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Application Number: 16659893 Document Date: 10/22/2019

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**Doc Code: TRACK1.REQ**
**Document Description: TrackOne Request**

PTO/SB/424 (12-11)

## CERTIFICATION AND REQUEST FOR PRIORITIZED EXAMINATION UNDER 37 CFR 1.102(e) (Page 1 of 1)

| | | | |
|---|---|---|---|
| First Named Inventor: | Mark E. Deem | Nonprovisional Application Number (if known): | |
| Title of Invention: | SYSTEMS AND METHODS FOR DELIVERY OF A THERAPEUTIC AGENT | | |

**APPLICANT HEREBY CERTIFIES THE FOLLOWING AND REQUESTS PRIORITIZED EXAMINATION FOR THE ABOVE-IDENTIFIED APPLICATION.**

1. The processing fee set forth in 37 CFR 1.17(i), the prioritized examination fee set forth in 37 CFR 1.17(c), and if not already paid, the publication fee set forth in 37 CFR 1.18(d) have been filed with the request. The basic filing fee, search fee, examination fee, and any required excess claims and application size fees are filed with the request or have been already been paid.

2. The application contains or is amended to contain no more than four independent claims and no more than thirty total claims, and no multiple dependent claims.

3. The applicable box is checked below:

**I. ☑ Original Application (Track One) - Prioritized Examination under § 1.102(e)(1)**

i. (a) The application is an original nonprovisional utility application filed under 35 U.S.C. 111(a). This certification and request is being filed with the utility application via EFS-Web.

---OR---

(b) The application is an original nonprovisional plant application filed under 35 U.S.C. 111(a). This certification and request is being filed with the plant application in paper.

ii. An executed oath or declaration under 37 CFR 1.63 is filed with the application.

**II. ☐ Request for Continued Examination - Prioritized Examination under § 1.102(e)(2)**

i. A request for continued examination has been filed with, or prior to, this form.
ii. If the application is a utility application, this certification and request is being filed via EFS-Web.
iii. The application is an original nonprovisional utility application filed under 35 U.S.C. 111(a), or is a national stage entry under 35 U.S.C. 371.
iv. This certification and request is being filed prior to the mailing of a first Office action responsive to the request for continued examination.
v. No prior request for continued examination has been granted prioritized examination status under 37 CFR 1.102(e)(2).

| | |
|---|---|
| Signature /Daidre L. Burgess/ | Date 10/22/2019 |
| Name (Print/Typed) Daidre L. Burgess | Practitioner Registration Number 60389 |

***Note:*** *Signatures of all the inventors or assignees of record of the entire interest or their representative(s) are required in accordance with 37 CFR 1.33 and 11.18. Please see 37 CFR 1.4(d) for the form of the signature. If necessary, submit multiple forms for more than one signature, see below*.*

☐ *Total of _____ forms are submitted.

# Privacy Act Statement

The **Privacy Act of 1974 (P.L. 93-579)** requires that you be given certain information in connection with your submission of the attached form related to a patent application or patent. Accordingly, pursuant to the requirements of the Act, please be advised that: (1) the general authority for the collection of this information is 35 U.S.C. 2(b)(2); (2) furnishing of the information solicited is voluntary; and (3) the principal purpose for which the information is used by the U.S. Patent and Trademark Office is to process and/or examine your submission related to a patent application or patent. If you do not furnish the requested information, the U.S. Patent and Trademark Office may not be able to process and/or examine your submission, which may result in termination of proceedings or abandonment of the application or expiration of the patent.

The information provided by you in this form will be subject to the following routine uses:

1. The information on this form will be treated confidentially to the extent allowed under the Freedom of Information Act (5 U.S.C. 552) and the Privacy Act (5 U.S.C 552a). Records from this system of records may be disclosed to the Department of Justice to determine whether disclosure of these records is required by the Freedom of Information Act.
2. A record from this system of records may be disclosed, as a routine use, in the course of presenting evidence to a court, magistrate, or administrative tribunal, including disclosures to opposing counsel in the course of settlement negotiations.
3. A record in this system of records may be disclosed, as a routine use, to a Member of Congress submitting a request involving an individual, to whom the record pertains, when the individual has requested assistance from the Member with respect to the subject matter of the record.
4. A record in this system of records may be disclosed, as a routine use, to a contractor of the Agency having need for the information in order to perform a contract. Recipients of information shall be required to comply with the requirements of the Privacy Act of 1974, as amended, pursuant to 5 U.S.C. 552a(m).
5. A record related to an International Application filed under the Patent Cooperation Treaty in this system of records may be disclosed, as a routine use, to the International Bureau of the World Intellectual Property Organization, pursuant to the Patent Cooperation Treaty.
6. A record in this system of records may be disclosed, as a routine use, to another federal agency for purposes of National Security review (35 U.S.C. 181) and for review pursuant to the Atomic Energy Act (42 U.S.C. 218(c)).
7. A record from this system of records may be disclosed, as a routine use, to the Administrator, General Services, or his/her designee, during an inspection of records conducted by GSA as part of that agency's responsibility to recommend improvements in records management practices and programs, under authority of 44 U.S.C. 2904 and 2906. Such disclosure shall be made in accordance with the GSA regulations governing inspection of records for this purpose, and any other relevant (*i.e.*, GSA or Commerce) directive. Such disclosure shall not be used to make determinations about individuals.
8. A record from this system of records may be disclosed, as a routine use, to the public after either publication of the application pursuant to 35 U.S.C. 122(b) or issuance of a patent pursuant to 35 U.S.C. 151. Further, a record may be disclosed, subject to the limitations of 37 CFR 1.14, as a routine use, to the public if the record was filed in an application which became abandoned or in which the proceedings were terminated and which application is referenced by either a published application, an application open to public inspection or an issued patent.
9. A record from this system of records may be disclosed, as a routine use, to a Federal, State, or local law enforcement agency, if the USPTO becomes aware of a violation or potential violation of law or regulation.

PTO/AIA/14 (02-18)
Approved for use through 11/30/2020. OMB 0651-0032
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it contains a valid OMB control number.

| Application Data Sheet 37 CFR 1.76 | Attorney Docket Number | 5187.01US01AP |
|---|---|---|
| | Application Number | |
| Title of Invention | SYSTEMS AND METHODS FOR DELIVERY OF A THERAPEUTIC AGENT | |

The application data sheet is part of the provisional or nonprovisional application for which it is being submitted. The following form contains the bibliographic data arranged in a format specified by the United States Patent and Trademark Office as outlined in 37 CFR 1.76.
This document may be completed electronically and submitted to the Office in electronic format using the Electronic Filing System (EFS) or the document may be printed and included in a paper filed application.

## Secrecy Order 37 CFR 5.2:

☐ Portions or all of the application associated with this Application Data Sheet may fall under a Secrecy Order pursuant to 37 CFR 5.2 (Paper filers only. Applications that fall under Secrecy Order may not be filed electronically.)

## Inventor Information:

**Inventor 1** Remove

**Legal Name**

| Prefix | Given Name | Middle Name | Family Name | Suffix |
|---|---|---|---|---|
| | Mark | E. | Deem | |

**Residence Information (Select One)** ● US Residency Non US Residency Active US Military Service

| City | State/Province | Country of Residence |
|---|---|---|
| Mountain View | CA | US |

**Mailing Address of Inventor:**

| | |
|---|---|
| Address 1 | c/o The Foundry, LLC |
| Address 2 | 199 Jefferson Drive |
| City | Menlo Park |
| State/Province | CA |
| Postal Code | 94025 |
| Country | US |

**Inventor 2** Remove

**Legal Name**

| Prefix | Given Name | Middle Name | Family Name | Suffix |
|---|---|---|---|---|
| | Hanson | | Gifford | |

**Residence Information (Select One)** ◉ US Residency Non US Residency Active US Military Service

| City | State/Province | Country of Residence |
|---|---|---|
| Woodside | CA | US |

**Mailing Address of Inventor:**

| | |
|---|---|
| Address 1 | c/o The Foundry, LLC |
| Address 2 | 199 Jefferson Drive |
| City | Menlo Park |
| State/Province | CA |
| Postal Code | 94025 |
| Country | US |

All Inventors Must Be Listed - Additional Inventor Information blocks may be generated within this form by selecting the **Add** button. Add

## Correspondence Information:

**Enter either Customer Number or complete the Correspondence Information section below.**
**For further information see 37 CFR 1.33(a).**

| Application Data Sheet 37 CFR 1.76 | Attorney Docket Number | 5187.01US01AP |
|---|---|---|
| | Application Number | |
| Title of Invention | SYSTEMS AND METHODS FOR DELIVERY OF A THERAPEUTIC AGENT | |

☐ **An Address is being provided for the correspondence Information of this application.**

| | | | |
|---|---|---|---|
| **Customer Number** | 24113 | | |
| **Email Address** | | Add Email | Remove Email |

## Application Information:

| | | | |
|---|---|---|---|
| **Title of the Invention** | SYSTEMS AND METHODS FOR DELIVERY OF A THERAPEUTIC AGENT | | |
| **Attorney Docket Number** | 5187.01US01AP | **Small Entity Status Claimed** | ☒ |
| **Application Type** | Nonprovisional | | |
| **Subject Matter** | | | |
| **Total Number of Drawing Sheets (if any)** | 27 | **Suggested Figure for Publication (if any)** | |

## Filing By Reference:

Only complete this section when filing an application by reference under 35 U.S.C. 111(c) and 37 CFR 1.57(a). Do not complete this section if application papers including a specification and any drawings are being filed. Any domestic benefit or foreign priority information must be provided in the appropriate section(s) below (i.e., "Domestic Benefit/National Stage Information" and "Foreign Priority Information").

For the purposes of a filing date under 37 CFR 1.53(b), the description and any drawings of the present application are replaced by this reference to the previously filed application, subject to conditions and requirements of 37 CFR 1.57(a).

| Application number of the previously filed application | Filing date (YYYY-MM-DD) | Intellectual Property Authority or Country |
|---|---|---|
| | | |

## Publication Information:

☐ Request Early Publication (Fee required at time of Request 37 CFR 1.219)

☐ **Request Not to Publish.** I hereby request that the attached application not be published under 35 U.S.C. 122(b) and certify that the invention disclosed in the attached application **has not and will not** be the subject of an application filed in another country, or under a multilateral international agreement, that requires publication at eighteen months after filing.

## Representative Information:

Representative information should be provided for all practitioners having a power of attorney in the application. Providing this information in the Application Data Sheet does not constitute a power of attorney in the application (see 37 CFR 1.32).
Either enter Customer Number or complete the Representative Name section below. If both sections are completed the customer Number will be used for the Representative Information during processing.

| | | | |
|---|---|---|---|
| Please Select One: | ● Customer Number | US Patent Practitioner | ○ Limited Recognition (37 CFR 11.9) |
| Customer Number | 24113 | | |

| Application Data Sheet 37 CFR 1.76 | Attorney Docket Number | 5187.01US01AP |
|---|---|---|
| | Application Number | |
| Title of Invention | SYSTEMS AND METHODS FOR DELIVERY OF A THERAPEUTIC AGENT | |

## Domestic Benefit/National Stage Information:

This section allows for the applicant to either claim benefit under 35 U.S.C. 119(e), 120, 121, 365(c), or 386(c) or indicate National Stage entry from a PCT application. Providing benefit claim information in the Application Data Sheet constitutes the specific reference required by 35 U.S.C. 119(e) or 120, and 37 CFR 1.78.
When referring to the current application, please leave the "Application Number" field blank.

| Prior Application Status | Pending | | | Remove |
|---|---|---|---|---|
| Application Number | Continuity Type | Prior Application Number | Filing or 371(c) Date (YYYY-MM-DD) | |
| | Continuation of | 16/036381 | 2018-07-16 | |

| Prior Application Status | Patented | | | Remove |
|---|---|---|---|---|
| Application Number | Continuity Type | Prior Application Number | Filing Date (YYYY-MM-DD) | Patent Number | Issue Date (YYYY-MM-DD) |
| 16/036381 | Continuation of | 15/358187 | 2016-11-22 | 10022529 | 2018-07-17 |

| Prior Application Status | Patented | | | Remove |
|---|---|---|---|---|
| Application Number | Continuity Type | Prior Application Number | Filing Date (YYYY-MM-DD) | Patent Number | Issue Date (YYYY-MM-DD) |
| 15/358187 | Continuation of | 14/601529 | 2015-01-21 | 9498283 | 2016-11-22 |

| Prior Application Status | Patented | | | Remove |
|---|---|---|---|---|
| Application Number | Continuity Type | Prior Application Number | Filing Date (YYYY-MM-DD) | Patent Number | Issue Date (YYYY-MM-DD) |
| 14/601529 | Continuation of | 13/660629 | 2012-10-25 | 8961391 | 2015-02-24 |

| Prior Application Status | Patented | | | Remove |
|---|---|---|---|---|
| Application Number | Continuity Type | Prior Application Number | Filing Date (YYYY-MM-DD) | Patent Number | Issue Date (YYYY-MM-DD) |
| 13/660629 | Continuation of | 13/253595 | 2011-10-05 | 8338164 | 2012-12-25 |

| Prior Application Status | Patented | | | Remove |
|---|---|---|---|---|
| Application Number | Continuity Type | Prior Application Number | Filing Date (YYYY-MM-DD) | Patent Number | Issue Date (YYYY-MM-DD) |
| 13/253595 | Continuation of | 12/559278 | 2009-09-14 | 8133497 | 2012-03-13 |

| Prior Application Status | Patented | | | Remove |
|---|---|---|---|---|
| Application Number | Continuity Type | Prior Application Number | Filing Date (YYYY-MM-DD) | Patent Number | Issue Date (YYYY-MM-DD) |
| 12/559278 | Division of | 11/459090 | 2006-07-21 | 7608275 | 2009-10-27 |

| Prior Application Status | Expired | | | Remove |
|---|---|---|---|---|
| Application Number | Continuity Type | Prior Application Number | Filing or 371(c) Date (YYYY-MM-DD) | |
| 11/459090 | Claims benefit of provisional | 60/702077 | 2005-07-22 | |

Additional Domestic Benefit/National Stage Data may be generated within this form by selecting the **Add** button. Add

| Application Data Sheet 37 CFR 1.76 | Attorney Docket Number | 5187.01US01AP |
|---|---|---|
| | Application Number | |
| Title of Invention | SYSTEMS AND METHODS FOR DELIVERY OF A THERAPEUTIC AGENT | |

## Foreign Priority Information:

This section allows for the applicant to claim priority to a foreign application. Providing this information in the application data sheet constitutes the claim for priority as required by 35 U.S.C. 119(b) and 37 CFR 1.55. When priority is claimed to a foreign application that is eligible for retrieval under the priority document exchange program (PDX)[i] the information will be used by the Office to automatically attempt retrieval pursuant to 37 CFR 1.55(i)(1) and (2). Under the PDX program, applicant bears the ultimate responsibility for ensuring that a copy of the foreign application is received by the Office from the participating foreign intellectual property office, or a certified copy of the foreign priority application is filed, within the time period specified in 37 CFR 1.55(g)(1).

Remove

| Application Number | Country[i] | Filing Date (YYYY-MM-DD) | Access Code[i] (if applicable) |
|---|---|---|---|
| | | | |

Additional Foreign Priority Data may be generated within this form by selecting the **Add** button. Add

## Statement under 37 CFR 1.55 or 1.78 for AIA (First Inventor to File) Transition Applications

☐ This application (1) claims priority to or the benefit of an application filed before March 16, 2013 and (2) also contains, or contained at any time, a claim to a claimed invention that has an effective filing date on or after March 16, 2013.
NOTE: By providing this statement under 37 CFR 1.55 or 1.78, this application, with a filing date on or after March 16, 2013, will be examined under the first inventor to file provisions of the AIA.

| Application Data Sheet 37 CFR 1.76 | Attorney Docket Number | 5187.01US01AP |
|---|---|---|
| | Application Number | |
| Title of Invention | SYSTEMS AND METHODS FOR DELIVERY OF A THERAPEUTIC AGENT | |

## Authorization or Opt-Out of Authorization to Permit Access:

When this Application Data Sheet is properly signed and filed with the application, applicant has provided written authority to permit a participating foreign intellectual property (IP) office access to the instant application-as-filed (see paragraph A in subsection 1 below) and the European Patent Office (EPO) access to any search results from the instant application (see paragraph B in subsection 1 below).

Should applicant choose not to provide an authorization identified in subsection 1 below, applicant **must opt-out** of the authorization by checking the corresponding box A or B or both in subsection 2 below.

**NOTE**: This section of the Application Data Sheet is **ONLY** reviewed and processed with the **INITIAL** filing of an application. After the initial filing of an application, an Application Data Sheet cannot be used to provide or rescind authorization for access by a foreign IP office(s). Instead, Form PTO/SB/39 or PTO/SB/69 must be used as appropriate.

**1. Authorization to Permit Access by a Foreign Intellectual Property Office(s)**

**A. Priority Document Exchange (PDX)** - Unless box A in subsection 2 (opt-out of authorization) is checked, the undersigned hereby **grants the USPTO authority** to provide the European Patent Office (EPO), the Japan Patent Office (JPO), the Korean Intellectual Property Office (KIPO), the State Intellectual Property Office of the People's Republic of China (SIPO), the World Intellectual Property Organization (WIPO), and any other foreign intellectual property office participating with the USPTO in a bilateral or multilateral priority document exchange agreement in which a foreign application claiming priority to the instant patent application is filed, access to: (1) the instant patent application-as-filed and its related bibliographic data, (2) any foreign or domestic application to which priority or benefit is claimed by the instant application and its related bibliographic data, and (3) the date of filing of this Authorization. See 37 CFR 1.14(h)(1).

**B. Search Results from U.S. Application to EPO** - Unless box B in subsection 2 (opt-out of authorization) is checked, the undersigned hereby **grants the USPTO authority** to provide the EPO access to the bibliographic data and search results from the instant patent application when a European patent application claiming priority to the instant patent application is filed. See 37 CFR 1.14(h)(2).

The applicant is reminded that the EPO's Rule 141(1) EPC (European Patent Convention) requires applicants to submit a copy of search results from the instant application without delay in a European patent application that claims priority to the instant application.

**2. Opt-Out of Authorizations to Permit Access by a Foreign Intellectual Property Office(s)**

☐ A. Applicant **DOES NOT** authorize the USPTO to permit a participating foreign IP office access to the instant application-as-filed. If this box is checked, the USPTO will not be providing a participating foreign IP office with any documents and information identified in subsection 1A above.

☐ B. Applicant **DOES NOT** authorize the USPTO to transmit to the EPO any search results from the instant patent application. If this box is checked, the USPTO will not be providing the EPO with search results from the instant application.

**NOTE:** Once the application has published or is otherwise publicly available, the USPTO may provide access to the application in accordance with 37 CFR 1.14.

| Application Data Sheet 37 CFR 1.76 | Attorney Docket Number | 5187.01US01AP |
|---|---|---|
| | Application Number | |
| Title of Invention | SYSTEMS AND METHODS FOR DELIVERY OF A THERAPEUTIC AGENT | |

## Applicant Information:

Providing assignment information in this section does not substitute for compliance with any requirement of part 3 of Title 37 of CFR to have an assignment recorded by the Office.

**Applicant** 1 — Remove

If the applicant is the inventor (or the remaining joint inventor or inventors under 37 CFR 1.45), this section should not be completed. The information to be provided in this section is the name and address of the legal representative who is the applicant under 37 CFR 1.43; or the name and address of the assignee, person to whom the inventor is under an obligation to assign the invention, or person who otherwise shows sufficient proprietary interest in the matter who is the applicant under 37 CFR 1.46. If the applicant is an applicant under 37 CFR 1.46 (assignee, person to whom the inventor is obligated to assign, or person who otherwise shows sufficient proprietary interest) together with one or more joint inventors, then the joint inventor or inventors who are also the applicant should be identified in this section.

Clear

| Assignee | Legal Representative under 35 U.S.C. 117 | Joint Inventor |
|---|---|---|
| ● Person to whom the inventor is obligated to assign. | Person who shows sufficient proprietary interest | |

If applicant is the legal representative, indicate the authority to file the patent application, the inventor is:

Name of the Deceased or Legally Incapacitated Inventor:

If the Applicant is an Organization check here. ☒

| Organization Name | The Foundry, LLC | | |
|---|---|---|---|
| **Mailing Address Information For Applicant:** | | | |
| **Address 1** | 199 Jefferson Drive | | |
| Address 2 | | | |
| **City** | Menlo Park | **State/Province** | CA |
| **Country** | US | Postal Code | 94025 |
| Phone Number | | Fax Number | |
| Email Address | | | |

Additional Applicant Data may be generated within this form by selecting the Add button. Add

## Assignee Information including Non-Applicant Assignee Information:

Providing assignment information in this section does not substitute for compliance with any requirement of part 3 of Title 37 of CFR to have an assignment recorded by the Office.

| **Application Data Sheet 37 CFR 1.76** | Attorney Docket Number | 5187.01US01AP |
|---|---|---|
| | Application Number | |
| Title of Invention | SYSTEMS AND METHODS FOR DELIVERY OF A THERAPEUTIC AGENT | |

**Assignee 1**

Complete this section if assignee information, including non-applicant assignee information, is desired to be included on the patent application publication. An assignee-applicant identified in the "Applicant Information" section will appear on the patent application publication as an applicant. For an assignee-applicant, complete this section only if identification as an assignee is also desired on the patent application publication.

Remove

If the Assignee or Non-Applicant Assignee is an Organization check here. ☐

| Prefix | **Given Name** | Middle Name | **Family Name** | Suffix |
|---|---|---|---|---|
| | | | | |

**Mailing Address Information For Assignee including Non-Applicant Assignee:**

| | | | |
|---|---|---|---|
| **Address 1** | | | |
| Address 2 | | | |
| **City** | | **State/Province** | |
| **Country** i | | Postal Code | |
| Phone Number | | Fax Number | |
| Email Address | | | |

Additional Assignee or Non-Applicant Assignee Data may be generated within this form by selecting the Add button. Add

## Signature:

Remove

**NOTE:** This Application Data Sheet must be signed in accordance with 37 CFR 1.33(b). **However, if this Application Data Sheet is submitted with the INITIAL filing of the application and either box A or B is not checked in subsection 2 of the "Authorization or Opt-Out of Authorization to Permit Access" section, then this form must also be signed in accordance with 37 CFR 1.14(c).**

This Application Data Sheet **must** be signed by a patent practitioner if one or more of the applicants is a **juristic entity** (e.g., corporation or association). If the applicant is two or more joint inventors, this form must be signed by a patent practitioner, **all** joint inventors who are the applicant, or one or more joint inventor-applicants who have been given power of attorney (e.g., see USPTO Form PTO/AIA/81) on behalf of **all** joint inventor-applicants.

See 37 CFR 1.4(d) for the manner of making signatures and certifications.

| **Signature** | /Daidre L. Burgess/ | | | Date (YYYY-MM-DD) | 2019-10-22 |
|---|---|---|---|---|---|
| First Name | Daidre | Last Name | Burgess | Registration Number | 60389 |

Additional Signature may be generated within this form by selecting the Add button. Add

| **Application Data Sheet 37 CFR 1.76** | Attorney Docket Number | 5187.01US01AP |
|---|---|---|
| | Application Number | |
| Title of Invention | SYSTEMS AND METHODS FOR DELIVERY OF A THERAPEUTIC AGENT | |

This collection of information is required by 37 CFR 1.76. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 23 minutes to complete, including gathering, preparing, and submitting the completed application data sheet form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

# Privacy Act Statement

The Privacy Act of 1974 (P.L. 93-579) requires that you be given certain information in connection with your submission of the attached form related to a patent application or patent. Accordingly, pursuant to the requirements of the Act, please be advised that: (1) the general authority for the collection of this information is 35 U.S.C. 2(b)(2); (2) furnishing of the information solicited is voluntary; and (3) the principal purpose for which the information is used by the U.S. Patent and Trademark Office is to process and/or examine your submission related to a patent application or patent. If you do not furnish the requested information, the U.S. Patent and Trademark Office may not be able to process and/or examine your submission, which may result in termination of proceedings or abandonment of the application or expiration of the patent.

The information provided by you in this form will be subject to the following routine uses:

1 The information on this form will be treated confidentially to the extent allowed under the Freedom of Information Act (5 U.S.C. 552) and the Privacy Act (5 U.S.C. 552a). Records from this system of records may be disclosed to the Department of Justice to determine whether the Freedom of Information Act requires disclosure of these records.

2. A record from this system of records may be disclosed, as a routine use, in the course of presenting evidence to a court, magistrate, or administrative tribunal, including disclosures to opposing counsel in the course of settlement negotiations.

3 A record in this system of records may be disclosed, as a routine use, to a Member of Congress submitting a request involving an individual, to whom the record pertains, when the individual has requested assistance from the Member with respect to the subject matter of the record.

4. A record in this system of records may be disclosed, as a routine use, to a contractor of the Agency having need for the information in order to perform a contract. Recipients of information shall be required to comply with the requirements of the Privacy Act of 1974, as amended, pursuant to 5 U.S.C. 552a(m).

5. A record related to an International Application filed under the Patent Cooperation Treaty in this system of records may be disclosed, as a routine use, to the International Bureau of the World Intellectual Property Organization, pursuant to the Patent CooperationTreaty.

6. A record in this system of records may be disclosed, as a routine use, to another federal agency for purposes of National Security review (35 U.S.C. 181) and for review pursuant to the Atomic Energy Act (42 U.S.C. 218(c)).

7. A record from this system of records may be disclosed, as a routine use, to the Administrator, General Services, or his/her designee, during an inspection of records conducted by GSA as part of that agency's responsibility to recommend improvements in records management practices and programs, under authority of 44 U.S.C. 2904 and 2906. Such disclosure shall be made in accordance with the GSA regulations governing inspection of records for this purpose, and any other relevant (i.e., GSA or Commerce) directive. Such disclosure shall not be used to make determinations about individuals.

8. A record from this system of records may be disclosed, as a routine use, to the public after either publication of the application pursuant to 35 U.S.C. 122(b) or issuance of a patent pursuant to 35 U.S.C. 151. Further, a record may be disclosed, subject to the limitations of 37 CFR 1.14, as a routine use, to the public if the record was filed in an application which became abandoned or in which the proceedings were terminated and which application is referenced by either a published application, an application open to public inspections or an issued patent.

9. A record from this system of records may be disclosed, as a routine use, to a Federal, State, or local law enforcement agency, if the USPTO becomes aware of a violation or potential violation of law or regulation.

# Electronic Patent Application Fee Transmittal

| | |
|---|---|
| **Application Number:** | |
| **Filing Date:** | |
| **Title of Invention:** | SYSTEMS AND METHODS FOR DELIVERY OF A THERAPEUTIC AGENT |
| **First Named Inventor/Applicant Name:** | Mark E. Deem |
| **Filer:** | Daidre L. Burgess/Valerie Mitchell |
| **Attorney Docket Number:** | 5187.01US01AP |

Filed as Small Entity

**Filing Fees for Track I Prioritized Examination - Nonprovisional Application under 35 USC 111(a)**

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| Document Number | Document Description | File Name | File Size(Bytes)/ Message Digest | Multi Part /.zip | Pages (if appl.) |
|---|---|---|---|---|---|
| 1 | | 5187_01US01AP_APP.pdf | 202788<br>1bd4da68665860a9bcbea904fb6d1953d5f3f848 | yes | 60 |
| | **Multipart Description/PDF files in .zip description** | | | | |
| | **Document Description** | | **Start** | **End** | |
| | Abstract | | 60 | 60 | |
| | Claims | | 55 | 59 | |
| | Specification | | 1 | 54 | |
| **Warnings:** | | | | | |
| **Information:** | | | | | |
| 2 | Drawings-other than black and white line drawings | 5187_01US01AP_DRW.pdf | 2395831<br>9809b1ae670d06b5216a05a1cc78c4cdf1a4bcc1 | no | 27 |
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| 3 | Oath or Declaration filed | 5187_01US01AP_Declaration.pdf | 317506<br>46e0e18143479c657d48b96af76c5e91fb0b3d54 | no | 1 |
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| 4 | TrackOne Request | 5187_01US01AP_Track_One_Request.pdf | 140835<br>86cc1a28f0c1ecfcc9ccdc89651e684256b7d0c7 | no | 2 |
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| 5 | Application Data Sheet | 5187_01US01AP_ADS.pdf | 1256914<br>8c3a1cea29a5010809cca538452bc5786ee4c9f3 | no | 9 |

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| 6 | Fee Worksheet (SB06) | fee-info.pdf | 41366<br>557eb88cf04d4fa2f25fff27a8bdce4da0a71176 | no | 2 |
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## ABSTRACT

Methods and apparatus are provided for applying an fragment of a neurotoxin such as the active light chain (LC) of the botulinum toxin (BoNT), such as one of the serotype A, B, C, D, E, F or G botulinum toxins, via permeabilization of targeted cell membranes to enable translocation of the botulinum neurotoxin light chain (BoNT-LC) molecule across the targeted cell membrane to the cell cytosol where a therapeutic response is produced in a mammalian system. The methods and apparatus include use of catheter based delivery systems, non-invasive delivery systems, and transdermal delivery systems.

WHAT IS CLAIMED IS:

1. A method of treating a nasal condition of a patient comprising:

positioning a distal portion of a treatment device proximate to target tissue in a nasopharyngeal passage of a patient; and

administering therapy to the target tissue with the treatment device so as to disrupt neural activity such that mucus secretion is reduced in the nasopharyngeal passage;

wherein administering therapy comprises at least one of delivering energy to the target tissue and changing the temperature of the target tissue.

2. The method of claim 1, wherein administering therapy comprises delivering energy from at least one energy delivery element on the treatment device.

3. The method of claim 2, wherein the energy comprises RF energy.

4. The method of claim 2, wherein the energy comprises ultrasound energy.

5. The method of claim 2, wherein the energy comprises microwave energy.

6. The method of claim 2, wherein the energy comprises AC or DC current.

7. The method of claim 1, wherein changing the temperature comprises transferring thermal energy between the treatment device and the target tissue.

8. The method of claim 1, wherein the energy is delivered or the temperature is changed so as to electroporate cells in the target tissue.

9. The method of claim 1, wherein administering therapy comprises contacting target tissue with a delivery portion of the treatment device.

10. The method of claim 9, wherein the target tissue is contacted without penetrating the target tissue.

11. The method of claim 9, wherein the target tissue is penetrated by the treatment delivery portion of the treatment device.

12. The method of claim 1, wherein administering therapy further comprises delivering an agent to the target tissue.

13. The method of claim 12, wherein the agent comprises a neurotoxin.

14. The method of claim 1, wherein administering therapy disables adrenergic cells in the target tissue.

15. The method of claim 1, wherein administering therapy blocks or disrupts acetycholine release in cells in the target tissue.

16. The method of claim 15, wherein the cells comprise goblet cells or epithelial cells.

17. A method of treating a nasal condition of a patient comprising:

positioning a distal portion of a treatment device proximate to target tissue in a nasopharyngeal passage of a patient; and

administering therapy to the target tissue with the treatment device to alter nasopharyngeal cells such that congestion in the nasopharyngeal passage is reduced;

wherein administering therapy comprises delivering energy to the target tissue.

18. The method of claim 17, wherein the energy is delivered from an energy delivery element on the treatment device.

19. The method of claim 18, wherein the energy comprises RF energy.

20. The method of claim 19, wherein the energy delivery element comprises a monopolar or bipolar electrode.

21. The method of claim 18, wherein the energy delivery element comprises a plurality of electrodes.

22. The method of claim 18, wherein the energy delivery element is configured to concentrate energy laterally relative to the distal portion of the treatment device.

23. The method of claim 22, wherein the energy delivery element comprises at least one electrode disposed on a lateral side of the distal portion of the treatment device.

24. The method of claim 18, further comprising a monitoring electrode or system on the treatment device.

25. The method of claim 24, wherein the monitoring electrode or system comprises a thermocouple, ultrasound transducer, fiberoptic, or sensing or stimulating electrode.

26. The method of claim 17, wherein the energy is delivered so as to disable adrenergic cells.

27. The method of claim 26, wherein the adrenergic cells are disabled such that mucus production in the nasopharyngeal passage is reduced.

28. The method of claim 26, wherein the energy is delivered to as to electroporate the adrenergic cells.

29. The method of claim 28, further comprising delivering an agent to disable the adrenergic cells.

30. The method of claim 29, wherein the agent comprises a neurotoxin.

# SYSTEMS AND METHODS FOR DELIVERY OF A THERAPEUTIC AGENT

## RELATED APPLICATIONS

This application is a continuation of Application No. 16/036,381 filed July 16, 2018, which in turn is a continuation of Application No. 15/358,187 filed November 22, 2016, now U.S. Patent No. 10,022,529 issued July 17, 2018, which in turn is a continuation of Application No. 14/601,529 filed January 21, 2015, now U.S. Patent No. 9,498,283 issued November 22, 2016, which in turn is a continuation of Application No. 13/660,629 filed October 25, 2012, now U.S. Patent No. 8,961,391 issued February 24, 2015, in turn which is a continuation of Application No. 13/253,595 filed October 5, 2011, now U.S. Patent No. 8,338,164 issued December 25, 2012, which in turn is a continuation of Application No. 12/559,278 filed September 14, 2009, now U.S. Patent No. 8,133,497 issued March 13, 2012, which in turn is a divisional of Application No. 11/459,090 filed July 21, 2006, now U.S. Patent No. 7,608,275 issued October 27, 2009, which claims the benefit of U.S. Provisional Application No. 60/702,077 filed July 22, 2005, each of which is hereby fully incorporated herein by reference. U.S. Patent No. 7,608,275 also claims the benefit of, and incorporated by reference in its entirety U.S. Provisional Application No. and 60/747,771, filed on May 19, 2006, which is thereby also fully incorporated herein by reference.

## BACKGROUND OF THE INVENTION

### Field of the Invention

The present invention relates to methods and apparatus for the control of autonomic nerve function comprising delivery via permeabilization of targeted cell membranes a therapeutically effective amount of a portion or fragment of a neurotoxin such as botulinum toxin

(BoNT), the active portion known as the light chain (LC), to cause a clinical benefit in various regions within the body. More particularly, the present invention relates to methods and systems for delivering toxins, such as botulinum toxin light chain fragments, to target cells in a nasal cavity.

First used for medical purposes over 20 years ago for treatment of blepharospasm and strabismus and other skeletal muscle abnormalities, certain neurotoxins have found widespread use in millions of patients worldwide for a variety of conditions.

Controlled injection of neurotoxins has become a common procedure to control skeletal muscle spasms. While the primary application of neurotoxins such as BOTOX®, commercially sold by Allergan, Inc. (Irvine, Calif.), has been focused on cosmetic applications, such as treatment of facial wrinkles, other uses for the compound are now common. Certain applications include treatment of cervical dystonia, tremor, headache (migraine), spasticity, torticollis, hemifacial spasm, blepharospasm, meige syndrome, spastic dysphonia, writers cramp, hyperhydrosis, hypersalivation, bladder dysfunction multiple sclerosis, spinal cord injury, cystic fibrosis, stroke paralysis, stuttering, and all types of pain.

Clostridium botulinum neurotoxins (BoNTs) block the release of acetylcholine from peripheral cholinergic nerve endings thereby disabling the release of neurotransmitters from the cells (Bigalke, H. and Shoer, L. F. (1999) Clostridial Neurotoxins in Handbook of Experimental Pharmacology 45, 407-443). This mechanism of action is well defined. Seven immunologically distinct serotypes of neurotoxin, designated types A through G, have been identified as discussed by Simpson, L. L., Schmidt, J. J. and Middlebrook, J. L. (1988) in Methods Enzymol. 165, 76-85. There are general structural and functional similarities among the various types of

neurotoxins, but they all have preferred recipients, for example some favor use in humans and other in non-human species.

A frequently used neurotoxin for many applications in the human body is Botulinum Toxin Type A (BoNT\A), a protein produced by the bacterium Clostridium botulinum and sold commercially by Allergan, Inc., as BOTOX®. Botulinum toxin blocks the release of neurotransmitter from the nerves that control the contraction of the target muscles. When used in medical settings, small doses of the toxin are injected into the affected muscles and block the release of a chemical acetylcholine that signals the muscle to contract. The toxin thus paralyzes or weakens the injected muscle.

In addition, use of neurotoxin for control of the following conditions has been proposed in U.S. Patent No. 6,063,768 to First, and U.S. Patent No. 5,766,605 to Sanders, including: rhinorrhea, asthma, COPD, excessive stomach acid secretion, spastic colitis, otitus media, arthritis, tensoynovitis, lupus, connective tissue disease, inflammatory bowel disease, gout, tumors, musculo-skeletal abnormalities, reflex sympathetic dystrophies, tendonitis, bursitis, and peripheral neuropathy. Various other patents contemplate the use of a neurotoxin for additional applications such as, neuromuscular disorders (U.S. Patent No. 6,872,397), essential tremor (U.S. Patent No. 6,861,058), pancreatitis (U.S. Patent No. 6,843,998), muscle spasm (U.S. Patent No. 6,841,156), sinus headache (U.S. Patent No. 6,838,434), endocrine disorders (U.S. Patent No. 6,827,931), priapism (U.S. Patent No. 6,776,991), thyroiditis (U.S. Patent No. 6,773,711), cardiovascular disease (U.S. Patent No. 6,767,544), thyroid disorders (U.S. Patent No. 6,740,321), hypocalcemia (U.S. Patent No. 6,649,161), hypercalcemia (U.S. Patent No. 6,447,785), tardive dyskenesia (U.S. Patent No. 6,645,496), fibromyalgia (U.S. Patent No.

6,623,742), Parkinson's Disease (U.S. Patent No. 6,620,415) cerebral palsy (U.S. Patent No. 6,448,231), inner ear disorders (U.S. Patent No. 6,358,926), cancers (U.S. Patent No. 6,139,845), otic disorders (U.S. Patent No. 6,265,379), appetite reduction (US2004/0253274), compulsive disorders (US2004/0213814, US2004/0213813), uterine disorders (US2004/0175399), neuropsychiatric disorders (US2003/0211121), dermatological or transdermal applications (US2004/00091880), focal epilepsy (US2003/0202990) the contents of which are expressly incorporated herein by reference in their entirety.

The patent authors have further detailed devices and methods for treating asthma with local delivery of the intact botulinum toxin in U.S. Patent Application No. 10/437,882, filed on May 13, 2003, the contents of which are expressly incorporated by reference herein in its entirety.

Due to their extreme toxicity, neurotoxins are highly controlled and can have disastrous consequences if not used and controlled properly, especially when used *in vivo*. In addition, due to their toxicity, the body tends to build up a resistance to their use, resulting in lower efficacy, the need for increased treatments, or the need to discontinue their use all together in certain patients.

In light of the foregoing, it would be desirable to provide methods and apparatus for delivering neurotoxins such as botulinum toxins non-toxically.

It would also be desirable to provide methods and apparatus for treating various conditions with a neurotoxin such as botulinum toxin fragments via *in vivo* cell permeabilization.

In would also be desirable to provide a system of devices, including catheters, trocars, needles, endoscopes, inhalers, nebulizers and aerosolizers and other mechanisms to deliver fragmented neurotoxins non-toxically.

Further, it would be desirable to couple energy delivery devices with the delivery of fragmented neurotoxins to deliver active neurotoxins, non-toxically, including catheter based energy systems, and non-invasive energy systems.

For example, rhinitis, which includes the symptoms of rhinorrhea, is a condition resulting from inflammation and swelling of the patient's mucus membranes which line the nasal cavity. Rhinitis and/or rhinorrea can arise from a number of conditions, most often results from allergies to pollen, dust, seasonal allergens or other airborne substances, but can also be caused by anatomic pathologies such as blockages (as in the case of sinusitis). Symptoms may include sneezing, itching, nasal congestion, and a runny nose.

While numerous treatments for rhinitis have been proposed over the years, no single treatment is optimum for all patients or all conditions. Most commonly, hay fever and other forms of rhinitis are treated with antihistamines which block the inflammatory response. While effective, many antihistamines can cause drowsiness, have a limited duration of effect, and present the patient with an on-going cost to continuously purchase the drugs.

Recently, a longer term therapy for rhinitis which relies on the use of botulinum toxin ("BoNT") for blocking mucus production by mucus-producing cells in the nasal membrane has been proposed. Botulinum and other neurotoxins are capable of disabling adrenergic cells, including epithelial or goblet cells which are responsible for the majority of mucus production in the nasal cavity membrane. Dr. Ira Sanders has demonstrated that introduction of intact

botulinum toxin molecules into the nasal passages of canines can reduce mucus secretion by a significant amount.

While the experimental work of Dr. Sanders holds promise for long term rhinitis treatment, it faces a number of challenges before it is suitable for wide spread use in humans. In particular, botulinum toxin is a neurotoxin which could have significant negative effects on a patient if accidentally released outside of the targeted nasal passages. Inadvertent distribution of the toxin to muscles of the oropharynx, mouth, tongue, or elsewhere could result in serious complications to the patient. Additionally, the use of botulinum-soaked gauze pads for delivering the toxin to the nasal cavities, as demonstrated by Dr. Sanders, will have limited ability to uniformly and selectively deliver the botulinum to the regions having high concentrations of preferred target cells, such as epithelial or goblet cells in the nasopharynx.

For these reasons, it would be desirable to provide improved methods and systems for delivering toxins, such as botulinum and active botulinum fragments, to the nasal membrane of a patient, particularly a patient suffering from rhinitis or other conditions associated with nasal inflammation and conditions, such as sinus headaches and migraine headaches. The methods and systems should be capable of providing for selective and repeatable delivery of the toxins to defined target areas within the nasal cavities, including particular paranasal sinuses, the nasopharynx, and in some cases substantially the entire nasal cavity. The systems and methods should provide for the safe and effective delivery of the toxins, and in particular should reduce or eliminate the risk of toxin being delivered to non-targeted tissues outside of the nasal cavity. At least some of these objectives will be met by the inventions described herein below.

U.S. Pat. No. 5,766,605, to Sanders et al. has been described above. Sharri et al. (1995) Otolaryngol. Head Neck Surg. 112: 566-571 also reports the work of Dr. Sanders described in the '605 patent. Ünal et al. (2002) Acta Otolaryngol 123: 1060-1063 describes the injection of botulinum toxin A into the turbinates of patients suffering from allergic rhinitis. See also, U.S. Pat. No. 6,974,578. The purification and possible therapeutic uses of botulinum light chain are described in US2004/0151741, US2005/0019346, and Chaddock et al. (2002) Protein Expression and Purification 25: 219-228. Energy-mediated transdermal delivery of intact botulinum toxin is suggested in US2005/007441 and 2004/0009180. The use of catheters and other devices for the energy-mediated delivery of botulinum light chain is described in commonly owned co-pending provisional application 60/702,077, filed Jul. 22, 2005, the full disclosure of which has previously been incorporated herein by reference.

All publications and patents or patent applications mentioned in this specification are herein incorporated by reference to the same extent as if each individual publication, patent or patent application was specifically and individually so incorporated by reference.

## BRIEF SUMMARY OF THE INVENTION

According to the present invention, an active fragment (sometimes referred to as a catalytic portion) of a neurotoxin such as the botulinum neurotoxin (BoNT), preferably the light chain (LC) portion of BoNT, is delivered to target cells via cell membrane permeabilization. Such delivery provides a non-toxic delivery scheme for deriving a variety of clinical benefits. Although botulinum toxins are used broadly for a variety of clinical applications, the present invention provides enhanced methods of delivery and use of the isolated active fragments or

portions of the toxin. Other neurotoxins which may be used in the methods and systems of the present invention include ricin and its active fragments, exotoxin A and its active fragments, diphtheria toxin and its active fragments, cholera toxin and its active fragments, tetanus toxin and its active fragments, and the like.

The present invention contemplates application to all of the conditions listed herein, collectively defined as "therapeutic target conditions", and any other conditions for which BoNT and other neurotoxins are known to or can be shown to provide a therapeutic benefit. Certain examples have been detailed below for specific applications, but it is within the scope of the present invention that the methods and devices detailed herein have specific applications to many or all of the conditions wherein the intact neurotoxins have shown or proposed to show a therapeutic benefit or effect.

In one aspect of the present invention, BoNT-LC or other active neurotoxin fragment is delivered with the application of energy to achieve cell membrane permeabilization.

In another aspect of the present invention methods and apparatus are provided for altering autonomic nerve function by utilizing an electric field or ultrasonic energy generated by a pulse or pulses of a designated duration and amplitude to alter tissue at the cellular level via permeabilization of the cell membrane to facilitate the translocation of the BoNT-LC or other active neurotoxin fragment to the cell cytosol.

A further aspect of the invention is to provide methods and apparatus for treating or inhibiting a variety of diseases or syndromes that have an underlying neurogenic component, by disrupting the neurogenic activities of the promoters or mediators of the disease or syndrome. Such disruption is facilitated by delivering an active fragment of botulinum toxin, such as the

light chain portion of botulinum toxin serotype A (BoNT-LC/A), in the presence of an electric field or ultrasonic energy applied to permeabilize the wall of targeted cell under conditions which induce reversible poration of the cellular membrane and efficient passage of the BoNT-LC fragment to the cell cytosol, its catalytic environment.

In addition to the methods described thus far, the present invention further provides systems for delivering toxins to target cells in a mammalian host. The target cells may be in any of the target regions described above or in any other target region which may benefit from the specific and enhanced delivery of a neurotoxin to cells within the region. Systems comprise catheter or other structure adapted to introduce the toxin or toxin fragment to a region adjacent the target cells. The systems further comprise an energy applicator for applying energy to the target cells under condition which cause poration of the cell membranes to enhance delivery of the toxins and/or their active fragments. The systems still further comprise a source of the toxin or active fragments suitable for introduction from the catheter or other delivery structure.

The energy applicator will typically be adapted to selectively apply energy to target cells within the region where the toxin is to be introduced, e.g., by focusing energy distribution to the particular target cells or regions which are rich with the target cells. Alternatively, the energy applicator may be adapted to apply energy non-selectively within the target region where both target cells and other cell types may receive the energy.

In some instances, the toxin may comprise an intact toxin, but more usually will comprise an active toxin fragment as defined elsewhere in this application. In the exemplary embodiments, the active toxin fragment is the light chain fragment of the botulinum toxin

(BoNT-LC). The light chain fragment may be derived from any one of at least botulinum toxins A, B, C, D, E, F, and G.

The energy applicators of the systems of the present invention may be adapted to apply electric energy, typically pulses between 1 V and 500 V to the targeted region. The electric energy may be radiofrequency (RF) energy, where the energy may be pulsed for durations between 5 microseconds to 100 milliseconds. Alternatively, the electrical energy can be direct current (DC), alternating current (AC), or combinations thereof.

`In addition to electrical energy, the energy applicator may be adapted to deliver ultrasonic energy, X-ray beam energy, microwave energy, or any other energy type which can achieve a reversible poration of the target cell walls.

There are at least two general power categories of medical ultrasound waves which may be utilized in the present invention. One category of medical ultrasound wave is high acoustic pressure ultrasound. Another category of medical ultrasound wave is low acoustic pressure ultrasound. Acoustic power is expressed in a variety of ways by those skilled in the art. One method of estimating the acoustic power of an acoustic wave on tissue is the Mechanical Index. The Mechanical Index (MI) is a standard measure of the acoustic output in an ultrasound system. High acoustic pressure ultrasound systems generally have a MI greater than 10. Low acoustic pressure systems generally have a MI lower than 5. For example, diagnostic ultrasound systems are limited by law to a Mechanical Index not to exceed 1.9. Another measurement used by those skilled in the art is the spatial peak, peak average intensity (Isppa). The intensity of an ultrasound beam is greater at the center of its cross section than at the periphery. Similarly, the intensity varies over a given pulse of ultrasound energy. Isppa is measured at the location where

intensity is maximum averaged over the pulse duration. Isppa for high acoustic pressure or high intensity focused ultrasound (HIFU) applications ranges from approximately 1500 W/cm$^2$ to 9000 W/cm$^2$. Diagnostic ultrasound equipment, for instance, will generally have, and an Isppa less than 700 W/cm$^2$. Yet another way in which ultrasound waves can be characterized is by the amplitude of their peak negative pressure. High acoustic pressure or HIFU applications employ waves with peak amplitudes in excess of 10 MPa. Low acoustic pressure ultrasound will generally have peak negative pressures in the range of 0.01 to 5.0 MPa. Diagnostic ultrasound equipment, for example, will generally have a peak amplitude less than 3.0 MPa. Both high and low acoustic pressure ultrasound systems generally operate within the frequency range of 20 KHz-10.0 MHz Interventional applications (such as in blood vessels) operate clinically up to about 50 MHz. Also opthalmologic applications up to about 15 MHz. Diagnostic imaging typically uses frequencies of about 3 to about 10 MHz. Physical therapy ultrasound systems generally operate at frequencies of either 1.0 MHz or 3.3 MHz. High acoustic pressure ultrasound or high intensity focused ultrasound has been used for tissue disruption, for example for direct tumor destruction. High intensity focused ultrasound using high acoustic pressure ultrasound is most commonly focused at a point in order to concentrate the energy from the generated acoustic waves in a relatively small focus of tissue.

Systems and methods for permeabilization of target tissue cell membranes according to the present invention may employ either high acoustic pressure or low acoustic pressure ultrasound. Some embodiments may preferably employ relatively low acoustic pressure, for example the systems described herein where the transducers are mounted on the delivery devices and operate inside the body. Other systems may operate at interim acoustic pressure ranges. For

example, systems described herein which employ an external ultrasound generator and transducer and which conduct the ultrasound to the target tissues through the use of a wave guide. In these systems, losses due to transduction through the wave guide can be compensated for by increasing the input power to the wave guide until adequate power is delivered to the target tissue. Finally, some systems described herein may employ focused or partially focused higher pressure ultrasound, for example the systems which employ an external mask to conduct the ultrasonic power through the tissues to the target tissues. It should be appreciated that combinations of high and low acoustic pressure systems may also be employed.

The catheter or other structure may be adapted to introduce the toxin to the target cells in a variety of ways. For example, catheters may comprise a needle for injecting the toxin, optionally a needle which is deployable axially or radially from the catheter body. Alternatively or additionally, catheters may be provided with nozzles or other ports for aerosolizing the toxin, particularly within regions of the lung as described herein. Still further alternatively or additionally, the catheters may comprise balloons or other expandable elements for deflecting an end of the catheter to engage one or more ports on the catheter against the tissue where the toxin fragments are released through the port(s). In a specific embodiment, the ports may be in the balloon itself where the toxin fragments are released through the ports in the balloon as the balloon is inflated with the medium containing the fragments. With such balloon embodiments, the electrodes or other energy transducers will typically be located within the balloon for applying the poration energy to the target tissue. Further optionally, the energy applicators may be mounted directly on the catheters, for example in the form of acoustic transducers, RF or other electrical electrodes, or the like. Alternatively, the energy applicator may be provided

separately from the toxin delivery catheter or other source, typically being an external source, such as an external high intensity focused ultrasound (HIFU) source or an external electrode array for delivering radiofrequency or other electroporation energy.

In a further aspect of the invention, it may be desirable to provide methods and devices that utilize a non-toxic delivery mechanism to target cells to reduce the potential for an immunogenic response to the delivered toxin over time.

In a further aspect of the invention, it may be desirable to deliver the therapeutic neurotoxin fragment and energy via a catheter.

In a further aspect of the invention, it may be desirable to deliver the therapeutic neurotoxin fragment via an aerosolizer or nebulizer.

In a further aspect of the invention, it may be desirable to deliver the therapeutic neurotoxin fragment via an inhaler.

In a further aspect of the invention, it may be desirable to deliver the therapeutic neurotoxin fragment and membrane transport energy transdermally.

In a further aspect of the invention, it may be desirable to deliver the therapeutic neurotoxin fragment via a catheter, or aerosolizer or inhaler, and the energy via a catheter placed in the vicinity of the targeted cell.

In a further aspect of the invention, it may be desirable to deliver the therapeutic neurotoxin fragment and the membrane transport energy via an implantable generator and drug delivery pump.

In a further aspect of the invention, it may be desirable to deliver the therapeutic neurotoxin fragment via a catheter, or aerosolizer (nebulizer) or inhaler, and the energy via an external energy source adapted to target the applied energy in the vicinity of the targeted cell.

In other aspects, embodiments of the present invention provide treatments for any disease or condition for which rhinorrhea is a result or symptom.

Rhinorrhea is the term describing the effluence of mucus from the lining of the nasal passages, nasopharynx, or paranasal sinuses. Rhinorrhea can be a symptom of a number of diseases such as the common cold, sinusitis or rhinitis, Rhinitis (inflammation of the airways) falls into two major categories—allergic and non-allergic (or vasomotor) rhinitis. Each can have several subcategories. Sinusitis is an infection or inflammation of the paranasal sinuses. Sinusitis may have a number of different causes, and can be the result of chronic inflammation of the nasal passages, for example as a result of chronic rhinitis.

Allergic rhinitis is an immunologic response modulated by IgE and characterized predominantly by sneezing, rhinorrhea, nasal congestion, and pruritus of the nose. It may be seasonal (a condition commonly referred to as hay fever) or perennial. The seasonal form is caused by allergens released during tree, grass, or weed pollination, whereas the perennial form is caused by allergies to animal dander, dust mites, or mold spores with or without associated pollinosis. Data also suggest that urban air pollutants from automobiles and other sources may have an adjunctive effect.

Nonallergic rhinitis is a diagnosis of rhinitis without any immunoglobulin E (IgE) mediation, as documented by allergen skin testing. Hence, the rhinorrhea, sneezing, pruritus, and congestion do not result from allergy or hypersensitivity and continue to persist, whether

continuously or sporadically. Nonallergic rhinitis affects 5-10% of the population. Nonallergic rhinitis has 7 basic subclassifications, including infectious rhinitis, nonallergic rhinitis with eosinophilia syndrome (NARES), occupational rhinitis, hormonal rhinitis, drug-induced rhinitis, gustatory rhinitis, and vasomotor rhinitis. Patients may or may not present with the same symptoms seen in allergic rhinitis.

According to the present invention, botulinum toxin, ricin, exotoxin A, diphtheria toxin, cholera toxin, tetanus toxin, other neurotoxins, and active fragments thereof are delivered to a patient's nasal membrane while applying energy to target cells within the membrane under conditions which cause a reversible (or in some instances non-reversible) poration of the cell membranes to enhance delivery of the toxin into the cells. The region where the toxin is introduced may comprise any portion of the nasal cavity, such as a single paranasal sinus or portion thereof, a main nasal passage, two or more paranasal sinuses, or in some cases may comprise substantially the entire nasal cavity of the patient. A particular target region for the toxin may comprise the nasopharynx which is at the back of the nasal passage. The nasopharynx comprises a cluster of goblet cells which are responsible for mucus secretion and which are susceptible to the disabling mechanism of the botulinum toxin and other neurotoxins.

The energy is preferably selectively applied to a targeted region containing a variety of cell types, including goblet cells, epithelial cells, ciliated and non-ciliated columnar cells, basal cells, and less or no energy applied to untargeted regions. It will be appreciated that the energy may be applied to regions of the nasal membrane which are the same or different from the regions to which the toxin has been introduced. By controlling the delivery area of both the toxin delivery and the energy delivery, the methods and apparatus of the present invention can more

specifically target the epithelial or goblet and other recipient cells of interest while minimizing the amount of toxin which enters non-targeted cells. That is, only those cells in the nasal membrane which are exposed to both the toxin and the applied energy will preferentially be permeablized or porated to receive the toxin within the cytoplasm of the cell.

The toxin to be delivered may comprise any neurotoxin capable of disabling mucus secretion in epithelial or goblet cells and other mucus-producing nasal cells. Preferably, the toxin comprises botulinum toxin, although other toxins such as ricin, exotoxin A, diphtheria toxin, cholera toxin, tetanus toxin, other neurotoxins, and active fragments thereof may also find use. In preferred aspects of the present invention, only an active fragment of the toxin will be delivered to the nasal cavity. botulinum toxin and the other toxins listed above commonly comprise both a heavy chain and a light chain. The heavy chain is responsible for binding to the target cells and mediating passage of the light chain into the cytoplasm of the target cells. By delivering only the light or active chain of these toxins (after removal of the heavy chain or recombinant production of only the light chain), the risk of accidental delivery of the toxin to non-target cells is greatly reduced. Delivery of the active or light chain fragments into the target cells, according to the present invention, is mediated and enhanced by the selective application of an energy which porates the cell membrane to allow entry of the light chain or active fragment. The presently preferred botulinum light chain fragment may be derived from any one of the seven presently known botulinum types A-G.

Any type of energy which is capable of reversibly permeablizing or porating the cell wall to allow passage of the toxin molecule, either whole toxin or preferably light chain fragment, into the cell cytoplasm may be applied to the cell membrane. Thus, energy may comprise various

forms of electrical pulses, acoustic pulses, X-ray energy, microwave energy, or the like, and combinations thereof. Preferably, the energy will be either pulsed electrical energy of the type which is commonly used for cellular electroporation or will be ultrasonic energy of the type commonly employed for sonoporation of cells. The energy may be applied using the same catheters or other structures which are used for delivering the toxins. Alternatively, the energy may be applied using separate external or internal sources, such as using separate external ultrasonic transducers and/or ultrasound wave guides capable of delivering focused or unfocused ultrasound into the target tissues of the nasal cavity.

In specific embodiments of the methods of the present invention, the toxin may be introduced to the target region through a catheter. For example, the catheter may carry a balloon which engages the nasal membrane in order to effect delivery of the toxin to the target cells. In a particular example, the balloon is porous over at least a portion of its area so that the toxin may be released to specific areas of the nasal membrane, typically being incorporated into a suitable liquid, gel, or other fluid or fluidizable carrier. In other embodiments, the toxin may be introduced through one or more needles carried on the catheter, and in still other embodiments the toxin may be aerosolized from a small port, nozzle, or other orifice or structure on the catheter.

While the energy may be applied from a separate external source, as generally described above, the energy will most often be applied from the same catheter or other apparatus used to deliver the toxin. For example, when ultrasonic or other acoustic energy is being applied, the transducer may be on or associated with the catheter. In a particular example, it is shown that the transducer may be located within or beneath the porous balloon which is used to deliver toxin to

the nasal membrane. When electrical energy is used for poration, the electrodes may be on the catheter within or surrounding the region which delivers the energy to the nasal membrane. In other instances, the energy may be applied from a separate catheter or other device adapted for intranasal introduction. In still other instances, the energy application will apply energy transcutaneously, for example from the skin of the face, typically surrounding the nose over the sinus cavities.

In addition to the methods described above, the present invention further provides systems for delivering toxins to goblet and other target cells as defined above in a nasal membrane. The systems may typically comprise a catheter adapted to introduce a toxin to a region adjacent to the target cells. An energy applicator is further provided for applying energy to the target cells under conditions which cause a reversible poration of the cell membranes to enhance delivery of the toxin. Systems may still further comprise a source of the toxin suitable for introduction from or through the catheter. The energy applicator may be mounted on or incorporated within the catheter, or may be a separate or intrabronchial external source. In an exemplary embodiment illustrated below, an external applicator may comprise a mask or other structure which fits over the nose and/or sinus region of the patient and which is capable of delivering acoustic to the target cells within the target regions.

When the energy applicator is incorporated with or within the catheter, the delivery pattern of the energy will usually be at least partially overlapping with the toxin delivery pattern of the catheter. For example, when a porous balloon is used for toxin delivery, the acoustic transducer, electroporation electrodes, or the like, will usually be disposed to deliver energy which at least partly overlaps with the dispersion pattern of the toxin. In some instances, the

region of applied energy will be coextensive with the region of toxin dispersion. In other instances, the two regions will only partially overlap. In the latter case, the delivery of the toxin will be enabled or enhanced principally within the regions of overlap.

## BRIEF DESCRIPTION OF THE DRAWINGS

Further features of the invention, its nature and various advantages will be more apparent from the accompanying drawings and the following detailed description, in which:

FIG. 1 - depicts a schematic of the creation of neurotoxin Botulinum Toxin Type A (BoNT/A), including the light chain (LC) fragment or portion.

FIG. 2A - depicts a schematic of a target cell, including the cell membrane, and inner cellular matrices.

FIG. 2B - depicts a schematic of the target cell wherein LC molecule has been introduced.

FIG. 3A-3B - depicts a the target cell of FIG. 2 showing application of an energy field (EF) to produce permeabilization or pores (P) in the cell membrane, and introduction of the LC fragment therethrough.

FIG. 4 - depicts a schematic of a cell wherein the energy field has been discontinued, and neurotransmission of the cell has been effectively blocked.

FIGS. 5, 5A-5B - depicts various embodiments of a delivery device of the present invention utilizing multiple energy transmission elements and an energy transmission system.

FIGS. 6A-D, 6AA, and 6CC - depict various electrode catheter configurations adapted to deliver energy or energy and therapeutic agents to target tissue.

FIG. 7 - depicts an alternative embodiment of the present invention wherein one of the multiple energy transmission elements is placed at the targeted cell site, and the other in a location remote therefrom.

FIG. 8 - depicts an embodiment of the present invention utilizing an ultrasound element on a catheter device.

FIG. 9 - depicts an embodiment of the present invention utilizing an inhaler with an in vivo energy delivery source.

FIG. 10 - depicts an interstitial method of use of the present invention.

FIG. 11 - depicts an embodiment of the present invention utilizing an aerosolizing element.

FIG. 12 - depicts a fully implantable pulse generator, lead and agent delivery pump of the present invention.

FIG. 13 - depicts an embodiment of the present invention utilizing an external energy delivery source applied to the therapeutic agent applied in the vicinity of a targeted cell.

FIG. 14 - depicts an embodiment of the present invention wherein the energy and therapeutic agent are delivered transdermally.

FIG. 15 - depicts a method of use of a noninvasive agent delivery device coupled with a non-invasive energy source for treating a lumen or tract of the respiratory system.

FIGS. 15A and 15B - depict use of a balloon for delivering toxin fragments in a lung.

FIGS. 16A and 16B - depict use of a deflected catheter tip for delivering toxin fragments in a lung.

FIG. 17 - depicts use on an external hand held transducer for enhancing cellular uptake of toxin delivered from a separate nasal aerosolizer.

FIGS. 18 and 19 - depict use of balloon catheters for delivering toxin to the nasopharynx.

FIGS. 20A-20C - depict use of a self-expanding toxin delivery structure on a catheter.

FIGS. 21 and 22 - depict a protocol for limiting toxin introduction by partial filling of a porous delivery balloon.

FIGS. 23 and 24 – depicts sizing of a delivery balloon to control distribution of toxin released into the nasal cavity.

FIG. 25 - depicts the use of multiple small balloons for selective toxin delivery into the nasal cavity.

FIG. 26 - depicts sonoporation using an external mask placed over the sinuses and nose.

FIG. 27 - depicts a front view of an external sonoporation mask showing placement of ultrasound transducers.

FIGS. 28 and 29 - depict an orally-introduced occlusion catheter and energy applicator system.

FIGS. 30 and 31 - depict nose plugs for occluding and optionally delivery poration energy to the nasal cavity.

FIGS. 32 and 33 - depict an alternate occlusion catheter system for targeted toxin delivery to the nasopharynx.

FIGS. 34 and 35 - depict use of a toxin delivery catheter having side holes and a distal occlusion balloon for isolating and protecting the olefactory bulb.

FIGS. 36 and 38 - depict use of a simple catheter having a shaped distal end for aerosolizing a toxin into a target nasal sinus though an ostium open to the sinus.

FIG. 37 -depicts toxin delivery using a nasal spray and energy delivery using a face mask.

FIGS. 39 and 40 - depict use of a catheter having a shaped distal end for positioning separate infusion structures with a target sinus cavity.

## DETAILED DESCRIPTION OF THE INVENTION

The present invention is directed to methods and apparatus for targeting the non toxic delivery of a fragment of a neurotoxin, while still maintaining the catalytic or toxic effect of the neurotoxin fragment once it is non-toxically delivered to its targeted cell. For purposes of this specification, the term "non-toxic", "non-toxically" and the like refer to the state of the fragment molecule prior to delivery to a target location. In this description, the fragment neurotoxin is intended to retain its toxic effect once delivered to its catalytic environment; the intracellular matrix or cytosol of the targeted cell.

Devices and methods of the present invention may be directed to suitable "targeted regions" such as muscle cells in various regions of the body related to the various "therapeutic target conditions" or syndromes to be treated, as detailed in this specification above. Some particular examples include targeting mucosal and muscular lining of the lung, cholinergic cells in the region of tumors, myofacial regions, vascular smooth muscle cells, musculoskeletal regions and the like.

According to the present invention, energy fields (EF) may be applied to target regions in conjunction with the delivery of a fragmented neurotoxin such as BoNT-LC to facilitate the transfer of the neurotoxin fragment into the targeted cell, non-toxically via in vivo target cell permeabilization.

Use of Isolated Light Chain of Botulinum Neurotoxins

Generally, the BoNT molecule is synthesized as a single polypeptide chain of 150 kD molecular weight. The neurotoxin is then exposed to enzymes, either during cultivation of the *Clostridium botulinum* organism or subsequent to purification of the toxin, wherein specific peptide bonds are cleaved or "nicked" resulting in the formation of a dichain molecule referred to as BoNT. As shown in FIG. 1, dichain neurotoxin is composed of a light chain (LC) region 50 kD molecular weight linked by disulfide bonds to a heavy chain (HC) 100 kD molecular weight (Kistner, A., Habermann, E. (1992) *Naunyn Schmiedebergs Arch. Pharmacol.* 345, 227-334). When the light chain is separated from the heavy chains of botulinum toxin, neither chain is capable of blocking neurotransmitter release, however, the light chain alone is capable of blocking acetylcholine release if transported directly into the cell cytosol. (Ahnert-Hilger, G., Bader, M. F., Bhakdi, S., Gratzl, M. (1989) *J. Neurochem.* 52, 1751-1758 and Simpson, L. L. (1981) *Pharmacol. Rev.* 33, 155-188.) Focusing on the light chain, the isolation or separation process essentially renders the light chain "non-toxic" in a general environment, while still maintaining its effect or toxicity, once it is transported through the target cell membrane.

Over the past several years, the separation and purification of the light chain and heavy chain of BoNT has seen significant development activity. In the case of the heavy chain (HC),

researchers are interested in its ability to bond with a target cell and deliver certain molecules into that cell. For example, various drug delivery applications have been suggested, for example, using the HC to bind to tPA so that a patient could inhale the HC bound tPA allowing it to cross the membrane of the lungs and be transported into the bloodstream for anticoagulation. Of particular interest to the present invention are the efforts to isolate and purify the light chain (LC) of the botulinum molecule. In its isolated and purified form, all HC elements are removed, rendering the LC incapable of crossing the cell membrane without assistance. Thus, the LC is non-toxic until delivered to the target cell cytosol by the delivery protocols of the present invention.

Various groups have been active in the area of isolation and purification. For example, companies such as Metabiologics, a group affiliated with the University of Wisconsin, the Center for Applied Microbiology and Research (CAMR), a division of the UK Health Protection Agency, List Biological Laboratories, Inc. of California, and other research groups throughout the world. Many of these companies provide purified preparations of botulinum neurotoxins from *Clostridium botulinum* types A and B. List Laboratories in particular provides recombinantly produced light chains from both types A, B, C, D and E.

According to the present invention, the therapeutic use and delivery of the light chain only may significantly improve the safety profile of certain applications of therapies utilizing BoNT. BoNT are some of the most lethal toxins known to man. All concerns about migration of the neurotoxin into unintended regions, and harm or toxicity to the patient or physician are eliminated by storing, handling, injecting and metabolizing the light chain only. In the absence of a specific membrane binding technology, the LC is completely non-toxic. In certain

applications, such as the treatment of asthma, this is of critical import. In using BoNT to treat asthma, a large quantity of the purified LC substance may be introduced directly into the lung, and then specifically transported to target cells in the exact location and only during the period of use of application of the membrane transport technology, such as cell membrane permeabilization by energy. Once the membrane transport technology has been removed, turned off or otherwise inactivated, the remaining LC which has not been transported into target cells can simply be removed from the body by standard biologic processes for expelling foreign materials, e.g. coughing, immune system or lymphatic system transport and the like.

In addition, therapeutic use of only the LC of the neurotoxin BoNT may reduce the likelihood of the body developing an immunogenic response to the therapy that is seen with delivery of the intact toxin. This could be a major advantage in light of the repetitive application or injection of the toxin that is required to maintain a therapeutic effect.

Non-Toxic Membrane Transport Mechanisms

To date, the main application of purified or isolated light chain has been the study of its mechanism of action. To further this research, literature has reported the use of certain detergent based permeabilization techniques to deliver fragment BoNT (Bittner M A, DasGupta B R, Holz R W. Isolated light chains of botulinum neurotoxins inhibit exocytosis. Studies in digitonin-permeabilized chromaffin cells. J Biol Chem 1989 June 25; 264(18):10354-10360.) Further reference to the mechanism of permeability of cell membranes to deliver botulinum toxin are mentioned in U.S. Patent No. 6,063,768 to First, and U.S. Patent No. 6,632,440 to Quinn, Chaddock, et al "Expression and Purification of Catalytically Active Non-Toxic Endopeptidase

Derivatives of Clostridium botulinum toxin type A", *Protein Expression and Purification*, 25 (2002) 219-228, contemplating the insertion of the light chain of BoNT into a target cell without the heavy chain for purposes of deriving vaccines or in bench top studies of cell mechanisms of action. The contents of these references are expressly incorporated by reference in their entirety. None of the teachings contemplate a delivery of a fragment of neurotoxin using a clinically acceptable permeabilization technique in vivo for therapeutic uses as is contemplated by the present invention.

For purposes of this specification, the term "poration" includes various forms of electroporation, such as the use of pulsed electric fields (PEFs), nanosecond pulsed electric fields (nsPEFs), ionophoreseis, electrophoresis, electropermeabilization, as well as other energy mediated permeabilization, including sonoporation (mediated by ultrasonic or other acoustic energy), and/or combinations thereof, to create temporary pores in a targeted cell membrane. Similarly, the term "electrode" or "energy source" used herein, encompasses the use of various types of energy producing devices, including x-ray, radiofrequency (RF), DC current, AC current, microwave, ultrasound, adapted and applied in ranges to produce membrane permeabilization in the targeted cell.

Reversible electroporation, first observed in the early 1970's, has been used extensively in medicine and biology to transfer chemicals, drugs, genes and other molecules into targeted cells for a variety of purposes such as electrochemotherapy, gene transfer, transdermal drug delivery, vaccines, and the like.

In general, electroporation may be achieved utilizing a device adapted to activate an electrode set or series of electrodes to produce an electric field. Such a field can be generated in

a bipolar or monopolar electrode configuration. When applied to cells, depending on the duration and strength of the applied pulses, this field operates to increase the permeabilization of the cell membrane and reversibly open the cell membrane for a short period of time by causing pores to form in the cell lipid bilayer allowing entry of various therapeutic elements or molecules, after which, when energy application ceases, the pores spontaneously close without killing the cell after a certain time delay. As characterized by Weaver, *Electroporation: A General Phenomenon for Manipulating Cells and Tissues* Journal of Cellular Biochemistry, 51:426-435 (1993), short (1-100 .mu.s) and longer (1-10 ms) pulses have induced electroporation in a variety of cell types. In a single cell model, most cells will exhibit electroporation in the range of 1-1.5V applied across the cell (membrane potential).

In addition, it is known in the art that macromolecules can be made to cross reversibly created pores at voltages of 120V or less applied to cells for durations of 20 microseconds to many milliseconds. For applications of electroporation to cell volumes, ranges of 10 V/cm to 10,000 V/cm and pulse durations ranging from 1 nanosecond to 0.1 seconds can be applied. In one example, a relatively narrow (pee) high voltage (200V) pulse can be followed by a longer (>msec) lower voltage pulse (<100V). The first pulse or series of pulses open the pores and the second pulse or series of pulses assist in the movement of the BoNT-LC across the cell membrane and into the cell.

Certain factors affect how a delivered electric field will affect a targeted cell, including cell size, cell shape, cell orientation with respect to the applied electric field, cell temperature, distance between cells (cell-cell separation), cell type, tissue heterogeneity, properties of the cellular membrane and the like.

Various waveforms or shapes of pulses may be applied to achieve electroporation, including sinusoidal AC pulses, DC pulses, square wave pulses, exponentially decaying waveforms or other pulse shapes such as combined AC/DC pulses, or DC shifted RF signals such as those described by *Chang in Cell Potation and Cell Fusion using and Oscillating Electric Field*, Biophysical Journal October 1989, Volume 56 pgs 641-652, depending on the pulse generator used or the effect desired. The parameters of applied energy may be varied, including all or some of the following: waveform shape, amplitude, pulse duration, interval between pulses, number of pulses, combination of waveforms and the like.

There are at least two general power categories of medical ultrasound waves. One category of medical ultrasound wave is high acoustic pressure ultrasound. Another category of medical ultrasound wave is low acoustic pressure ultrasound.

Acoustic power is expressed in a variety of ways by those skilled in the art. One method of estimating the acoustic power of an acoustic wave on tissue is the Mechanical Index. The Mechanical Index (MI) is a standard measure of the acoustic output in an ultrasound system.

High acoustic pressure ultrasound systems generally have a MI greater than 10. Low acoustic pressure systems generally have a MI lower than 5. For example, diagnostic ultrasound systems are limited by law to a Mechanical Index not to exceed 1.9.

Another measurement used by those skilled in the art is the spatial peak, peak average intensity (Isppa). The intensity of an ultrasound beam is greater at the center of its cross section than at the periphery. Similarly, the intensity varies over a given pulse of ultrasound energy. Isppa is measured at the location where intensity is maximum averaged over the pulse duration. Isppa for high acoustic pressure or high intensity focused ultrasound (HIFU) applications ranges

from approximately 1500W/cm2. to 9000 W/cm2. Diagnostic ultrasound equipment, for instance, will generally have, and an Isppa less than 700 W/cm2.

Yet another way in which ultrasound waves can be characterized is by the amplitude of their peak negative pressure. High acoustic pressure or HIFU applications employ waves with peak amplitudes in excess of 10 MPa. Low acoustic pressure ultrasound will generally have peak negative pressures in the range of 0.01 to 5.0 MPa. Diagnostic ultrasound equipment, for example, will generally have a peak amplitude less than 3.0 MPa.

Both high and low acoustic pressure ultrasound systems generally operate within the frequency range of 20 KHz-10.0 MHz Interventional applications (such as in blood vessels) operate clinically up to about 50 MHz. Also opthalmologic applications up to about 15 MHz. Diagnostic imaging typically uses frequencies of about 3 to about 10 MHz. Physical therapy ultrasound systems generally operate at frequencies of either 1.0 MHz or 3.3 MHz.

High acoustic pressure ultrasound or high intensity focused ultrasound has been used for tissue disruption, for example for direct tumor destruction. High intensity focused ultrasound using high acoustic pressure ultrasound is most commonly focused at a point in order to concentrate the energy from the generated acoustic waves in a relatively small focus of tissue.

Systems for permeabilization of target tissue cell membranes may employ either high acoustic pressure or low acoustic pressure ultrasound. Some embodiments may preferably employ relatively low acoustic pressure, for example the systems described herein where the transducers are mounted on the delivery devices and operate inside the body. Other systems may operate at interim acoustic pressure ranges. For example, systems described herein which employ an external ultrasound generator and transducer and which conduct the ultrasound to the target

tissues through the use of a wave guide. In these systems, losses due to transduction through the wave guide can be compensated for by increasing the input power to the wave guide until adequate power is delivered to the target tissue. Finally, some systems described herein may employ focused or partially focused higher pressure ultrasound, for example the systems which employ an external mask to conduct the ultrasonic power through the tissues to the target tissues. It should be appreciated that combinations of high and low acoustic pressure systems may also be employed.

A schematic example of the methods of the present invention are shown in FIGS. 2-4 in a simplified single cell model. A targeted cell 10, e.g. a goblet cell of the type which line the nasal cavity membrane, is shown in FIG. 2A. Fragmented neurotoxin such as BoNT-LC (LC) is introduced into the vicinity of the targeted cell as depicted in FIG. 2B. An energy field (EF) is applied in accordance with the present invention resulting in the transfer of the BoNT-LC through pores P to the intracellular matrix (cytosol) as shown in FIGS. 3A and 3B. Once this transfer has occurred, the release of neurotransmitters of the target cell are then blocked or disrupted, and once energy application is discontinued, the pores P in the cell membrane recover or close as depicted in FIG. 4.

Of particular interest for application in certain therapeutic target conditions is the developing field of sonoporation, and the terms “poration” and “permeablization” will also cover forms of cellular sonoporation. Just as pulses of high voltage electricity can open transient pores in the cell membrane, ultrasonic energy can do the same. See for example Guzman et al. "Equilibrium Loading of Cells with Macromolecules by Ultrasound: Effects of Molecular Sizing

and Acoustic Energy," Journal of Pharmaceutical Sciences, 91:7, 1693-1701, which examines the viability of ultrasound to deliver molecules of a variety of sizes into target cells. In addition, techniques for nebulizing fluids and aqueous drugs are well known in the art, and as such, devices of the present invention may be adapted to introduce a BoNT-LC solution to a target region, such as the lung or the nasal passage and then effect selective membrane transport of the BoNT-LC into the cell using sonoporation.

For example, U.S. Patent No. 6,601,581 to Babaev, hereby incorporated by reference in its entirety, describes certain techniques for delivering therapeutic agents using ultrasound for pulmonary delivery via an aerosolizing technique. Further, Guzman, et al, depicts delivery of molecules from a low of 62 Da up to 464 kDa (a range of 0.6-18.5 nm radius). Since the LC of the botulinum toxin is in the 50 kDa range, the LC would be very susceptible to sonoporetic delivery. Furthermore, Guzman, et al also showed that for all size ranges tested, levels of macromolecule within the cell reached thermodynamic equilibrium with the extracellular environment, and the cell uptake also depended on the energy delivered, as expressed in J/cm2. As such, the sonoporetic delivery of LC to the targeted regions may be controlled by adjusting the concentration of the LC exposed to the target region (e.g. wall or membrane of the lung), the energy delivered to the target region, or both.

Catheter Devices

To achieve the goals of the present invention, it may be desirable to employ methods and apparatus for achieving cell membrane permeabilization via the application of an energy source, either from a catheter located directly in the vicinity of the targeted cells, or an externally

focused energy system. For purposes of this specification, the term "catheter" may be used to refer to an elongate element, hollow or solid, flexible or rigid and capable of percutaneous introduction to a body (either by itself, or through a separately created incision or puncture), such as a sheath, a trocar, a needle, a lead. Further descriptions of certain electroporation catheters are described in U.S. Patent Application 60/701,747 (Attorney Docket No. 020979-003500US), filed on July 22, 2005, the full disclosure of which is expressly incorporated herein by reference.

FIGS. 5 and 5A-5B depict a system 20 utilizing an electroporation catheter 22 for selective electroporation of targeted cells. In certain configurations of the present invention, voltages may be applied via the electroporation catheter 22 to induce reversible electroporation at the same time as the catheter delivers the fragmented neurotoxin to the targeted region.

Referring to FIG. 5, electroporation catheter system 20 further comprises a pulse generator 24 such as those generators available from Cytopulse Sciences, Inc. (Columbia, Md.) or the Gene Pulser Xcell (Bio-Rad, Inc.), or IGEA (Carpi, Italy), electrically connected to a catheter having a proximal end and a distal end and adapted for minimally invasive insertion into the desired region of the body as described herein. The catheter further comprises an electroporation element 26 at a distal 28 end thereof The electroporation element may include for example a first and second electrode 30 and 32 operatively connected to the pulse generator for delivering the desired number, duration, amplitude and frequency of pulses to affect the targeted cells. These parameters can be modified either by the system or the user, depending on the location of the catheter within the body (intervening tissues or structures), and the timing and duration of reversible cell poration desired.

FIG. 5A depicts an arrangement of electrodes 30 and 32 that produces an electric field concentrated in a lateral direction from the catheter body whereas, FIG. 5B shows a device constructed to create a more uniform electric field about the shaft of the catheter body. Further catheter device and electrode configurations are shown in FIGS. 6A-6D. FIG. 6A depicts an elongate catheter 40 having first and second electrodes 42 and 44 near the distal tip thereof, and including a monitoring or stimulation electrode 46 in the vicinity of the active porating electrodes for localizing the treatment area. In some embodiments, the monitoring or stimulating function may be performed by one or more of the treatment electrodes. The catheter device may have an optional sharp tip 48 to facilitate percutaneous introduction. Cross-sectional view FIG. 6A A shows various lumens provided for neurotoxin fragment delivery and other purposes.

FIG. 6B is a similar catheter device 50 having electrodes 52, 54, and 56, but is further adapted to be steerable, or articulate at a region 53 near the distal end of the device, e.g., including a pull wire for deflecting the tip. Such steering ability enables the operator to introduce the device into tight or tortuous spaces (such as the bronchial passages or cardiovascular vessels) so that optimal placement of the device at the target location may be achieved.

FIG. 6C depicts a catheter device 60 having a needle 62 or other injection element to allow for the injection of a therapeutic agent such as a fragmented neurotoxin before, during or after the application of the pulsed energy or electroporation. The catheter 60 further includes electrodes 64 and 66 or other poration components as discussed herein. The injection element may be a needle 62 as shown in FIG. 6C, an infusion port, or other infusion means. Needle 62 may also be used as an electrode in addition to an injection port. Electrode 68 comprises a

monitoring or stimulating electrode. FIG. 10 depicts the use of a catheter of FIG. 6C to treat bronchial tissue in the lung for a variety of respiratory ailments such as asthma. FIG. 6CC is a cross-sectional view taken along line 6CC-6CC in FIG. 6, showing a co-axial sleeve design.

FIG. 6D depicts a catheter device 70 having electrode elements 72 and 74 that are adapted to extend laterally from the main catheter body, and in some cases, penetrate the surrounding tissue prior to application of energy. In doing so the depth and direction of the energy field created by the electroporative process, may be further controlled. A monitoring/stimulating electrode 76 will usually also be provided. Elements 72 and 74 may also be used as injection ports for introduction of toxin or toxin fragments.

FIG. 7 depicts the use of a catheter device 80 of the present invention for treatment of a respiratory tract, by positioning at least one electrode (82) at the target region, and a second electrode (84) remote from the target region, the target region being positioned between 82 and 84, such that activation of the electrodes produces an energy field (EF) therebetween, the size and intensity of which can be controlled by the placement of the electrodes relative to each other and the targeted region.

FIG. 8 depicts catheter 90 constructed in accordance with the principles of the present invention utilizing an ultrasonic element 92 that may be particularly useful in delivery of the BoNT-LC to bronchial tissue (lung) and/or nasal tissue that provides a broad but targeted transport of the LC across the target cell walls, for example, epithelial and goblet cell walls. In this device, ultrasound energy is delivered to the distal end of the catheter device via an ultrasonic waveguide 94 that is operatively connected to an ultrasound energy source (U/SES). The LC fragment would be delivered from a receptacle 96 via the same lumen as the waveguide

via a lumen provided the distal tip of the device. In operation, the ultrasonic energy would cause the LC solution to be nebulized, forming a mist or aerosol 98 within the lung, as shown in FIG. 11. The aerosol 98 itself, in the appropriate concentrations, may act as an ultrasound coupler, conveying the ultrasonic energy to the wall of the lung or other targeted cellular structures, causing sonoporation of the targeted cells whereby the LC fragment is transmitted across the cell membranes to become an effective neurotransmitter blocker. In an alternative embodiment, an ultrasonic transducer may be located directly at the tip of the delivery device, eliminating the need for a wave guide. Various catheters useful for delivering vibrational energy to tissue are described in U.S. Patent Nos. 6,361,554 and 6,464,680 to Brisken, the contents of which are expressly incorporated herein by reference in their entirety, for various therapeutic effects, such as enhancing cellular absorption of a substance.

Since air is a very effective insulator against transmission of ultrasonic energy, the treatment area in the lung may be more precisely controlled by the concentration of the LC mist and the intensity of the ultrasonic energy. A fairly steep drop off in energy delivery would occur as mist concentration diffused, effectively protecting areas outside the predetermined radius surrounding the distal end of the delivery device. According to the present invention, since no functional neurotoxin exists without an effective membrane transport technology, terminating the energy application leaves a harmless mist that is then coughed up (if resident in the lungs) or otherwise metabolized and excreted by the body.

Any of the catheter devices described herein, or described in the contemporaneously filed U.S. Patent Application 60/701,747 (Attorney Docket No. 020979-003500US), previously incorporated by reference in its entirety, may be adapted to include an energy delivery element

such as those described herein for purposes of providing a membrane transport system for delivery of a fragment of neurotoxin. In addition, certain catheter devices and methods such as those set forth in U.S. Patent Nos. 5,964,223 and 6,526,976 to Baran may be adapted to include energy transmission elements capable of producing a porative effect at the cellular level, including electrodes, ultrasonic elements and the like, for treatment in the respiratory tract.

Furthermore, any of the foregoing systems may include electrodes or other monitoring systems either located on the treatment catheter, or external to the patient, to determine the degree of treatment to the region, including, thermocouple, ultrasound transducers, fiberoptics, sensing or stimulating electrodes. Further, it may be desirable to incorporate multiple pairs of electrodes that may be activated in pairs, in groups, or in a sequential manner in order to maximize the desired shape of the energy field (EF) while minimizing the field strength requirements.

Implantable Devices

Just as energy may be delivered to a targeted region to facilitate the delivery of fragmented neurotoxin via a catheter system, it is also within the scope of the present invention to deliver neurotoxins via an implantable system, including a pulse generator, lead and drug pump as depicted in FIGS. 12. A neuromodulation system 200 may be fully implantable, having a pulse generator and a power supply or battery and be operatively connected to a programmable drug delivery pump all housed within a module 202, including a reservoir in which the BoNT-LC is stored for delivery over time using the principles of the present invention and technology

of the programmable drug pump. A catheter 204 can be adapted to deliver the drug and poration energy to a desired target location in the patient's body.

Examples of useful implantable devices of the present invention arc, devices such as those set forth in U.S. Patent No. 5,820,589 to Torgerson et al, the entire contents of which are hereby incorporated by reference, the SynchroMed® programmable pump available from Medtronic, Inc. (Minneapolis, Minn.), and the neurostimulation units such as the RESTORE* or SynergyPlus® available from Medtronic, Inc., modified if necessary to deliver the desired voltage range for cell membrane permeabilization. Implantation of the neurostimulation device is further described in U.S. Patent No. 6,847,849, incorporated herein by reference in its entirety.

The non-toxic nature of the BoNT in the absence of applied energy makes it possible to contemplate placing a bolus of neurotoxin in the body of a patient in what might otherwise be a toxic amount. This is particularly advantageous, since the traditional treatment regime using neurotoxins, is typically repeat injections of the toxins every 3 to 6 months and sometimes more frequently depending on the application. Certainly in more chronic conditions such as chronic pain, tremor, spasm, palsy and the like, such a fully implantable system may be highly desirable.

Non-Invasive Devices

It is within the scope of the invention to deliver either the energy or the therapeutic BoNT-LC non-invasively, or both. For example, FIG. 13 depicts delivery of the BoNT-LC via a catheter 100 placed in the bronchial passageway with the energy field (EF) delivered from outside the patient in the form of an energy system 102 such as focused ultrasound (HIFU), stereotactic x-ray beams, magnetic resonance transmission, and the like. As detailed in U.S.

Patent Nos. 6,626,855 and 6,719,694 to Weng, the contents of which are expressly incorporated herein by reference in their entirety, an ultrasound beam can be controlled from outside the patient to focus the ultrasound beam in the desired location and intensity. For use in the present invention, it may be desirable to pulse or otherwise attenuate the ultrasound beam to achieve reversible cellular poration at the targeted site. Further, due to its non-toxic state, the BoNT-LC may be inhaled by the patient using a standard inhaler device such as those using pressurized aerosols known as metered dose inhalers (MDI) available from Cardinal Health (Somerset, N.J.), the OPTIHALER® available from National Allergy Supply Incorporated (Georgia, USA), or a nebulizer breathing machine such as a Pari DURANEB 3000 portable nebulizer available from Medinfinity, Co. (Fountain Valley, Calif.). In addition, certain technology currently under development employing thermal aerosols, such as a the STACCATO.TM. vaporization technology from Alexza Molecular Delivery (Palo Alto, Calif.) may also be useful within the scope of the present invention. Such devices 110 may be used as depicted in FIG. 9 for treating a respiratory ailment such as asthma. Optionally, the drug can be delivered with the catheter 22 (as shown) or with the external sources of FIG. 13.

A combination of these non-invasive approaches may also be advantageous as shown in FIG. 15, wherein an non-invasive inhaler 110 is used to deliver the BoNT-LC to the target region (such as the lung), and the energy is delivered to the target region by the non-invasive source 102 such as the focused ultrasound (HIFU), stereotactic x-ray, or magnetic resonance transmission as previously described. Due to its non-invasive technique, this approach may have broad appeal to a large patient population, including pediatric use, on an outpatient basis in a clinic designated for the treatment of specific respiratory ailments.

In a further aspect of the present invention, the fragmented molecule BoNT-LC may be delivered intravenously to a patient to achieve a systemic affect. A non-invasive energy application device, such as those described above, may then be targeted at the area of interest to porate the target area, thereby locally delivering the BoNT-LC to the region sufficiently porated by the applied energy.

Cosmetic and Myofacial Applications. For some conditions, it may be desirable to apply the energy field from the surface of the skin to produce a porative effect, while injecting the BoNT-LC fragment into the targeted facial muscles as shown in FIG. 14. In operation, an injection device 220 places the BoNT-LC in the muscle to be treated (target region), and an energy transmission device such as an ultrasonic pen 222 with a single, or a series of ultrasonic elements located on the distal end and coupled to an energy transmission system 224, follows along the target region to controllably discharge the BoNT-LC fragments to the targeted cells leaving a highly controlled treated region. In some instances for treatments around the eye, it may be desirable to limit the penetration of the BoNT-LC to dermal or subdermal layers. In these applications, BoNT-LC may be applied transdermally with ultrasound assistance using techniques similar to those set forth in U.S. Patent No. 4,767,402 to Kost the contents of which is expressly incorporated herein in its entirety or through transdermal electroporation.

Intraluminal Devices

It may further be advantageous to position catheters of the present invention through vessels in the body to direct them to various regions to affect neurotransmitters in the cardiovascular system. Intraluminal catheters such as those shown in United States Patent

Applications 2001/0044596 to Jaafar and 2002/0198512 to Seward, hereby incorporated by reference in their entirety, may be used in this application of the present invention.

Treatment Enhancements

In some applications of the present invention, it may be desirable to assess the appropriate location for the therapy prior to treatment, the therapeutic effect as it is delivered, and ultimately the resulting effect. To achieve this, once the treatment device is in place adjacent the tissue to be treated, the energy generator may be activated, causing an energized field to be generated in the target area. Prior to activation of therapeutic voltages and agent, stimulation using one or more electrodes may be used to elicit a nerve response or reflex. By observing the nerve response, a target treatment location can be confirmed. Similarly, once the therapy has been delivered, a similar stimulation response may be sought, to determine presence or lack of neurogenic response.

In operation, effects of electroporation and delivery of a therapeutic dose of BoNT LC may be selective due to the cellular structure and orientation of the targeted cells. For example, targeted cells may be preferentially affected due to size, avoiding smaller or cross-oriented tissue cells.

In a further aspect of the present invention, the method of delivering the LC fragment of the BoNT molecule may include the use of a media that contains microspheres or microbubbles, such as Optison.TM. sold by GE Healthcare (www.amershamhealth-us.com/optison/). Delivery of an ultrasound energy (or other form of energy, for example, laser, RF, thermal, energy) to the media causes the microspheres to rupture, which causes a release of energy toward the targeted

region. Such a technique may assist in the desired porative effect by reducing the amount of applied energy required to create poration in the targeted cell membrane. *Bioeffects Caused by Changes in Acoustic Cavitation Bubble Density and Cell Concentration: A Unified Explanation Based on Cell-to-Bubble Ratio and Blast Radius*, Guzman, et al. Ultrasound in Med. & Biol., Vol. 29, No. 8, pp. 1211-1222 (2003). In an alternative embodiment, the LC fragment may actually be contained or encapsulated within a microsphere to assist in delivery. Such enhancing elements may be delivered prior to energy application or during energy application.

In a further aspect of the present invention, it may be advantageous to heat the targeted cells or surrounding tissue by either applying thermal energy directly to the region, or directing a heated fluid, such as saline to the region through an injection element, to aid the cell poration process. Other substances may also be injected to aid in the transmission of the BoNT-LC into the intracellular membrane, such as amino acids, detergents or other agents that may facilitate the catalytic activity of the LC, in addition to the applied energy.

Referring now to FIGS. 15A and 15B, a balloon catheter 300 may be delivered to a target site in the bronchus B of a lung (FIG. 15B). Typically, the catheter 300 will be delivered through an endoscope E, and the shaft 302 of the catheter will comprise at least one lumen for inflating the balloon 304. The inflation medium may carry the toxin fragment which is released through ports 306 formed in the balloon itself. Thus, inflation of the balloon both engages the ports against the wall of the bronchus B and provides the pressure necessary to infuse the neurotoxin fragments into the wall of the bronchus B. Usually, energy will be applied from electrodes 308 or other transducers located within the balloon 304.

Referring now FIGS. 16A and 16B, the catheter 400 may also be delivered to a bronchus B of a lung through an endoscope E. Catheter shaft 402 terminates with a delivery port 404 near its distal end. A deflection balloon 406 (or other expandable element capable of pressing against the wall of the bronchus B to engage the port 404 against target tissue) is provided on a side of the catheter shaft 402 which is opposite to that of the port 404. Electrodes 408 are provided on either side of the port 404 in order to deliver the poration energy into the target tissue.

Delivery to Nasal Cavity

In other embodiments, the present invention is directed to methods and systems for delivering toxins to target cells within a patient's nasal cavity. The toxins may be intact toxins, such as botulinum toxin, ricin, exotoxin A, diphtheria toxin, cholera toxin, tetanus toxin, other neurotoxins, and active fragments thereof. Each of these toxins comprises a heavy chain responsible for cell binding and a light chain having enzyme activity responsible for cell toxicity.

Botulinum toxin blocks acetylcholine release from cells, such as the epithelial or goblet cells in the nasal membranes responsible for mucus hypersecretion, and can thus be effective even without energy-mediated delivery in accordance with the principles of the present invention. The use of energy to permeablize or porate the cell membranes of the epithelial or goblet cells or other mucus-secreting cells of the nasal lining, in accordance with the present invention, allows botulinum and other toxins to be preferentially delivered to the targeted epithelial or goblet and other mucus-producing cells. Additionally, it allows use of the active or light chains of these toxins (having the heavy chains removed or inactivated) for treatments in accordance with the present invention. Normally, the light chains when separated from the cell-

binding heavy chains of botulinum and the other toxins are incapable of entering the cells and thus will be free from significant cell toxicity. By using the energy-mediated protocols of the present invention, the toxin light chains may be locally and specifically introduced into the target cells located within defined regions of the nasal membrane. Thus, even if the toxin fragments are accidentally dispersed beyond the desired target regions, the fragments will not generally enter cells without the additional application of cell permeablizing or porating energy. For that reason, the toxin delivery methods of the present invention are particularly safe when performed with toxin fragments, such as the light chain of botulinum and other toxins.

While the remaining portion of this disclosure will be presented with specific reference to the botulinum toxin light chain, it will be appreciated that the energy-mediated delivery protocols and systems may also be used with other intact toxins and in particular with other light chain toxin fragments as just discussed.

It is within the scope of the present invention to deliver the toxin, the energy, or both, non-invasively. For example, as illustrated in FIG. 17, the patient may draw the toxin into the nasal cavity from a hand-held dispersion device DD. After a sufficient amount of the toxin has been infused into the nasal cavity, a separate hand-held transducer TD connected to an appropriate power supply PS will be energized and applied to the nasal cavities by passing the transducer over the appropriate regions of the forehead and nose. Optionally, the transducer can have a focused output so that the acoustic energy is focused in an appropriate depth beneath the skin surface. Typically, from about 0.1 cm to 2 cm.

While the toxins and porating energy of the present invention may be delivered to the nasal cavity in a variety of ways, the following provides a number of specific examples of

catheters and other structures for delivering toxins to preselected portions of the nasal cavity. For example, as shown in FIG. 18, a balloon catheter 1000 may be provided with a porous balloon 1002 at its distal end. The balloon would be porous over at least a portion of its body so that solution delivered to inflate the balloon, which would contain desired levels of the toxin or toxin fragment, would release the solution through the balloon at a controlled rate. By further providing one or more ultrasonic transducers 1004 within the balloon, optionally mounted on the catheter body, ultrasonic poration energy can be delivered to the adjacent nasal membranes which are receiving the toxin solution. As illustrated in FIG. 18, the toxin is being delivered to a lower surface of the inferior meatus IM to localize and enhance cellular delivery at the balloon tissue interface. Alternatively, the balloon could carry the toxin in a releasable form over its exterior surface in order to deliver to any adjacent tissue structure. In some instances, the toxin could be carried or encapsulated in delivery vesicles which are preferentially fractured by the same acoustic energy which permeablizes the cell wall. Other coatings include hydrogels, such as those produced by Surmodics, Inc., BioCoat, Inc., or the like. In some instances, it may be desirable to provide a coupling agent over and/or within the balloon in order to enhance the delivery of ultrasonic energy from the internal transducer. In still other instances, it would be possible to place polymeric transducers on or within the balloon surface in order to directly deliver ultrasonic or other acoustic energy into the adjacent tissues.

In all the above cases, the ultrasonic transducers can be configured in order to selectively deliver the energy to desired portions of the adjacent tissues. For example, in the embodiment of FIG. 18, the internal transducers 1004 can be configured to focus the ultrasonic energy generally

upwardly (as viewed in FIG. 18) in order to preferentially deliver the toxins into the inferior meatus IM while minimizing delivery elsewhere.

As a further option, the balloon could be inflated by a coupling agent in order to enhance the transmission of the ultrasonic or other acoustic energy, while the toxin solution could be infused into the treatment area before or simultaneously using either a separate lumen in the catheter or a separate tube or other delivery catheter. In this way, it would not be necessary to inflate the balloon with a relatively large volume of the toxin solution.

The balloon catheters can be introduced by any conventional technique, for example, in some instances, it may be desirable to use a guidewire to place the catheter into a desired sinus or other location, optionally using fluoroscopic, MRI or ultrasound imaging.

Referring now to FIG. 19, a front view of particular balloons placed as generally shown in FIG. 18, is shown in more detail. A single balloon 1002 can be around the structures H in the inferior meatus. Alternatively, a pair of balloon structures 1003 may be placed in the same space, as shown in the right hand portion of FIG. 19. Optionally, the balloons could be formed from an elastic material, such as a silicone, urethane, latex, thermoplastic elastomers, or other materials where the material is treated to be appropriately porous, for example by laser drilling. Alternatively, the balloons could be formed from non-distensible materials which are pre-formed to conform to the desired target cavities. The non-distensible balloons could also be laser drilled or otherwise made permeable in order to release the toxin solutions of the present invention. Alternatively, either type of balloon could be coated with the toxin solutions, coupling solutions, or other materials which are useful in the protocols of the present invention.

Referring now to FIGS. 20A, 20B, and 20C, as an alternative to inflatable balloons, toxin delivery structures may be made to be various shapes, for example a generally "flattened" balloons 1002, whose profile is narrower in one axis than the other, for example by placement of an internal nitinol or other elastic frame or scaffold, or a stainless steel wire 103 that is fed into the balloon outer structure to form such shape, within a suitable porous cover or membrane. Thus, the structure 1020 may be expanded by the scaffold 1022 after release from a delivery tube 1024. The structures can be used to deliver energy and/or toxin in any of the ways described previously with respect to balloons, including by carrying a transducer or electrode on or within the structure and delivering a toxin solution from the interior of the self-expanding structure through a porous portion of the structure wall.

In some instances, it will be desirable to protect the olfactory bulb of the sinuses from treatment with the toxin solutions of the present invention. Referring now to FIGS. 21 and 22, the porous portion of a delivery balloon 1002 can be positioned so that the remaining non-porous segment is in contact with the olfactory bulb (FIG. 21). Thus, when the balloon is inflated and the toxin solution delivered, it will not be directed at the tissues of the olfactory bulb (OB).

As shown in FIG. 22, which is a cross-sectional view of FIG. 21, instead of rendering the top portion of the delivery balloon non-porous, it would be possible to simply refrain from filling the top portion with the toxin solution and/or a coupling solution. This can be achieved by filling the balloon with a known volume of air 1011 in addition to the toxin solution. With the patient positioned appropriately, the air will fill the portion of the balloon in proximity to the olfactory bulb, excluding this tissue from toxin contact. Additionally, the air bubble may act as an ultrasound insulator to inhibit energy delivery to the non-targeted or protected tissue. Thus,

delivery of the toxin to the region around the olfactory bulb and/or delivery of the energy to the region around the olfactory bulb can be partially or wholly prevented.

Referring now to FIGS. 23 and 24, the balloon may be sized and positioned to target an area of high goblet cell (G) concentration, for example in the back of the nasal passages in the area of the nasopharynx. By targeting this area of the nasal membrane, a high percentage of mucus-secreting epithelial or goblet cells can be treated with a device which is relatively small and which may carry a relatively low infusion volume and require less energy. Moreover, the olfactory bulb is inherently protected with this technique since the balloon is positioned well away from that area. If desired, of course, additional shielding, shaping or other protective balloons could be positioned between the olfactory bulb and the toxin and energy delivering components of the present invention.

As shown in FIG. 25, direct infusion and treatment of particular sinuses may be effected using relatively small occlusion balloons 1002 which occlude and isolate natural openings into those sinuses. Once the balloon is in place and the occlusion balloon employed, the toxic solution can be delivered by infusion, dispersion, or other conventional techniques. Once the toxin solution is present in the sinus, all or a portion of the membrane of the sinus can then be treated with an external or other ultrasonic source.

For example, as shown in FIGS. 26 and 27, the external transducer may comprise a mask which conforms to the nose and optionally over the sinuses, where the mask carries one or more ultrasonic or other acoustic transducers (TD) adapted to deliver energy transcutaneously into the sinuses. The mask may comprise a plurality of individual transducers (TD), which may be made from one, two, or several generally continuous piezoelectric films which are formed over or

lamented within the mask. Alternatively, multiple individual piezoelectric crystal transducers can be built into the mask.

The effect of such externally applied ultrasonic energy can be enhanced by introducing microbubbles (free air) into the isolated sinuses and/or nasal passages which have been filled with toxin solution. For example, encapsulated microbubbles, which are generally useful as echocardiographic contrast agents, or specialty perfluorocarbons, are useful as such ultrasonic enhancing agents. By encapsulating the toxin molecules in spheres or bubbles, or by simply placing the spheres or bubbles in proximity to toxin molecules, the ultrasonic or other acoustic energy can be captured and stored until it is abruptly released with fracture of the sphere or bubble. Such microspheres will also act as resonance bodies as defined below.

Referring now to FIGS. 28 and 29, a catheter 400 is placed at the posterior outlet of the nasal passages in the region of the nasopharynx. The catheters configured to occlude outflow from these sinuses and passages into the throat. As shown in FIG. 28, a balloon catheter 1002 or other occlusion device could be configured to block such passage. As shown in FIG. 28, the catheter is delivered in through the mouth and guided into the posterior portion of the nasal cavities, typically using a guidewire. Once the nasopharynx of the posterior portion of the nasal cavity is occluded, toxin solution (BoNT) can be infused through the occluding catheter lumen, or through a separate infusion catheter or tube, in order to treat substantially the entire sinus and/or nasal cavity membrane at once (FIG. 29). When the toxin solution is introduced through the catheter at the posterior region of the cavities, it will frequently be desirable to occlude the nostrils, for example using a nasal clip 1005.

As shown in FIGS. 30 and 32, specially designed nose plugs 1005 can be provided with air bleed valves 1006 which are used to occlude the nostrils in order to evacuate or bleed air from the nasal passages while filling the passages with the toxin solution. The nose plugs 1005 could optionally include ultrasonic transducers in order to deliver ultrasonic or other acoustic energy into the solutions entrapped within the nasal cavities using the nostril plugs. Alternatively, of course, the ultrasound or other acoustic energy could be delivered from an external transducer as described previously.

Referring now to FIGS. 32 and 33, an alternate occlusion catheter system for nasopharynx occlusion is illustrated. An occlusion catheter 400 is introduced through a nostril, where the tip includes an ultrasonic transducer to provide sonoporation. A nostril plug 1005 is provided proximally on the shaft of the catheter, while the cavity is blocked with a separate occlusion balloon 1002 introduced through the mouth and into the posterior nasopharynx region. The toxin solution can be introduced into the cavity through either the catheters which pass through or reside in the nostrils or the catheter which occludes the posterior nasopharynx.

FIGS. 34 and 35 illustrate how a catheter 400 with side holes 1008 can be configured to deliver toxin away from the olfactory bulb, even when used alone without separate nasopharynx occlusion catheters. The catheters preferably carry an occlusion balloon or other structure near their distal ends 1007 to prevent or inhibit toxin from reaching the olefactory bulb.

Use of these or other catheter devices can deliver toxin incorporated into vesicles which may be configured as “resonance” bodies, which reduce the need to fill the nasal cavities with a liquid or other form of toxin. For example, lipid microspheres which incorporate the toxin may be sprayed or aerosolized onto target surfaces of the nasal epithelium. After the lipid or other

resonance bodies are attached to the targeted epithelium membrane surface(s), the ultrasound energy can be delivered from the catheter or externally through the skin in order to selectively porate the epithelial or goblet cells to enhance introduction of the toxin vis-à-vis resonance bodies. A protection device at the end of the shaft can be provided to shield the olfactory bulb from the toxin.

Referring to FIG. 37, the toxin may be delivered as a conventional nasal spray (BoNT), as mentioned hereinbefore, and the poration energy can be delivered through a face mask. The poration energy might alternatively be delivered as ultrasound energy delivered through a mist, without direct contact to the tissues. This mist might be the same mist which contains the toxin, or it might be a different, possibly denser mist delivered at some time after the toxin has been delivered. The delivery devices for these mists might be introduced a relatively short distance into the nose. Thus the entire therapy might comprise the specialized delivery of two mists.

Referring now to FIGS. 36 and 38, an infusion catheter 400 can be engaged against the ostium of a sinus cavity (FIG. 36). A guidewire 1010 may then be advanced through the infusion catheter and into the sinus cavity (FIG. 38). The guidewire can be formed as a wave guide to deliver ultrasonic energy, as an electrode to deliver electroporation energy, or as an infusion wire to deliver the toxin solution itself. The wire could further be configured to perform two or more of these functions. The catheter could be configured to act as a counter electrode when the guidewire is acting as an electroporation electrode in bipolar energy delivery.

Referring now to FIG. 39, the catheter advanced to the os of a sinus cavity, as illustrated, can also be used to deliver a helical or randomly shaped delivery tube 1012 which is deployed within the sinus. Preferably, the tube will expand to engage a major portion of the wall of the

sinus cavity. Alternatively, the geometry could be selected to selectively engage only a particular portion of the wall of the sinus cavity. The wire can further be adapted to deliver energy, either electrical or acoustic, and/or may be configured to deliver and distribute the toxin solution within the cavity. In still other configurations, the wire could be coated to deliver the agent to the wall, and still further the wire could deliver ultrasound gels, saline, degassed water, or the like, to enhance coupling of a separate ultrasonic energy source.

Referring now to FIG. 40, two or more deployment catheters can be used to advance any of the guidewires or other wire structures discussed above. As illustrated in FIG. 40, an electrode basket 1013 may be deployed through the delivery catheter. Alternatively, a multiply tined catheter 1014 structure may be delivered through the delivery catheter.

Throughout this disclosure, the LC solution has typically been referred to as an infused, aerosolized or sprayed liquid. LC incorporated into coatings on devices has also been described. It should be noted, however, that other forms of LC delivery may be desirable.

For instance, commercially available botulinum toxins (such as Botox™—Allergan) are supplied as a dry lyophilized powder, and must be reconstituted prior to delivery by the addition of saline to the packaging vial. Similarly, light chain would be most readily available and stable in a powdered form. It may be desirable to spray or blow the powdered form of the LC into the target airways directly, without any reconstitution by liquid.

The lyophilized powder could also be formed into sheets, ribbons, pellets microspheres, or any other desirable form, and introduced to the target tissues.

Instead of a saline or low viscosity carrier, it may be desirable to deliver the light chain in a gel carrier, such as the types of gels which are commonly used for ultrasound coupling. Other

appropriate gel carriers include such biocompatible gels as hyaluronic acid (HA). HA has the added benefit of being a thixotropic liquid—its viscosity drops as it begins to flow or as increasing shear stress is applied, and then returns to a higher viscosity state as it comes to rest. This would aid in delivery of the solution through catheters and the like, while allowing the gel to remain in place once delivered. HA is also extremely biocompatible, and would allow efficient ultrasonic coupling to the target tissues. The application of ultrasonic energy might also reduce the viscosity of the HA gel, possibly improving the delivery of toxin into the tissues.

It may also be desirable to incorporate the light chain into a foam, or to foam the LC solution upon or during delivery of the LC to the target tissues. Foams may better fill the entire targeted airway, and may trap water or coupling agents to allow efficient ultrasonic coupling. In a further embodiment, the foam may be energized within or as it exits the catheter shaft to further enhance the delivery of the LC to cells that are contacted by the energized foam and LC foam solution.

In addition to BTX-LC, it may be desirable to deliver additional agents to the nasal passages and sinuses prior to, coincident with, or after delivery of the LC. Adjunctive therapies may include agents designed to slow down or halt the motion of the cilia, in order to aid in delivery of the LC to the target tissues by prevention of their mobilization by the cilia. Agents known to slow or halt the motion of cilia include but are not limited to epinephrine dilutions of 1:1000 (which causes ciliary death), 1:10,000 (which causes reversible paralysis), 10% cocaine (induces paralysis) or 2.5% cocaine (slows or stops cilia).

Other adjunctive therapies may include the use of or pretreatment with mucolytics, which will thin mucus secretions within the nose and may allow better penetration of LC into the target cells.

Decongestants such as epinephrine also cause constriction of the vasculature in the nasal passages, which in addition to temporarily reducing swelling of the target tissues, may decrease the risks of LC entering the blood stream during poration and delivery. Epinephrine also constricts the blood vessels locally, which may increase the residence time of other locally delivered agents or decrease their likelihood of entering systemic circulation.

Steroids may be used to reduce swelling and inflammation prior to LC treatment in order to improve LC delivery to target tissues. In the abovementioned embodiments, it may be important to note that by far the most significant effects will be seen in areas where both the LC and the permeablizing energy are delivered. Therefore, although it may be best to deliver both LC and energy to substantially the same area, for reasons of anatomy, ease of delivery, etc., either the LC or the energy might be delivered more broadly, or to a somewhat different area. As an extreme example, the LC might be delivered systemically or to the entire respiratory pathway, followed by very localized delivery of energy to the desired area. Alternatively, the LC could be delivered to a specific sinus, followed by energy to the entire nose and sinus using a standardized external energy delivery mask.

Although various illustrative embodiments of the present invention are described above, it will be evident to one skilled in the art that various changes and modifications may be made without departing from the scope of the invention. It will also be apparent that various changes

and modifications may be made herein without departing from the invention. The appended claims are intended to cover all such changes and modifications that fall within the true spirit and scope of the invention.

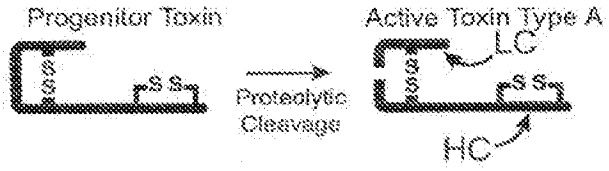

Progenitor Toxin
Active Toxin Type A
LC
HC
Proteolytic Cleavage

FIG. 1

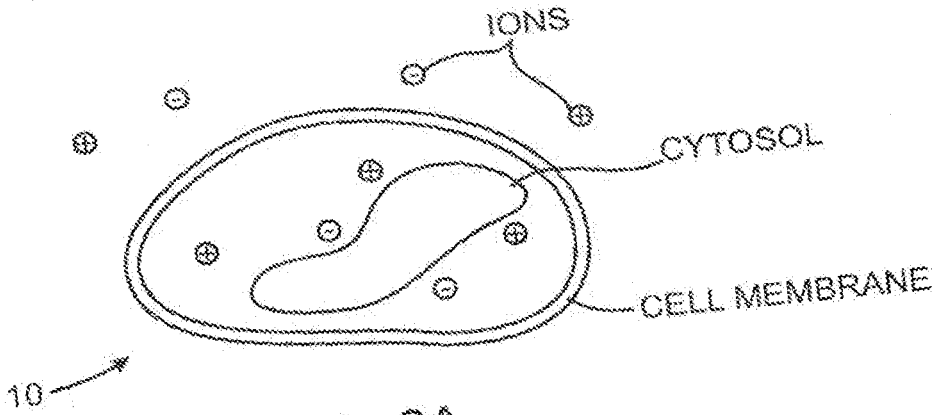



FIG. 2A

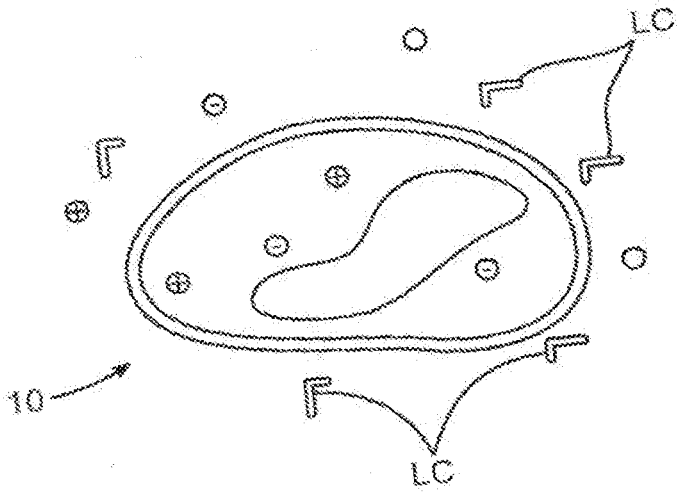



FIG. 2B

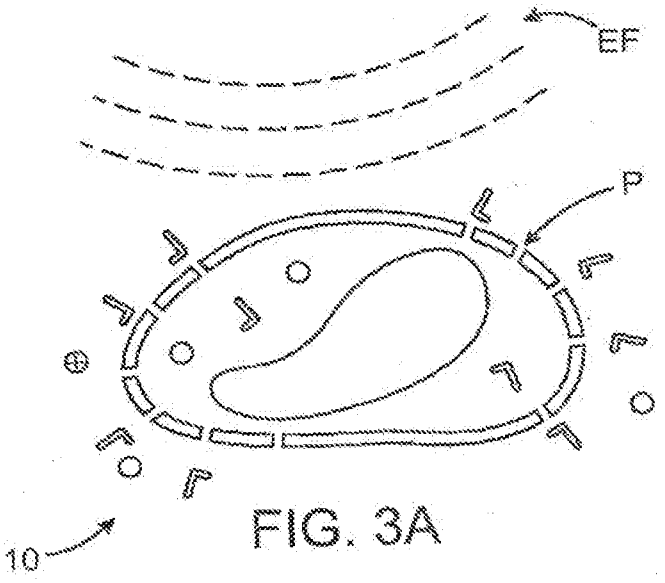



FIG. 3A

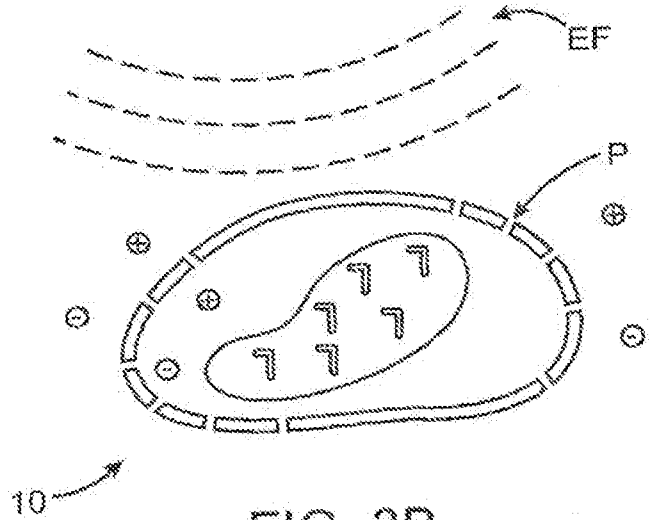



FIG. 3B

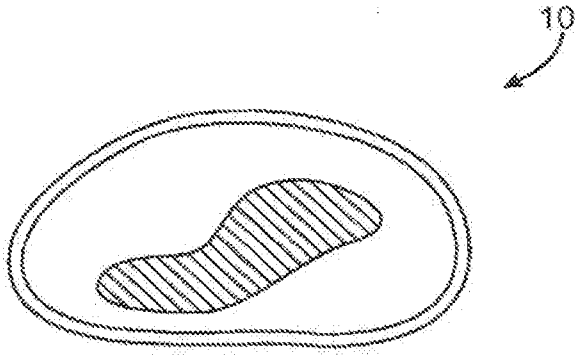



FIG. 4

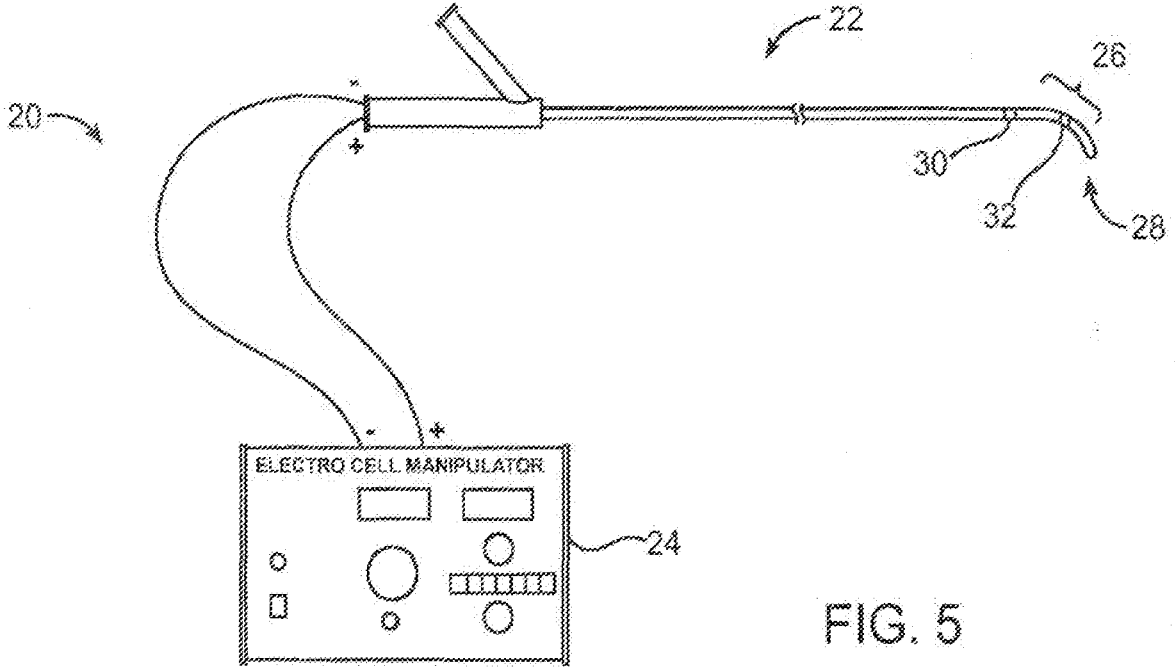



FIG. 5

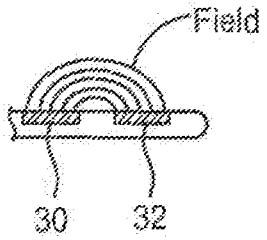



FIG. 5A

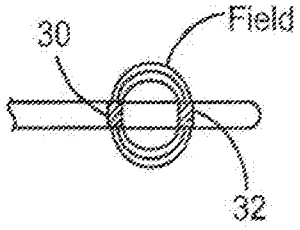



FIG. 5B

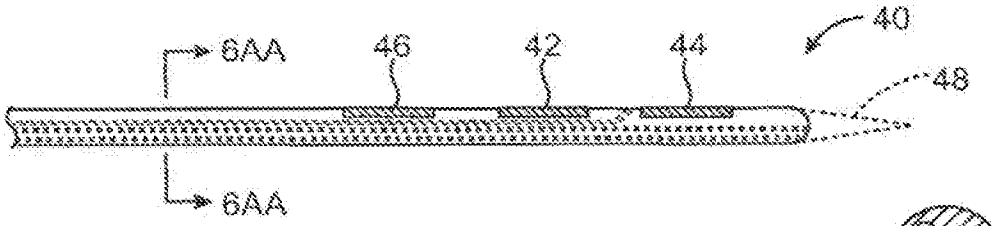



FIG. 6A

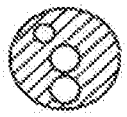


FIG. 6AA

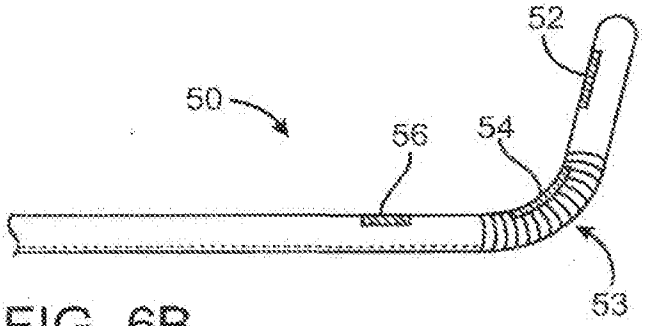



FIG. 6B

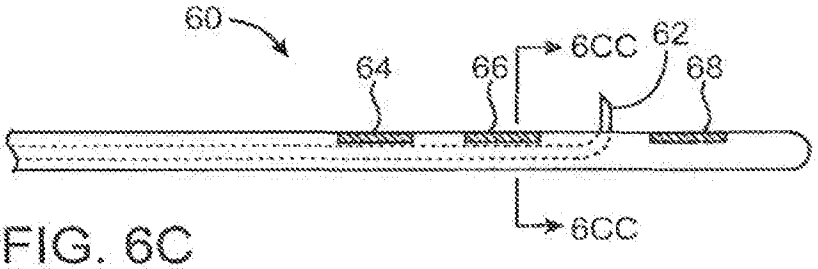



FIG. 6C

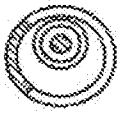


FIG. 6CC

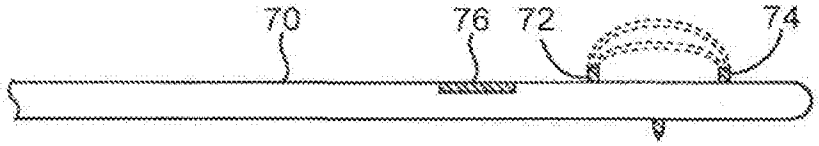



FIG. 6D

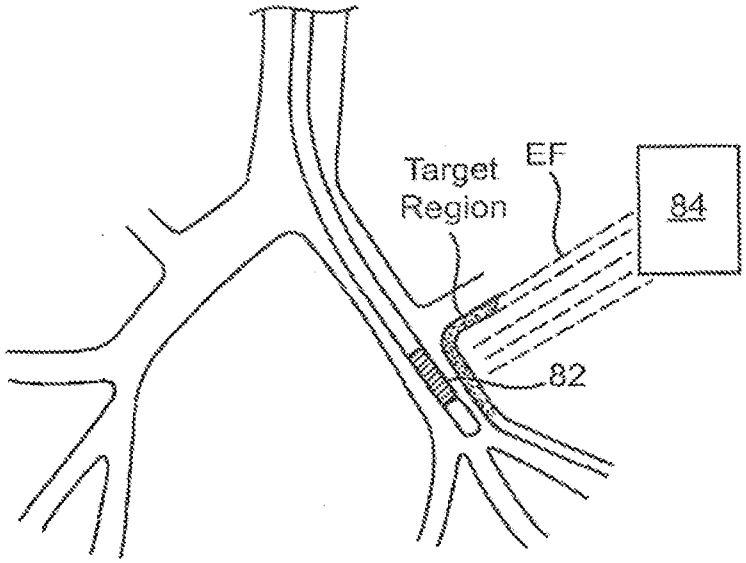



FIG. 7

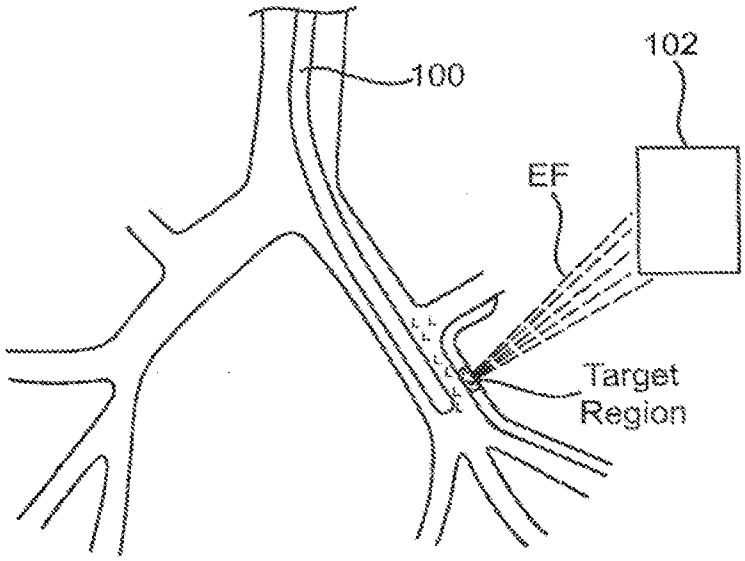



FIG. 13

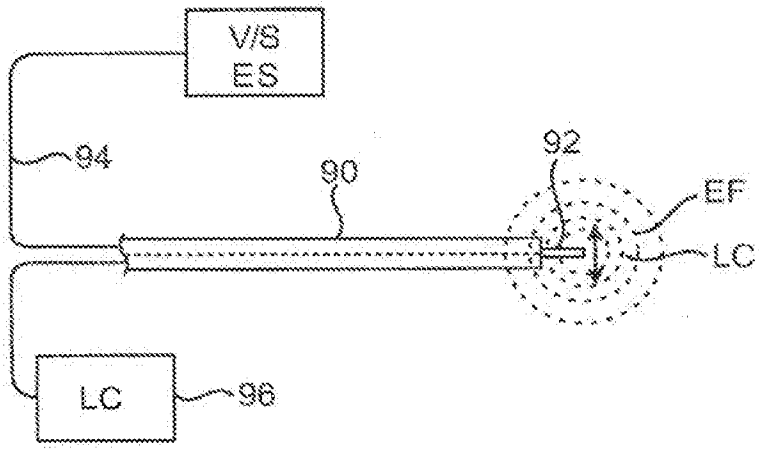



FIG. 8

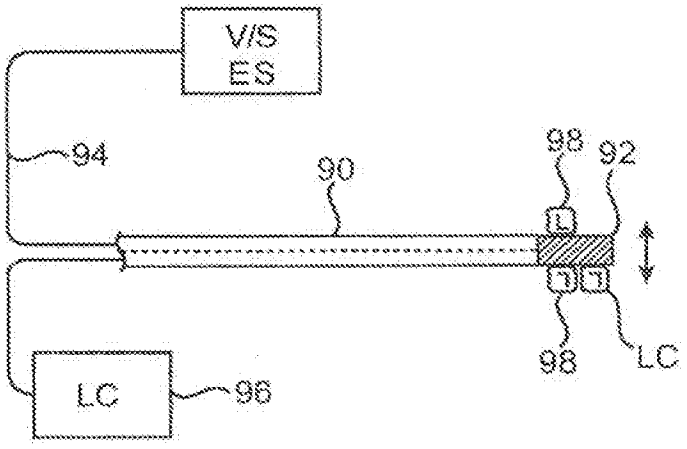



FIG. 11

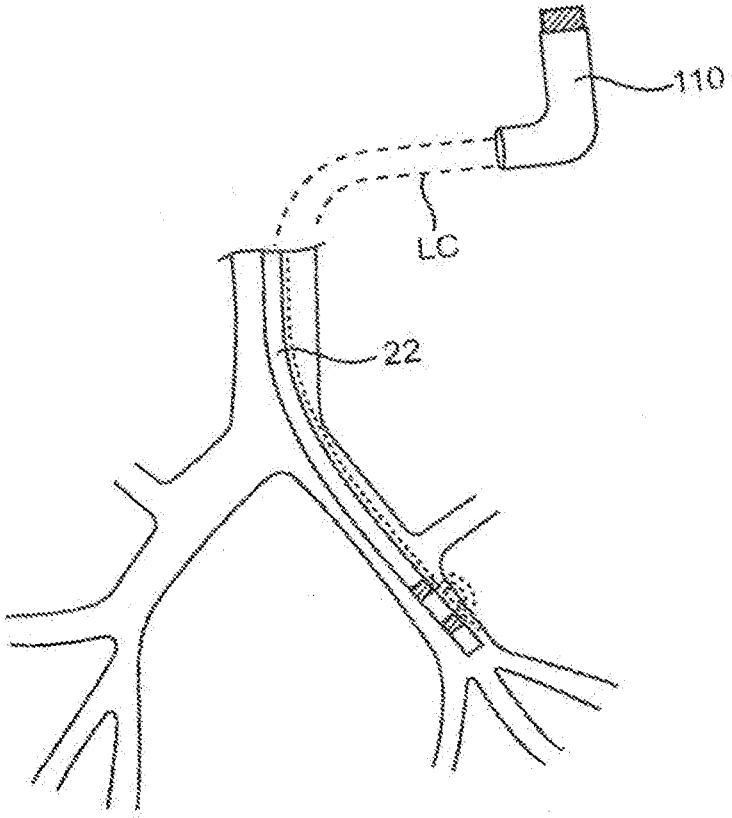



FIG. 9

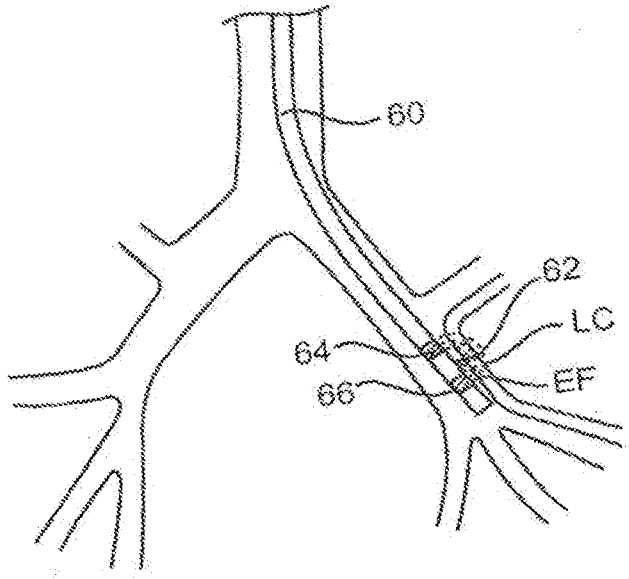



FIG. 10

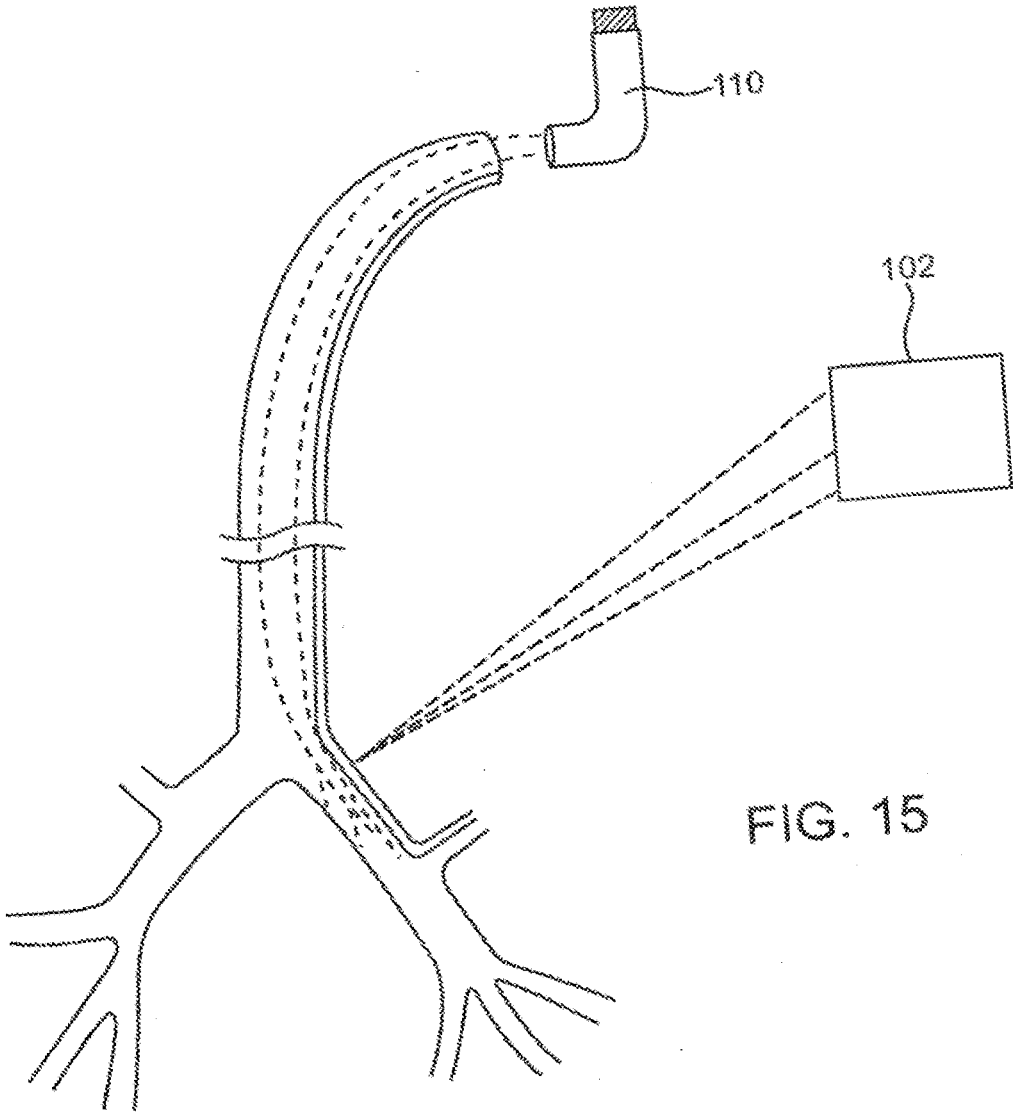



FIG. 15

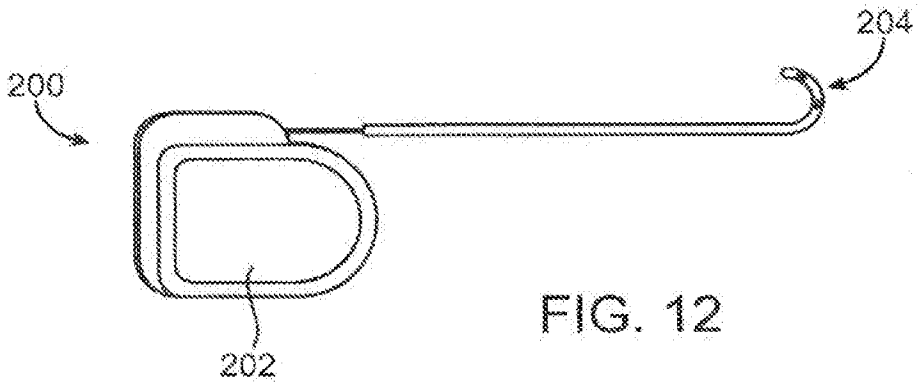



FIG. 12

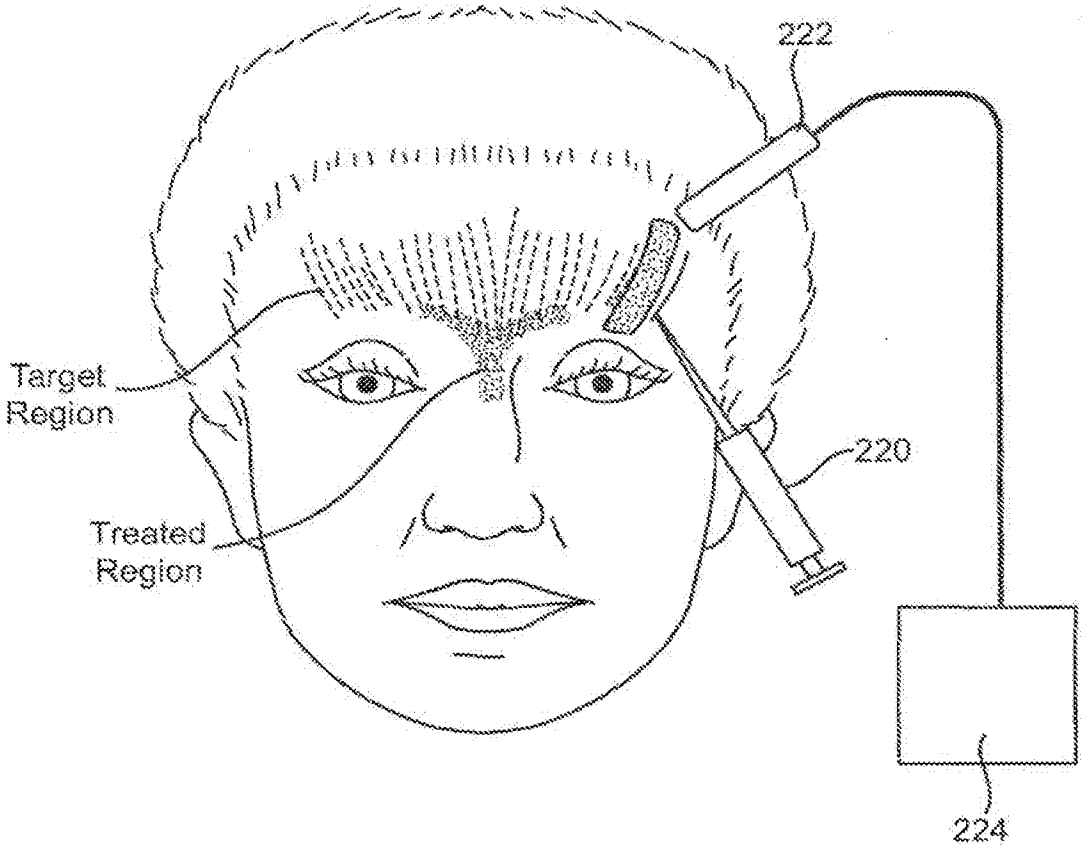



FIG. 14

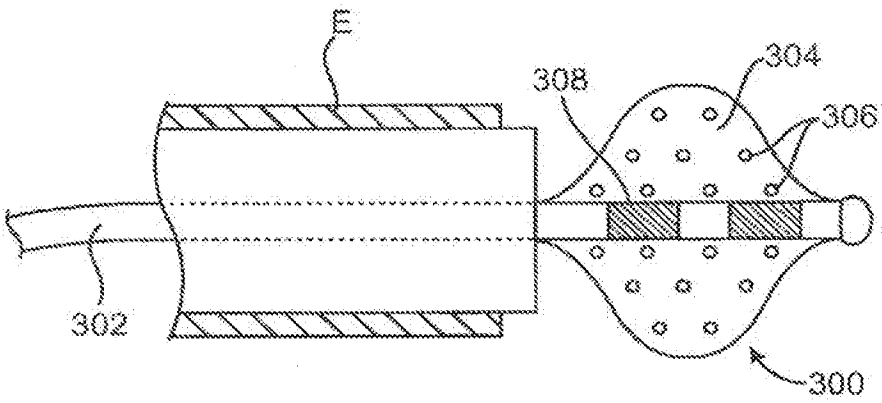



FIG. 15A

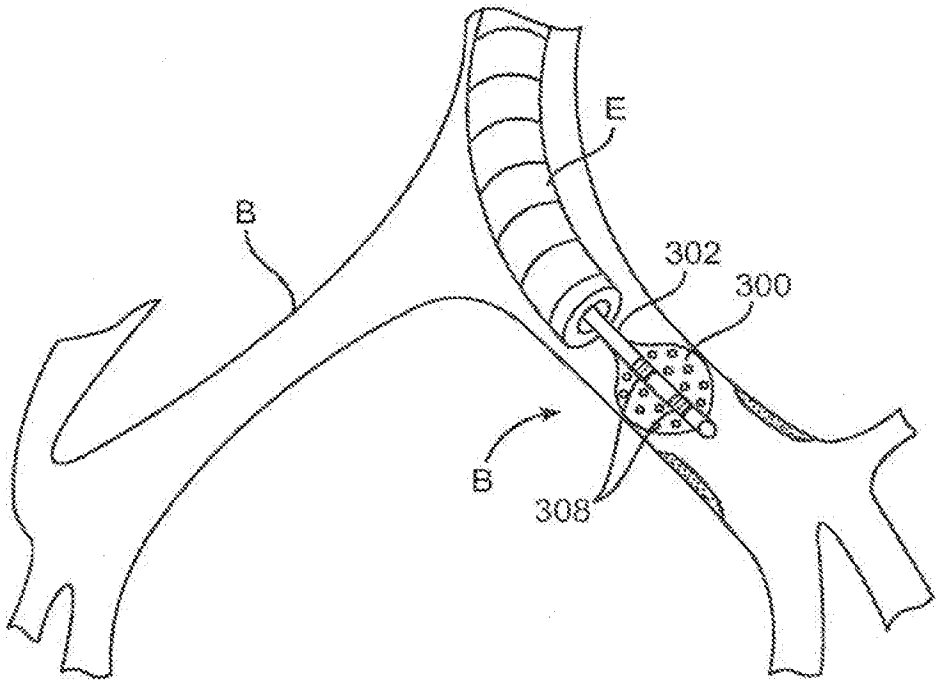



FIG. 15B

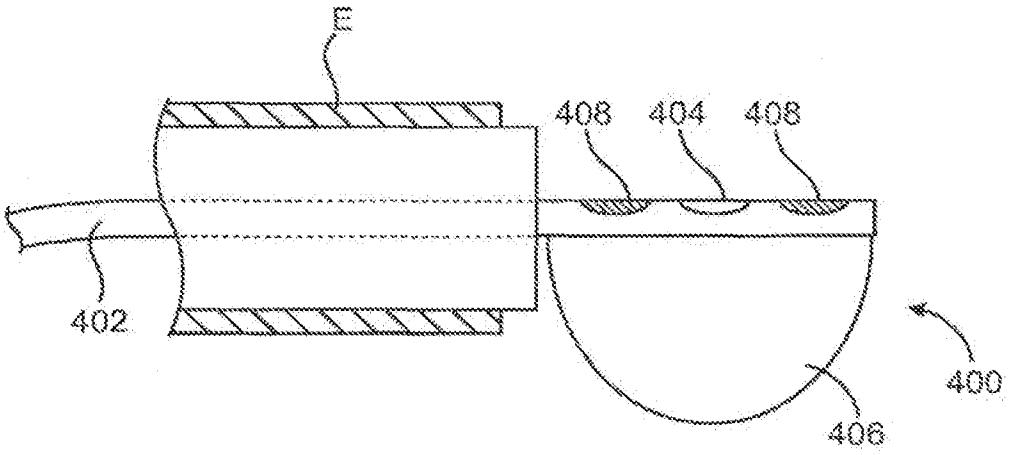



FIG. 16A

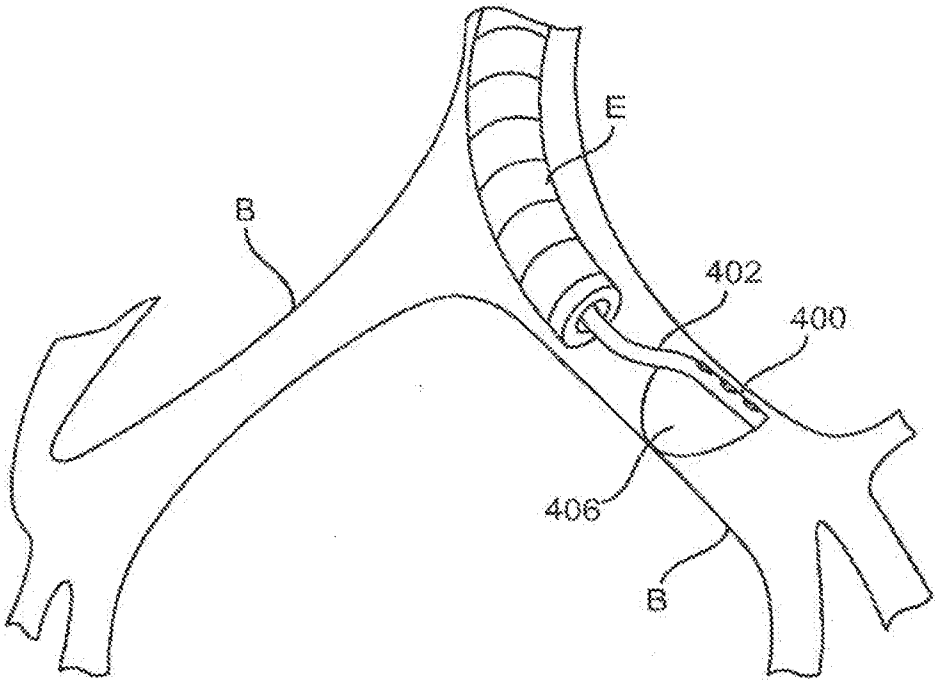



FIG. 16B

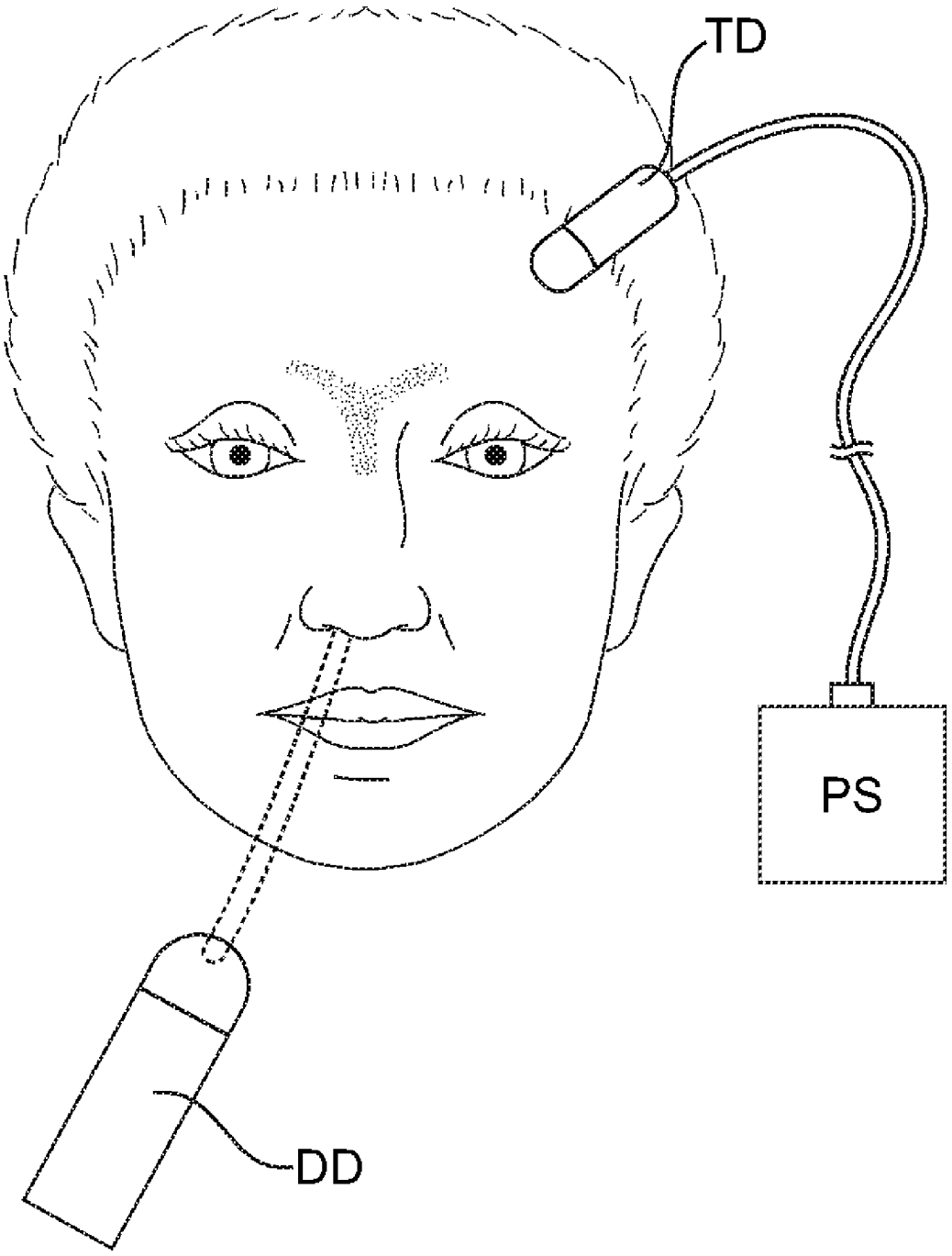



FIG. 17

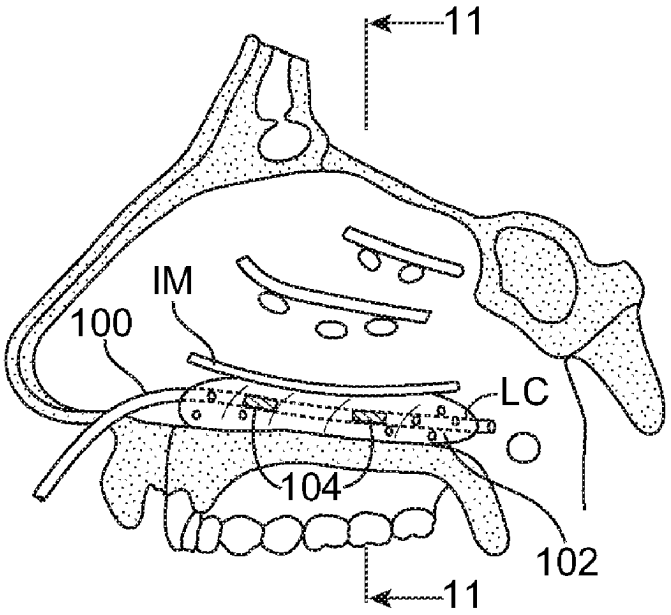



FIG. 18

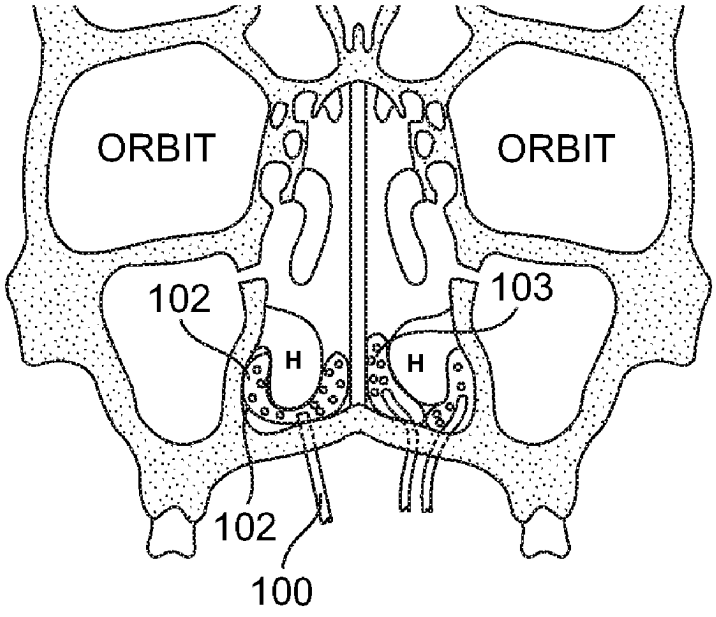



FIG. 19

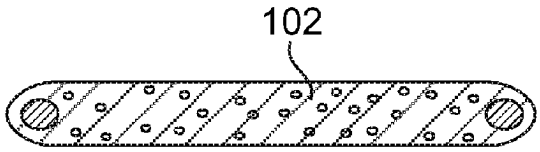



FIG. 20A

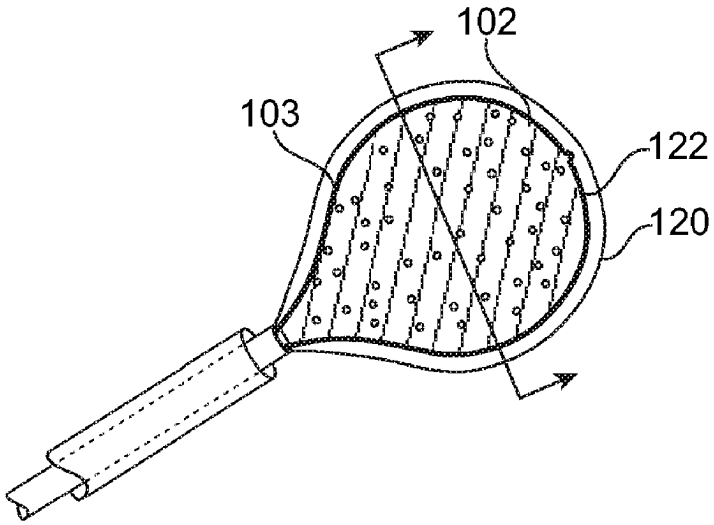



FIG. 20B

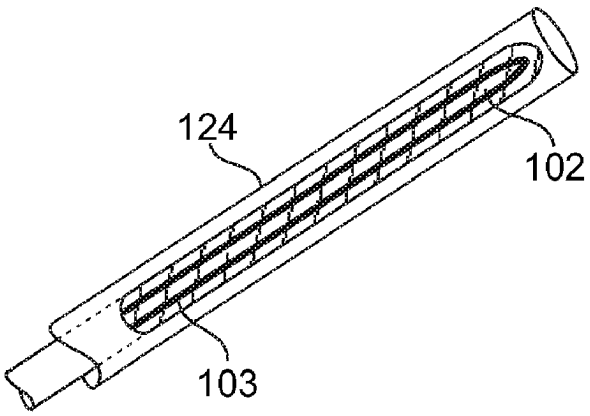



FIG. 20C

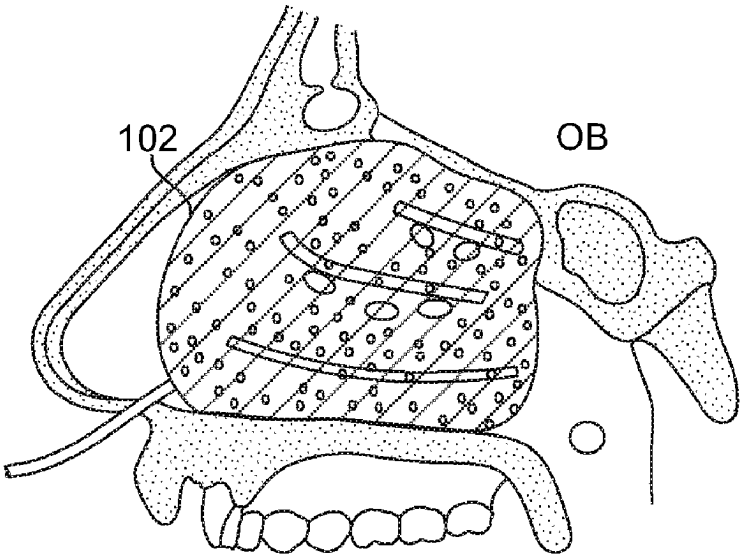



FIG. 21

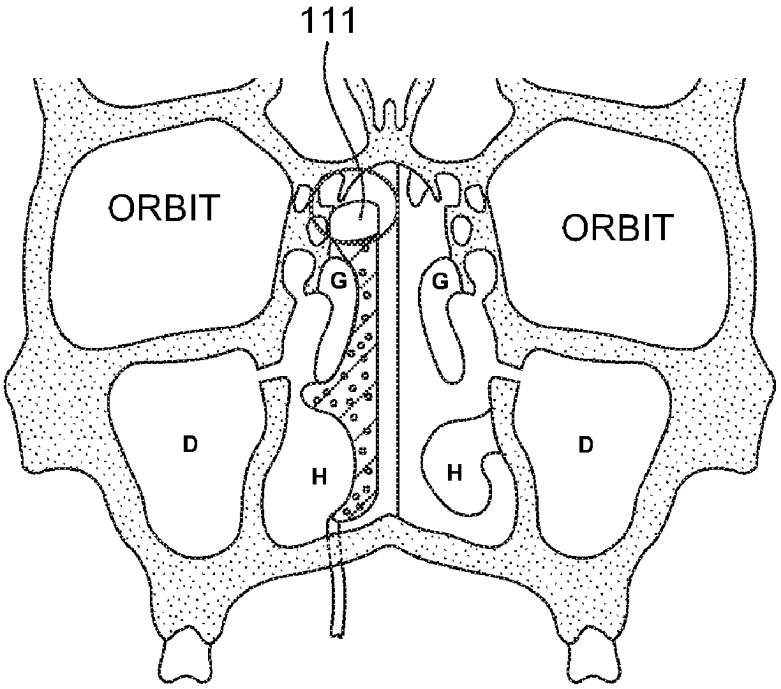



FIG. 22

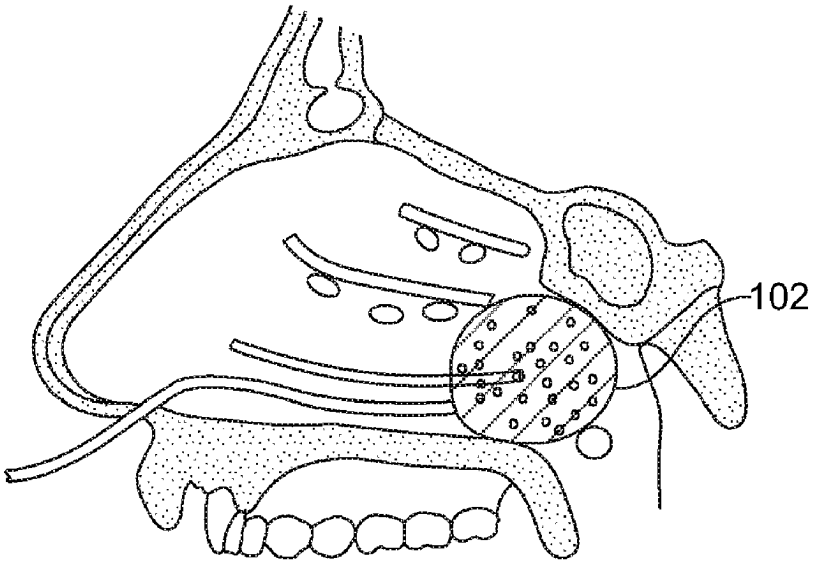



FIG. 23

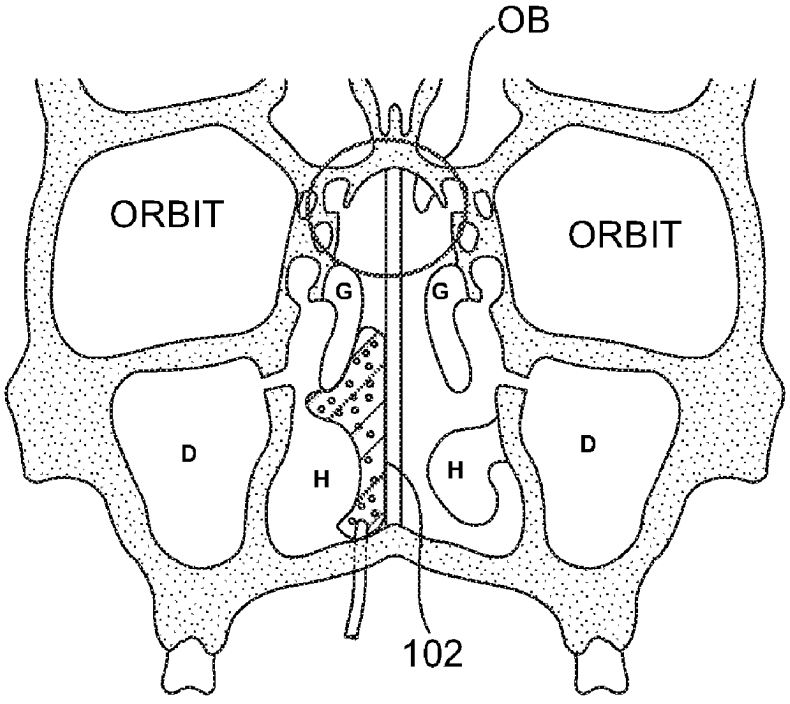



FIG. 24

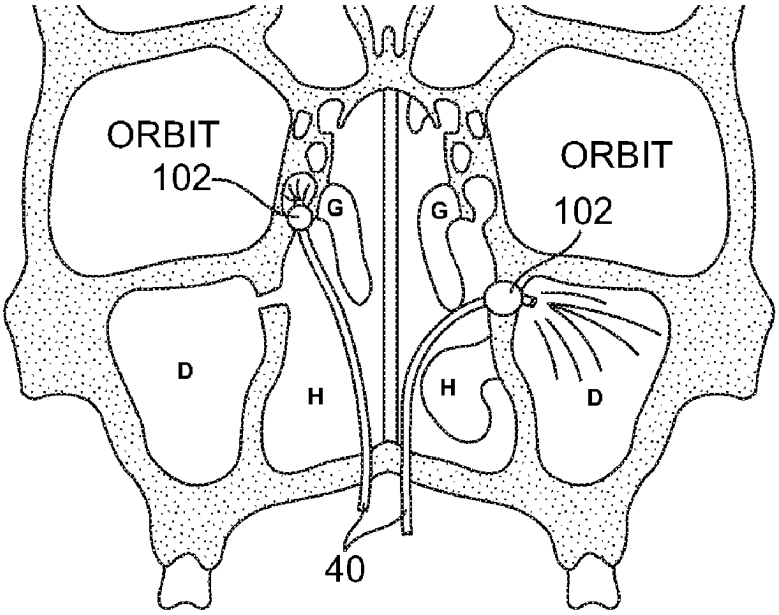



FIG. 25

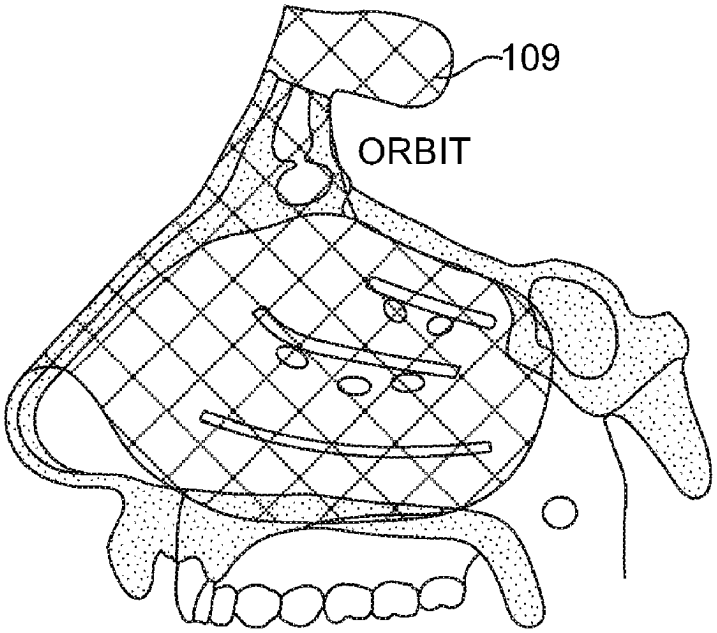



FIG. 26

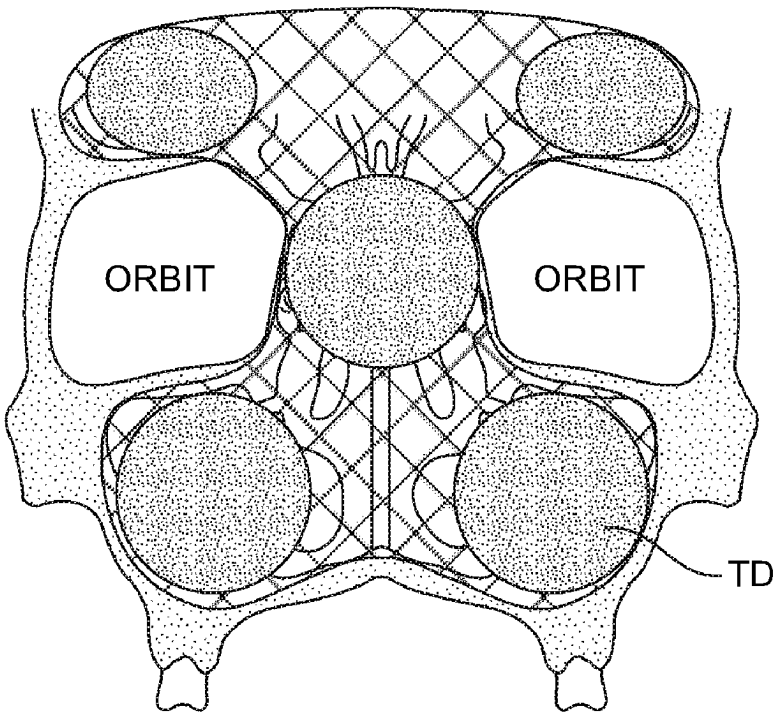



FIG. 27

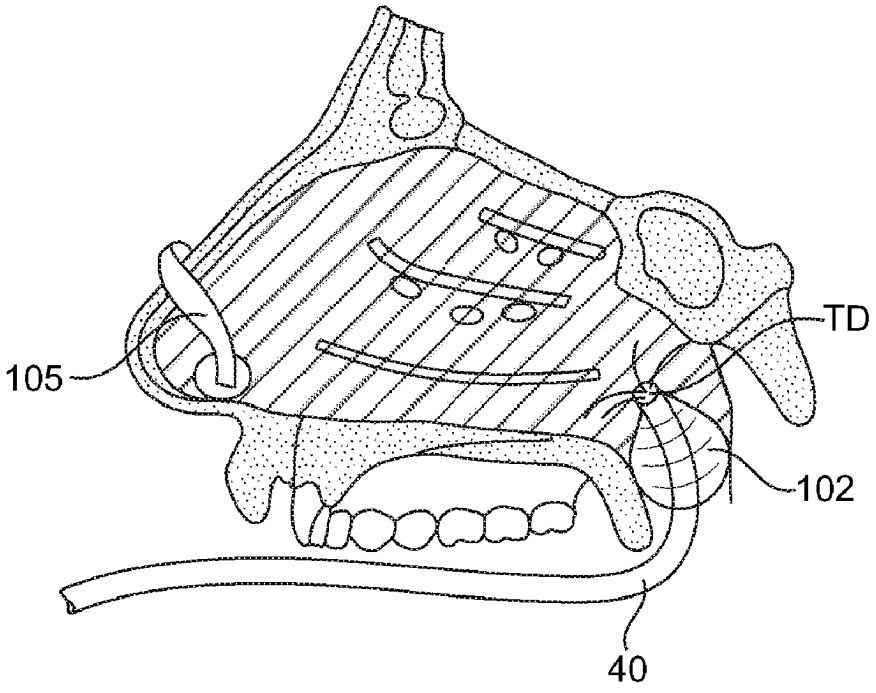



FIG. 28

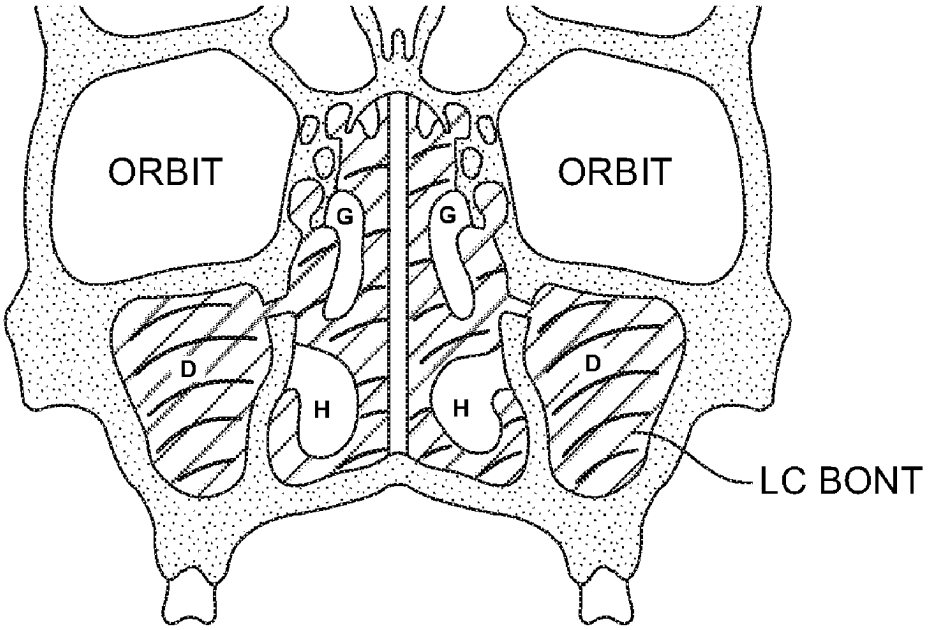



FIG. 29

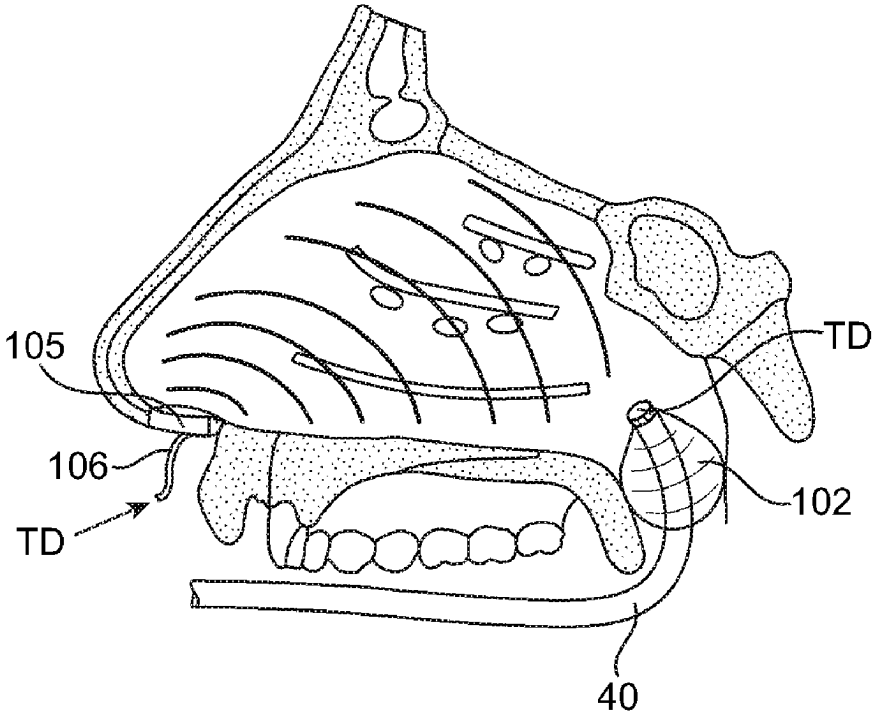



FIG. 30

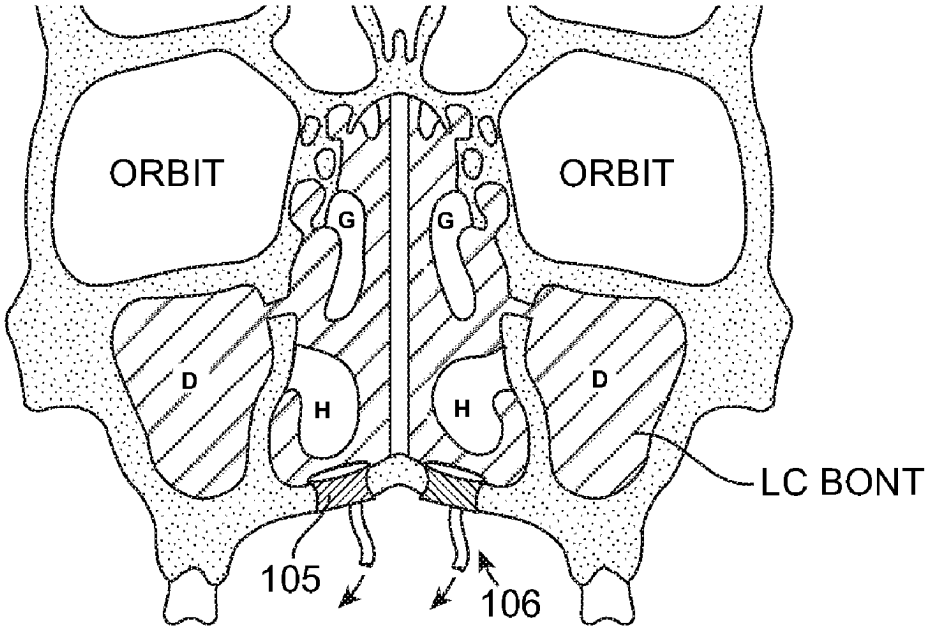



FIG. 31

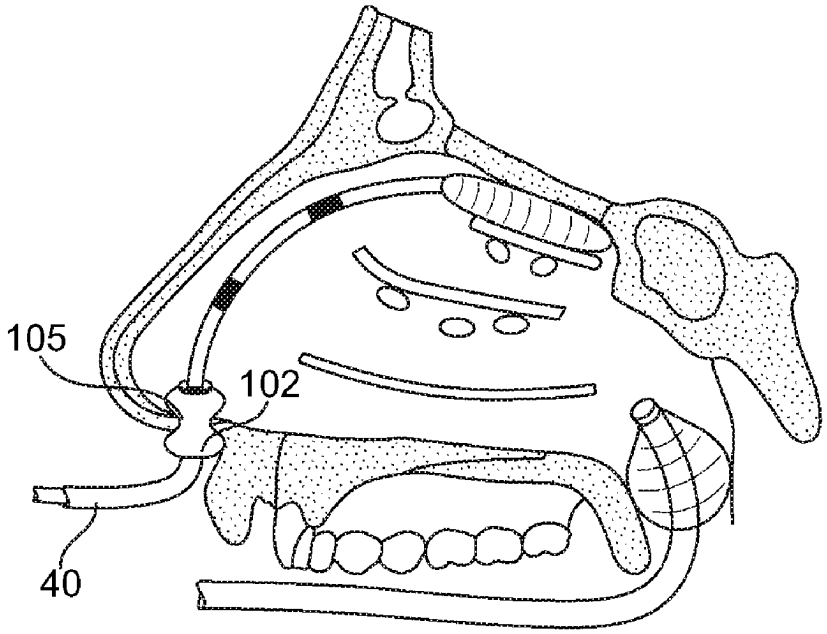



FIG. 32

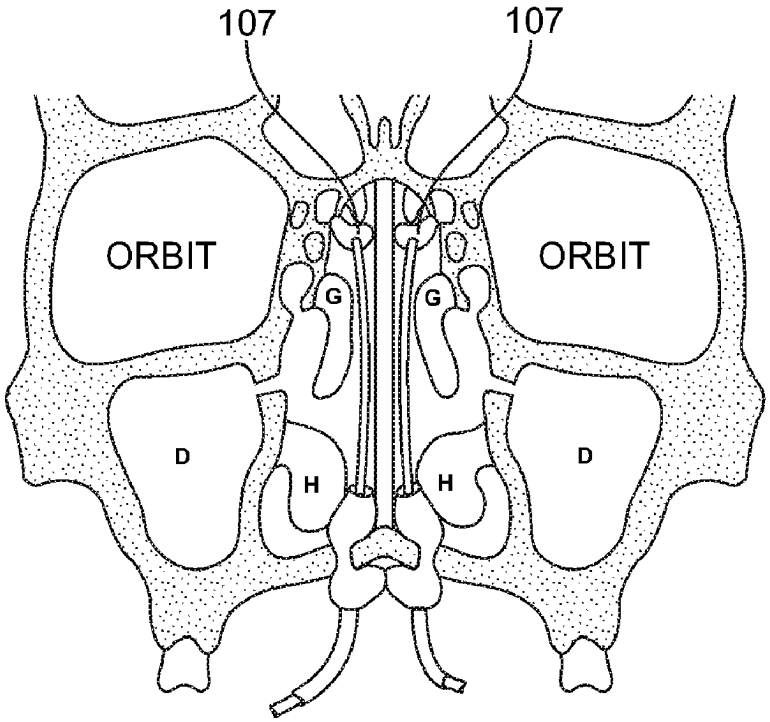



FIG. 33

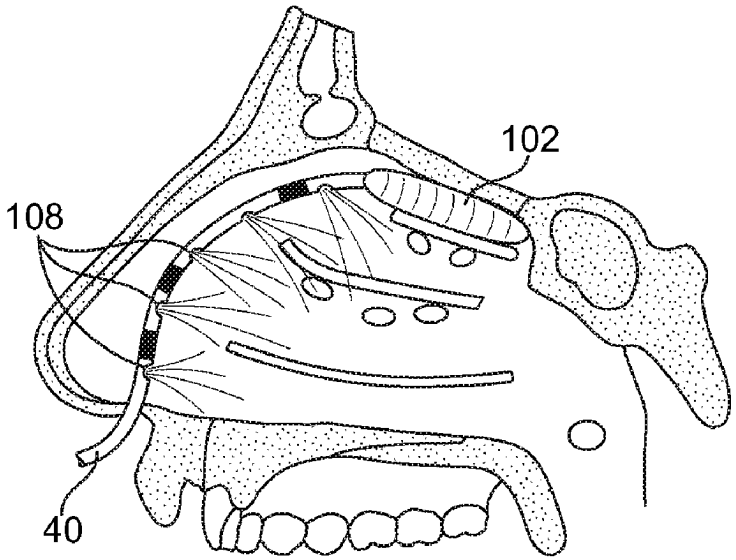



FIG. 34

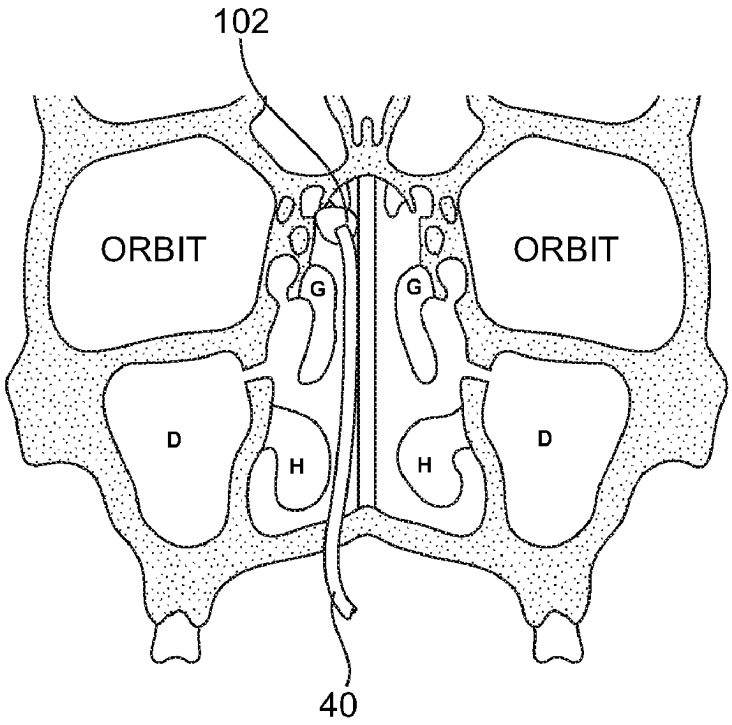



FIG. 35

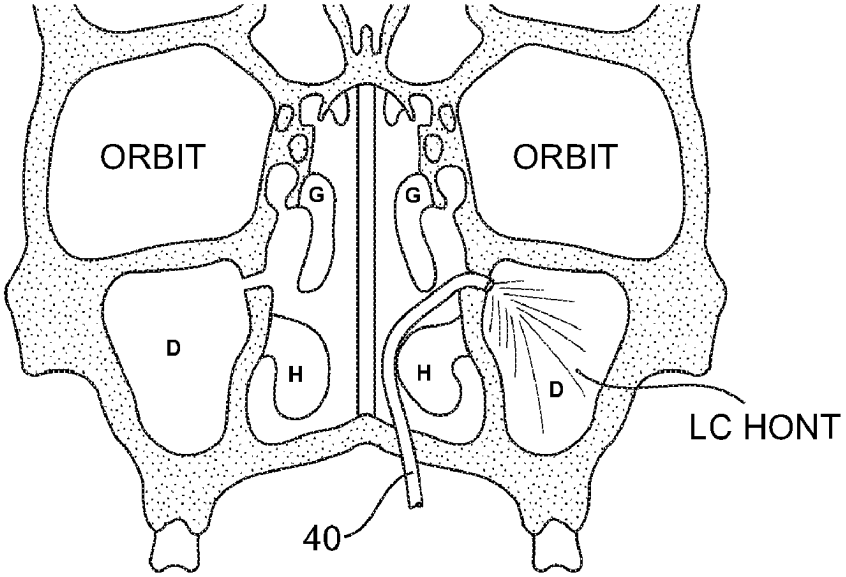



FIG. 36

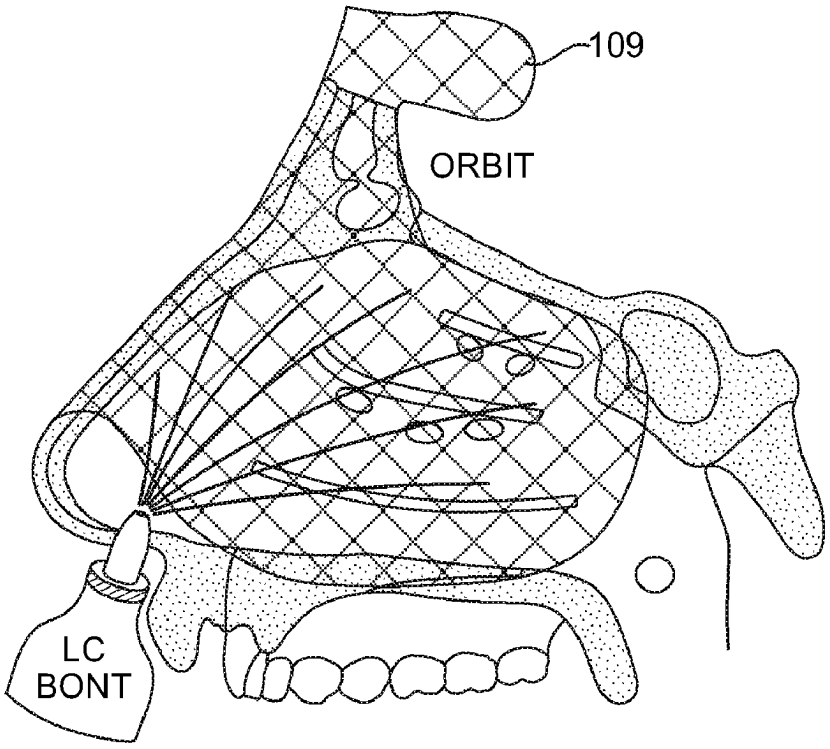



FIG. 37

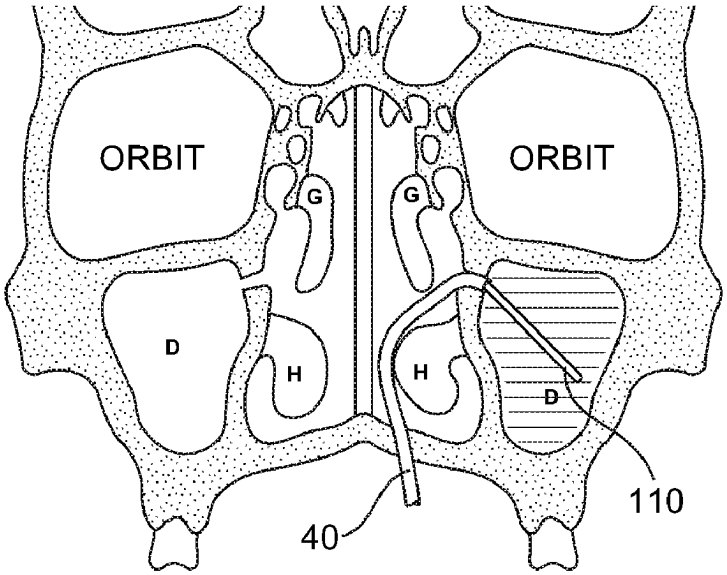



FIG. 38

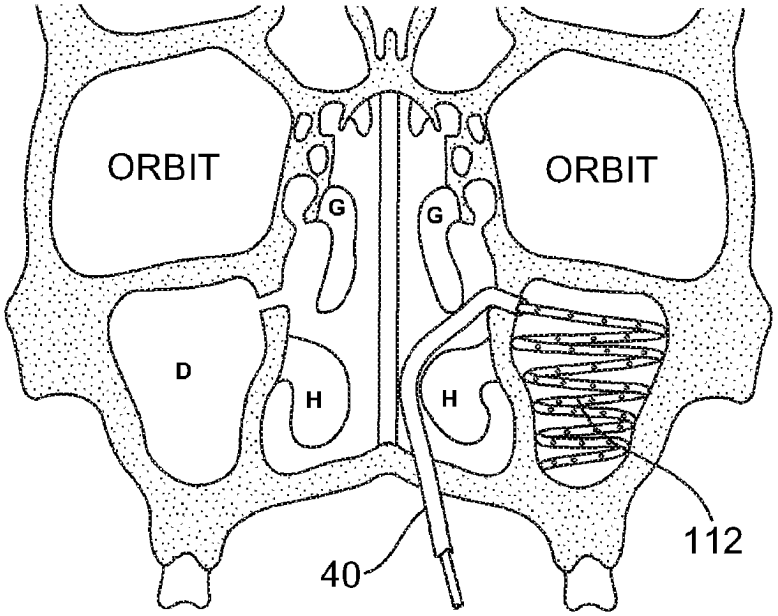



FIG. 39

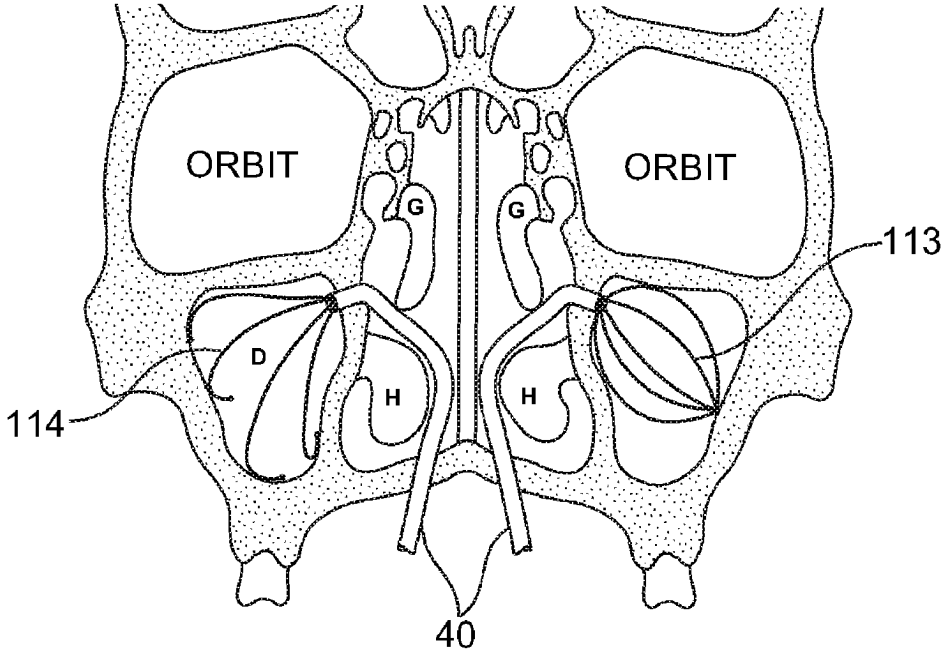



FIG. 40

# DECLARATION

As a below named inventor, I declare that:

My residence, post office address and citizenship are as stated below next to my name.

I believe that I am the original inventor or an original joint inventor of a claimed invention in the application.

This application, entitled: SYSTEMS AND METHODS FOR DELIVERY OF A THERAPEUTIC AGENT, the specification of which ___ is attached hereto or XX was filed on October 25, 2012, as Application No. 13/660,629 and was amended on _____ (if applicable).

I have reviewed and understand the contents of the above identified specification, including the claims, as amended by any amendment referred to above. I acknowledge the duty to disclose information which is material to patentability as defined in Title 37, Code of Federal Regulations, Section 1.56.

| | | | | | | |
|---|---|---|---|---|---|---|
| Full Name of Inventor 1: | Last Name: DEEM | Suffix: | First Name: Mark | Middle Name or Initial: E. | | |
| Residence & Citizenship: | City: Mountain View | | State/Foreign Country: CA | Country of Citizenship: US | | |
| Post Office Address: | Post Office Address: 685 Sierra Avenue | | City: Mountain View | State/Country: CA/USA | Postal Code: 94041 | |
| Full Name of Inventor 2: | Last Name: GIFFORD | Suffix: | First Name: Hanson | Middle Name or Initial: | | |
| Residence & Citizenship: | City: Woodside | | State/Foreign Country: CA | Country of Citizenship: US | | |
| Post Office Address: | Post Office Address: 3180 Woodside Road | | City: Woodside | State/Country: CA/USA | Postal Code: 94062 | |

I further declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

The above-identified application was made or authorized to be made by me.

I hereby acknowledge that any willful false statement made in this declaration (or oath) is punishable under 18 U.S.C. §1001 by fine or imprisonment of not more than five (5) years, or both.

| Signature of Inventor 1 | Signature of Inventor 2 |
|---|---|
| Mark E. Deem | Hanson Gifford |
| Date 12-15-14 | Date Dec. 15, 2014 |

Doc Code: PA..
Document Description: Power of Attorney

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# POWER OF ATTORNEY BY APPLICANT

I hereby revoke all previous powers of attorney given in the application identified in either the attached transmittal letter or the boxes below.

| Application Number | Filing Date |
|---|---|
| | |

(Note: The boxes above may be left blank if information is provided on form PTO/AIA/82A.)

☑ I hereby appoint the Patent Practitioner(s) associated with the following Customer Number as my/our attorney(s) or agent(s), and to transact all business in the United States Patent and Trademark Office connected therewith for the application referenced in the attached transmittal letter (form PTO/AIA/82A) or identified above: 24113

OR

☐ I hereby appoint Practitioner(s) named in the attached list (form PTO/AIA/82C) as my/our attorney(s) or agent(s), and to transact all business in the United States Patent and Trademark Office connected therewith for the patent application referenced in the attached transmittal letter (form PTO/AIA/82A) or identified above. (Note: Complete form PTO/AIA/82C.)

**Please recognize or change the correspondence address for the application identified in the attached transmittal letter or the boxes above to:**

☑ The address associated with the above-mentioned Customer Number

OR

☐ The address associated with Customer Number:

OR

| | | | | | |
|---|---|---|---|---|---|
| Firm or Individual Name | | | | | |
| Address | | | | | |
| City | | State | | Zip | |
| Country | | | | | |
| Telephone | | Email | | | |

I am the Applicant (if the Applicant is a juristic entity, list the Applicant name in the box):

The Foundry, LLC

☐ Inventor or Joint Inventor (title not required below)

☐ Legal Representative of a Deceased or Legally Incapacitated Inventor (title not required below)

☑ Assignee or Person to Whom the Inventor is Under an Obligation to Assign (provide signer's title if applicant is a juristic entity)

☐ Person Who Otherwise Shows Sufficient Proprietary Interest (e.g., a petition under 37 CFR 1.46(b)(2) was granted in the application or is concurrently being filed with this document) (provide signer's title if applicant is a juristic entity)

**SIGNATURE of Applicant for Patent**

The undersigned (whose title is supplied below) is authorized to act on behalf of the applicant (e.g., where the applicant is a juristic entity).

| | | | |
|---|---|---|---|
| Signature | | Date (Optional) | 2/13/13 |
| Name | Hunter Jeffress | | |
| Title | Manager member | | |

NOTE: Signature - This form must be signed by the applicant in accordance with 37 CFR 1.33. See 37 CFR 1.4 for signature requirements and certifications. If more than one applicant, use multiple forms.

☐ Total of forms are submitted.

This collection of information is required by 37 CFR 1.131, 1.32, and 1.33. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.11 and 1.14. This collection is estimated to take 3 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

*If you need assistance in completing the form, call 1-800-PTO-9199 and select option 2.*

# Electronic Acknowledgement Receipt

| | |
|---|---|
| **EFS ID:** | 37558987 |
| **Application Number:** | 16659893 |
| **International Application Number:** | |
| **Confirmation Number:** | 4259 |
| **Title of Invention:** | SYSTEMS AND METHODS FOR DELIVERY OF A THERAPEUTIC AGENT |
| **First Named Inventor/Applicant Name:** | Mark E. Deem |
| **Customer Number:** | 24113 |
| **Filer:** | Daidre L. Burgess/Valerie Mitchell |
| **Filer Authorized By:** | Daidre L. Burgess |
| **Attorney Docket Number:** | 5187.01US01AP |
| **Receipt Date:** | 25-OCT-2019 |
| **Filing Date:** | |
| **Time Stamp:** | 09:44:13 |
| **Application Type:** | Utility under 35 USC 111(a) |

## Payment information:

| | |
|---|---|
| Submitted with Payment | no |

## File Listing:

| Document Number | Document Description | File Name | File Size(Bytes)/ Message Digest | Multi Part /.zip | Pages (if appl.) |
|---|---|---|---|---|---|
| 1 | | 5187_01US01AP_Power_of_Atty.pdf | 416285<br>47f0d7ece5a4a47260a2a5fe98469e18964d8e79 | yes | 2 |

| | Multipart Description/PDF files in .zip description | | |
|---|---|---|---|
| | **Document Description** | **Start** | **End** |
| | Transmittal Letter | 1 | 1 |
| | Power of Attorney | 2 | 2 |
| **Warnings:** | | | |
| **Information:** | | | |
| | **Total Files Size (in bytes):** | 416285 | |

**This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.**

**New Applications Under 35 U.S.C. 111**
**If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.**
**National Stage of an International Application under 35 U.S.C. 371**
**If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.**
**New International Application Filed with the USPTO as a Receiving Office**
**If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.**

PTO/AIA/82A (07-13)
Approved for use through 03/31/2021. OMB 0651-0035
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it displays a valid OMB control number.

# TRANSMITTAL FOR POWER OF ATTORNEY TO ONE OR MORE REGISTERED PRACTITIONERS

NOTE: This form is to be submitted with the Power of Attorney by Applicant form (PTO/AIA/82B) to identify the application to which the Power of Attorney is directed, in accordance with 37 CFR 1.5, unless the application number and filing date are identified in the Power of Attorney by Applicant form. If neither form PTO/AIA/82A nor form PTO/AIA82B identifies the application to which the Power of Attorney is directed, the Power of Attorney will not be recognized in the application.

| | |
|---|---|
| Application Number | 16/659,893 |
| Filing Date | October 22, 2019 |
| First Named Inventor | Mark E. Deem |
| Title | SYSTEMS AND METHODS FOR DELIVERY OF A THERAPEUTIC AGENT |
| Art Unit | |
| Examiner Name | |
| Attorney Docket Number | 5187.01US01AP |

**SIGNATURE of Applicant or Patent Practitioner**

| | | | |
|---|---|---|---|
| Signature | /Daidre L. Burgess/ | Date (Optional) | 10/25/2019 |
| Name | Daidre L. Burgess | Registration Number | 60389 |
| Title (if Applicant is a juristic entity) | | | |
| Applicant Name (if Applicant is a juristic entity) | | | |

**NOTE:** This form must be signed in accordance with 37 CFR 1.33. See 37 CFR 1.4(d) for signature requirements and certifications. If more than one applicant, use multiple forms.

☐ *Total of _____ forms are submitted.

This collection of information is required by 37 CFR 1.131, 1.32, and 1.33. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.11 and 1.14. This collection is estimated to take 3 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

*If you need assistance in completing the form, call 1-800-PTO-9199 and select option 2.*

# PATENT APPLICATION FEE DETERMINATION RECORD

Substitute for Form PTO-875

Application or Docket Number: 16/659,893

## APPLICATION AS FILED - PART I

| FOR | (Column 1) NUMBER FILED | (Column 2) NUMBER EXTRA | SMALL ENTITY RATE($) | SMALL ENTITY FEE($) | OR | OTHER THAN SMALL ENTITY RATE($) | OTHER THAN SMALL ENTITY FEE($) |
|---|---|---|---|---|---|---|---|
| BASIC FEE (37 CFR 1.16(a), (b), or (c)) | N/A | N/A | N/A | 75 | | N/A | |
| SEARCH FEE (37 CFR 1.16(k), (i), or (m)) | N/A | N/A | N/A | 330 | | N/A | |
| EXAMINATION FEE (37 CFR 1.16(o), (p), or (q)) | N/A | N/A | N/A | 380 | | N/A | |
| TOTAL CLAIMS (37 CFR 1.16(i)) | 30 minus 20 = | * 10 | x 50 = | 500 | OR | | |
| INDEPENDENT CLAIMS (37 CFR 1.16(h)) | 2 minus 3 = | * | x 230 = | 0.00 | | | |
| APPLICATION SIZE FEE (37 CFR 1.16(s)) | If the specification and drawings exceed 100 sheets of paper, the application size fee due is $310 ($155 for small entity) for each additional 50 sheets or fraction thereof. See 35 U.S.C. 41(a)(1)(G) and 37 CFR 1.16(s). | | | 0.00 | | | |
| MULTIPLE DEPENDENT CLAIM PRESENT (37 CFR 1.16(j)) | | | | 0.00 | | | |
| * If the difference in column 1 is less than zero, enter "0" in column 2. | | | TOTAL | 1285 | | TOTAL | |

## APPLICATION AS AMENDED - PART II

| | | (Column 1) CLAIMS REMAINING AFTER AMENDMENT | | (Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR | (Column 3) PRESENT EXTRA | SMALL ENTITY RATE($) | SMALL ENTITY ADDITIONAL FEE($) | OR | OTHER THAN SMALL ENTITY RATE($) | OTHER THAN SMALL ENTITY ADDITIONAL FEE($) |
|---|---|---|---|---|---|---|---|---|---|---|
| AMENDMENT A | Total (37 CFR 1.16(i)) | * | Minus | ** | = | x = | | OR | x = | |
| | Independent (37 CFR 1.16(h)) | * | Minus | *** | = | x = | | OR | x = | |
| | Application Size Fee (37 CFR 1.16(s)) | | | | | | | | | |
| | FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j)) | | | | | | | OR | | |
| | | | | | | TOTAL ADD'L FEE | | OR | TOTAL ADD'L FEE | |

| | | (Column 1) CLAIMS REMAINING AFTER AMENDMENT | | (Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR | (Column 3) PRESENT EXTRA | RATE($) | ADDITIONAL FEE($) | | RATE($) | ADDITIONAL FEE($) |
|---|---|---|---|---|---|---|---|---|---|---|
| AMENDMENT B | Total (37 CFR 1.16(i)) | * | Minus | ** | = | x = | | OR | x = | |
| | Independent (37 CFR 1.16(h)) | * | Minus | *** | = | x = | | OR | x = | |
| | Application Size Fee (37 CFR 1.16(s)) | | | | | | | | | |
| | FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j)) | | | | | | | OR | | |
| | | | | | | TOTAL ADD'L FEE | | OR | TOTAL ADD'L FEE | |

* If the entry in column 1 is less than the entry in column 2, write "0" in column 3.

** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 20, enter "20".

*** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 3, enter "3".

The "Highest Number Previously Paid For" (Total or Independent) is the highest found in the appropriate box in column 1.

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UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

| APPLICATION NUMBER | FILING or 371(c) DATE | GRP ART UNIT | FIL FEE REC'D | ATTY.DOCKET.NO | TOT CLAIMS | IND CLAIMS |
|---|---|---|---|---|---|---|
| 16/659,893 | 10/22/2019 | 1645 | 1285 | 5187.01US01AP | 30 | 2 |

**CONFIRMATION NO. 4259**

24113
PATTERSON THUENTE PEDERSEN, P.A.
80 SOUTH 8TH STREET
4800 IDS CENTER
MINNEAPOLIS, MN 55402-2100

**FILING RECEIPT**

OC000000112456219

Date Mailed: 11/08/2019

Receipt is acknowledged of this non-provisional utility patent application. The application will be taken up for examination in due course. Applicant will be notified as to the results of the examination. Any correspondence concerning the application must include the following identification information: the U.S. APPLICATION NUMBER, FILING DATE, NAME OF FIRST INVENTOR, and TITLE OF INVENTION. Fees transmitted by check or draft are subject to collection.

**Please verify the accuracy of the data presented on this receipt.** If an error is noted on this Filing Receipt, please submit a written request for a corrected Filing Receipt, including a properly marked-up ADS showing the changes with strike-through for deletions and underlining for additions. If you received a "Notice to File Missing Parts" or other Notice requiring a response for this application, please submit any request for correction to this Filing Receipt with your reply to the Notice. When the USPTO processes the reply to the Notice, the USPTO will generate another Filing Receipt incorporating the requested corrections provided that the request is grantable.

**Inventor(s)**

Mark E. Deem, Mountain View, CA;
Hanson Gifford, Woodside, CA;

**Applicant(s)**

The Foundry, LLC, Menlo Park, CA

**Power of Attorney:** The patent practitioners associated with Customer Number 24113

**Domestic Priority data as claimed by applicant**

This application is a CON of 16/036,381 07/16/2018
which is a CON of 15/358,187 11/22/2016 PAT 10022529
which is a CON of 14/601,529 01/21/2015 PAT 9498283
which is a CON of 13/660,629 10/25/2012 PAT 8961391
which is a CON of 13/253,595 10/05/2011 PAT 8338164
which is a CON of 12/559,278 09/14/2009 PAT 8133497
which is a DIV of 11/459,090 07/21/2006 PAT 7608275
which claims benefit of 60/702,077 07/22/2005

**Foreign Applications** for which priority is claimed (You may be eligible to benefit from the **Patent Prosecution Highway** program at the USPTO. Please see http://www.uspto.gov for more information.) - None.
*Foreign application information must be provided in an Application Data Sheet in order to constitute a claim to foreign priority. See 37 CFR 1.55 and 1.76.*

**Permission to Access Application via Priority Document Exchange:** Yes

**Permission to Access Search Results:** Yes

Applicant may provide or rescind an authorization for access using Form PTO/SB/39 or Form PTO/SB/69 as appropriate.

**If Required, Foreign Filing License Granted:** 11/06/2019

The country code and number of your priority application, to be used for filing abroad under the Paris Convention, is **US 16/659,893**

**Projected Publication Date:** 02/13/2020

**Non-Publication Request:** No

**Early Publication Request:** No

**** SMALL ENTITY ****

**Title**

SYSTEMS AND METHODS FOR DELIVERY OF A THERAPEUTIC AGENT

**Preliminary Class**

424

**Statement under 37 CFR 1.55 or 1.78 for AIA (First Inventor to File) Transition Applications:** No

## PROTECTING YOUR INVENTION OUTSIDE THE UNITED STATES

Since the rights granted by a U.S. patent extend only throughout the territory of the United States and have no effect in a foreign country, an inventor who wishes patent protection in another country must apply for a patent in a specific country or in regional patent offices. Applicants may wish to consider the filing of an international application under the Patent Cooperation Treaty (PCT). An international (PCT) application generally has the same effect as a regular national patent application in each PCT-member country. The PCT process **simplifies** the filing of patent applications on the same invention in member countries, but **does not result** in a grant of "an international patent" and does not eliminate the need of applicants to file additional documents and fees in countries where patent protection is desired.

Almost every country has its own patent law, and a person desiring a patent in a particular country must make an application for patent in that country in accordance with its particular laws. Since the laws of many countries differ in various respects from the patent law of the United States, applicants are advised to seek guidance from specific foreign countries to ensure that patent rights are not lost prematurely.

Applicants also are advised that in the case of inventions made in the United States, the Director of the USPTO must issue a license before applicants can apply for a patent in a foreign country. The filing of a U.S. patent application serves as a request for a foreign filing license. The application's filing receipt contains further information and guidance as to the status of applicant's license for foreign filing.

Applicants may wish to consult the USPTO booklet, "General Information Concerning Patents" (specifically, the section entitled "Treaties and Foreign Patents") for more information on timeframes and deadlines for filing foreign patent applications. The guide is available either by contacting the USPTO Contact Center at 800-786-9199, or it can be viewed on the USPTO website at http://www.uspto.gov/web/offices/pac/doc/general/index.html.

For information on preventing theft of your intellectual property (patents, trademarks and copyrights), you may wish to consult the U.S. Government website, http://www.stopfakes.gov. Part of a Department of Commerce initiative, this website includes self-help "toolkits" giving innovators guidance on how to protect intellectual property in specific countries such as China, Korea and Mexico. For questions regarding patent enforcement issues, applicants may call the U.S. Government hotline at 1-866-999-HALT (1-866-999-4258).

## LICENSE FOR FOREIGN FILING UNDER

## Title 35, United States Code, Section 184

## Title 37, Code of Federal Regulations, 5.11 & 5.15

**GRANTED**

The applicant has been granted a license under 35 U.S.C. 184, if the phrase "IF REQUIRED, FOREIGN FILING LICENSE GRANTED" followed by a date appears on this form. Such licenses are issued in all applications where the conditions for issuance of a license have been met, regardless of whether or not a license may be required as set forth in 37 CFR 5.15. The scope and limitations of this license are set forth in 37 CFR 5.15(a) unless an earlier license has been issued under 37 CFR 5.15(b). The license is subject to revocation upon written notification. The date indicated is the effective date of the license, unless an earlier license of similar scope has been granted under 37 CFR 5.13 or 5.14.

This license is to be retained by the licensee and may be used at any time on or after the effective date thereof unless it is revoked. This license is automatically transferred to any related applications(s) filed under 37 CFR 1.53(d). This license is not retroactive.

The grant of a license does not in any way lessen the responsibility of a licensee for the security of the subject matter as imposed by any Government contract or the provisions of existing laws relating to espionage and the national security or the export of technical data. Licensees should apprise themselves of current regulations especially with respect to certain countries, of other agencies, particularly the Office of Defense Trade Controls, Department of State (with respect to Arms, Munitions and Implements of War (22 CFR 121-128)); the Bureau of Industry and Security, Department of Commerce (15 CFR parts 730-774); the Office of Foreign AssetsControl, Department of Treasury (31 CFR Parts 500+) and the Department of Energy.

**NOT GRANTED**

No license under 35 U.S.C. 184 has been granted at this time, if the phrase "IF REQUIRED, FOREIGN FILING LICENSE GRANTED" DOES NOT appear on this form. Applicant may still petition for a license under 37 CFR 5.12, if a license is desired before the expiration of 6 months from the filing date of the application. If 6 months has lapsed from the filing date of this application and the licensee has not received any indication of a secrecy order under 35 U.S.C. 181, the licensee may foreign file the application pursuant to 37 CFR 5.15(b).

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## *SelectUSA*

The United States represents the largest, most dynamic marketplace in the world and is an unparalleled location for business investment, innovation, and commercialization of new technologies. The U.S. offers tremendous resources and advantages for those who invest and manufacture goods here. Through SelectUSA, our nation works to promote and facilitate business investment. SelectUSA provides information assistance to the international investor

community; serves as an ombudsman for existing and potential investors; advocates on behalf of U.S. cities, states, and regions competing for global investment; and counsels U.S. economic development organizations on investment attraction best practices. To learn more about why the United States is the best country in the world to develop technology, manufacture products, deliver services, and grow your business, visit http://www.SelectUSA.gov or call +1-202-482-6800.

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UNITED STATES DEPARTMENT OF COMMERCE
**United States Patent and Trademark Office**
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
|---|---|---|---|---|
| 16/659,893 | 10/22/2019 | Mark E. Deem | 5187.01US01AP | 4259 |

24113 7590 11/15/2019

PATTERSON THUENTE PEDERSEN, P.A.
80 SOUTH 8TH STREET
4800 IDS CENTER
MINNEAPOLIS, MN 55402-2100

| EXAMINER | |
|---|---|
| NAVARRO, ALBERT MARK | |

| ART UNIT | PAPER NUMBER |
|---|---|
| 1645 | |

| NOTIFICATION DATE | DELIVERY MODE |
|---|---|
| 11/15/2019 | ELECTRONIC |

**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

efsuspto@ptslaw.com
johnson@ptslaw.com

| *Decision Granting Request for Prioritized Examination (Track I)* | **Application No.** 16/659,893 | **Applicant(s)** Deem et al. | |
|---|---|---|---|
| | **Examiner** CHERYL P GIBSON BAYLOR | **Art Unit** OPET | **AIA (FITF) Status** No |

1. THE REQUEST FILED 22 October 2019 IS **GRANTED** .

The above-identified application has met the requirements for prioritized examination

A. ☑ for an original nonprovisional application (Track I).
B. ☐ for an application undergoing continued examination (RCE).

2. **The above-identified application will undergo prioritized examination**. The application will be accorded special status throughout its entire course of prosecution until one of the following occurs:

A. filing a **petition for extension of time** to extend the time period for filing a reply;

B. filing an **amendment to amend the application to contain more than four independent claims, more than thirty total claims** , or a multiple dependent claim;

C. filing a **request for continued examination** ;

D. filing a notice of appeal;

E. filing a request for suspension of action;

F. mailing of a notice of allowance;

G. mailing of a final Office action;

H. completion of examination as defined in 37 CFR 41.102; or

I. abandonment of the application.

Telephone inquiries with regard to this decision should be directed to CHERYL GIBSON BAYLOR at (571 )272-3213. In his/her absence, calls may be directed to Petition Help Desk at (571) 272-3282.

| /CHERYL GIBSON BAYLOR/<br>Paralegal Specialist, OPET | |
|---|---|

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
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# NOTICE OF ALLOWANCE AND FEE(S) DUE

24113 7590 11/22/2019

PATTERSON THUENTE PEDERSEN, P.A.
80 SOUTH 8TH STREET
4800 IDS CENTER
MINNEAPOLIS, MN 55402-2100

| EXAMINER | |
|---|---|
| NAVARRO, ALBERT MARK | |
| ART UNIT | PAPER NUMBER |
| 1645 | |

DATE MAILED: 11/22/2019

| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
|---|---|---|---|---|
| 16/659,893 | 10/22/2019 | Mark E. Deem | 5187.01US01AP | 4259 |

TITLE OF INVENTION: SYSTEMS AND METHODS FOR DELIVERY OF A THERAPEUTIC AGENT

| APPLN. TYPE | ENTITY STATUS | ISSUE FEE DUE | PUBLICATION FEE DUE | PREV. PAID ISSUE FEE | TOTAL FEE(S) DUE | DATE DUE |
|---|---|---|---|---|---|---|
| nonprovisional | SMALL | $500 | $0.00 | $0.00 | $500 | 02/24/2020 |

**THE APPLICATION IDENTIFIED ABOVE HAS BEEN EXAMINED AND IS ALLOWED FOR ISSUANCE AS A PATENT. PROSECUTION ON THE MERITS IS CLOSED. THIS NOTICE OF ALLOWANCE IS NOT A GRANT OF PATENT RIGHTS. THIS APPLICATION IS SUBJECT TO WITHDRAWAL FROM ISSUE AT THE INITIATIVE OF THE OFFICE OR UPON PETITION BY THE APPLICANT. SEE 37 CFR 1.313 AND MPEP 1308.**

**THE ISSUE FEE AND PUBLICATION FEE (IF REQUIRED) MUST BE PAID WITHIN THREE MONTHS FROM THE MAILING DATE OF THIS NOTICE OR THIS APPLICATION SHALL BE REGARDED AS ABANDONED. THIS STATUTORY PERIOD CANNOT BE EXTENDED. SEE 35 U.S.C. 151. THE ISSUE FEE DUE INDICATED ABOVE DOES NOT REFLECT A CREDIT FOR ANY PREVIOUSLY PAID ISSUE FEE IN THIS APPLICATION. IF AN ISSUE FEE HAS PREVIOUSLY BEEN PAID IN THIS APPLICATION (AS SHOWN ABOVE), THE RETURN OF PART B OF THIS FORM WILL BE CONSIDERED A REQUEST TO REAPPLY THE PREVIOUSLY PAID ISSUE FEE TOWARD THE ISSUE FEE NOW DUE.**

**HOW TO REPLY TO THIS NOTICE:**

I. Review the ENTITY STATUS shown above. If the ENTITY STATUS is shown as SMALL or MICRO, verify whether entitlement to that entity status still applies.

If the ENTITY STATUS is the same as shown above, pay the TOTAL FEE(S) DUE shown above.

If the ENTITY STATUS is changed from that shown above, on PART B - FEE(S) TRANSMITTAL, complete section number 5 titled "Change in Entity Status (from status indicated above)".

For purposes of this notice, small entity fees are 1/2 the amount of undiscounted fees, and micro entity fees are 1/2 the amount of small entity fees.

II. PART B - FEE(S) TRANSMITTAL, or its equivalent, must be completed and returned to the United States Patent and Trademark Office (USPTO) with your ISSUE FEE and PUBLICATION FEE (if required). If you are charging the fee(s) to your deposit account, section "4b" of Part B - Fee(s) Transmittal should be completed and an extra copy of the form should be submitted. If an equivalent of Part B is filed, a request to reapply a previously paid issue fee must be clearly made, and delays in processing may occur due to the difficulty in recognizing the paper as an equivalent of Part B.

III. All communications regarding this application must give the application number. Please direct all communications prior to issuance to Mail Stop ISSUE FEE unless advised to the contrary.

**IMPORTANT REMINDER: Maintenance fees are due in utility patents issuing on applications filed on or after Dec. 12, 1980. It is patentee's responsibility to ensure timely payment of maintenance fees when due. More information is available at www.uspto.gov/PatentMaintenanceFees.**

## PART B - FEE(S) TRANSMITTAL

Complete and send this form, together with applicable fee(s), by mail or fax, or via EFS-Web.

By mail, send to: Mail Stop ISSUE FEE
Commissioner for Patents
P.O. Box 1450
Alexandria, Virginia 22313-1450

By fax, send to: (571)-273-2885

INSTRUCTIONS: This form should be used for transmitting the ISSUE FEE and PUBLICATION FEE (if required). Blocks 1 through 5 should be completed where appropriate. All further correspondence including the Patent, advance orders and notification of maintenance fees will be mailed to the current correspondence address as indicated unless corrected below or directed otherwise in Block 1, by (a) specifying a new correspondence address; and/or (b) indicating a separate "FEE ADDRESS" for maintenance fee notifications.

CURRENT CORRESPONDENCE ADDRESS (Note: Use Block 1 for any change of address)

24113 7590 11/22/2019
PATTERSON THUENTE PEDERSEN, P.A.
80 SOUTH 8TH STREET
4800 IDS CENTER
MINNEAPOLIS, MN 55402-2100

Note: A certificate of mailing can only be used for domestic mailings of the Fee(s) Transmittal. This certificate cannot be used for any other accompanying papers. Each additional paper, such as an assignment or formal drawing, must have its own certificate of mailing or transmission.

**Certificate of Mailing or Transmission**

I hereby certify that this Fee(s) Transmittal is being deposited with the United States Postal Service with sufficient postage for first class mail in an envelope addressed to the Mail Stop ISSUE FEE address above, or being transmitted to the USPTO via EFS-Web or by facsimile to (571) 273-2885, on the date below.

| |
|---|
| (Typed or printed name) |
| (Signature) |
| (Date) |

| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
|---|---|---|---|---|
| 16/659,893 | 10/22/2019 | Mark E. Deem | 5187.01US01AP | 4259 |

TITLE OF INVENTION: SYSTEMS AND METHODS FOR DELIVERY OF A THERAPEUTIC AGENT

| APPLN. TYPE | ENTITY STATUS | ISSUE FEE DUE | PUBLICATION FEE DUE | PREV. PAID ISSUE FEE | TOTAL FEE(S) DUE | DATE DUE |
|---|---|---|---|---|---|---|
| nonprovisional | SMALL | $500 | $0.00 | $0.00 | $500 | 02/24/2020 |

| EXAMINER | ART UNIT | CLASS-SUBCLASS |
|---|---|---|
| NAVARRO, ALBERT MARK | 1645 | 424-190100 |

1. Change of correspondence address or indication of "Fee Address" (37 CFR 1.363).

❑ Change of correspondence address (or Change of Correspondence Address form PTO/SB/122) attached.

❑ "Fee Address" indication (or "Fee Address" Indication form PTO/SB/47; Rev 03-09 or more recent) attached. **Use of a Customer Number is required.**

2. For printing on the patent front page, list
(1) The names of up to 3 registered patent attorneys or agents OR, alternatively,
(2) The name of a single firm (having as a member a registered attorney or agent) and the names of up to 2 registered patent attorneys or agents. If no name is listed, no name will be printed.

1 _____
2 _____
3 _____

3. ASSIGNEE NAME AND RESIDENCE DATA TO BE PRINTED ON THE PATENT (print or type)

PLEASE NOTE: Unless an assignee is identified below, no assignee data will appear on the patent. If an assignee is identified below, the document must have been previously recorded, or filed for recordation, as set forth in 37 CFR 3.11 and 37 CFR 3.81(a). Completion of this form is NOT a substitute for filing an assignment.

(A) NAME OF ASSIGNEE (B) RESIDENCE: (CITY and STATE OR COUNTRY)

Please check the appropriate assignee category or categories (will not be printed on the patent) : ❑ Individual ❑ Corporation or other private group entity ❑ Government

4a. Fees submitted: ❑ Issue Fee ❑ Publication Fee (if required) ❑ Advance Order - # of Copies _____

4b. Method of Payment: *(Please first reapply any previously paid fee shown above)*

❑ Electronic Payment via EFS-Web ❑ Enclosed check ❑ Non-electronic payment by credit card (Attach form PTO-2038)

❑ The Director is hereby authorized to charge the required fee(s), any deficiency, or credit any overpayment to Deposit Account No. _____

5. **Change in Entity Status** (from status indicated above)

❑ Applicant certifying micro entity status. See 37 CFR 1.29

❑ Applicant asserting small entity status. See 37 CFR 1.27

❑ Applicant changing to regular undiscounted fee status.

NOTE: Absent a valid certification of Micro Entity Status (see forms PTO/SB/15A and 15B), issue fee payment in the micro entity amount will not be accepted at the risk of application abandonment.
NOTE: If the application was previously under micro entity status, checking this box will be taken to be a notification of loss of entitlement to micro entity status.
NOTE: Checking this box will be taken to be a notification of loss of entitlement to small or micro entity status, as applicable.

NOTE: This form must be signed in accordance with 37 CFR 1.31 and 1.33. See 37 CFR 1.4 for signature requirements and certifications.

Authorized Signature _____ Date _____

Typed or printed name _____ Registration No. _____

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
|---|---|---|---|---|
| 16/659,893 | 10/22/2019 | Mark E. Deem | 5187.01US01AP | 4259 |

24113 7590 11/22/2019

PATTERSON THUENTE PEDERSEN, P.A.
80 SOUTH 8TH STREET
4800 IDS CENTER
MINNEAPOLIS, MN 55402-2100

| EXAMINER | |
|---|---|
| NAVARRO, ALBERT MARK | |
| ART UNIT | PAPER NUMBER |
| 1645 | |

DATE MAILED: 11/22/2019

**Determination of Patent Term Adjustment under 35 U.S.C. 154 (b)**
(Applications filed on or after May 29, 2000)

The Office has discontinued providing a Patent Term Adjustment (PTA) calculation with the Notice of Allowance.

Section 1(h)(2) of the AIA Technical Corrections Act amended 35 U.S.C. 154(b)(3)(B)(i) to eliminate the requirement that the Office provide a patent term adjustment determination with the notice of allowance. See Revisions to Patent Term Adjustment, 78 Fed. Reg. 19416, 19417 (Apr. 1, 2013). Therefore, the Office is no longer providing an initial patent term adjustment determination with the notice of allowance. The Office will continue to provide a patent term adjustment determination with the Issue Notification Letter that is mailed to applicant approximately three weeks prior to the issue date of the patent, and will include the patent term adjustment on the patent. Any request for reconsideration of the patent term adjustment determination (or reinstatement of patent term adjustment) should follow the process outlined in 37 CFR 1.705.

Any questions regarding the Patent Term Extension or Adjustment determination should be directed to the Office of Patent Legal Administration at (571)-272-7702. Questions relating to issue and publication fee payments should be directed to the Customer Service Center of the Office of Patent Publication at 1-(888)-786-0101 or (571)-272-4200.

## OMB Clearance and PRA Burden Statement for PTOL-85 Part B

The Paperwork Reduction Act (PRA) of 1995 requires Federal agencies to obtain Office of Management and Budget approval before requesting most types of information from the public. When OMB approves an agency request to collect information from the public, OMB (i) provides a valid OMB Control Number and expiration date for the agency to display on the instrument that will be used to collect the information and (ii) requires the agency to inform the public about the OMB Control Number's legal significance in accordance with 5 CFR 1320.5(b).

The information collected by PTOL-85 Part B is required by 37 CFR 1.311. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 30 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, Virginia 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, Virginia 22313-1450. Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it displays a valid OMB control number.

## Privacy Act Statement

**The Privacy Act of 1974 (P.L. 93-579)** requires that you be given certain information in connection with your submission of the attached form related to a patent application or patent. Accordingly, pursuant to the requirements of the Act, please be advised that: (1) the general authority for the collection of this information is 35 U.S.C. 2(b)(2); (2) furnishing of the information solicited is voluntary; and (3) the principal purpose for which the information is used by the U.S. Patent and Trademark Office is to process and/or examine your submission related to a patent application or patent. If you do not furnish the requested information, the U.S. Patent and Trademark Office may not be able to process and/or examine your submission, which may result in termination of proceedings or abandonment of the application or expiration of the patent.

The information provided by you in this form will be subject to the following routine uses:

1. The information on this form will be treated confidentially to the extent allowed under the Freedom of Information Act (5 U.S.C. 552) and the Privacy Act (5 U.S.C 552a). Records from this system of records may be disclosed to the Department of Justice to determine whether disclosure of these records is required by the Freedom of Information Act.
2. A record from this system of records may be disclosed, as a routine use, in the course of presenting evidence to a court, magistrate, or administrative tribunal, including disclosures to opposing counsel in the course of settlement negotiations.
3. A record in this system of records may be disclosed, as a routine use, to a Member of Congress submitting a request involving an individual, to whom the record pertains, when the individual has requested assistance from the Member with respect to the subject matter of the record.
4. A record in this system of records may be disclosed, as a routine use, to a contractor of the Agency having need for the information in order to perform a contract. Recipients of information shall be required to comply with the requirements of the Privacy Act of 1974, as amended, pursuant to 5 U.S.C. 552a(m).
5. A record related to an International Application filed under the Patent Cooperation Treaty in this system of records may be disclosed, as a routine use, to the International Bureau of the World Intellectual Property Organization, pursuant to the Patent Cooperation Treaty.
6. A record in this system of records may be disclosed, as a routine use, to another federal agency for purposes of National Security review (35 U.S.C. 181) and for review pursuant to the Atomic Energy Act (42 U.S.C. 218(c)).
7. A record from this system of records may be disclosed, as a routine use, to the Administrator, General Services, or his/her designee, during an inspection of records conducted by GSA as part of that agency's responsibility to recommend improvements in records management practices and programs, under authority of 44 U.S.C. 2904 and 2906. Such disclosure shall be made in accordance with the GSA regulations governing inspection of records for this purpose, and any other relevant (i.e., GSA or Commerce) directive. Such disclosure shall not be used to make determinations about individuals.
8. A record from this system of records may be disclosed, as a routine use, to the public after either publication of the application pursuant to 35 U.S.C. 122(b) or issuance of a patent pursuant to 35 U.S.C. 151. Further, a record may be disclosed, subject to the limitations of 37 CFR 1.14, as a routine use, to the public if the record was filed in an application which became abandoned or in which the proceedings were terminated and which application is referenced by either a published application, an application open to public inspection or an issued patent.
9. A record from this system of records may be disclosed, as a routine use, to a Federal, State, or local law enforcement agency, if the USPTO becomes aware of a violation or potential violation of law or regulation.

| Notice of Allowability | Application No. 16/659,893 | Applicant(s) Deem et al. | |
|---|---|---|---|
| | Examiner Mark NAVARRO | Art Unit 1645 | AIA (FITF) Status No |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address--*

All claims being allowable, PROSECUTION ON THE MERITS IS (OR REMAINS) CLOSED in this application. If not included herewith (or previously mailed), a Notice of Allowance (PTOL-85) or other appropriate communication will be mailed in due course. **THIS NOTICE OF ALLOWABILITY IS NOT A GRANT OF PATENT RIGHTS.** This application is subject to withdrawal from issue at the initiative of the Office or upon petition by the applicant. See 37 CFR 1.313 and MPEP 1308.

1. ☐ This communication is responsive to _____.
   ☐ A declaration(s)/affidavit(s) under **37 CFR 1.130(b)** was/were filed on _____.

2. ☐ An election was made by the applicant in response to a restriction requirement set forth during the interview on _____; the restriction requirement and election have been incorporated into this action.

3. ☑ The allowed claim(s) is/are 1-30 . As a result of the allowed claim(s), you may be eligible to benefit from the **Patent Prosecution Highway** program at a participating intellectual property office for the corresponding application. For more information, please see **http://www.uspto.gov/patents/init_events/pph/index.jsp** or send an inquiry to **PPHfeedback@uspto.gov.**

4. ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

   **Certified copies:**

   a) ☐ All  b) ☐ Some  *c) ☐ None of the:

   1. ☐ Certified copies of the priority documents have been received.
   2. ☐ Certified copies of the priority documents have been received in Application No. _____ .
   3. ☐ Copies of the certified copies of the priority documents have been received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

   * Certified copies not received: _____ .

Applicant has THREE MONTHS FROM THE "MAILING DATE" of this communication to file a reply complying with the requirements noted below. Failure to timely comply will result in ABANDONMENT of this application.
**THIS THREE-MONTH PERIOD IS NOT EXTENDABLE.**

5. ☐ CORRECTED DRAWINGS (as "replacement sheets") must be submitted.
   ☐ including changes required by the attached Examiner's Amendment / Comment or in the Office action of Paper No./Mail Date _____ .

   **Identifying indicia such as the application number (see 37 CFR 1.84(c)) should be written on the drawings in the front (not the back) of each sheet. Replacement sheet(s) should be labeled as such in the header according to 37 CFR 1.121(d).**

6. ☐ DEPOSIT OF and/or INFORMATION about the deposit of BIOLOGICAL MATERIAL must be submitted. Note the attached Examiner's comment regarding REQUIREMENT FOR THE DEPOSIT OF BIOLOGICAL MATERIAL.

**Attachment(s)**

1. ☑ Notice of References Cited (PTO-892)
2. ☐ Information Disclosure Statements (PTO/SB/08), Paper No./Mail Date _____.
3. ☐ Examiner's Comment Regarding Requirement for Deposit of Biological Material _____.
4. ☐ Interview Summary (PTO-413), Paper No./Mail Date. _____.
5. ☐ Examiner's Amendment/Comment
6. ☑ Examiner's Statement of Reasons for Allowance
7. ☐ Other _____.

/ALBERT M NAVARRO/
Primary Examiner, Art Unit 1645

***Notice of Pre-AIA or AIA Status***

The present application is being examined under the pre-AIA first to invent provisions.

***Reasons for Allowance***

The following is an examiner's statement of reasons for allowance:

The closest prior art is Makower et al (US Publication 2005/0240147) of record. Makower et al teach of treating disorders of the ear, nose and throat via inserting an energy emitting device into the nasopharynx. (See abstract). However, Makower et al do not teach or fairly suggest treating nasal conditions with a device so as to disrupt neural activity such that mucus secretion is reduced in the nasopharyngeal passage, and wherein the target tissue has a change in temperature.

Any comments considered necessary by applicant must be submitted no later than the payment of the issue fee and, to avoid processing delays, should preferably accompany the issue fee. Such submissions should be clearly labeled "Comments on Statement of Reasons for Allowance."

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Mark NAVARRO whose telephone number is (571)272-0861.

Examiner interviews are available via telephone, in-person, and video conferencing using a USPTO supplied web-based collaboration tool. To schedule an

interview, applicant is encouraged to use the USPTO Automated Interview Request (AIR) at http://www.uspto.gov/interviewpractice.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Nickol can be reached on 571 272-0835. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/ALBERT M NAVARRO/
Primary Examiner, Art Unit 1645
November 19, 2019

| Notice of References Cited | Application/Control No. 16/659,893 | Applicant(s)/Patent Under Reexamination Deem et al. | |
|---|---|---|---|
| | Examiner Mark NAVARRO | Art Unit 1645 | Page 1 of 1 |

**U.S. PATENT DOCUMENTS**

| * | | Document Number Country Code-Number-Kind Code | Date MM-YYYY | Name | CPC Classification | US Classification |
|---|---|---|---|---|---|---|
| * | A | US-20050240147-A1 | 10-2005 | Makower, Joshua | A61B17/24 | 604/96.01 |
| | B | | | | | |
| | C | | | | | |
| | D | | | | | |
| | E | | | | | |
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**FOREIGN PATENT DOCUMENTS**

| * | | Document Number Country Code-Number-Kind Code | Date MM-YYYY | Country | Name | CPC Classification |
|---|---|---|---|---|---|---|
| | N | | | | | |
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**NON-PATENT DOCUMENTS**

| * | | Include as applicable: Author, Title Date, Publisher, Edition or Volume, Pertinent Pages) |
|---|---|---|
| | U | |
| | V | |
| | W | |
| | X | |

*A copy of this reference is not being furnished with this Office action. (See MPEP § 707.05(a).)
Dates in MM-YYYY format are publication dates. Classifications may be US or foreign.

| Issue Classification | Application/Control No. | Applicant(s)/Patent Under Reexamination |
|---|---|---|
| | 16/659,893 | Deem et al. |
| | **Examiner** | **Art Unit** |
| | Mark NAVARRO | 1645 |

| CPC | | | | | | |
|---|---|---|---|---|---|---|
| **Symbol** | | | | | **Type** | **Version** |
| A61M | / | 37 | / | 00 | F | 2013-01-01 |
| A61M | / | 37 | / | 0092 | I | 2013-01-01 |
| A61K | / | 41 | / | 0047 | I | 2013-01-01 |
| A61N | / | 5 | / | 10 | I | 2013-01-01 |
| A61B | / | 18 | / | 1815 | I | 2013-01-01 |
| A61B | / | 18 | / | 1492 | I | 2013-01-01 |
| A61N | / | 7 | / | 00 | I | 2013-01-01 |
| A61N | / | 1 | / | 303 | I | 2013-01-01 |
| A61K | / | 9 | / | 0078 | I | 2013-01-01 |
| A61K | / | 9 | / | 0021 | I | 2013-01-01 |
| A61N | / | 1 | / | 327 | I | 2013-01-01 |
| A61N | / | 1 | / | 08 | I | 2013-01-01 |
| A61K | / | 41 | / | 0028 | I | 2013-01-01 |
| A61K | / | 41 | / | 00 | I | 2013-01-01 |
| A61K | / | 38 | / | 4893 | I | 2013-01-01 |
| A61K | / | 38 | / | 168 | I | 2013-01-01 |
| A61K | / | 38 | / | 164 | I | 2013-01-01 |
| C12Y | / | 304 | / | 24069 | I | 2013-01-01 |
| Y02A | / | 50 | / | 471 | A | 2018-01-01 |
| A61M | / | 2210 | / | 1035 | A | 2013-01-01 |
| A61N | / | 2007 | / | 003 | A | 2013-01-01 |
| A61B | / | 2018 | / | 1861 | A | 2013-01-01 |
| A61B | / | 2018 | / | 00434 | A | 2013-01-01 |
| A61B | / | 2018 | / | 00214 | A | 2013-01-01 |
| A61B | / | 2018 | / | 0016 | A | 2013-01-01 |

| CPC Combination Sets | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| **Symbol** | | | | | **Type** | **Set** | **Ranking** | **Version** |
| | / | | / | | | | | |

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|---|---|---|---|
| NONE | | **Total Claims Allowed:** | |
| (Assistant Examiner) | (Date) | 30 | |
| /ALBERT M NAVARRO/<br>Primary Examiner, Art Unit 1645 | 19 November 2019 | O.G. Print Claim(s) | O.G. Print Figure |
| (Primary Examiner) | (Date) | 1 | NONE |

U.S. Patent and Trademark Office

Part of Paper No.: 20191119

| Issue Classification | Application/Control No. | Applicant(s)/Patent Under Reexamination |
|---|---|---|
| | 16/659,893 | Deem et al. |
| | **Examiner** | **Art Unit** |
| | Mark NAVARRO | 1645 |

| INTERNATIONAL CLASSIFICATION | | | | | |
|---|---|---|---|---|---|
| **CLAIMED** | | | | | |
| A61K | / | 39 | / | 02 | |
| **NON-CLAIMED** | | | | | |
| | / | | / | | |

| US ORIGINAL CLASSIFICATION | |
|---|---|
| **CLASS** | **SUBCLASS** |
| 424 | 236.1 |

| CROSS REFERENCES(S) | | | | | | |
|---|---|---|---|---|---|---|
| **CLASS** | **SUBCLASS (ONE SUBCLASS PER BLOCK)** | | | | | |
| | | | | | | |

| NONE<br>(Assistant Examiner) | (Date) | **Total Claims Allowed:**<br>30 | |
|---|---|---|---|
| /ALBERT M NAVARRO/<br>Primary Examiner, Art Unit 1645<br>(Primary Examiner) | 19 November 2019<br>(Date) | O.G. Print Claim(s)<br>1 | O.G. Print Figure<br>NONE |

U.S. Patent and Trademark Office

Part of Paper No.: 20191119

| Issue Classification | Application/Control No. | Applicant(s)/Patent Under Reexamination |
|---|---|---|
| | 16/659,893 | Deem et al. |
| | **Examiner** | **Art Unit** |
| | Mark NAVARRO | 1645 |

☑ Claims renumbered in the same order as presented by applicant ☐ CPA ☐ T.D. ☐ R.1.47

**CLAIMS**

| Final | Original | Final | Original | Final | Original | Final | Original | Final | Original | Final | Original | Final | Original | Final | Original |
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|---|---|---|---|
| NONE | | **Total Claims Allowed:** | |
| (Assistant Examiner) | (Date) | 30 | |
| /ALBERT M NAVARRO/<br>Primary Examiner, Art Unit 1645 | 19 November 2019 | O.G. Print Claim(s) | O.G. Print Figure |
| (Primary Examiner) | (Date) | 1 | NONE |

U.S. Patent and Trademark Office

Part of Paper No.: 20191119

| Search Notes | Application/Control No. | Applicant(s)/Patent Under Reexamination |
|---|---|---|
| | 16/659,893 | Deem et al. |
| | Examiner | Art Unit |
| | Mark NAVARRO | 1645 |

| CPC - Searched* | | |
|---|---|---|
| Symbol | Date | Examiner |
| A61M 37/00 | 11/19/2019 | MN |

| CPC Combination Sets - Searched* | | |
|---|---|---|
| Symbol | Date | Examiner |
| | | |

| US Classification - Searched* | | | |
|---|---|---|---|
| Class | Subclass | Date | Examiner |
| | | | |

* See search history printout included with this form or the SEARCH NOTES box below to determine the scope of the search.

| Search Notes | | |
|---|---|---|
| Search Notes | Date | Examiner |
| Medline, Biosis, Ca, Caplus, EMbase, USPatfull, terms: update search history 16/036,381; 15/358,187; 14/601,529; 13/660,629; 13/253,595; 12/559,278; 11/459,090 | 11/19/2019 | MN |

| Interference Search | | | |
|---|---|---|---|
| US Class/CPC Symbol | US Subclass/CPC Group | Date | Examiner |
| A61M | 37/00 | 11/19/2019 | MN |

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 FILE 'MEDLINE, BIOSIS, CA, CAPLUS, EMBASE, USPATFULL' ENTERED AT 16:14:18
     ON 14 NOV 2019
L1        139953 S NASOPHARYNGEAL?
L2           528 S L1 (35A) (RF OR ULTRASOUND OR MICROWAVE OR AC OR DC OR ENERGY
L3             0 S L2 (300A) (NEURAL (5A) ACTIV?)
L4             0 S L2 (300A) (CONGEST?)
                 E DEEM MARK?/AU
                 E DEEM MA?/AU
L5           650 S E4-5
L6            34 S L5 AND NASAL?
L7            29 DUP REM L6 (5 DUPLICATES REMOVED)
                 E GIFFORD H?/AU
L8           678 S E5-12
L9            48 S L8 AND NASAL?
L10           40 DUP REM L9 (8 DUPLICATES REMOVED)

=>
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# Bibliographic Data

Application No: 16/659,893

Foreign Priority claimed: ○ Yes ◉ No

35 USC 119 (a-d) conditions met: ☐ Yes ☑ No ☐ Met After Allowance

Verified and Acknowledged: /ALBERT M NAVARRO/ Examiner's Signature | Initials

Title: SYSTEMS AND METHODS FOR DELIVERY OF A THERAPEUTIC AGENT

| FILING or 371(c) DATE | CLASS | GROUP ART UNIT | ATTORNEY DOCKET NO. |
|---|---|---|---|
| 10/22/2019 | 424 | 1645 | 5187.01US01AP |
| RULE | | | |

**APPLICANTS**

The Foundry, LLC, Menlo Park, CA, UNITED STATES

**INVENTORS**

Mark E. Deem Mountain View, CA, UNITED STATES

Hanson Gifford Woodside, CA, UNITED STATES

**CONTINUING DATA**

This application is a CON of 16036381 07/16/2018

16036381 is a CON of 15358187 11/22/2016 PAT 10022529

15358187 is a CON of 14601529 01/21/2015 PAT 9498283

14601529 is a CON of 13660629 10/25/2012 PAT 8961391

13660629 is a CON of 13253595 10/05/2011 PAT 8338164

13253595 is a CON of 12559278 09/14/2009 PAT 8133497

12559278 is a DIV of 11459090 07/21/2006 PAT 7608275

11459090 has PRO of 60702077 07/22/2005

**FOREIGN APPLICATIONS**

**IF REQUIRED, FOREIGN LICENSE GRANTED****

11/06/2019

**** SMALL ENTITY ****

**STATE OR COUNTRY**

UNITED STATES

**ADDRESS**

PATTERSON THUENTE PEDERSEN, P.A.

80 SOUTH 8TH STREET

4800 IDS CENTER

MINNEAPOLIS, MN 55402-2100

UNITED STATES

**FILING FEE RECEIVED**

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**Courtesy Reminder for**
**Application Serial No: 16/659,893**

Attorney Docket No: 5187.01US01AP
Customer Number: 24113
Date of Electronic Notification: 11/22/2019

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# INFORMATION DISCLOSURE STATEMENT BY APPLICANT

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Sheet 1 of 17

| Complete if Known | |
|---|---|
| Application Number | 16659893 |
| Filing Date | 10-22-2019 |
| First Named Inventor | MARK; E. Deem |
| Art Unit | 1645 |
| Examiner Name | Albert Mark Navarro |
| Attorney Docket Number | 5187.01US01AP |

| Examiner Initials* | Cite No.[1] | Document Number<br>Number-Kind Code[2] (if known) | Publication Date MM-DD-YYYY | Name of Patentee or Applicant of Cited Document |
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| Examiner Name | Albert Mark Navarro |
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# INFORMATION DISCLOSURE STATEMENT BY APPLICANT

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Sheet 7 of 17

| Complete if Known | |
|---|---|
| Application Number | 16659893 |
| Filing Date | 10-22-2019 |
| First Named Inventor | MARK; E. Deem |
| Art Unit | 1645 |
| Examiner Name | Albert Mark Navarro |
| Attorney Docket Number | 5187.01US01AP |

| Examiner Initials* | Cite No.[1] | Document Number<br>Number-Kind Code[2] (if known) | Publication Date MM-DD-YYYY | Name of Patentee or Applicant of Cited Document |
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Sheet 8 of 17

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| Application Number | 16659893 |
| Filing Date | 10-22-2019 |
| First Named Inventor | MARK; E. Deem |
| Art Unit | 1645 |
| Examiner Name | Albert Mark Navarro |
| Attorney Docket Number | 5187.01US01AP |

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| Application Number | 16659893 |
| Filing Date | 10-22-2019 |
| First Named Inventor | MARK; E. Deem |
| Art Unit | 1645 |
| Examiner Name | Albert Mark Navarro |
| Attorney Docket Number | 5187.01US01AP |

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Sheet 10 of 17

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| Application Number | 16659893 |
| Filing Date | 10-22-2019 |
| First Named Inventor | MARK; E. Deem |
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| Examiner Name | Albert Mark Navarro |
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| Application Number | 16659893 |
| Filing Date | 10-22-2019 |
| First Named Inventor | MARK; E. Deem |
| Art Unit | 1645 |
| Examiner Name | Albert Mark Navarro |
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| | | WO-2007014003-A2 | 02-01-2007 | THE FOUNDRY INC. [US] | ☐ |

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| Filing Date | 10-22-2019 |
| First Named Inventor | MARK; E. Deem |
| Art Unit | 1645 |
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Sheet 14 of 17

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| Application Number | 16659893 |
| Filing Date | 10-22-2019 |
| First Named Inventor | MARK; E. Deem |
| Art Unit | 1645 |
| Examiner Name | Albert Mark Navarro |
| Attorney Docket Number | 5187.01US01AP |

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| First Named Inventor | MARK; E. Deem |
| Art Unit | 1645 |
| Examiner Name | Albert Mark Navarro |
| Attorney Docket Number | 5187.01US01AP |

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| Application Number | 16659893 |
| Filing Date | 10-22-2019 |
| First Named Inventor | MARK; E. Deem |
| Art Unit | 1645 |
| Examiner Name | Albert Mark Navarro |
| Attorney Docket Number | 5187.01US01AP |

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| | | International Search Report and Written Opinion for Application No. PCT/US2006/028310, mailed on 8 August 2007, 7 pages. | ☐ |
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| Application Number | 16659893 |
| Filing Date | 10-22-2019 |
| First Named Inventor | MARK; E. Deem |
| Art Unit | 1645 |
| Examiner Name | Albert Mark Navarro |
| Attorney Docket Number | 5187.01US01AP |

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| **International Application Number:** | |
| **Confirmation Number:** | 4259 |
| **Title of Invention:** | SYSTEMS AND METHODS FOR DELIVERY OF A THERAPEUTIC AGENT |
| **First Named Inventor/Applicant Name:** | Mark E. Deem |
| **Customer Number:** | 24113 |
| **Filer:** | Daidre L. Burgess/Valerie Mitchell |
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(62) Document number(s) of the earlier application(s) in accordance with Art. 76 EPC:
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## (54) APPARATUS, METHODS AND SYSTEMS FOR TOXIN DELIVERY TO THE NASAL CAVITY

(57) Apparatus, methods and systems for delivering toxin and toxin fragments to a patient's nasal cavity provide for both release of the toxin and delivery of energy which selectively porates target cells to enhance uptake of the toxin. The use of energy-mediated delivery is particularly advantageous with light chain fragment toxins which lack cell binding capacity.

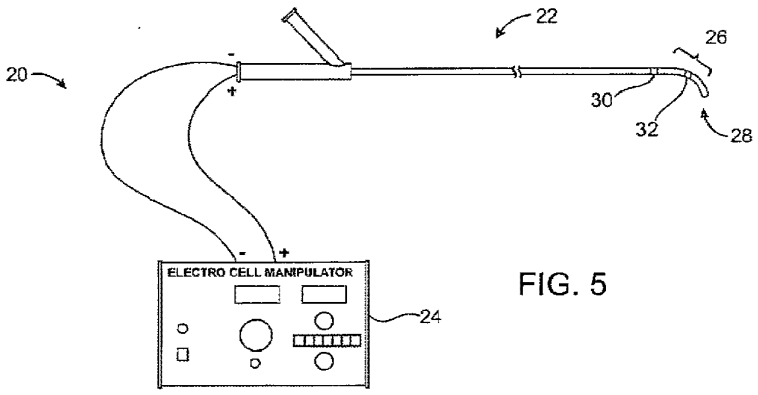



FIG. 5

EP 3 248 612 A1

## Description

### BACKGROUND OF THE INVENTION

**[0001]** 1. Field of the Invention. The present invention relates generally to medical methods and systems. More particularly, the present invention relates to methods and systems for delivering toxins, such as botulinum toxin light chain fragments, to target cells in a nasal cavity.

**[0002]** Rhinitis, which includes the symptoms of rhinorrhea, is a condition resulting from inflammation and swelling of the patient's mucus membranes which line the nasal cavity. Rhinitis and/or rhinorrea can arise from a number of conditions, most often results from allergies to pollen, dust, seasonal allergens or other airborne substances, but can also be caused by anatomic pathologies such as blockages (as in the case of sinusitis). Symptoms may include sneezing, itching, nasal congestion, and a runny nose.

**[0003]** While numerous treatments for rhinitis have been proposed over the years, no single treatment is optimum for all patients or all conditions. Most commonly, hay fever and other forms of rhinitis are treated with antihistamines which block the inflammatory response. While effective, many antihistamines can cause drowsiness, have a limited duration of effect, and present the patient with an on-going cost to continuously purchase the drugs.

**[0004]** Recently, a longer term therapy for rhinitis which relies on the use of botulinum toxin ("BoNT") for blocking mucus production by mucus-producing cells in the nasal membrane has been proposed. Botulinum and other neurotoxins are capable of disabling adrenergic cells, including epithelial or goblet cells which are responsible for the majority of mucus production in the nasal cavity membrane. Dr. Ira Sanders has demonstrated that introduction of intact botulinum toxin molecules into the nasal passages of canines can reduce mucus secretion by a significant amount.

**[0005]** While the experimental work of Dr. Sanders holds promise for long term rhinitis treatment, it faces a number of challenges before it is suitable for wide spread use in humans. In particular, botulinum toxin is a neurotoxin which could have significant negative effects on a patient if accidentally released outside of the targeted nasal passages. Inadvertent distribution of the toxin to muscles of the oropharynx, mouth, tongue, or elsewhere could result in serious complications to the patient. Additionally, the use of botulinum-soaked gauze pads for delivering the toxin to the nasal cavities, as demonstrated by Dr. Sanders, will have limited ability to uniformly and selectively deliver the botulinum to the regions having high concentrations of preferred target cells, such as epithelial or goblet cells in the nasopharynx.

**[0006]** For these reasons, it would be desirable to provide improved methods and systems for delivering toxins, such as botulinum and active botulinum fragments, to the nasal membrane of a patient, particularly a patient suffering from rhinitis or other conditions associated with nasal inflammation and conditions, such as sinus headaches and migraine headaches. The methods and systems should be capable of providing for selective and repeatable delivery of the toxins to defined target areas within the nasal cavities, including particular paranasal sinuses, the nasopharynx, and in some cases substantially the entire nasal cavity. The systems and methods should provide for the safe and effective delivery of the toxins, and in particular should reduce or eliminate the risk of toxin being delivered to non-targeted tissues outside of the nasal cavity. At least some of these objectives will be met by the inventions described herein below.

**[0007]** 2. Description of the Background Art. U.S. Patent No. 5,766,605, to Sanders et al. has been described above. Sharri et al. (1995) Otolaryngol. Head Neck Surg. 112: 566-571 also reports the work of Dr. Sanders described in the '605 patent. Ünal et al. (2002) Acta Otolaryngol 123: 1060-1063 describes the injection of botulinum toxin A into the turbinates of patients suffering from allergic rhinitis. See also, U.S. 6,974,578. The purification and possible therapeutic uses of botulinum light chain are described in US2004/0151741, US2005/0019346, and Chaddock et al. (2002) Protein Expression and Purification 25: 219-228. Energy-mediated transdermal delivery of intact botulinum toxin is suggested in US2005/007441 and 2004/0009180. The use of catheters and other devices for the energy-mediated delivery of botulinum light chain is described in commonly owned co-pending provisional application 60/702,077 (Attorney Docket No. 020979-003400US, filed July 22, 2005, the full disclosure of which has previously been incorporated herein by reference.

### BRIEF SUMMARY OF THE INVENTION

**[0008]** Briefly and in general terms, the present invention provides methods and systems for toxin delivery to the nasal cavity. The invention provides for the delivery of toxin to and across the nasal membrane tissue to treat various conditions and symptoms associated with nasal inflammation, including, rhinorrhea, rhinitis, sinusitis and hay fever.

**[0009]** Rhinorrhea is the term describing the effluence of mucus from the lining of the nasal passages, nasopharynx, or paranasal sinuses. Rhinorrhea can be a symptom of a number of diseases such as the common cold, sinusitis or rhinitis, Rhinitis (inflammation of the airways) falls into two major categories - allergic and non-allergic (or vasomotor) rhinitis. Each can have several subcategories. Sinusitis is an infection or inflammation of the paranasal sinuses. Sinusitis may have a number of different causes, and can be the result of chronic inflammation of the nasal passages, for example as a result of chronic rhinitis.

**[0010]** Allergic rhinitis is an immunologic response modulated by IgE and characterized predominantly by sneezing, rhinorrhea, nasal congestion, and pruritus of

the nose. It may be seasonal (a condition commonly referred to as hay fever) or perennial. The seasonal form is caused by allergens released during tree, grass, or weed pollination, whereas the perennial form is caused by allergies to animal dander, dust mites, or mold spores with or without associated pollinosis. Data also suggest that urban air pollutants from automobiles and other sources may have an adjunctive effect. (from attached articles by Nathan et al)

**[0011]** Nonallergic rhinitis is a diagnosis of rhinitis without any immunoglobulin E (IgE) mediation, as documented by allergen skin testing. Hence, the rhinorrhea, sneezing, pruritus, and congestion do not result from allergy or hypersensitivity and continue to persist, whether continuously or sporadically. Nonallergic rhinitis affects 5-10% of the population. Nonallergic rhinitis has 7 basic subclassifications, including infectious rhinitis, nonallergic rhinitis with eosinophilia syndrome (NARES), occupational rhinitis, hormonal rhinitis, drug-induced rhinitis, gustatory rhinitis, and vasomotor rhinitis. Patients may or may not present with the same symptoms seen in allergic rhinitis.

**[0012]** According to embodiments of the present invention, a toxin, such as botulinum toxin, is administered to the tissue of the nasal cavity using an apparatus comprising a handle and at least one applicator tip configured for insertion into a patient's nostril and placement within the patient's nasal passageway to facilitate deliver of the toxin via the applicator.

**[0013]** In one aspect of the present invention, the apparatus can be configured to facilitate contact between the applicator tips and the turbinates of the nasal wall and optimize toxin deliver to the nasal membrane. This can be achieved by incorporating a spring element into the handle of the apparatus, such as a v-shaped spring or closed-loop spring. The outward bias from this spring element can result in an expanded treatment configuration for delivering toxin to the nasal tissue.

**[0014]** In another aspect of the present invention, the applicator tips can be configured with a low volume delivery configuration to facilitate placement of the apparatus within the nasal passageway and an expanded volume treatment configuration to facilitate contact with the nasal wall. A spring element can be used to expand the applicator tip. Additionally, an actuator and engagement member can be used to transition the spring-loaded applicator tip from a compressed state to an expanded state.

**[0015]** In another aspect of the present invention, the toxin is loaded onto the applicator tips prior to insertion into the nasal passageway by, for example, dipping the applicator tips in a solution of toxin, coating the applicator tips with a lyophilized compound of toxin, incorporating the toxin into a bioresorbable coating on the applicator or configuring the applicator with a muco-adhesive pad that carries toxin.

**[0016]** In another aspect of the present invention, the apparatus further comprises an infusion channel and access port connected to a toxin source so that toxin can be infused into the applicator tips either prior to or following placement in the nasal passageway. Alternatively, a liquid such as saline can be infused to the applicator tips to reconstituted lyophilized toxin that was preloaded on the applicator tips.

**[0017]** In another aspect of the present invention, a toxin fragment, such as light chain botulinum toxin, can be administered to the nasal tissue and energy can be delivered to the tissue to cause poration in the cells of the nasal membrane and enhance delivery of the toxin to the tissue.

**[0018]** In another aspect of the present invention, the applicator is configured to deliver predetermined quantity in a controlled fashion. The applicator comprises a inner member for transitioning the applicator form a low volume configuration to an expanded volume configuration and an outer member for carrying the predetermined quantity of toxin and delivering the toxin to the nasal wall. The expansion of the inner member can also facilitate the controlled delivery of toxin to the nasal wall. The applicator may further comprise an impermeable lining separating the inner member and outer member and preventing toxin from dispersing to and through the inner member.

**[0019]** The present invention provides treatments for any disease or condition for which rhinorrhea is a result or symptom.

**[0020]** Rhinorrhea is the term describing the effluence of mucus from the lining of the nasal passages, nasopharynx, or paranasal sinuses. Rhinorrhea can be a symptom of a number of diseases such as the common cold, sinusitis or rhinitis, Rhinitis (inflammation of the airways) falls into two major categories - allergic and non-allergic (or vasomotor) rhinitis. Each can have several subcategories. Sinusitis is an infection or inflammation of the paranasal sinuses. Sinusitis may have a number of different causes, and can be the result of chronic inflammation of the nasal passages, for example as a result of chronic rhinitis.

**[0021]** Allergic rhinitis is an immunologic response modulated by IgE and characterized predominantly by sneezing, rhinorrhea, nasal congestion, and pruritus of the nose. It may be seasonal (a condition commonly referred to as hay fever) or perennial. The seasonal form is caused by allergens released during tree, grass, or weed pollination, whereas the perennial form is caused by allergies to animal dander, dust mites, or mold spores with or without associated pollinosis. Data also suggest that urban air pollutants from automobiles and other sources may have an adjunctive effect.

**[0022]** Nonallergic rhinitis is a diagnosis of rhinitis without any immunoglobulin E (IgE) mediation, as documented by allergen skin testing. Hence, the rhinorrhea, sneezing, pruritus, and congestion do not result from allergy or hypersensitivity and continue to persist, whether continuously or sporadically. Nonallergic rhinitis affects 5-10% of the population. Nonallergic rhinitis has 7 basic sub-

classifications, including infectious rhinitis, nonallergic rhinitis with eosinophilia syndrome (NARES), occupational rhinitis, hormonal rhinitis, drug-induced rhinitis, gustatory rhinitis, and vasomotor rhinitis. Patients may or may not present with the same symptoms seen in allergic rhinitis.

**[0023]** According to the present invention, botulinum toxin, ricin, exotoxin A, diphtheria toxin, cholera toxin, tetanus toxin, other neurotoxins, and active fragments thereof are delivered to a patient's nasal membrane while applying energy to target cells within the membrane under conditions which cause a reversible (or in some instances non-reversible) poration of the cell membranes to enhance delivery of the toxin into the cells. The region where the toxin is introduced may comprise any portion of the nasal cavity, such as a single paranasal sinus or portion thereof, a main nasal passage, two or more paranasal sinuses, or in some cases may comprise substantially the entire nasal cavity of the patient. A particular target region for the toxin may comprise the nasopharynx which is at the back of the nasal passage. The nasopharynx comprises a cluster of epithelial or goblet cells which are responsible for mucus secretion and which are susceptible to the disabling mechanism of the botulinum toxin and other neurotoxins.

**[0024]** The energy is preferably selectively applied to a targeted region containing a variety of cell types, including goblet cells, epithelial cells, ciliated and non-ciliated columnar cells, basal cells, and less or no energy applied to untargeted regions. It will be appreciated that the energy may be applied to regions of the nasal membrane which are the same or different from the regions to which the toxin has been introduced. By controlling the delivery area of both the toxin delivery and the energy delivery, the methods and apparatus of the present invention can more specifically target the epithelial or goblet and other recipient cells of interest while minimizing the amount of toxin which enters non-targeted cells. That is, only those cells in the nasal membrane which are exposed to both the toxin and the applied energy will preferentially be permeablized or porated to receive the toxin within the cytoplasm of the cell.

**[0025]** The toxin to be delivered may comprise any neurotoxin capable of disabling mucus secretion in epithelial or goblet cells and other mucus-producing nasal cells. Preferably, the toxin comprises botulinum toxin, although other toxins such as ricin, exotoxin A, diphtheria toxin, cholera toxin, tetanus toxin, other neurotoxins, and active fragments thereof may also find use. In preferred aspects of the present invention, only an active fragment of the toxin will be delivered to the nasal cavity. Botulinum toxin and the other toxins listed above commonly comprise both a heavy chain and a light chain. The heavy chain is responsible for binding to the target cells and mediating passage of the light chain into the cytoplasm of the target cells. By delivering only the light or active chain of these toxins (after removal of the heavy chain or recombinant production of only the light chain), the risk of accidental delivery of the toxin to non-target cells is greatly reduced. Delivery of the active or light chain fragments into the target cells, according to the present invention, is mediated and enhanced by the selective application of an energy which porates the cell membrane to allow entry of the light chain or active fragment. The presently preferred botulinum light chain fragment may be derived from any one of the seven presently known botulinum types A-G.

**[0026]** Any type of energy which is capable of reversibly permeablizing or porating the cell wall to allow passage of the toxin molecule, either whole toxin or preferably light chain fragment, into the cell cytoplasm may be applied to the cell membrane. Thus, energy may comprise various forms of electrical pulses, acoustic pulses, X-ray energy, microwave energy, or the like, and combinations thereof. Preferably, the energy will be either pulsed electrical energy of the type which is commonly used for cellular electroporation or will be ultrasonic energy of the type commonly employed for sonoporation of cells. The energy may be applied using the same catheters or other structures which are used for delivering the toxins. Alternatively, the energy may be applied using separate external or internal sources, such as using separate external ultrasonic transducers and/or ultrasound wave guides capable of delivering focused or unfocused ultrasound into the target tissues of the nasal cavity.

**[0027]** In specific embodiments of the methods of the present invention, the toxin may be introduced to the target region through a catheter. For example, the catheter may carry a balloon which engages the nasal membrane in order to effect delivery of the toxin to the target cells. In a particular example, the balloon is porous over at least a portion of its area so that the toxin may be released to specific areas of the nasal membrane, typically being incorporated into a suitable liquid, gel, or other fluid or fluidizable carrier. In other embodiments, the toxin may be introduced through one or more needles carried on the catheter, and in still other embodiments the toxin may be aerosolized from a small port, nozzle, or other orifice or structure on the catheter.

**[0028]** While the energy may be applied from a separate external source, as generally described above, the energy will most often be applied from the same catheter or other apparatus used to deliver the toxin. For example, when ultrasonic or other acoustic energy is being applied, the transducer may be on or associated with the catheter. In a particular example, it is shown that the transducer may be located within or beneath the porous balloon which is used to deliver toxin to the nasal membrane. When electrical energy is used for poration, the electrodes may be on the catheter within or surrounding the region which delivers the energy to the nasal membrane. In other instances, the energy may be applied from a separate catheter or other device adapted for intranasal introduction. In still other instances, the energy application will apply energy transcutaneously, for example from the skin of the face, typically surrounding the nose over

the sinus cavities.

**[0029]** In addition to the methods described above, the present invention further provides systems for delivering toxins to epithelial or goblet and other target cells as defined above in a nasal membrane. The systems may typically comprise a catheter adapted to introduce a toxin to a region adjacent to the target cells. An energy applicator is further provided for applying energy to the target cells under conditions which cause a reversible poration of the cell membranes to enhance delivery of the toxin. Systems may still further comprise a source of the toxin suitable for introduction from or through the catheter. The energy applicator may be mounted on or incorporated within the catheter, or may be a separate or external source. In an exemplary embodiment, as illustrated in Figure 18, an external applicator may comprise a mask or other structure which fits over the nose and/or sinus region of the patient and which is capable of delivering acoustic or microwave energy to the target cells within the target regions.

**[0030]** When the energy applicator is incorporated with or within the catheter, the delivery pattern of the energy will usually be at least partially overlapping with the toxin delivery pattern of the catheter. For example, when a porous balloon is used for toxin delivery, the acoustic transducer, electroporation electrodes, or the like, will usually be disposed to deliver energy which at least partly overlaps with the dispersion pattern of the toxin. In some instances, the region of applied energy will be coextensive with the region of toxin dispersion. In other instances, the two regions will only partially overlap. In the latter case, the delivery of the toxin will be enabled or enhanced principally within the regions of overlap.

## BRIEF DESCRIPTION OF THE DRAWINGS

**[0031]**

Figure 1 - depicts a schematic of the creation of neurotoxin Botulinum Toxin Type A (BoNT/A), including the light chain (LC) fragment or portion.

Figure 2A - depicts a schematic of a target cell, including the cell membrane, and inner cellular matrices.

Figure 2B - depicts a schematic of the target cell wherein LC molecule has been introduced.

Figures 3A-3B - depicts a the target cell of Figure 2 showing application of an energy field (EF) to produce permeabilization or pores (P) in the cell membrane, and introduction of the LC fragment therethrough.

Figure 4 - depicts a schematic of a cell wherein the energy field has been discontinued, and neurotransmission of the cell has been effectively blocked.

Figures 5, 5A-5B - depicts various embodiments of a delivery device of the present invention utilizing multiple energy transmission elements and an energy transmission system.

Figures 6A-6D, 6AA and 6CC - depict various electrode catheter configurations adapted to deliver energy or energy and therapeutic agents to target tissue.

Figure 7 - depicts an embodiment of the present invention utilizing an ultrasound element on a catheter device.

Figure 8 - depicts an embodiment of the present invention utilizing an aerosolizing element.

Figure 9 - depicts use on an external hand held transducer for enhancing cellular uptake of toxin delivered from a separate nasal aerosolizer.

Figures 10 and 11 - depicts depict use of balloon catheters for delivering toxin to the nasopharynx.

Figures 12A-12C - depict use of a self-expanding toxin delivery structure on a catheter.

Figures 13 and 14 - depict a protocol for limiting toxin introduction by partial filling of a porous delivery balloon.

Figure 15 - depicts sizing of a delivery balloon to control distribution of toxin released into the nasal cavity.

Figure 16 - depicts placement of a delivery balloon to protect the olfactory bulb.

Figure 17 - depicts the use of multiple small balloons for selective toxin delivery into the nasal cavity.

Figure 18 - depicts sonoporation using an external mask placed over the sinuses and nose.

Figure 19 - depicts a front view of an external sonoporation mask showing placement of ultrasound transducers.

Figures 20 and 21 - depict an orally-introduced occlusion catheter and energy applicator system.

Figures 22 and 23 - depict nose plugs for occluding and optionally delivery poration energy to the nasal cavity.

Figures 24 and 25 - depict an alternate occlusion catheter system for targeted toxin delivery to the nasopharynx.

Figures 26 and 27 - depict use of a toxin delivery catheter having side holes and a distal occlusion balloon for isolating and protecting the olefactory bulb.

Figures 28 and 30- depict use of a simple catheter having a shaped distal end for aerosolizing a toxin into a target nasal sinus though an ostium open to the sinus.

Figure 29 - depicts toxin delivery using a nasal spray and energy delivery using a face mask.

Figures 31 and 32, depict use of a catheter having a shaped distal end for positioning separate infusion structures with a target sinus cavity.

Figure 33 - depicts an applicator device for delivering toxin to the nasal cavity having a handle and two applicator tips for placement within the nasal passageway.

Figure 34 - depicts a top view of the applicator device illustrated in Figure 33.

Figure 35 - depicts the applicator device illustrated in Figure 33 when placed within the nasal passageway.

Figure 36 - depicts an applicator device configured with an infusion channel and access port for infusing solution to the applicator tip.

Figures 37A-37C - depict the handle of an applicator device in an isometric view, a top view in an expanded state and a top view in a compressed state, respectively.

Figure 38 - depicts an applicator device comprising a spring element.

Figures 39A-39B - depict a sponge applicator tip for an applicator device in a dry low volume configuration and a wet expanded configuration, respectively.

Figures 40A-40B - depict an applicator tip comprising a spring element in an expanded configuration and a compressed configuration, respectively.

Figure 41 - depicts an applicator device comprising loop spring element.

Figure 42 - depicts a spring-loaded applicator tip held in a compressed state by an engaged actuator.

Figure 43 - depicts an applicator device with the actuators of both applicator tips engaged by an engagement element.

## DETAILED DESCRIPTION OF THE INVENTION

**[0032]** The present invention is directed to methods and systems for delivering toxins to target cells within a patient's nasal cavity. The toxins may be intact toxins, such as botulinum toxin, ricin, exotoxin A, diphtheria toxin, cholera toxin, tetanus toxin, other neurotoxins, and active fragments thereof. Each of these toxins comprises a heavy chain responsible for cell binding and a light chain having enzyme activity responsible for cell toxicity.

**[0033]** Botulinum toxin blocks acetylcholine release from cells, such as the epithelial or goblet cells in the nasal membranes responsible for mucus hypersecretion, and can thus be effective even without energy-mediated delivery in accordance with the principles of the present invention. The use of energy to permeablize or porate the cell membranes of the epithelial or goblet cells or other mucus-secreting cells of the nasal lining, in accordance with the present invention, allows botulinum and other toxins to be preferentially delivered to the targeted epithelial or goblet and other mucus-producing cells. Additionally, it allows use of the active or light chains of these toxins (having the heavy chains removed or inactivated) for treatments in accordance with the present invention. Normally, the light chains when separated from the cell-binding heavy chains of botulinum and the other toxins are incapable of entering the cells and thus will be free from significant cell toxicity. By using the energy-mediated protocols of the present invention, the toxin light chains may be locally and specifically introduced into the target cells located within defined regions of the nasal membrane. Thus, even if the toxin fragments are accidentally dispersed beyond the desired target regions, the fragments will not generally enter cells without the additional application of cell permeablizing or porating energy. For that reason, the toxin delivery methods of the present invention are particularly safe when performed with toxin fragments, such as the light chain of botulinum and other toxins.

**[0034]** While the remaining portion of this disclosure will be presented with specific reference to the botulinum toxin light chain, it will be appreciated that the energy-mediated delivery protocols and systems may also be used with other intact toxins and in particular with other light chain toxin fragments as just discussed.

**[0035]** Generally, the botulinum toxin molecule (BoNT) is synthesized as a single polypeptide chain of 150kD molecular weight. The neurotoxin is then exposed to enzymes, either during cultivation of the *Clostridium botulinum* organism or subsequent to purification of the toxin, wherein specific peptide bonds are cleaved or "nicked" resulting in the formation of a dichain molecule referred to as BoNT. As shown in Figure 1, dichain neurotoxin is composed of a light chain region 50kD molecular weight linked by disulfide bonds to a heavy chain 100kD molecular weight (Kistner, A., Habermann, E. (1992) Naunyn Schmiedebergs Arch. Pharmacol. 345, 227-334). When the light chain is separated from the heavy chains of bot-

ulinum toxin, neither chain is capable of blocking neurotransmitter release, however, the light chain alone is capable of blocking acetylcholine release if transported directly into the cell cytosol. (Ahnert-Hilger, G., Bader, M.F., Bhakdi, S., Gratzl, M. (1989) J. Neurochem. 52, 1751-1758 and Simpson, L.L. (1981) Pharmacol. Rev. 33, 155-188.) Focusing on the light chain, the isolation or separation process essentially renders the light chain "non-toxic" in a general environment, while still maintaining its effect or toxicity, once it is transported through the target cell membrane.

**[0036]** Over the past several years, the separation and purification of the light chain and heavy chain of BoNT has seen significant development activity. In the case of the heavy chain (HC), researchers are interested in its ability to bond with a target cell and deliver certain molecules into that cell. For example, various drug delivery applications have been suggested, for example, using the HC to bind to tPA so that a patient could inhale the HC-bound tPA allowing it to cross the membrane of the lungs and be transported into the bloodstream for anticoagulation. Of particular interest to the present invention are the efforts to isolate and purify the light chain (LC) of the botulinum molecule. In its isolated and purified form, all HC elements are removed, rendering the LC incapable of crossing the cell membrane without assistance. This renders the LC a non-toxic protein to the cell environment, while still maintaining its encoded toxicity by, once it is effectively delivered to its appropriate catalytic environment; the cell cytosol.

**[0037]** Various groups have been active in the area of isolation and purification. For example, companies such as Metabiologics, a group affiliated with the University of Wisconsin, the Center for Applied Microbiology and Research (CAMR), a division of the UK Health Protection Agency, List Biological Laboratories, Inc. of California, and other research groups throughout the world. Many of these companies provide purified preparations of botulinum neurotoxins from *Clostridium botulinum* types A and B. List Laboratories in particular provides recombinantly produced light chains from both types A, B, C, D and E.

**[0038]** For purposes of this specification, the terms "poration" and/or "permeablization" include various forms of electrically-medicated poration, such as the use of pulsed electric fields (PEFs), nanosecond pulsed electric fields (nsPEFs), ionophoreseis, electrophoresis, electropermeabilization, as well as other energy mediated permeabilization, including sonoporation (mediated by ultrasonic or other acoustic energy), and/or combinations thereof, to create temporary pores in a targeted cell membrane. Similarly, the term "electrode" or "energy source" used herein, encompasses the use of various types of energy producing devices, including x-ray, radiofrequency (RF), DC current, AC current, microwave, ultrasound, adapted and applied in ranges to produce membrane permeabilization in the targeted cell.

**[0039]** Reversible electroporation, first observed in the early 1970's, has been used extensively in medicine and biology to transfer chemicals, drugs, genes and other molecules into targeted cells for a variety of purposes such as electrochemotherapy, gene transfer, transdermal drug delivery, vaccines, and the like.

**[0040]** In general, electroporation may be achieved utilizing a device adapted to activate an electrode set or series of electrodes to produce an electric field. Such a field can be generated in a bipolar or monopolar electrode configuration. When applied to cells, depending on the duration and strength of the applied pulses, this field operates to increase the permeabilization of the cell membrane and reversibly open the cell membrane for a short period of time by causing pores to form in the cell lipid bilayer allowing entry of various therapeutic elements or molecules, after which, when energy application ceases, the pores spontaneously close without killing the cell after a certain time delay. As characterized by Weaver, Electroporation: A General Phenomenon for Manipulating Cells and Tissues Journal of Cellular Biochemistry, 51:426-435 (1993), short(1-100$\mu$s) and longer (1-10 ms) pulses have induced electroporation in a variety of cell types. In a single cell model, most cells will exhibit electroporation in the range of 1-1.5V applied across the cell (membrane potential).

**[0041]** In addition, it is known in the art that macromolecules can be made to cross reversibly created pores at voltages of 120V or less applied to cells for durations of 20 microseconds to many milliseconds. For applications of electroporation to cell volumes, ranges of 10 V/cm to 10,000 V/cm and pulse durations ranging from 1 nanosecond to 0.1 seconds can be applied. In one example, a relatively narrow ($\mu$sec) high voltage (200V)pulse can be followed by a longer (>msec) lower voltage pulse (<100V). The first pulse or pulses open the pores and the second pulse or series of pulses assist in the movement of the BoNT-LC across the cell membrane and into the cell.

**[0042]** Certain factors affect how a delivered electric field will affect a targeted cell, including cell size, cell shape, cell orientation with respect to the applied electric field, cell temperature, distance between cells (cell-cell separation), cell type, tissue heterogeneity, properties of the cellular membrane and the like.

**[0043]** Various waveforms or shapes of pulses may be applied to achieve electroporation, including sinusoidal AC pulses, DC pulses, square wave pulses, exponentially decaying waveforms or other pulse shapes such as combined AC/DC pulses, or DC shifted RF signals such as those described by Chang in Cell Poration and Cell Fusion using an Oscillating Electric Field, Biophysical Journal October 1989, Volume 56 pgs 641-652, depending on the pulse generator used or the effect desired. The parameters of applied energy may be varied, including all or some of the following: waveform shape, amplitude, pulse duration, interval between pulses, number of pulses, combination of waveforms and the like.

**[0044]** There are at least two general power categories

of medical ultrasound waves. One category of medical ultrasound wave is high acoustic pressure ultrasound. Another category of medical ultrasound wave is low acoustic pressure ultrasound.

**[0045]** Acoustic power is expressed in a variety of ways by those skilled in the art. One method of estimating the acoustic power of an acoustic wave on tissue is the Mechanical Index. The Mechanical Index (MI) is a standard measure of the acoustic output in an ultrasound system.

**[0046]** High acoustic pressure ultrasound systems generally have a MI greater than 10. Low acoustic pressure systems generally have a MI lower than 5. For example, diagnostic ultrasound systems are limited by law to a Mechanical Index not to exceed 1.9.

**[0047]** Another measurement used by those skilled in the art is the spatial peak, peak average intensity (Isppa). The intensity of an ultrasound beam is greater at the center of its cross section than at the periphery. Similarly, the intensity varies over a given pulse of ultrasound energy. Isppa is measured at the location where intensity is maximum averaged over the pulse duration. Isppa for high acoustic pressure or high intensity focused ultrasound (HIFU) applications ranges from approximately 1500W/cm2. to 9000 W/cm2. Diagnostic ultrasound equipment, for instance, will generally have, and an Isppa less than 700 W/cm2.

**[0048]** Yet another way in which ultrasound waves can be characterized is by the amplitude of their peak negative pressure. High acoustic pressure or HIFU applications employ waves with peak amplitudes in excess of 10MPa. Low acoustic pressure ultrasound will generally have peak negative pressures in the range of 0.01 to 5.0 MPa. Diagnostic ultrasound equipment, for example, will generally have a peak amplitude less than 3.0MPa.

**[0049]** Both high and low acoustic pressure ultrasound systems generally operate within the frequency range of 20KHz - 10.0 MHz Interventional applications (such as in blood vessels) operate clinically up to about 50 MHz. Also ophthalmologic applications up to about 15 MHz. Diagnostic imaging typically uses frequencies of about 3 to about 10 MHz. Physical therapy ultrasound systems generally operate at frequencies of either 1.0MHz or 3.3MHz.

**[0050]** High acoustic pressure ultrasound or high intensity focused ultrasound has been used for tissue disruption, for example for direct tumor destruction. High intensity focused ultrasound using high acoustic pressure ultrasound is most commonly focused at a point in order to concentrate the energy from the generated acoustic waves in a relatively small focus of tissue.

**[0051]** Systems for permeabilization of target tissue cell membranes may employ either high acoustic pressure or low acoustic pressure ultrasound. Some embodiments may preferably employ relatively low acoustic pressure, for example the systems described herein where the transducers are mounted on the delivery devices and operate inside the body. Other systems may operate at interim acoustic pressure ranges. For example, systems described herein which employ an external ultrasound generator and transducer and which conduct the ultrasound to the target tissues through the use of a wave guide. In these systems, losses due to transduction through the wave guide can be compensated for by increasing the input power to the wave guide until adequate power is delivered to the target tissue. Finally, some systems described herein may employ focused or partially focused higher pressure ultrasound, for example the systems which employ an external mask to conduct the ultrasonic power through the tissues to the target tissues. It should be appreciated that combinations of high and low acoustic pressure systems may also be employed.

**[0052]** It should also be appreciated that any embodiment employing ultrasonic energy and ultrasound transducers can alternatively be configured as a microwave energy system using microwave antennas. For example, the embodiments disclosed herein relating to delivering energy from an external mask equipped with ultrasound transducers can also be configured to deliver microwave energy using one or more microwave antennas.

**[0053]** A schematic example of the methods of the present invention are shown in Figures 2A, 2B, 3A, 3B and 4 in a simplified single cell model. A targeted cell, e.g., an epithelial or goblet cell of the type which line the nasal cavity membrane, is shown in Figure 2A. Fragmented neurotoxin such as BoNT-LC (LC)is introduced into the vicinity of the targeted cell as depicted in Figure 2B. An energy field (EF) is applied in accordance with the present invention resulting in the transfer of the BoNT-LC to the intracellular matrix (cytosol or cytoplasm) as shown in Figures 3A and 3B. Once this transfer has occurred, the release of acetylcholine from the presynaptic neurons at the neuromuscular junctions of the epithelial or goblet or other target cells is then blocked or disrupted. Once energy application is discontinued, the pores in the cell membrane recover or close as depicted in Figure 4.

**[0054]** The terms "poration" and "permeablization" will also cover forms of cellular sonoporation. Just as pulses of high voltage electricity can open transient pores in the cell membrane, ultrasonic energy can do the same. See for example Guzman et al. "Equilibrium Loading of Cells with Macromolecules by Ultrasound: Effects of Molecular Sizing and Acoustic Energy", Journal of Pharmaceutical Sciences, 91:7, 1693-1701, which examines the viability of ultrasound to deliver molecules of a variety of sizes into target cells. In addition, techniques for nebulizing fluids and aqueous drugs are well known in the art, and as such, devices of the present invention may be adapted to introduce a BoNT-LC solution to a target region, such as the nasal passages and then effect selective membrane transport of the BoNT-LC into the cell using sonoporation.

**[0055]** To achieve the goals of the present invention, it may be desirable to employ methods and apparatus for achieving cell membrane permeabilization via the application of an energy source, either from a catheter located directly in the vicinity of the targeted cells, or an

externally focused energy system. For purposes of this specification, the term "catheter" may be used to refer to an elongate element, hollow or solid, flexible or rigid and capable of percutaneous introduction to a body (either by itself, or through a separately created incision or puncture), such as a sheath, a trocar, a needle, a lead. Further descriptions of certain electroporation catheters are described in United States Provisional Patent Application No. 60/701,747 (Attorney Docket No. 020979-003500US) and Non-provisional Patent Application No. 11/459,582 (Attorney Docket No. 020979-003510US), the full disclosures of which are expressly incorporated herein by reference.

**[0056]** Figures 5 and 5A-5B depict a system utilizing an electroporation catheter for selective electroporation of targeted cells. In certain configurations of the present invention, voltages may be applied via the electroporation catheter to induce reversible electroporation at the same time as the catheter delivers the fragmented neurotoxin to the targeted region.

**[0057]** Referring to Figure 5, electroporation catheter system 20 comprises a pulse generator 24 such as those generators available from Cytopulse Sciences, Inc. (Columbia, MD) or the Gene Pulser Xcell (Bio-Rad, Inc.), or IGEA (Carpi, Italy), electrically connected to a catheter 22 having a proximal end and a distal region 26 adapted for minimally invasive insertion into the desired region of the body as described herein. The catheter further comprises an electroporation element 28 at the distal region thereof The electroporation element consists for example of a first electrode 30 and a second electrode 32 operatively connected to the pulse generator for delivering the desired number, duration, amplitude and frequency of pulses to affect the targeted cells. These parameters can be modified either by the system or the user, depending on the location of the catheter within the body (intervening tissues or structures), and the timing and duration of reversible cell poration desired.

**[0058]** Figure 5A depicts an arrangement of electrodes 30 and 32 that produces an electric field concentrated in a lateral direction from the catheter body whereas, Figure 5B shows a device with electrodes 30 and 32 configured to create a more uniform electric field about the shaft of the catheter body. Further catheter device and electrode configurations are shown in Figures 6A-6D. Figure 6A depicts an elongate catheter 40 having a first and second electrode (42 and 44) near the distal tip thereof, and including a monitoring or stimulation electrode 46 in the vicinity of the active porating electrodes for localizing the treatment area. In some embodiments, the monitoring or stimulating function may be performed by one or more of the treatment electrodes. The catheter device may have an optional sharp tip 48 to facilitate percutaneous introduction. Figure 6B is a similar catheter device, but is further adapted to be steerable, or articulate at a region 53 near the distal end of the device. Such steering ability enables the operator to introduce the device into tight or tortuous spaces (such as the bronchial passages, or cardiovascular vessels) so that optimal placement of electrodes 52, 54 and 56 of the device at the target location may be achieved.

**[0059]** Figure 6C depicts a further embodiment of the catheter device described above, that includes an injection element such as needle 62 to allow for the injection of a therapeutic agent such as a fragmented neurotoxin before, during or after the application of the pulsed energy or electroporation. The injection element may be a needle as shown in Figure 6C, an infusion port, or other infusion means. Electrodes 64, 66 and 68 are provided as discussed with respect to Figs. 6A and 6B.

**[0060]** Figure 6D depicts an alternative embodiment of the present invention, showing a catheter device 70 having electrode elements (72 and 74) that are adapted to extend laterally from the main catheter body, and in some cases, penetrate the surrounding tissue prior to application of energy. In doing so the depth and direction of the energy field created by the electroporative process, may be further controlled. A reference electrode 76 may also be provided.

**[0061]** Figure 7 depicts an embodiment of the present invention utilizing an ultrasonic element that may be particularly useful in delivery of the BoNT-LC to nasal tissue that provides a broad but targeted transport of the LC across the epithelial and goblet cell walls. In this device, ultrasound energy is delivered to the distal end 92 of the catheter device 90 via an ultrasonic waveguide that is operatively connected to an ultrasound energy source (U/SES) connected by cable 94. The LC fragment would be delivered from source 96 via the same lumen as the waveguide, or via a separate lumen that exits the distal tip of the device. In operation, the ultrasonic energy would cause the LC solution to be nebulized, forming mist clouds 98 within the lung, as shown in Figure 8. The mist itself, in the appropriate concentrations, may act as an ultrasound coupler, conveying the ultrasonic energy to the wall of the lung or other targeted cellular structures, causing sonoporation of the targeted cells whereby the LC fragment is transmitted across the cell membranes to become an effective neurotransmitter blocker. In an alternative embodiment, an ultrasonic transducer may be located directly at the tip of the delivery device, eliminating the need for a wave guide. Various catheters useful for delivering vibrational energy to tissue are described in United States Patent 6,361,554 and 6,464,680 to Brisken, the contents of which are expressly incorporated herein by reference in their entirety, for various therapeutic effects, such as enhancing cellular absorption of a substance.

**[0062]** Any of the catheter devices described herein, or described in the contemporaneously filed United States Provisional Patent Application No. 60/701,747 (Attorney Docket No. 020979-003500US) and Non-provisional Patent Application No. 11/459,582 (Attorney Docket No. 020979-003510US), previously incorporated by reference in their entirety, may be adapted to include an energy delivery element such as those described

herein for purposes of providing a membrane transport system for delivery of a toxin fragment of neurotoxin. In addition, certain catheter devices and methods such as those set forth in United States Patents 5,964,223 and 6,526,976 to Baran may be adapted to include energy transmission elements capable of producing a porative effect at the cellular level, including electrodes, ultrasonic elements and the like, for treatment in the nasal passages.

**[0063]** Furthermore, any of the foregoing systems may include electrodes or other monitoring systems either located on the treatment catheter, or external to the patient, to determine the degree of treatment to the region, including, thermocouple, ultrasound transducers, fiberoptics, sensing or stimulating electrodes. Further, it may be desirable to incorporate multiple pairs of electrodes that may be activated in pairs, in groups, or in a sequential manner in order to maximize the desired shape of the energy field (EF) while minimizing the field strength requirements.

**[0064]** It is within the scope of the present invention to deliver the toxin, the energy, or both, non-invasively. For example, as illustrated in Figure 9, the patient may draw the toxin into the nasal cavity from a hand-held dispersion device DD. After a sufficient amount of the toxin has been infused into the nasal cavity, a separate hand-held transducer TD connected to an appropriate power supply PS will be energized and applied to the nasal cavities by passing the transducer over the appropriate regions of the forehead and nose. Optionally, the transducer can have a focused output so that the acoustic energy is focused in an appropriate depth beneath the skin surface. Typically, from about 0.1 cm to 2 cm.

**[0065]** While the toxins and porating energy of the present invention may be delivered to the nasal cavity in a variety of ways, the following provides a number of specific examples of catheters and other structures for delivering toxins to preselected portions of the nasal cavity. For example, as shown in Figure 10, a balloon catheter 100 may be provided with a porous balloon 102 at its distal end. The balloon would be porous over at least a portion of its body so that solution delivered to inflate the balloon, which would contain desired levels of the toxin or toxin fragment, would release the solution through the balloon at a controlled rate. By further providing one or more ultrasonic transducers 104 within the balloon, optionally mounted on the catheter body, ultrasonic poration energy can be delivered to the adjacent nasal membranes which are receiving the toxin solution. As illustrated in Figure 10, the toxin is being delivered to a lower surface of the inferior meatus IM to localize and enhance cellular delivery at the balloon tissue interface. Alternatively, the balloon could carry the toxin in a releasable form over its exterior surface in order to deliver to any adjacent tissue structure. In some instances, the toxin could be carried or encapsulated in delivery vesicles which are preferentially fractured by the same acoustic energy which permeablizes the cell wall. Other coatings include hydrogels, such as those produced by Surmodics, Inc., BioCoat, Inc., or the like. In some instances, it may be desirable to provide a coupling agent over and/or within the balloon in order to enhance the delivery of ultrasonic energy from the internal transducer. In still other instances, it would be possible to place polymeric transducers on or within the balloon surface in order to directly deliver ultrasonic or other acoustic energy into the adjacent tissues.

**[0066]** In all the above cases, the ultrasonic transducers can be configured in order to selectively deliver the energy to desired portions of the adjacent tissues. For example, in the embodiment of Figure 10, the internal transducers 104 can be configured to focus the ultrasonic energy generally upwardly (as viewed in Figure 10) in order to preferentially deliver the toxins into the inferior meatus IM while minimizing delivery elsewhere.

**[0067]** As a further option, the balloon could be inflated by a coupling agent in order to enhance the transmission of the ultrasonic or other acoustic energy, while the toxin solution could be infused into the treatment area before or simultaneously using either a separate lumen in the catheter or a separate tube or other delivery catheter. In this way, it would not be necessary to inflate the balloon with a relatively large volume of the toxin solution.

**[0068]** The balloon catheters can be introduced by any conventional technique, for example, in some instances, it may be desirable to use a guidewire to place the catheter into a desired sinus or other location, optionally using fluoroscopic, MRI or ultrasound imaging.

**[0069]** Referring now to Figure 11, a front view of particular balloons placed as generally shown in Figure 10, is shown in more detail. A single balloon 102 can be around the structures H in the inferior meatus. Alternatively, a pair of balloon structures 103 may be placed in the same space, as shown in the right hand portion of Figure 11. Optionally, the balloons could be formed from an elastic material, such as a silicone, urethane, latex, thermoplastic elastomers, or other materials where the material is treated to be appropriately porous, for example by laser drilling. Alternatively, the balloons could be formed from non-distensible materials which are preformed to conform to the desired target cavities. The non-distensible balloons could also be laser drilled or otherwise made permeable in order to release the toxin solutions of the present invention. Alternatively, either type of balloon could be coated with the toxin solutions, coupling solutions, or other materials which are useful in the protocols of the present invention.

**[0070]** Referring now to Figures 12A. 12B, and 12C, as an alternative to inflatable balloons, toxin delivery structures may be made to be various shapes, for example a generally "flattened" balloons 102, whose profile is narrower in one axis than the other, for example by placement of an internal nitinol or other elastic frame or scaffold, or a stainless steel wire 103 that is fed into the balloon outer structure to form such shape, within a suitable porous cover or membrane. Thus, the structure 120 may

be expanded by the scaffold 122 after release from a delivery tube 124. The structures can be used to deliver energy and/or toxin in any of the ways described previously with respect to balloons, including by carrying a transducer or electrode on or within the structure and delivering a toxin solution from the interior of the self-expanding structure through a porous portion of the structure wall.

**[0071]** In some instances, it will be desirable to protect the olfactory bulb of the sinuses from treatment with the toxin solutions of the present invention. Referring now to Figures 13 and 14, the porous portion of a delivery balloon 102 can be positioned so that the remaining non-porous segment is in contact with the olfactory bulb (Figure 13). Thus, when the balloon is inflated and the toxin solution delivered, it will not be directed at the tissues of the olfactory bulb (OB).

**[0072]** As shown in Figure 14, which is a cross-sectional view of Figure 13, instead of rendering the top portion of the delivery balloon non-porous, it would be possible to simply refrain from filling the top portion with the toxin solution and/or a coupling solution. This can be achieved by filling the balloon with a known volume of air 111 in addition to the toxin solution. With the patient positioned appropriately, the air will fill the portion of the balloon in proximity to the olfactory bulb, excluding this tissue from toxin contact. Additionally, the air bubble may act as an ultrasound insulator to inhibit energy delivery to the non-targeted or protected tissue. Thus, delivery of the toxin to the region around the olfactory bulb and/or delivery of the energy to the region around the olfactory bulb can be partially or wholly prevented.

**[0073]** Referring now to Figures 15 and 16, the balloon may be sized and positioned to target an area of high epithelial or goblet cell (G) concentration, for example in the back of the nasal passages in the area of the nasopharynx. By targeting this area of the nasal membrane, a high percentage of mucus-secreting epithelial or goblet cells can be treated with a device which is relatively small and which may carry a relatively low infusion volume and require less energy. Moreover, the olfactory bulb is inherently protected with this technique since the balloon is positioned well away from that area. If desired, of course, additional shielding, shaping or other protective balloons could be positioned between the olfactory bulb and the toxin and energy delivering components of the present invention.

**[0074]** As shown in Figure 17, direct infusion and treatment of particular sinuses may be effected using relatively small occlusion balloons 102 which occlude and isolate natural openings into those sinuses. Once the balloon is in place and the occlusion balloon employed, the toxic solution can be delivered by infusion, dispersion, or other conventional techniques. Once the toxin solution is present in the sinus, all or a portion of the membrane of the sinus can then be treated with an external or other ultrasonic source.

**[0075]** For example, as shown in Figures 18 and 19, the external transducer may comprise a mask which conforms to the nose and optionally over the sinuses, where the mask carries one or more ultrasonic or other acoustic transducers (TD) adapted to deliver energy transcutaneously into the sinuses. The mask may comprise a plurality of individual transducers (TD), which may be made from one, two, or several generally continuous piezoelectric films which are formed over or lamented within the mask. Alternatively, multiple individual piezoelectric crystal transducers can be built into the mask.

**[0076]** The effect of such externally applied ultrasonic energy can be enhanced by introducing microbubbles (free air) into the isolated sinuses and/or nasal passages which have been filled with toxin solution. For example, encapsulated microbubbles, which are generally useful as echocardiographic contrast agents, or specialty perfluorocarbons, are useful as such ultrasonic enhancing agents. By encapsulating the toxin molecules in spheres or bubbles, or by simply placing the spheres or bubbles in proximity to toxin molecules, the ultrasonic or other acoustic energy can be captured and stored until it is abruptly released with fracture of the sphere or bubble. Such microspheres will also act as resonance bodies as defined below.

**[0077]** Referring now to Figures 20 and 21, a catheter 40 is placed at the posterior outlet of the nasal passages in the region of the nasopharynx. The catheters configured to occlude outflow from these sinuses and passages into the throat. As shown in Figure 20, a balloon catheter 102 or other occlusion device could be configured to block such passage. As shown in Figure 20, the catheter is delivered in through the mouth and guided into the posterior portion of the nasal cavities, typically using a guidewire. Once the nasopharynx of the posterior portion of the nasal cavity is occluded, toxin solution (BoNT)can be infused through the occluding catheter lumen, or through a separate infusion catheter or tube, in order to treat substantially the entire sinus and/or nasal cavity membrane at once (Figure 21). When the toxin solution is introduced through the catheter at the posterior region of the cavities, it will frequently be desirable to occlude the nostrils, for example using a nasal clip 105.

**[0078]** As shown in Figures 22 and 23, specially designed nose plugs 105 can be provided with air bleed valves 106 which are used to occlude the nostrils in order to evacuate or bleed air from the nasal passages while filling the passages with the toxin solution. The nose plugs 105 could optionally include ultrasonic transducers in order to deliver ultrasonic or other acoustic energy into the solutions entrapped within the nasal cavities using the nostril plugs. Alternatively, of course, the ultrasound or other acoustic energy could be delivered from an external transducer as described previously.

**[0079]** Referring now to Figures 24 and 25, an alternate occlusion catheter system for nasopharynx occlusion is illustrated. An occlusion catheter 40 is introduced through a nostril, where the tip includes an ultrasonic transducer to provide sonoporation. A nostril plug 105 is provided

proximally on the shaft of the catheter, while the cavity is blocked with a separate occlusion balloon 102 introduced through the mouth and into the posterior nasopharynx region. The toxin solution can be introduced into the cavity through either the catheters which pass through or reside in the nostrils or the catheter which occludes the posterior nasopharynx.

**[0080]** Figures 26 and 27 illustrate how a catheter 40 with side holes 108 can be configured to deliver toxin away from the olfactory bulb, even when used alone without separate nasopharynx occlusion catheters. The catheters preferably carry an occlusion balloon or other structure near their distal ends 107 to prevent or inhibit toxin from reaching the olefactory bulb

**[0081]** Use of these or other catheter devices can deliver toxin incorporated into vesicles which may be configured as "resonance" bodies, which reduce the need to fill the nasal cavities with a liquid or other form of toxin. For example, lipid microspheres which incorporate the toxin may be sprayed or aerosolized onto target surfaces of the nasal epithelium. After the lipid or other resonance bodies are attached to the targeted epithelium membrane surface(s), the ultrasound energy can be delivered from the catheter or externally through the skin in order to selectively porate the epithelial or goblet cells to enhance introduction of the toxin *vis-à-vis* resonance bodies. A protection device at the end of the shaft can be provided to shield the olfactory bulb from the toxin.

**[0082]** Referring to Figure 29, the toxin may be delivered as a conventional nasal spray (BoNT), as mentioned hereinbefore, and the poration energy can be delivered through a face mask. The poration energy might alternatively be delivered as ultrasound energy delivered through a mist, without direct contact to the tissues. This mist might be the same mist which contains the toxin, or it might be a different, possibly denser mist delivered at some time after the toxin has been delivered. The delivery devices for these mists might be introduced a relatively short distance into the nose. Thus the entire therapy might comprise the specialized delivery of two mists.

**[0083]** Referring now to Figures 28 and 30, an infusion catheter 40 can be engaged against the ostium of a sinus cavity (Figure 28). A guidewire 110 may then be advanced through the infusion catheter and into the sinus cavity (Figure 30). The guidewire can be formed as a wave guide to deliver ultrasonic energy, as an electrode to deliver electroporation energy, or as an infusion wire to deliver the toxin solution itself. The wire could further be configured to perform two or more of these functions. The catheter could be configured to act as a counter electrode when the guidewire is acting as an electroporation electrode in bipolar energy delivery.

**[0084]** Referring now to Figure 31, the catheter advanced to the os of a sinus cavity, as illustrated, can also be used to deliver a helical or randomly shaped delivery tube 112 which is deployed within the sinus. Preferably, the tube will expand to engage a major portion of the wall of the sinus cavity. Alternatively, the geometry could be selected to selectively engage only a particular portion of the wall of the sinus cavity. The wire can further be adapted to deliver energy, either electrical or acoustic, and/or may be configured to deliver and distribute the toxin solution within the cavity. In still other configurations, the wire could be coated to deliver the agent to the wall, and still further the wire could deliver ultrasound gels, saline, degassed water, or the like, to enhance coupling of a separate ultrasonic energy source.

**[0085]** Referring now to Figure 32, two or more deployment catheters can be used to advance any of the guidewires or other wire structures discussed above. As illustrated in Figure 32, an electrode basket 113 may be deployed through the delivery catheter. Alternatively, a multiply tined catheter 114 structure may be delivered through the delivery catheter.

**[0086]** Figures 33 and 34 illustrate a device for applying BoNT to the treatment area within the nasal cavity. This device comprises a handle 115 having a proximal section, a body and a distal section. The body of the handle comprises a first member 116 and a second member 117. The first member and second member merge at the proximal section and terminate at the distal section, wherein the distal section comprises a first end and second end corresponding to the first member and second member. The device further comprises applicator tips 118 connected to each of the first end and second, wherein the applicator tips are configured for insertion into the nasal passageway, as shown in Figure 35.

**[0087]** Once within the nasal cavity, the applicator tips 117 and 118 can apply BoNT to the nasal passageway and, specifically, the turbinates along the nasal wall. The BoNT can be applied or affixed to the applicator tips as a liquid solution, gel, foam, cream, lotion and/or a lyophilized compound prior to being positioned within the nasal passageway. Alternatively, as illustrated in Figure 36, the handle can be configured with an infusion channel 119 for delivering the BoNT to the applicator tips following placement in the nasal passageway. In this configuration, the handle may further comprise an access port at its proximal section that is in fluid communication with a BoNT source.

**[0088]** As shown in Figure 33, the loop member may be configured to provide an outward lateral force such that the applicator tips 118 are firmly contacted against the nasal turbinates when placed in the nasal passageway. With reference to Figure 37A, the operator would apply inward pressure in the direction of the arrows to the handle to achieve a compressed configuration, as shown in Figure 37C, prior to inserting the applicator tips into the nose. Once the applicator tips of the device are properly inserted into the nasal passageway, this pressure would be released such that the outward bias in the handle transitions the handle from a compressed configuration to an expanded configuration, as shown in Figure 37B, wherein the applicator tips are pressed against the nasal turbinates. The applicator tips can be held against the turbinates by the outward bias for sufficient time to

allow a therapeutically effective amount of BoNT to be absorbed by the nasal cavity wall.

**[0089]** This outward bias may be achieved by spring loading the device 120. Specifically, the handle itself may comprise a spring element, wherein the handle is dimensioned and configured with a residual spring force that exhibits this outward bias. Additionally or alternatively, the handle may comprise a material with mechanical properties to facilitate the spring action with little to no inelastic deformation resulting from the inward pressure applied by the operator. For example, at least a portion of the proximal section of the handle may comprise spring steel, stainless steel, nitinol, or MP35N alloy. Alternatively, as illustrated in Figure 38, a spring element 120 that is separate from the handle may be used to apply outward lateral pressure to the first and second members of the handle body.

**[0090]** To facilitate the insertion of the tip applicator through the nostril and into the nasal passageway, it may be desirable for the applicator tip to initially have a low volume configuration. Once properly positioned in the nasal passageway, it would be desirable for the applicator to have an expanded volume configuration for maximizing contact with the nasal turbinates. In one exemplary embodiment, the tip applicator may comprise a sponge such that the sponge 121 is in a low volume configuration when dry (Figure 39A) and an expanded configuration when wet (Figure 39B), wherein the sponge 121 is configured to fit securely within the nasal passageway.

**[0091]** In the embodiment illustrated in Figures 39A and 39B, the dry sponge applicator could be preloaded with lyophilized BoNT and wetted with a liquid (e.g., saline) following placement of the applicator in the nasal passageway. The liquid can be introduced into the nasal passageway using a spray or a catheter, or the BoNT may simply be rewetted by the nasal secretions themselves. Alternatively, as described with respect to Figure 36, the liquid can be infused into the applicator tip through a channel 119 in the device handle. Still alternatively, the liquid infused through the channel can be a solution comprising BoNT, thereby eliminating the need for the dry sponge applicator to be preloaded with BoNT.

**[0092]** To facilitate the expansion of the applicator tip, thereby maximizing the surface contact between the nasal cavity wall and applicator tip, it may be desirable to incorporate a spring element 122 within the applicator tip 118. The embodiment in Figures 40A and 40B shows an applicator tip comprising a sponge 121 and a spring element 122 in an expanded and compressed configuration. This configuration can be used instead of or in addition to the wet/dry sponge embodiment discussed above.

**[0093]** The spring clement may comprise any type of compressible spring and any number of elastically deformable polymers or metals, including, spring steel, stainless steel, nitinol, and MP35N alloy. As shown in many of the above embodiments, the spring element may comprise a v-shape spring. Alternatively, the spring element may comprise a closed-loop spring 123, as illustrated in Figure 41.

**[0094]** For embodiments utilizing a spring-loaded applicator tip, it will be necessary to hold the spring 122 in its compressed state until it is properly positioned within the nasal cavity, at which time the spring can be released to allow the applicator to expand into the nasal cavity. In the wet/dry sponge 121 embodiment described with respect to Figures 39A and 39B, a sponge and spring can be selected and matched such that the stiffness of the dry sponge is sufficient to overcome the spring stiffness and hold the spring in a compressed configuration until it becomes wet.

**[0095]** In another embodiment employing a spring-loaded applicator tip, an actuator can be used to hold the spring in a compressed state. Figure 42 illustrates a spring-loaded applicator tip 124 that is restrained in a compressed state by a slidably-engaged actuator 125. The slidably-engaged actuator may comprise a retractable sheath or collar 126 for holding the spring in its compressed configuration. Once the applicator is positioned within the nasal cavity, the actuator can be retracted to release the spring, thereby expanding the applicator.

**[0096]** The device may optionally comprise an engagement element 127 for engaging and retracting the actuators on both applicators. Figure 43 shows a device comprising a handle 115, two actuator-equipped applicator tips 124 and an engagement element 127 in contact with each applicator tip actuator 124. The engagement element is configured for movement along the longitudinal axis of the handle, wherein such movement may engage or retract the actuator resulting in compression or expansion of the spring-loaded applicator tip, respectively.

**[0097]** It may be desirable for the spring-assisted expansion of the applicator tip to be directionally biased to maximize contact with the wall of the nasal cavity and optimize contact pressure with the nasal turbinates. For example, the spring element can be dimensioned and configured such that the applicator expands laterally towards the turbinates of the nasal cavity. Alternatively or additionally, portions of the applicator tip may comprise an impermeable lining such that delivery of BoNT to certain portions of the nasal cavity is optimized and undesirable migration of BoNT solution is minimized.

**[0098]** Although toxins can be administered to the body to achieve a therapeutic benefit, the same toxins can cause local and systematic damage to non-targeted body tissues. Accordingly, it would also be desirable for the apparatus to be configured such that only the amount of toxin necessary to treat the nasal cavity is loaded on the applicator tip and applied to the nasal wall. It this embodiment, it would be desirable for the applicator to carry a predetermined quantity of toxin, wherein the predetermined quantity is the amount necessary to provide a therapeutic effect. It would also be desirable for the applicator to be configured such that most, if not all, of the toxin carried on the applicator is delivered to the nasal wall,

wherein little to no toxin runs, escapes or migrates to non-target portions of body tissue.

**[0099]** Additionally, it would be desirable for the applicator to be configured to provide a controlled delivery of toxin to facilitate absorption of the toxin into the walls of the nasal cavity. An applicator providing a controlled delivery of toxin can be configured such that the rate of toxin delivery is proportionate with the rate of BoNT absorption across the nasal membrane. Such a controlled delivery will ensure that the toxin is absorbed into the nasal tissue and not dispersed elsewhere in the body.

**[0100]** An apparatus for treating a nasal cavity of a patient via a controlled and uniform delivery of BoNT may comprise an applicator having an inner member, an outer member and an impermeable lining, wherein the impermeable lining separates the inner member and outer member. In this embodiment, the outer member serves as a carrier for a toxin (e.g., BoNT). The outer member may comprise any material or structure for carrying BoNT such as an open cell foam (e.g., sponge), mesh pad, porous or perforated balloon, polymeric sheet having microchannels, bioresorbable coating or muco-adhesive surface having wells or open-faced chambers. The outer member may also comprise an array of microneedles to facilitate the passage of BoNT across the nasal membrane. Alternatively, the outer member may comprise a combination of the structures and materials mentioned above. For example, the outer member may comprise a balloon coated with a sponge material, wherein the sponge material is configured to retain and subsequently release a predetermined quantity of toxin. The inner member is configured for occupying space when the applicator is positioned within the nasal cavity such that the outer member is placed in contact with the wall of the nasal cavity. The inner member may be any compliant material such as a sponge, balloon or foam rubber. The impermeable lining (e.g., tetrafluoroethylene) prevents the BoNT from retreating from the outer member to inner member and, accordingly, facilitates the transfer of BoNT from the applicator to the tissue of the nasal wall. As with applicator embodiments that have been previously discussed herein, the outer member can be pre soaked or filled with BoNT solution, infused with BoNT following placement in the nasal passageway, or pre-loaded with freeze-dried BoNT that can be reconstituted with infused saline.

**[0101]** In one embodiment, both the inner and outer members may comprise balloons, wherein the BoNT is carried in the space between the inner and outer balloons. The outer balloon can be a perforated polymer (e.g., polyethylene terephthalate or expanded polytetrafluoroethylene) for releasing BoNT in a controlled and uniform matter. The inner member can be a compliant balloon, wherein the volume occupied by the inner balloon can be adjusted by injecting a fluid (e.g., air or saline) into the inner balloon. In this configuration, the impermeable lining is comprised of the wall of the inner balloon and the applicator's BoNT carrying capacity is based on the volume of the outer balloon relative to that of the inner balloon. For example, an applicator could be configured to carry less BoNT by increasing the inner balloon's volume relative to the the outer balloon's volume.

**[0102]** In a preferred embodiment, the inner member comprises (1) a low volume configuration to facilitate the applicator's insertion into and placement within the nasal passageway and (2) an expanded volume configuration for pressing the outer member against the walls of the nasal cavity. The expansion of the inner member relative to the outer member can also facilitate the controlled release of BoNT from the outer member. Once the applicator is in its expanded volume configuration, additional fluid can be infused into the inner member to reduce the volume of the outer member relative to the inner member, thereby forcing the BoNT from the outer member. In fact, the expansion of the inner member may be configured such that the resulting stretching and compression of the outer member causes a controlled release of BoNT from the outer member, wherein the rate of BoNT release is proportional to the inner member's rate of expansion. In the embodiment comprising an inner balloon and outer balloon, the expansion of the inner member can be facilitated by the introduction of fluid into the inner member. In other embodiments, the expansion of the inner member can be facilitated by a spring member.

**[0103]** In any of the embodiments discussed herein, it may be desirable to adapt the applicator to the geometry of the nasal cavity. For example, in embodiments comprising an outer member and inner member, the outer member can be configured to match the shape of the nasal cavity or portions of the nasal passageway following the expansion of the inner member. By achieving better contact, the delivery of toxin to and across the nasal membrane can be optimized.

**[0104]** To achieve a more focal treatment, the applicator tip can be equipped with a muco-adhesive pad that is pre-loaded with BoNT solution rather than a sponge. This pad can be configured to optimize the delivery of BoNT to the mucosa. Alternatively, the applicator tip may further comprise a bioabsorbable coating or film carrying BoNT. In this embodiment, the applicator tip may comprise a BoNT-loaded bioresorbable polymer that can be absorbed into the nasal cavity tissue. The tip can be configured such that the BoNT can be delivered to the nasal wall both immediately and as the coating is absorbed into the tissue.

**[0105]** Similar to the other devices discussed in this application, the device described with respect to Figure 33 and 34 can be used to deliver BoNT-LC to the nasal cavity instead of the BoNT intact molecule. In cases where this device is used to deliver BoNT-LC to the nasal cavity, any of the previously-described, energy-based delivery systems can be used to cause poration in the nasal tissue to facilitate delivery of the BoNT-LC to the tissue. Additionally or alternatively, this device can be equipped with an energy delivery element for causing

poration in the target tissue in conjunction with delivery of BoNT-LC to the target tissue. For example, the device may comprise an electrode, antenna or ultrasonic transducer that is electrically connected to an energy generator configured for delivering energy via the energy delivery element to the target tissue at a voltage, amplitude, frequency, etc. sufficient to cause poration or permeabilization in the target tissue.

**[0106]** Throughout this disclosure, the LC solution has typically been referred to as an infused, aerosolized or sprayed liquid. LC incorporated into coatings on devices has also been described. It should be noted, however, that other forms of LC delivery may be desirable.

**[0107]** For instance, commercially available botulinum toxins (such as Botox tm - Allergan) are supplied as a dry lyophilized powder, and must be reconstituted prior to delivery by the addition of saline to the packaging vial. Similarly, light chain would be most readily available and stable in a powdered form. It may be desirable to spray or blow the powdered form of the LC into the target airways directly, without any reconstitution by liquid.

**[0108]** The lyophilized powder could also be formed into sheets, ribbons, pellets microspheres, or any other desirable form, and introduced to the target tissues.

**[0109]** Instead of a saline or low viscosity carrier, it may be desirable to deliver the light chain in a gel carrier, such as the types of gels which are commonly used for ultrasound coupling. Other appropriate gel carriers include such biocompatible gels as hyaluronic acid (HA). HA has the added benefit of being a thixotropic liquid - its viscosity drops as it begins to flow or as increasing shear stress is applied, and then returns to a higher viscosity state as it comes to rest. This would aid in delivery of the solution through catheters and the like, while allowing the gel to remain in place once delivered. HA is also extremely biocompatible, and would allow efficient ultrasonic coupling to the target tissues. The application of ultrasonic energy might also reduce the viscosity of the HA gel, possibly improving the delivery of toxin into the tissues.

**[0110]** It may also be desirable to incorporate the light chain into a foam, or to foam the LC solution upon or during delivery of the LC to the target tissues. Foams may better fill the entire targeted airway, and may trap water or coupling agents to allow efficient ultrasonic coupling. In a further embodiment, the foam may be energized within or as it exits the catheter shaft to further enhance the delivery of the LC to cells that are contacted by the energized foam and LC foam solution.

**[0111]** In addition to BTX-LC, it may be desirable to deliver additional agents to the nasal passages and sinuses prior to, coincident with, or after deliver of the LC. Adjunctive therapies may include agents designed to slow down or halt the motion of the cilia, in order to aid in delivery of the LC to the target tissues by prevention of their mobilization by the cilia. Agents known to slow or halt the motion of cilia include but are not limited to epinephrine dilutions of 1:1000 (which causes ciliary death), 1:10,000 (which causes reversible paralysis), 10% cocaine (induces paralysis) or 2.5% cocaine (slows or stops cilia).

**[0112]** Other adjunctive therapies may include the use of or pretreatment with mucolytics, which will thin mucus secretions within the nose and may allow better penetration of LC into the target cells.

**[0113]** Decongestants such as epinephrine also cause constriction of the vasculature in the nasal passages, which in addition to temporarily reducing swelling of the target tissues, may decrease the risks of LC entering the blood stream during poration and delivery. Epinephrine also constricts the blood vessels locally, which may increase the residence time of other locally delivered agents or decrease their likelihood of entering systemic circulation.

**[0114]** Steroids may be used to reduce swelling and inflammation prior to LC treatment in order to improve LC delivery to target tissues. In the abovementioned embodiments, it may be important to note that by far the most significant effects will be seen in areas where both the LC and the permeablizing energy are delivered. Therefore, although it may be best to deliver both LC and energy to substantially the same area, for reasons of anatomy, ease of delivery, etc., either the LC or the energy might be delivered more broadly, or to a somewhat different area. As an extreme example, the LC might be delivered systemically or to the entire respiratory pathway, followed by very localized delivery of energy to the desired area. Alternatively, the LC could be delivered to a specific sinus, followed by energy to the entire nose and sinus using a standardized external energy delivery mask.

**[0115]** While the above is a complete description of the preferred embodiments of the invention, various alternatives, moditications, and equivalents may be used. Therefore, the above description should not be taken as limiting the scope of the invention which is defined by the appended claims.

THE DISCLOSURE OF THIS APPPLICATION ALSO INCLUDES THE FOLLOWING NUMBERED CLAUSES:

**[0116]**

1. An apparatus for treating inflammation of a nasal membrane of a patient comprising: a handle comprising a proximal section, a first member and a second member, wherein the first member and second member are connected at the proximal section; a first applicator tip coupled to the first member; and a second applicator tip coupled to the second member; wherein the first applicator tip and second applicator tip are each configured for insertion into a nostril of the patient and placement within a nasal passageway of the patient and wherein each applicator tip is configured for delivering a toxin to a region of nasal tissue within the nasal cavity of the patient, thereby treating the inflammation.

2. The apparatus of clause 1, wherein the handle further comprises a spring element.

3. The apparatus of clause 2, wherein the spring element is either a v- shaped spring or closed-loop spring.

4. The apparatus of clause 2, wherein the handle is configured to be arranged in a compressed delivery configuration for placement of the applicator tips within the nasal passageway and an expanded treatment configuration for delivering toxin to the region of nasal tissue.

5. The apparatus of clause 1, wherein each applicator tip comprises a sponge.

6. The apparatus of clause 5, wherein each applicator tip is configured to be arranged in a low volume delivery configuration for placement within the nasal passageway and an expanded volume treatment configuration for delivering toxin to the region of nasal tissue.

7. The apparatus of clause 6, wherein each applicator tip in the expanded volume treatment configuration is adapted to fit substantially within the nasal cavity of the patient.

8. The apparatus of clause 5, wherein each applicator tip further comprises a spring element.

9. The apparatus of clause 8, wherein each applicator tip is configured to be arranged in a compressed delivery configuration for placement within the nasal passageway and an expanded treatment configuration for delivering toxin to the region of nasal tissue.

10. The apparatus of clause 9, wherein each applicator tip further comprises an actuator, wherein the actuator is configured for movement from an engaged position and a retracted position.

11. The apparatus of clause 10. wherein the applicator tip is in the compressed delivery configuration when the actuator is in the engaged position.

12. The apparatus of clause 10. wherein the applicator tip is in the expanded delivery configuration when the actuator is in the retracted position.

13. The apparatus of clause 10 further comprising an engagement element, wherein the engagement element is configured to control the movement of both actuators simultaneously.

14. The apparatus of clause 5, wherein each applicator tip further comprises an impermeable lining.

15. The apparatus of clause 1, wherein each applicator tip further comprises a muco-adhesive pad.

16. The apparatus of clause 1, wherein the toxin is carried by a bioresorbable coating.

17. The apparatus of clause 1 further comprising an infusion channel for delivering the toxin to the applicator tips.

18. The apparatus of clause 17 further comprising an access port, wherein the apparatus is in fluid communication with a toxin source via the access port.

19. The apparatus of clause 17, wherein the applicator tips are configured to receive the toxin prior to being positioned in the nasal passageway.

20. The apparatus of clause 17, wherein the applicator tips are configured to receive the toxin after being positioned in the nasal passageway.

21. The apparatus of clause 1, wherein the toxin comprises at least one selected from the group consisting of a liquid, gel, foam, cream, lotion and lyophilized compound.

22. The apparatus of clause 1, wherein the toxin comprises botulinum toxin.

23. The apparatus of clause 22. wherein the botulinum toxin is selected from the group of botulinum toxins consisting of A, B, C, D. E, F and G.

24. The apparatus of clause 22, wherein the toxin is a fragment of botulinum toxin.

25. The apparatus of clause 24, wherein the fragment is a light chain fragment of botulinum toxin.

26. The apparatus of clause 25 further comprising an energy delivery applicator configured for delivering energy to the region of nasal tissue to enhance delivery of the toxin to the nasal tissue.

27. The apparatus of clause 26, wherein the energy delivery applicator is adapted to deliver energy under conditions which cause poration of at least one cell in the region of nasal tissue.

28. The apparatus of clause 26, wherein the energy delivery applicator is adapted to deliver an electric pulse.

29. The apparatus of clause 28, wherein the electric pulse is an RF signal.

30. The apparatus of clause 26, wherein the energy

delivery is adapted to deliver energy selected from the group consisting of microwave, ultrasound and x-ray.

31. An apparatus for ti eating a condition associated with inflammation of a nasal membrane of a patient selected from the group consisting of rhinitis, rhinorrhea, hay fever and combinations thereof, said apparatus comprising. an applicator configured for (a) insertion into a nostril of the patient, (b) placement within a nasal passageway of the patient, and (c) delivering a therapeutically effective amount of a toxin to a region of nasal tissue within the nasal cavity of the patient, wherein the applicator comprises an inner member and outer member.

32. The apparatus of clause 31, wherein the applicator further comprises an impermeable lining configured for separating the inner member and outer member.

33. The apparatus of clause 31, wherein the applicator is configured to be arranged in a low volume configuration for placement within the nasal passageway and an expanded volume configuration for delivering the toxin to the nasal tissue

34. The apparatus of clause 33, wherein the inner member comprises a balloon.

35. The apparatus of clause 33, wherein the inner member comprises a sponge.

36. The apparatus of clause 35, wherein the inner member further comprises a spring element.

37. The apparatus of clause 31, wherein the outer member comprises one selected from the group consisting of a sponge, mesh pad, perforated balloon, porous polymer, bioresorbable coating, muco-adhesive surface and combinations thereof.

38. The apparatus of clause 31, wherein the outer member comprises a balloon and a sponge.

39. The apparatus of clause 31 , wherein the inner member is configured to expand.

40. The apparatus of clause 39, wherein expansion of the inner member facilitates delivery of the toxin to the nasal tissue

41. An apparatus for treating a condition associated with inflammation of a nasal membrane of a patient selected from the group consisting of rhinitis, rhinorrhea, hay fever and combinations thereof, said apparatus comprising: a handle comprising a first distal and a second distal end; a first applicator tip coupled to the first distal end; and a second applicator tip coupled to the second distal end; wherein the first applicator tip and second applicator tip are each configured for insertion into a nostril of the patient and placement within a nasal passageway of the patient and wherein each applicator tip is configured for delivering a therapeutically effective amount of a toxin to a region of nasal tissue within the nasal cavity of the patient, thereby treating the condition.

42. The apparatus of clause 41 further comprising a spring element, wherein the spring element is configured to provide the applicator tips with an outward bias when the applicator tips are placed within the nasal passageway.

43. The apparatus of clause 42, wherein the outward bias presses each applicator tip against a turbinate in the nasal cavity.

44. A method for delivering toxins to target cells in a nasal membrane of a patient, said method comprising: introducing a toxin to a region proximate the target cells; and applying energy to the target cells to enhance delivery of the toxin to the cells.

45. A method as in clause 44, wherein the region comprises at least one paranasal sinus, a main nasal passage or a nasal turbinate.

46. A method as in clause 44, wherein the region comprises substantially the entire nasal cavity.

47. A method as in clause 44, wherein the region comprises the nasopharynx.

48. A method as in clause 44, wherein the target cells comprise epithelial or goblet cells.

49. A method as in clause 44, wherein the energy is selectively applied to target cells within the region where toxin has been introduced.

50. A method as in clause 44, wherein the energy is applied non-selectively within the region where toxin has been introduced.

51. A method as in clause 44, wherein the patient suffers from or is at risk of suffering from rhinorreah.

52. A method as in clause 44, wherein the patient suffers from or is at risk of suffering from sinus headaches.

53. A method as in clause 44, wherein the patient suffers from or is at risk of suffering from migraine headaches.

54. A method as in clause 44, wherein the toxin comprises botulinum toxin.

55. A method as in clause 54, wherein the toxin is a fragment of botulinum toxin.

56. A method as in clause 55, wherein the fragment is a light chain fragment of botulinum toxin.

57. A method as in clause 56, wherein the light chain fragment is derived from at least one of botulinum toxins A, B, C, D, E, F, and G.

58. A method as in clause 44, wherein the energy applied to the targeted region is an electric pulse.

59. A method as in clause 58, wherein the electric pulse is applied from between IV to 500V.

60. A method as in clause 58, wherein the electric pulse is an RF signal.

61. A method of clause 58, wherein the electric pulse is pulsed for durations between 5 microseconds to 100 milliseconds.

62. A method as in clause 58, wherein the electric pulse is produced by a DC power source.

63. A method as in clause 58, wherein the electric pulse is produced by an AC power source.

64. A method as in clause 44, wherein the energy applied to the target region is ultrasonic.

65. A method as in clause 44, wherein the energy applied to the targeted region is an x-ray beam.

66. A method as in clause 44, wherein the energy applied to the targeted region is focused ultrasound.

67. A method as in clause 44, wherein the energy applied to the targeted region is microwave.

68. A method as in clause 44, wherein the toxin is introduced to the target region through a catheter.

69. A method as in clause 68, wherein the toxin is introduced through a balloon on the catheter.

70. A method as in clause 69, wherein the balloon is porous and the toxin is introduced through the balloon.

71. A method as in clause 68, wherein the toxin is introduced through a needle on the catheter.

72. A method as in clause 68, wherein the toxin is aerosolized from the catheter.

73. A method as in clause 68, wherein energy is applied from a source on the catheter.

74. A method as in clause 73, wherein acoustic energy is applied from a transducer on the catheter.

75. A method as in clause 73, wherein electrical energy is applied from an electrode on the catheter.

76. A method as in clause 44, wherein the energy is delivered from a source external to the patient.

77. A method as in clause 76, wherein the source is an acoustic energy transducer.

78. A method as in clause 77, wherein the acoustic energy transducer is a focused ultrasound transducer.

79. A system for delivering toxins to target cells in a nasal membrane, said system comprising: a catheter adapted to introduce a toxin to a region proximate the target cells; an energy applicator configured for applying energy to the target cells under conditions which cause poration of the cell membranes to enhance delivery of the toxin; and a source of toxin suitable for introduction from the catheter.

80. A system as in clause 79, wherein the energy applicator is adapted to selectively apply energy to target cells within the region where toxin has been introduced.

81. A system as in clause 79, wherein the energy applicator is adapted to apply energy non-selectively within the region where toxin has been introduced.

82. A system as in clause 79, wherein the toxin comprises botulinum toxin.

83. A system as in clause 82, wherein the toxin is a fragment of botulinum toxin.

84. A system as in clause 83, wherein the fragment is a light chain fragment of botulinum toxin.

85. A system as in clause 84, wherein the light chain fragment is derived from at least one of botulinum toxins A, B, C, D, E, F, and G.

86. A system as in clause 44, wherein the energy applicator is adapted to apply an electric pulse of between Iv and 500V to the targeted region.

87. A system as in clause 86, wherein the electric pulse is an RF signal

88. A system as in clause 86, wherein the electric pulse is pulsed for durations between 5 microseconds to 100 milliseconds

89. A system as in clause 86, wherein the electric pulse is produced by a DC power source

90. A system as in clause 86, wherein the electric pulse is produced by an AC power source

91. A system as in clause 44, wherein the energy applicator is adapted to apply ultrasonic energy to the targeted region

92. A system as in clause 79, wherein the energy applicator is adapted to apply an x-ray beam to the targeted region

93. A system as in clause 79, wherein the energy applicator is adapted to apply focused ultrasound to the targeted region

94. A system as in clause 79, wherein the energy applicator is adapted to apply microwave to the targeted region

95. A system as in clause 79, wherein the toxin is introduced by a balloon on the catheter

96. A system as in clause 95, wherein the balloon comprises one or more pores and the toxin is introduced through the pores of the balloon

97. A system as in clause 79, wherein the toxin is introduced through a needle on the catheter

98. A system as in clause 95, wherein the toxin is aerosolized from the catheter

99. A system as in clause 79, wherein energy applicator is on the catheter

100. A system as in clause 99, wherein energy applicator applies acoustic energy from a transducer on the catheter.

101. A system as in clause 99, wherein energy applicator applies electrical energy from an electrode on the catheter.

102. A system as in clause 79, wherein the applicator applies energy from a source external to the patient.

103. A system as in clause 102, wherein the source further comprises an acoustic energy transducer.

104. A system as in clause 102, wherein the acoustic energy transducer further comprises a focused ultrasound transducer.

105. A system as in clause 79, wherein the toxin is introduced through a membrane supported on a scaffold on the catheter.

106. A system as in clause 79, wherein the toxin is introduced by a needless injector.

107. A system as in clause 79, wherein the energy applicator comprises a wave guide configured to be positioned within a nasal passageway.

108. A system as in clause 95, wherein the balloon is configured to be positioned within a nasal passageway.

109. A system as in clause 95, wherein the balloon is configured to be positioned outside of a sinus cavity.

110. A method as in clause 44, wherein applying energy to the target cells further comprises applying energy to the target cells under conditions which cause poration of the cell membranes.

111. A system as in clause 102, wherein the source further comprises a microwave antenna.

112. A method as in clause 73, wherein microwave energy is applied from the catheter.

## Claims

1. A system for treating a condition associated with inflammation of a nasal membrane of a patient selected from the group consisting of rhinitis, rhinorrhea, hay fever and combinations thereof, said system comprising:

   an applicator carrying an agent and configured for (a) insertion into a nostril of the patient, (b) placement within a nasal passageway of the patient, and (c) delivering a therapeutically effective amount of the agent to a target region of nasal tissue within the nasal cavity of the patient; wherein the applicator comprises an inner member and outer member, the applicator having a low volume configuration for placement within the nasal passageway and an expanded volume configuration for delivering the agent to the nasal tissue, and having an impermeable lining, and the outer member having a porous portion to allow the agent to pass through the porous surface upon expansion of the inner member,
   wherein expansion of the inner member also expands the outer member such that the porous

surface of the outer member contacts and delivers the agent to the target region of nasal tissue in an amount selected to have a therapeutic effect on rhinitis, rhinorrhea, hay fever or combinations thereof.

2. The system of claim 1, wherein the agent is contained between the inner and outer members.

3. The system of claim 1 or 2, wherein the inner member and the outer member are configured to deliver the agent to the tissue at a rate no higher than the rate of absorption of the agent across the nasal membrane.

4. The system of claim 1, 2 or 3, wherein the applicator is configured to carry no more than a predetermined quantity of the agent selected to be an amount necessary to provide a therapeutic effect for the condition.

5. The system of any preceding claim, wherein the applicator is configured to preferentially deliver the agent to the target region of nasal tissue while inhibiting migration of the toxin to non-target regions of the nasal cavity outside the target region.

6. The system of any preceding claim, wherein the inner member comprises a balloon or a sponge.

7. The system of any preceding claim, wherein the inner member further comprises a spring element, usually a v-shaped spring or closed-loop spring.

8. The system of claim 7, wherein the spring element is outwardly biased, and optionally wherein the spring element is biased to expand laterally toward turbinates of the nasal cavity.

9. The system of claim 7 or 8, wherein the applicator comprises a handle and the spring element is incorporated into the handle.

10. The system of any preceding claim, wherein the outer member comprises one selected from the group consisting of a sponge, mesh pad, perforated balloon, porous polymer, bioresorbable coating, mucoadhesive surface, and combinations thereof.

11. The system of any preceding claim, wherein the outer member comprises a balloon and a sponge.

12. The system of any preceding claim, wherein the agent comprises a neurotoxin.

13. The system of claim 12, wherein:

the neurotoxin comprises one or more of botulinum toxin (BoNT), ricin, exotoxin A, diphtheria toxin, cholera toxin, tetanus toxin, or active fragments thereof; or

the neurotoxin comprises botulinum toxin (BoNT), a light chain fragment of BoNT, a heavy chain fragment of BoNT, or an active fragment of BoNT, and optionally wherein the botulinum toxin (BoNT) is selected from the group of botulinum toxin (BoNT) consisting of A, B, C, D, E, F, and G.

14. The system of any preceding claim, wherein the agent is carried in a liquid solution, gel, foam, cream lotion, a lyophilized powder or other compound, or other fluid or fluidizable carrier.

15. The system of any preceding claim, further comprising an energy delivery element for delivering energy to the target region of the nasal tissue to enhance delivery of the agent to the nasal tissue by causing a poration of at least one cell in the target region of the nasal tissue, and optionally wherein the energy delivery element is incorporated into the applicator, and optionally, wherein the applied energy comprises one or more of electrical pulses, acoustic pulses, X-ray energy, or microwave energy.

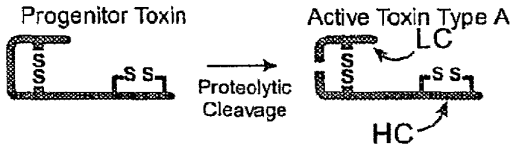

Progenitor Toxin
S S
Proteolytic
Cleavage
Active Toxin Type A
LC
S S
HC

FIG. 1

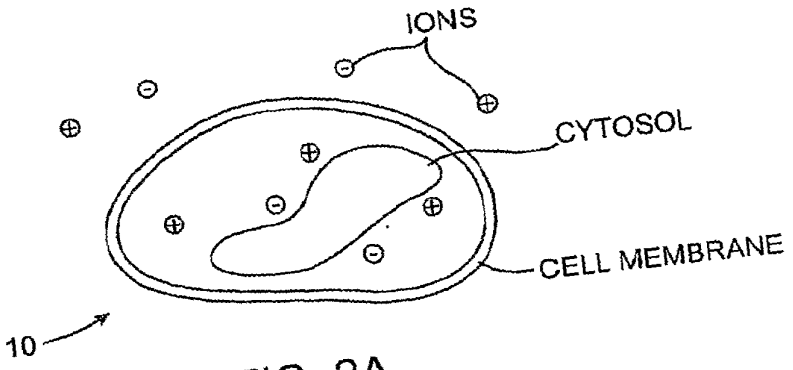



FIG. 2A

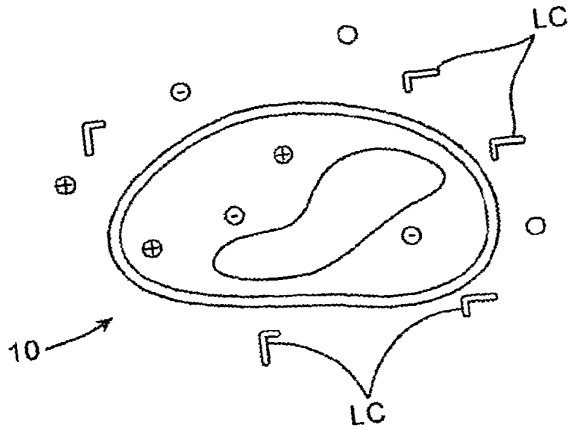



FIG. 2B

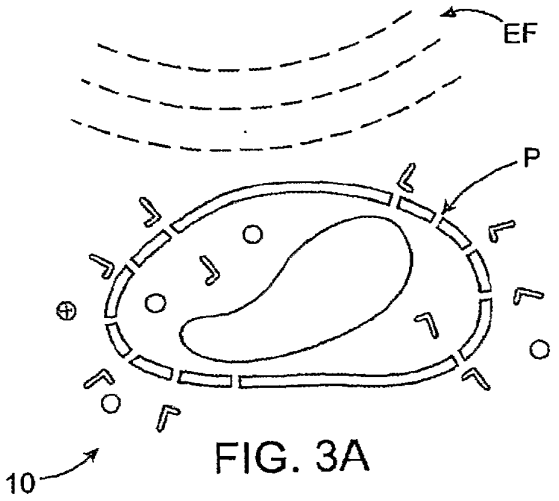



FIG. 3A

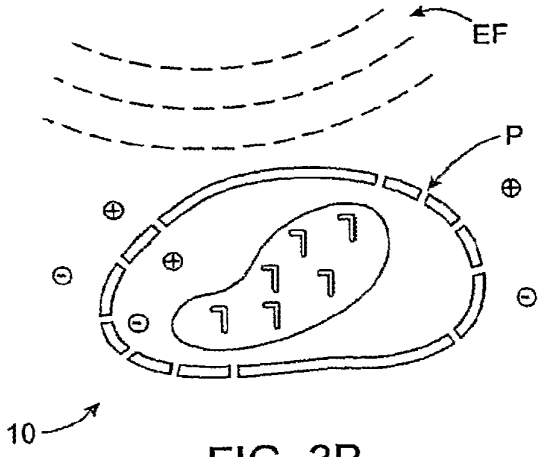



FIG. 3B

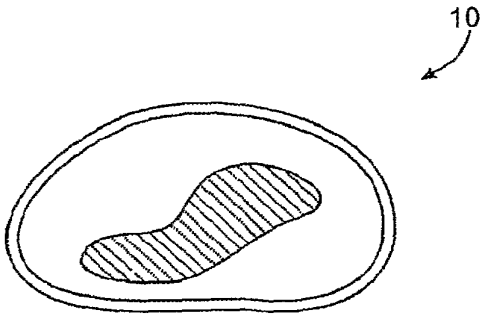



FIG. 4

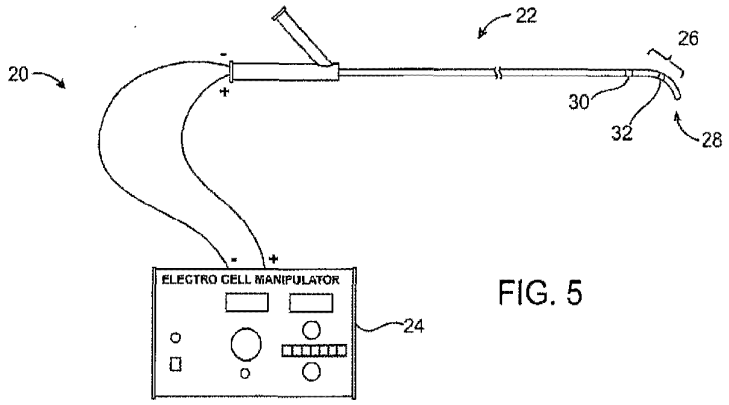



FIG. 5

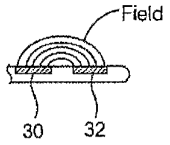



FIG. 5A

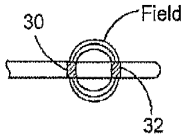



FIG. 5B

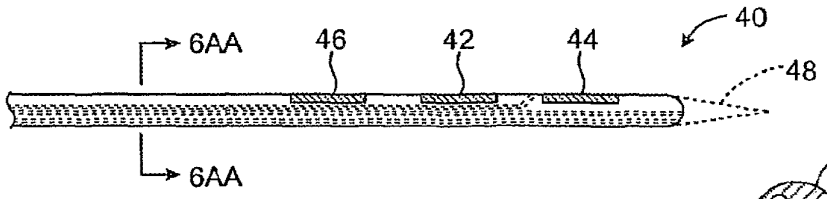



FIG. 6A

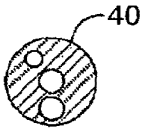



FIG. 6AA

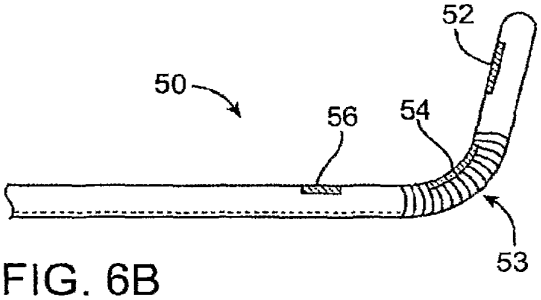



FIG. 6B

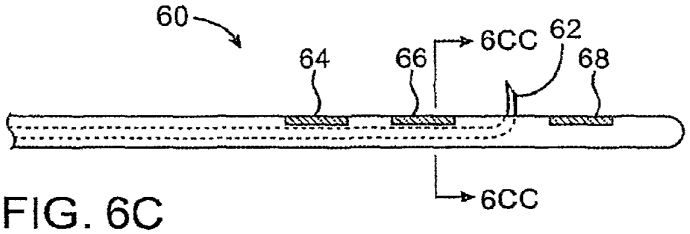



FIG. 6C

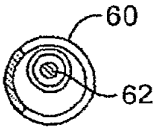



FIG. 6CC

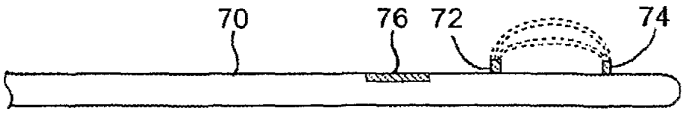



FIG. 6D

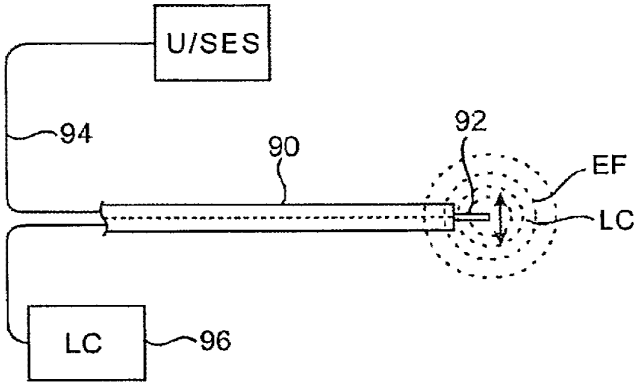



FIG. 7

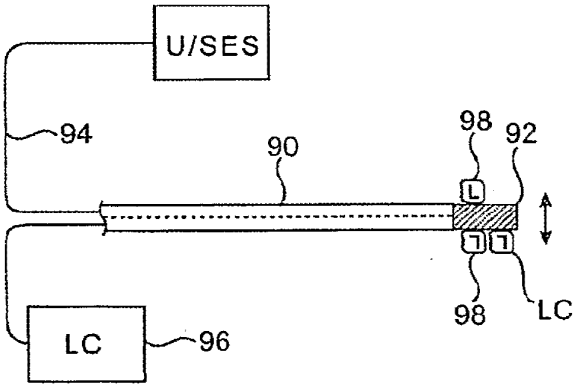



FIG. 8

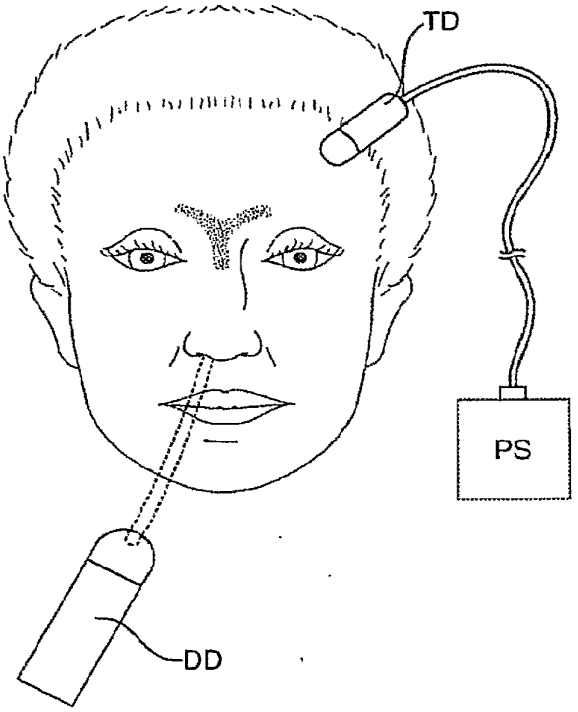



FIG. 9

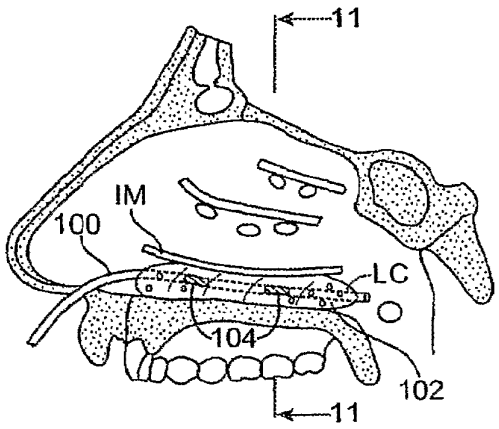



FIG. 10

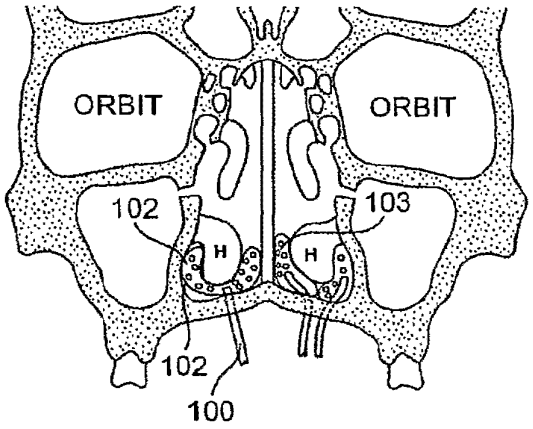



FIG. 11

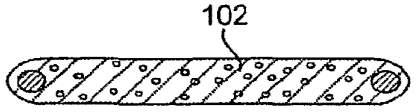



FIG. 12A

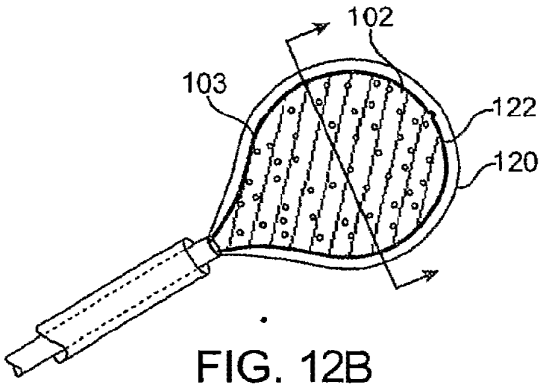



FIG. 12B

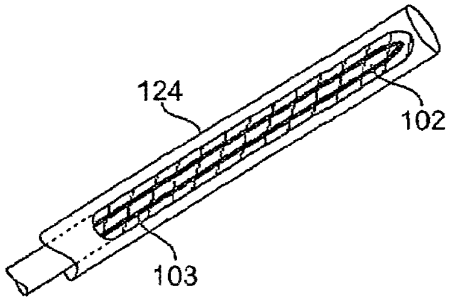



FIG. 12C

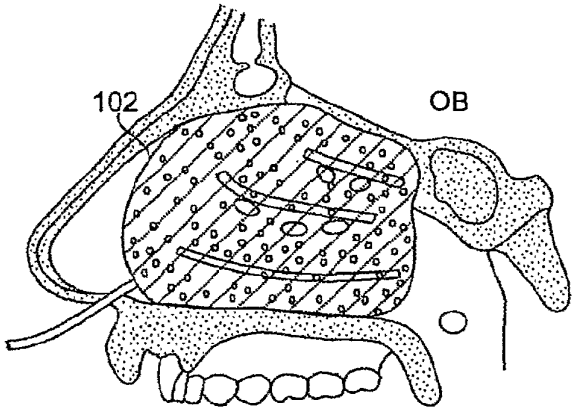



FIG. 13

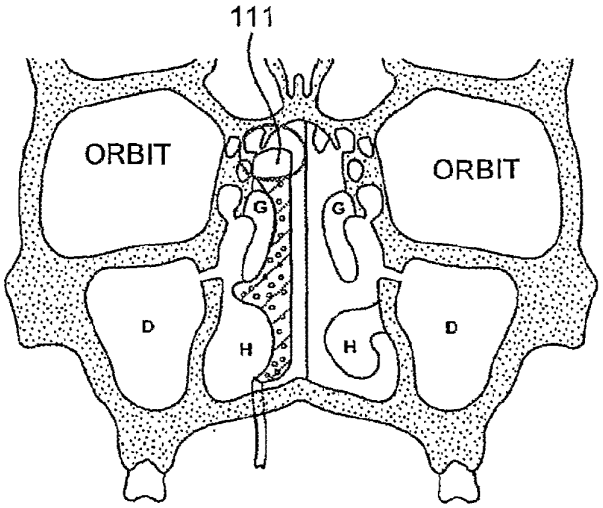



FIG. 14

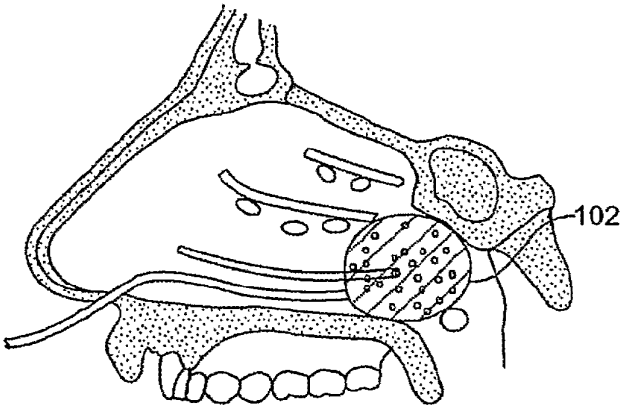



FIG. 15

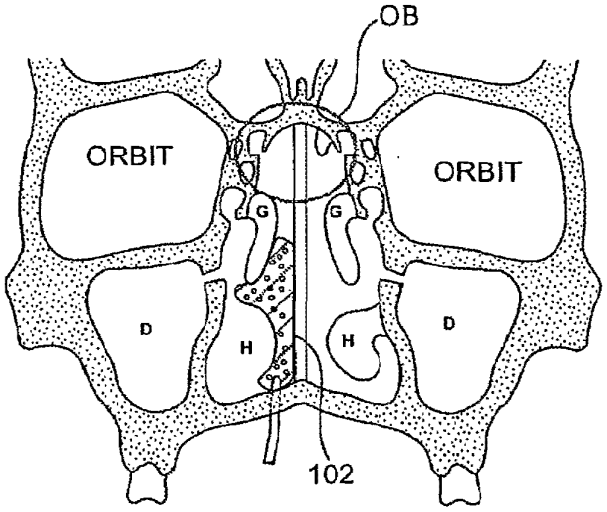



FIG. 16

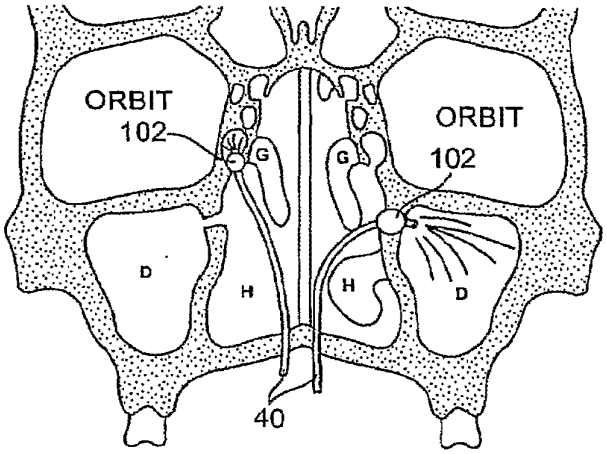



FIG. 17

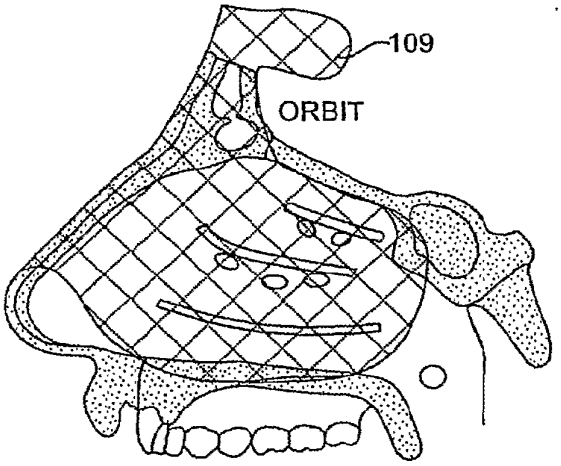



FIG. 18

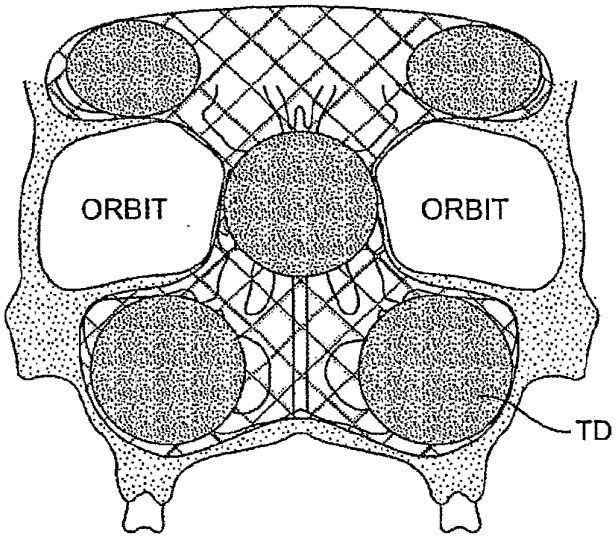



FIG. 19

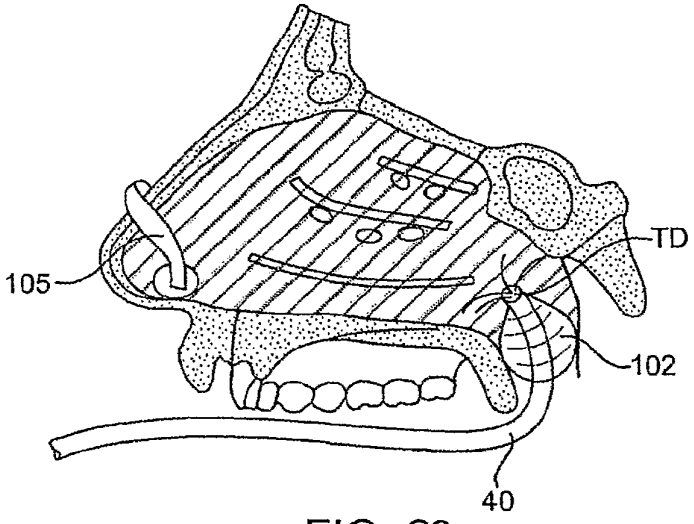



FIG. 20

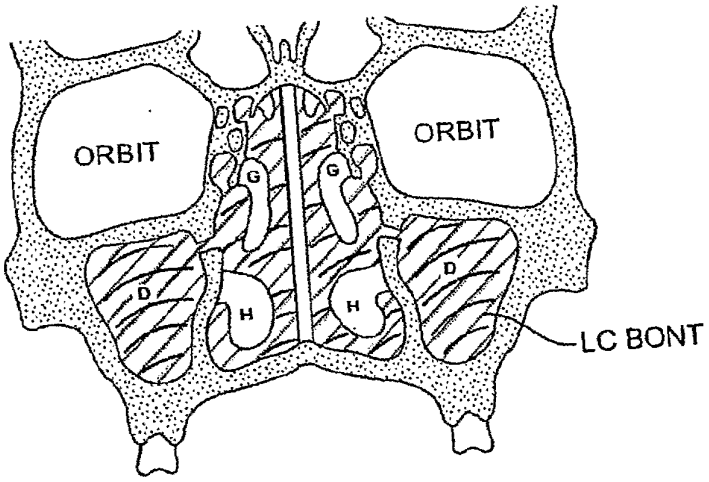



FIG. 21

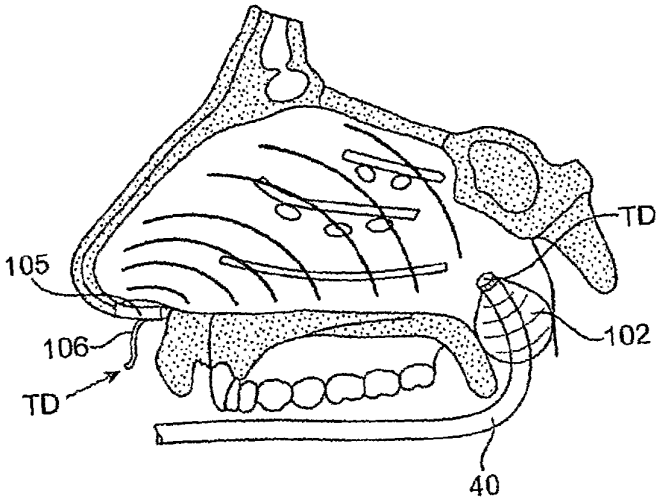



FIG. 22

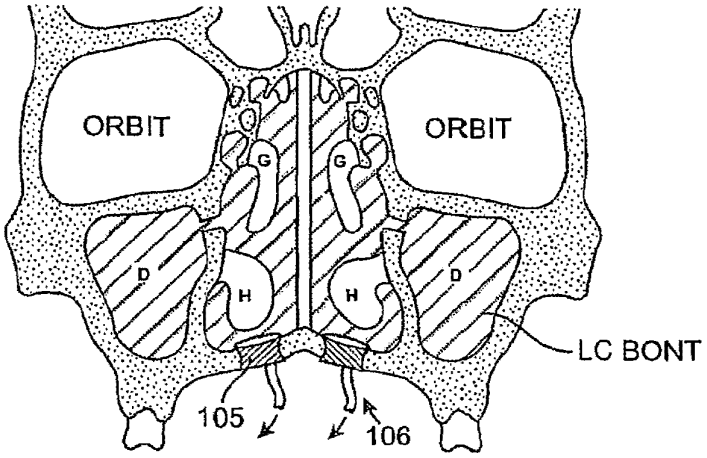



FIG. 23

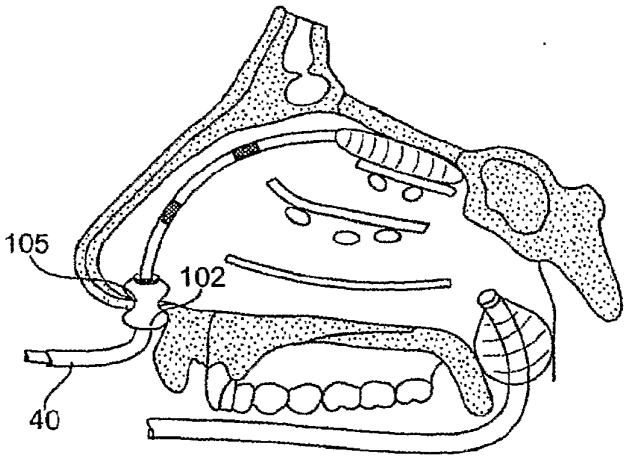



FIG. 24

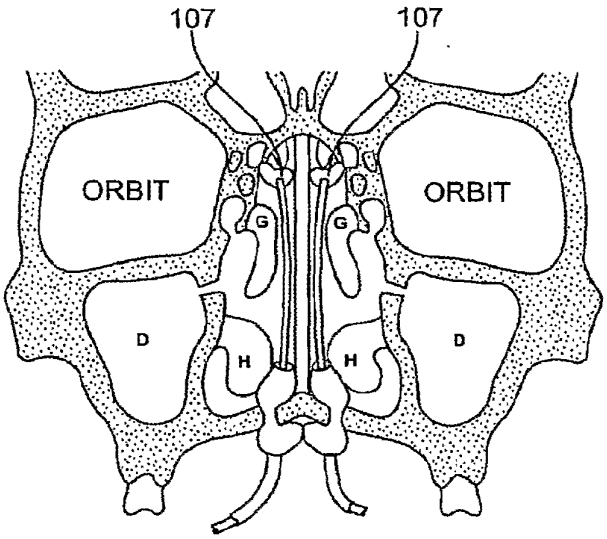



FIG. 25

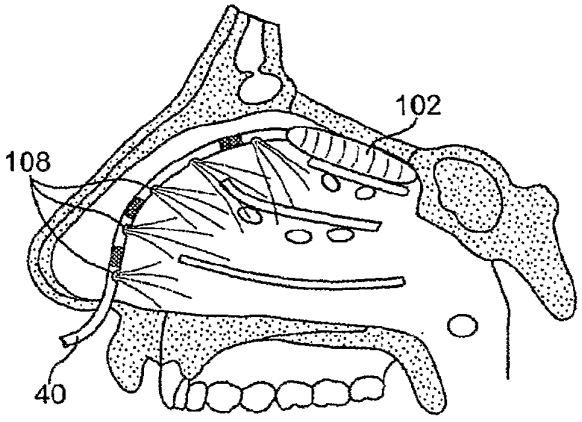



FIG. 26

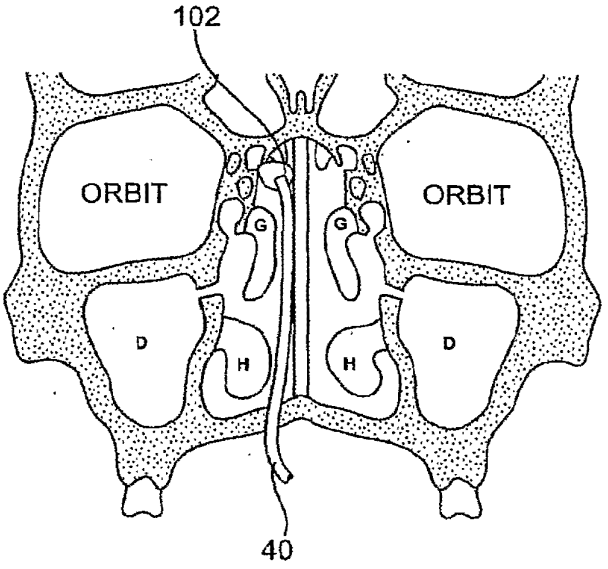



FIG. 27

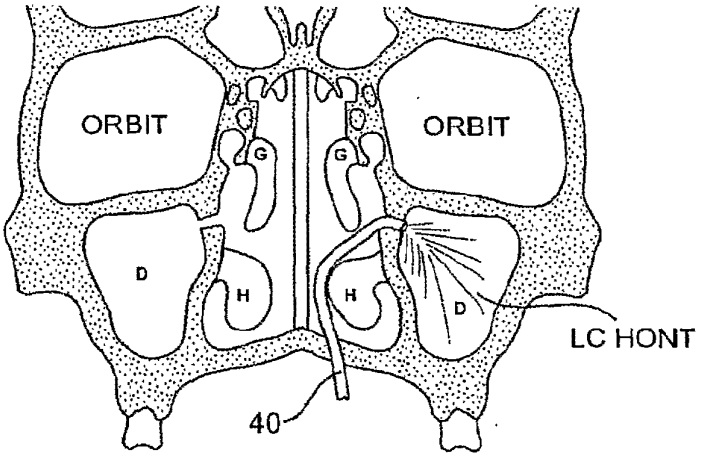



FIG. 28

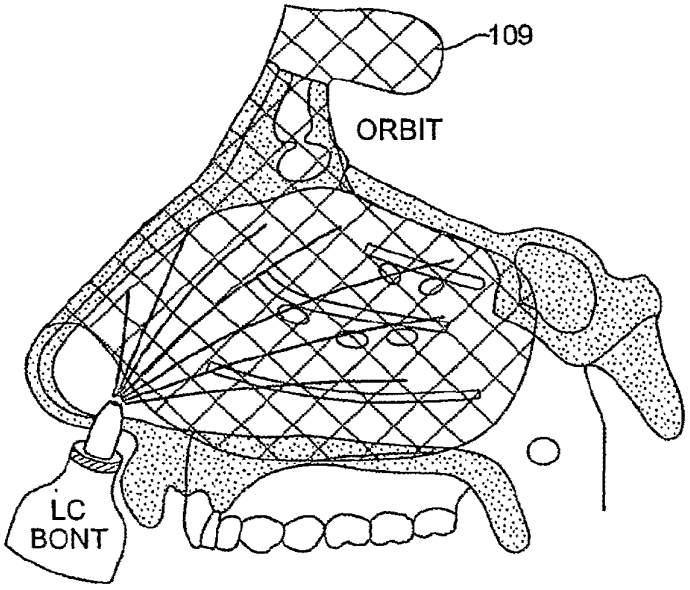



FIG. 29

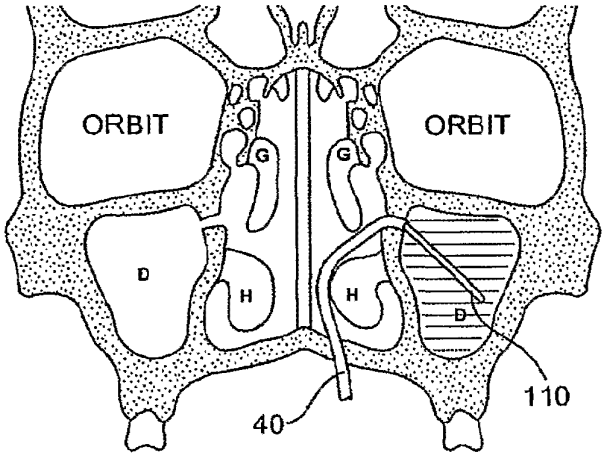



FIG. 30

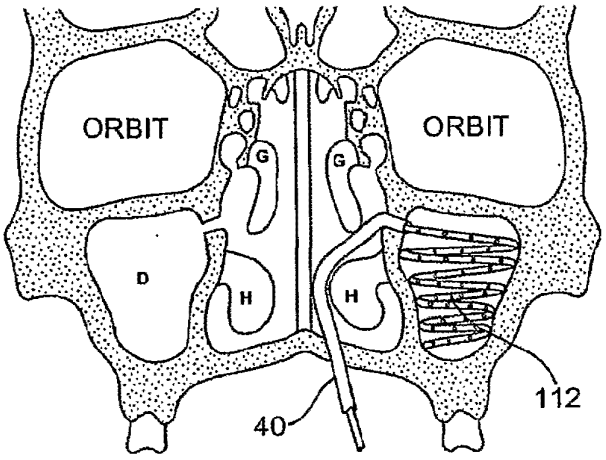



FIG. 31

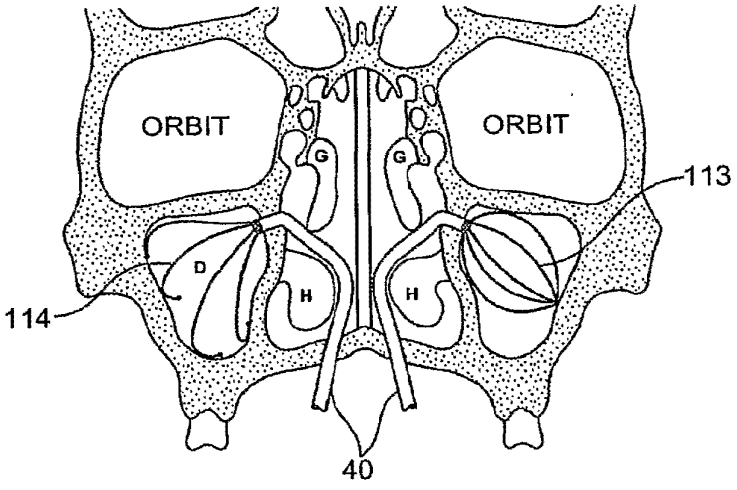



FIG. 32

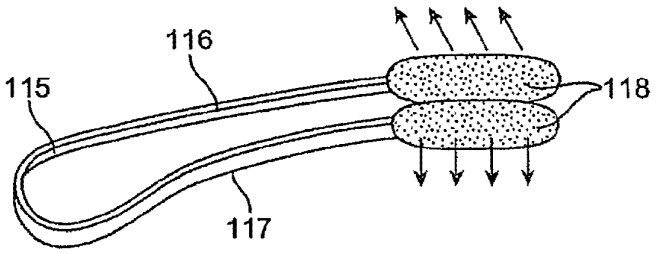



FIG. 33

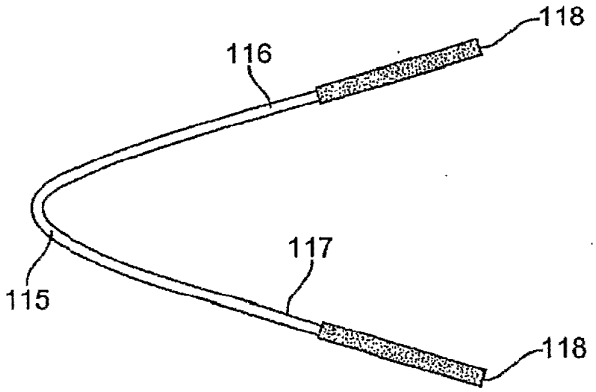



FIG. 34

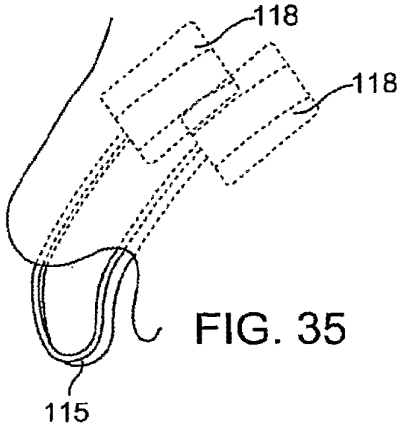



FIG. 35

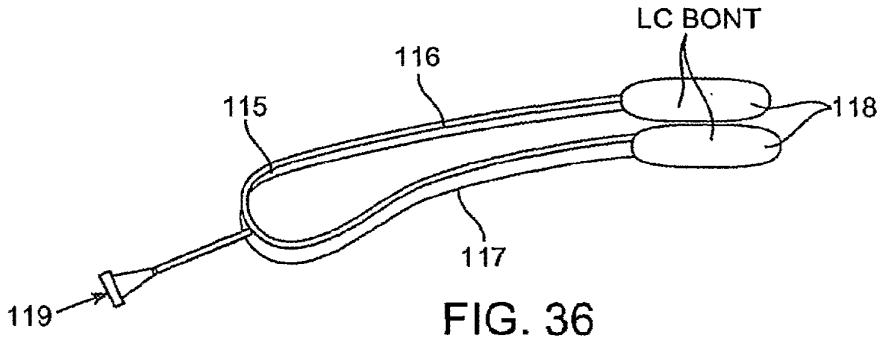



FIG. 36

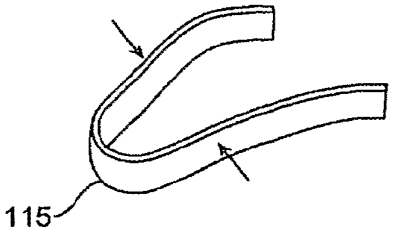



FIG. 37A

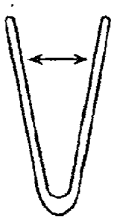


FIG. 37B

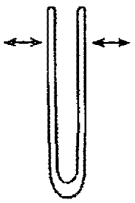


FIG. 37C

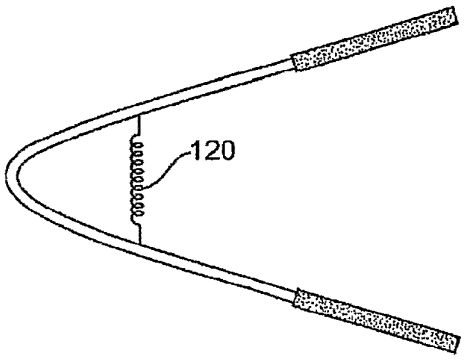



FIG. 38

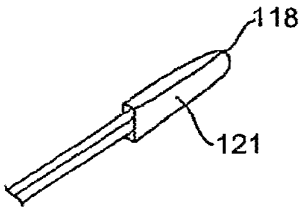



FIG. 39A

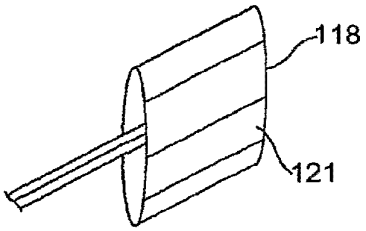



FIG. 39B

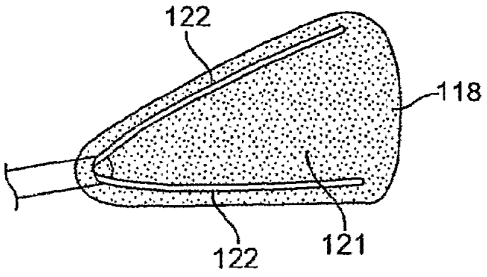



FIG. 40A

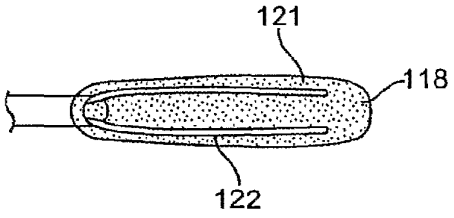



FIG. 40B

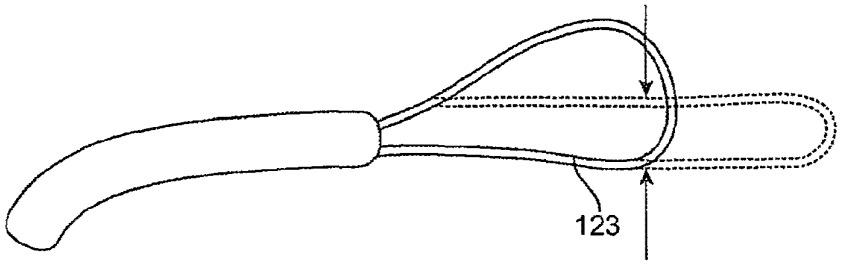



FIG. 41

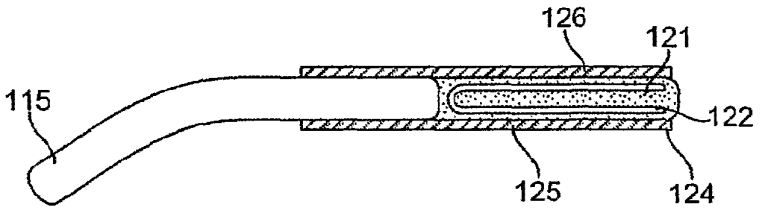



FIG. 42

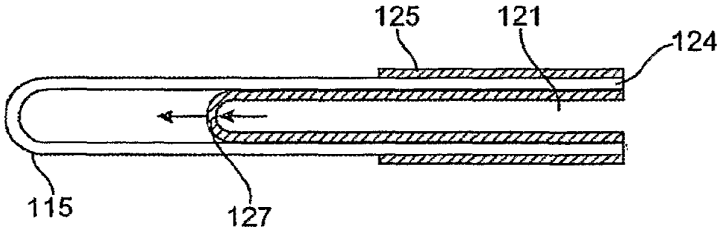



FIG. 43

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# EUROPEAN SEARCH REPORT

Application Number
EP 17 16 5407

## DOCUMENTS CONSIDERED TO BE RELEVANT

| Category | Citation of document with indication, where appropriate, of relevant passages | Relevant to claim | CLASSIFICATION OF THE APPLICATION (IPC) |
|---|---|---|---|
| X | EP 0 533 816 A1 (CORTRAK MEDICAL INC [US]) 31 March 1993 (1993-03-31) | 1-6,8-14 | INV. A61K9/12 |
| Y | * abstract; figure 3 * * pages 1-8 * | 7 | A61K39/02 A61K9/08 A61K9/72 |
| X | US 2006/106361 A1 (MUNI KETAN P [US] ET AL) 18 May 2006 (2006-05-18) * abstract; figures 4A-5A * * paragraphs [0075] - [0078], [0135] * | 1-6, 10-14 | A61N1/30 A61K38/16 A61N7/00 A61K38/48 A61K41/00 |
| X | US 5 807 306 A (SHAPLAND J EDWARD [US] ET AL) 15 September 1998 (1998-09-15) * abstract; figure 26 * * columns 21-24 * | 1-6, 10-15 | A61N1/08 A61N1/32 A61N7/02 A61N1/05 A61M25/00 |
| Y | US 5 192 290 A (HILAL SAID [US]) 9 March 1993 (1993-03-09) * abstract; figure 6 * * column 6 * | 7 | A61M25/10 A61B18/18 A61K9/00 |

TECHNICAL FIELDS SEARCHED (IPC)

A61K
A61N

The present search report has been drawn up for all claims

| Place of search | Date of completion of the search | Examiner |
|---|---|---|
| Munich | 3 August 2017 | Lins, Stephanie |

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# EUROPEAN SEARCH REPORT

Application Number
EP 17 16 5407

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|---|---|---|---|
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| | | | TECHNICAL FIELDS SEARCHED (IPC) |

The present search report has been drawn up for all claims

| Place of search | Date of completion of the search | Examiner |
|---|---|---|
| Munich | 3 August 2017 | Lins, Stephanie |

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D : document cited in the application
L : document cited for other reasons

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03-08-2017

| Patent document cited in search report | Publication date | Patent family member(s) | Publication date |
|---|---|---|---|
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| | | AU 8074591 A | 07-01-1992 |
| | | CA 2081896 A1 | 16-12-1991 |
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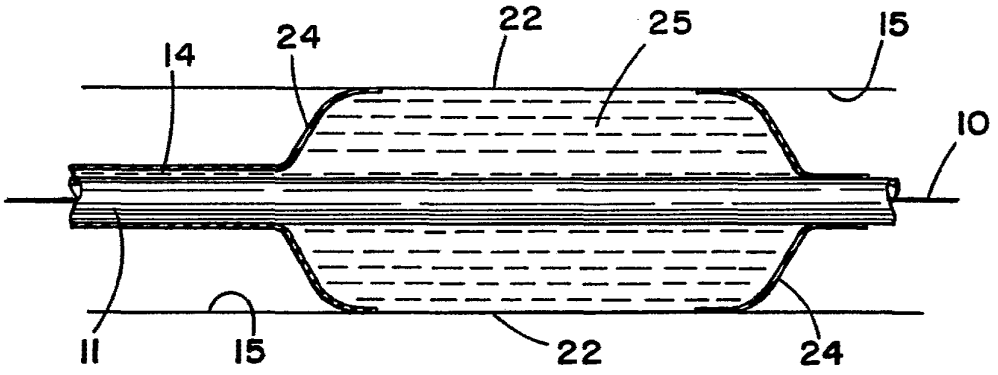
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(54) Title: DRUG DELIVERY APPARATUS AND METHOD




(57) Abstract

A drug delivery apparatus and method for delivering a drug locally to internal body tissue. The invention contemplates positioning a drug delivery device in a body passageway or within body tissue and then selectively introducing a selected drug so that it is transported across a drug transport wall of the device for direct contact with the passageway wall or body tissue.

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# DRUG DELIVERY APPARATUS AND METHOD

## BACKGROUND OF THE INVENTION

### 1. Field of the Invention

The present invention relates generally to a drug delivery apparatus and method, and more particularly, to an apparatus and method for selectively and locally delivering a drug to internal body tissue. More specific applications of the present invention relate to an apparatus and method for limiting restenosis of natural or an artificially dilated blood vessel and localized treatment of tumors or other tissue.

### 2. Description of the Prior Art

Many techniques currently exist for delivering drugs or other medicaments to body tissue. These include, among possible others, oral administration, injection directly into body tissue such as through an intramuscular injection or the like, topical or transcutaneous administration where the drug is passively absorbed, or caused to pass, into or across the skin or other surface tissue and intravenous administration which involves introducing a selected drug directly into the blood stream.

Except for topical or transcutaneous administration, the above drug delivery systems tend to be systemic. In other words, administration of the drug is delivered throughout the body by the blood stream. Although transcutaneous drug delivery systems tend to be localized delivery systems in that the drug is delivered locally to a selected area, such drug delivery systems are also, by definition, limited to application of a drug externally through the patient's skin or other surface tissue. Thus, the above described drug delivery systems are generally not appropriate for the localized treatment of internal body tissue.

Although many medical situations are satisfactorily treated by the general systemic administration of a drug, there are a great many treatments which could be facilitated and/or improved by the ability to deliver or administer a drug locally to a selected portion of internal body tissue, without appreciably affecting the surrounding tissue.

One example is the ability to treat the dilated vessel in percutaneous transluminal coronary angioplasty (PTCA), and thus limit or prevent restenosis. In PTCA, catheters are inserted into the cardiovascular system under local anesthesia and an expandable balloon portion is then inflated to compress the atherosclerosis and dilate the lumen of the artery. Despite the general success of such PTCA procedures, high restenosis rates (reported to be as high as 47%) continue to be a major problem. Various techniques have been tried to treat stenosed vessels including the use of lasers, application of heat and the use of intravascular stents. However, many of these are still under investigation with mixed results, while others have generally not been successful. The ability to administer a drug locally to the dilated portion of the artery in PTCA procedures, without significantly affecting other tissues, would greatly enhance the ability to address the restenosis problem.

A second example of specific application for a local drug delivery system for delivering a drug to an internal body tissue is in the treatment of cancerous tumors or the like. In the treatment of such tumors, an objective is to administer the cancer drug so that it localizes, as much as possible, in the tumor itself. Such drugs are commonly administered systemically through the blood stream. Various means are then utilized for causing the drug to localize in the cancer tumor. Nevertheless, significant portions of the drug still circulate through the blood stream, thereby

affecting noncancerous tissue, producing undesirable side effects, and limiting the dosages of the drug which can be safely administered.

Accordingly, there is a need in the art for a method and apparatus for delivering a drug selectively and locally to internal body tissue, without significantly affecting other tissue. There is a further need for such a system and method for the localized treatment of internal body tissues to limit restenosis following PTCA, to treat cancerous tumors or the like, or to treat various other medical situations.

## SUMMARY OF THE INVENTION

In accordance with the present invention, an apparatus and method is provided for delivering a drug or combination of drugs selectively and locally to an internal body tissue. More specifically, the invention involves an apparatus and method for delivering a drug or combination of drugs substantially transversely to the longitudinal axis of a body passageway such as blood vessel, urinary tract, intestinal tract, kidney ducts, etc., in order to treat a localized region of the passageway itself or to treat a localized region or tissue located adjacent to the passageway. The invention also involves an apparatus and method for delivering a drug or combination of drugs directly to an internal body tissue.

In the preferred embodiment, the apparatus includes a flexible member adapted for insertion into the body passageway or tissue and a drug delivery means connected with the flexible member for delivering the drug to or through a local area of the passageway wall or tissue. The drug delivery means includes a drug transport wall for engagement with a local area of the passageway wall or tissue and a drug chamber for receiving a selected drug. The chamber is defined in part by the drug transport wall which is constructed of

a material that permits selective transport of a drug therethrough, i.e. constructed of at least perforated, permeable or semipermeable material through which the drug is intended to selectively pass, that is, selectively permeable.

Preferably, in one embodiment the drug delivery means includes a modified catheter balloon or bag. The modified catheter balloon contacts the inner surface of the passageway wall and defines the localized passageway area to or through which the drug is to be administered.

In a second embodiment, to deliver a drug to an internal body tissue, the preferred apparatus includes a catheter body connected with a drug delivery component having a drug delivery passageway, an outer wall and a selectively permeable outer membrane portion.

The method of the present invention involves positioning a drug delivery member such as a modified catheter balloon in a body passageway such that the delivery member or balloon traverses the desired localized area of administration. The balloon is then inflated or otherwise expanded to define a local drug administration zone in the passageway. This involves introducing a selected drug into or through the localized zone or passageway. The method for delivering a drug to an internal body tissue involves positioning the drug delivery component at a target area of an internal body tissue and transporting the selected drug across the selectively permeable outer membrane of the drug delivery component and into the internal body tissue target area.

A specific application of the apparatus and method of the present invention involves the treatment of a dilated vessel to prevent restenosis following PTCA. In the preferred embodiment and procedure, this involves administering a fixation solution or fixative to the passageway walls in the localized area.

Administration of the fixative in this area renders the dilated artery biologically inert, resulting in a certain degree of hardening and the production of a biological stent. A further specific application of the apparatus and method of the present invention is in the treatment of cancerous tumors or other internal body tissue adjacent to a body passageway, such as the prostrate.

Accordingly, it is an object of the present invention to provide a drug delivery apparatus and method for delivering a drug or combination of drugs locally to internal body tissue.

Another object of the present invention is to provide an apparatus and method for delivering a drug or combination of drugs locally to internal body tissue through selected portions of a body passageway wall.

Another object of the present invention is to provide an apparatus and method for treatment of dilated vessels to prevent or limit restenosis following PTCA procedures.

Another object of the present invention is to provide an apparatus and method for local treatment of cancerous tumors or other internal body tissues.

A still further object of the present invention is to provide a modified dilation catheter having localized drug delivery capabilities for limiting restenosis and for the delivery of drugs locally to internal body tissues.

These and other objects of the present invention will become apparent with reference to the drawings, the description of the preferred embodiment and method and the appended claims.

## DESCRIPTION OF THE DRAWINGS

Figure 1 is a fragmentary view, partially in section, of a first embodiment of the drug delivery apparatus of the present invention in the form of a

catheter with a modified dilatation balloon in its deflated state.

Figure 2 is a fragmentary view, partially in section, of the drug delivery apparatus of Figure 1 positioned in a blood vessel with the dilatation balloon in its inflated state.

Figure 3 is a fragmentary view, partially in section, of an alternate design of a drug delivery apparatus in the form of a double balloon catheter positioned in a blood vessel.

Figure 4 is a fragmentary view, partially in section, of a further embodiment of the drug delivery apparatus of the present invention positioned in a blood vessel.

Figure 5 is an enlarged fragmentary view, partially in section, of the embodiment of Figure 4.

Figure 6 is a fragmentary view, partially in section, of the drug delivery apparatus of the present invention positioned in a blood vessel and embodying iontophoresis means to transport the drug across the balloon surface.

Figure 7 is a fragmentary view, partially in section, of a still further alternate design of a drug delivery apparatus in accordance with the present invention positioned in a blood vessel and illustrating alternate means for defining the local area for drug delivery.

Figure 8 is a fragmentary view, partially in section, of the drug delivery apparatus of the present invention positioned in a blood vessel, embodying iontophoresis to transport a drug across the balloon surface where the solution containing the drug is circulated through the balloon.

Figure 9 is a fragmentary view, partially in section, of a still further alternate design of a drug delivery apparatus in accordance with the present invention in the form of a catheter with a drug delivery

component to transport a drug to an internal body tissue.

Figure 10 is a fragmentary view, partially in section, of a still further alternate design of the drug delivery apparatus shown in Figure 9 for drug transport to an internal body tissue in which a selectively permeable membrane forms a portion of the outer wall of the drug delivery component.

## DESCRIPTION OF THE PREFERRED AND ALTERNATE EMBODIMENTS AND METHODS

Figures 1-8 illustrate the preferred and various alternate designs of the drug delivery apparatus in accordance with the present invention. In general, this apparatus provides a means and a system for delivering a drug or combination of drugs to or through a localized area of a passageway in order to treat the localized area of the passageway or to treat a localized area of tissue located adjacent to the passageway, with minimal, if any, undesirable effect on other body tissue. The drug delivery apparatus includes a modified catheter balloon design which can be used in conjunction with existing catheters. The term catheter as used in the present application is intended to broadly include any medical device designed for insertion into a body passageway to permit injection or withdrawal of fluids, to keep a passage open or for any other purpose. It is contemplated that the drug delivery apparatus of the present invention has applicability for use with any body passageways including, among others, blood vessels, urinary tract, intestinal tract, kidney ducts, wind pipe and the like.

Figures 9 and 10 illustrate further alternate designs of the drug delivery apparatus in accordance with the present invention. The embodiments shown in these figures are specifically designed to provide means and a system for delivering a drug or combination of drugs to a localized area of an internal body tissue.

For this purpose the apparatus includes a flexible catheter connected to a drug delivery component having a fluid delivery passageway with an outer wall and selectively permeable outer membrane portion through which a drug passes to an internal body tissue target area.

In particular, catheters are commonly used in percutaneous transluminal coronary angioplasty (PTCA) procedures to dilate stenosed blood vessels or arteries. These include so-called over the wire catheters of the type illustrated generally in U.S. Patent No. 4,323,071, the disclosure of which is incorporated herein by reference, and so-called fixed wire catheters of the type illustrated in U.S. Patent No. 4,582,181, the disclosure of which is incorporated herein by reference. These catheters may be modified according to the present invention.

In order to illustrate the method aspect of treating a localized area of a passageway, the specific application of the present invention to the reduction of restenosis will be described. Following a discussion of reducing restenosis, the present invention will be applied to the treatment of tumors.

As indicated in the discussion earlier, percutaneous transluminal coronary angioplasty (PTCA) has been demonstrated to be a highly successful procedure for the treatment of atherosclerosis and other diseases and conditions tending to narrow arterial passageways. In normal PTCA procedure, a dilatation catheter is advanced along an artery to the desired position in the arterial system. The catheter includes an inflatable balloon at its distal end and means for inflating the balloon. When the balloon is positioned so that it traverses or crosses a stenotic lesion, the balloon is inflated to compress the atherosclerosis and expand the artery in a direction generally perpendicular to its wall, thereby dilating the lumen of the artery.

Following this procedure, the balloon is deflated and the catheter withdrawn.

Despite the generally excellent success of PTCA, relatively high restenosis (the tendency of the dilated artery to close) rates continue to be a major problem. Restenosis can include abrupt reclosure resulting from thrombotic occlusion, vasospasms, or the like as well as the more common occurrence of gradual restenosis.

In accordance with the method of the present invention, a drug referred to as a fixation solution or a fixative is delivered locally to the dilated portion of the vessel to render the vessel wall biologically inert to prevent or reduce reactions that lead to reclosure. Because of the nature of the fixative and its ability to inactivate living cells and render the tissue in which it comes into contact biologically inert, it is essential that such fixative be exposed only to that portion of the arterial wall which has been dilated. A preferred method and apparatus for delivering the fixative locally to the dilated vessel is via a modified catheter balloon. The balloon catheter that delivers the drug may be the same balloon catheter that dilates the vessel, thus combining both functions in one catheter. Alternatively, a vessel may be dilated first with a catheter designed specifically for dilation, followed by insertion of a second catheter for drug delivery. One embodiment of a modified balloon useful for either approach is illustrated in Figures 1 and 2.

Figure 1 illustrates the distal end of a catheter with the modified catheter balloon in its deflated state. The catheter includes a guide wire 10, an elongated, flexible catheter body 11, a drug delivery means in the form of a balloon 12 positioned on the catheter body 11 near its distal end and a balloon lumen or passageway 14 extending along the catheter body 11 to

the proximal end of the body 11 for inflation and deflation of the balloon 12. In the preferred embodiment, the material from which the balloon 12 is constructed is a permeable or semipermeable material which is effective to permit transport or passage of the fixative or other drug across the balloon surface as a result of an appropriate driving force.

The structure of the guide wire 10, the catheter body 11 and the balloon lumen 14 is similar to conventional catheter design which is known in the art and an example of which is shown in U.S. Patent No. 4,323,071. The balloon 12 of Figure 1, however, is distinguishable from conventional catheter balloons in that the balloon 12 is constructed from a material which selectively permits the transport or passage of a drug or fixative across the balloon surface.

Figure 2 illustrates the drug delivery apparatus of Figure 1 with the balloon 12 in its inflated state within an arterial vessel in which the vessel walls are indicated by the reference numeral 15. During PTCA procedures, the guide wire 10 is first inserted into the selected artery to a point past the stenotic lesion. The dilatation catheter including the catheter body 11 and balloon 12 is then advanced along the guide wire 10 to the desired position in the arterial system in which the balloon portion 12 traverses or crosses the stenotic lesion. The balloon 12 is then inflated by introducing an inflation fluid through the balloon lumen 14 into the interior chamber 13 of the balloon 12. During inflation, the outer surfaces of the balloon 12 press outwardly against the inner surfaces of the vessel wall 15 to expand or dilate the vessel in the area of the stenotic lesion. In accordance with the present invention, and in particular in accordance with the embodiment of Figures 1 and 2, the balloon 12 is inflated by introducing a fixation or other drug solution through the balloon lumen 14 and

into the interior of the balloon portion 12. As a result of at least a portion of the balloon 12 being constructed of a permeable or semipermeable membrane, the pressure of the drug or fixative within the balloon 12 causes the drug or fixative to be transported across the walls of the balloon 12 into direct contact with the vessel wall 15.

Alternatively, the catheter of Figures 1 and 2 may be used after dilation has already been effected by another catheter earlier used to dilate the vessel. In this case, the fixative delivering catheter is expandable in order to bring the balloon 12 in contact with the vessel wall for drug delivery.

In the preferred embodiment, it is contemplated that the material from which the balloon of Figures 1 and 2 is constructed will be a semipermeable membrane material such as dialysis membrane (Cordis Dow 3500-cellulose acetate and Cordis Dow cellulose regenerated from acetate; anisotropic polyacrylonitrile available from Ashaki Medical). It is contemplated, however, that various other permeable or semipermeable materials may also be used including, without limitation, cellulose, cellulose acetate, polyvinyl chloride, polysulfone, polyacrylonitrile, silicon, polyurethanes, natural and synthetic elastomers. Also, it is contemplated that the particular material from which the balloon 12 is constructed will depend to some extent on the specific composition of the fixative or other drug to be delivered as well as the transport or driving pressures which are developed within the balloon chamber 13. In the structure of Figures 1 and 2, the preferred material from which the balloon 12 is constructed is an elastomer and the pressure generated within the balloon chamber 13 to result in transport of the drug or fixation solution across the balloon walls is between about 1 and about 90 psi.

A fixative or fixation agent is a compound or composition known in the art as a fixative. A fixative functions, among other things, to kill, penetrate and harden fresh tissues, to set the tissues so that they will not be altered by subsequent biological or other processing and to render the cell constituents insoluble. Fixatives are commonly used for stabilizing and fixing tissue at the moment such tissue is exposed to the fixative so that histologic slides of the tissue can be prepared or the tissue can otherwise be preserved for examination.

The particular fixative or fixation solution as contemplated by the present invention must be able to rapidly penetrate the plaque and vascular tissue of the vessel in the area of the stenotic lesion. It should quickly kill or otherwise preserve the tissue, while hardening the vascular structure. Such fixation maintains the vessel in an "opened" or dilated condition and prevents or substantially reduces reclosure due to vasospasm or other abrupt reclosure mechanisms. Such fixation also retards or stops the biological processes which lead to gradual restenosis. The preferred fixative should also have rapid, specific action in high concentrations, while generally nontoxic actions in lower concentrations.

Current fixatives include:

Glutaraldehyde
Formaldehyde
Acetaldehyde
Ethyl Alcohol

In accordance with the preferred apparatus and method of the present invention, the fixation solution may contain compounds or drugs to reduce vasomotor action (calcium antagonists) and inflammatory response (steroids) as well as antiplatelet inhibitors and anticoagulants. Calcium antagonists may include materials such as diltiazem HCl, nifedipine and

verapamil HCl, steroids such as dexamethasone and specific nonsteroidal anti-inflammatory agents. Antiplatelet inhibitors and anticoagulants may include materials such as heparin, dipyridamole, papaverine HCl, ethaverine HCl and prostacyclin inhibitors. It is also contemplated that agents inhibiting smooth muscle and fibroblast proliferation which is a primary factor in restenosis, or agents tending to reduce collagen response to injury could also be used either with or without the fixation agent. Fibroblast proliferation inhibiting agents may also be included as well as collagen response reduction agents. It is still further contemplated that compounds which reduce platelet aggregation may also be beneficial to administer with a fixation solution. Also, antitumor or other antimitogenic drugs can be used for prevention of restenosis.

The formulation for the preferred fixative solution in accordance with the present invention is 2% by volume glutaraldehyde in normal saline solution. A second preferred fixative solution includes formalin at a concentration of about 10% in a normal saline solution.

Figure 3 illustrates an alternate design for the catheter balloon utilizing a dual or concentric balloon concept. Specifically, a first, inner balloon 16 is provided which is constructed from a material such as polyethylene which is impermeable. The balloon 16 includes an inner chamber 17 which is connected through the inner balloon lumen 20 to the proximal end of the catheter. The embodiment of Figure 3 is also provided with a second or outer balloon 18 which is generally concentric to the balloon 16 and which extends completely around the balloon 16. This outer balloon 18 is constructed from a permeable or semipermeable material similar to that of the balloon 12 of Figures 1 and 2 and includes a balloon chamber 19 formed between

the outer surface of the balloon 16 and the inner surface of the balloon 18. The chamber 19 is connected through the outer balloon lumen 21 to the proximal end of the catheter. When using the structure of Figure 3, the inflated balloon portion is first inserted into the arterial passageway until it bridges a stenotic lesion in the manner described above and known in the art. During the balloon inflation process contemplated by the structure of Figure 3, the chamber 19 of the outer balloon 18 is first filled with the drug or fixative through the lumen 21. This is followed by inflation of the chamber 17 of the inner balloon 16 with standard inflation medium provided through the lumen 20. As a result of inflation of this inner balloon 16, sufficient pressure is developed against the chamber 19 to provide the pressure required to drive or transport the fixative through the outer balloon wall 18.

Although the structure of Figure 3 shows a separate lumen 21 for filling the outer balloon chamber 19, it is contemplated that the lumen 21 could be eliminated and the chamber 19 prefilled with the fixative or other drugs. In such a structure, the pressure causing transport of the fixation solution across the balloon wall 18 would be provided solely by inflation of the inner balloon 16.

A further modified balloon structure is illustrated in Figures 4 and 5. The embodiment of Figures 4 and 5 is similar to the embodiment of Figures 1 and 2 except that the balloon structure in Figures 4 and 5 is constructed of two different materials. It will be appreciated that as an alternative, the balloon structure in Figures 4 and 5 can be constructed of a permeable material that is modified to have one or more impermeable portions (i.e., increased thickness). In Figures 4 and 5, the balloon end portions 24 are a totally impermeable material, while an intermediate portion 22 of the balloon positioned between the end

portions 24 is a permeable or semipermeable material. The purpose of this structure is to enable more specific and precise delivery of the fixation solution or other drug desired to be administered. For example, with the end portions 24 constructed of an impermeable material, inadvertent passage of the fixation solution or other drug through such end portions is prevented. In the structure of Figures 4 and 5, the impermeable material may be polyethylene, or polyester or an area of permeable material that is functionally impermeable because of increased thickness or other modification that results in a non-permeable region or regions.

In the structure of Figures 4 and 5, the fixative or other drug is permitted to pass from the interior chamber 25 of the balloon only through the balloon portion 22. The material from which the portion 22 is constructed is similar to the material from which the balloon 12 of Figures 1 and 2 and the outer balloon 18 of Figure 3 is constructed.

As a further alternative, the catheters of Figures 1-5 may be coated on their outer surfaces, or at least that portion of the outer surface which is to contact the vessel wall, with hydrogel to improve contact with the vessel wall. The hydrogel so described may also contain the fixative or drug to be delivered where solution passing from the catheter through the hydrogel will dissolve the fixative or drug and transport the fixative or drug to the vessel wall. As a further alternative, drug impregnated hydrogel may be coated on the inside wall of a catheter for similar drug delivery as solution passes through the hydrogel and catheter wall.

In the embodiments of Figures 1-5, pressure is the force which is utilized to transport the fixative or other drug from the interior balloon chamber across the balloon wall to the vessel wall. However, it is contemplated that other transport forces could also be

used either with or in lieu of pressure to enhance or otherwise control the speed of drug transport. For example, one method could utilize DMSO as a carrier to transport a fixative or drug through the vessel wall. Other fluid diffusion enhancement compositions include propylene glycol, azone and ionic or non-ionic surfactants. Another method could utilize iontophoresis technology. Such technology is known in the art and is commonly used in transdermal drug delivery. In general, iontophoresis technology uses an electrical potential or current across a semipermeable barrier to drive ionic fixatives or drugs or drag nonionic fixatives or drugs in an ionic solution. Iontophoresis can be useful in certain applications of the present invention because it facilitates both transport of the fixative or drug across the selectively permeable membrane and enhances tissue penetration. In the application of iontophoresis, two electrodes, one on each side of the barrier, are utilized to develop the required potential or current flow. In particular, one electrode may be located inside of the catheter in opposed relation to the drug delivery wall of the catheter while the other electrode may be located at a remote site on a patient's skin. In addition to direct current, other wave forms may be utilized (e.g., a series of rectangular waves producing a frequency of 100 Hz or greater).

The embodiment of Figure 6 illustrates a structure utilizing iontophoresis to assist in driving the fixative or other drug across the balloon wall 26 and into contact with the vessel walls 15. In Figure 6, one electrode 28, the catheter electrode, is located on or within the catheter body 11 while the other electrode 31, the body surface electrode, is located on the body surface or within the body of the patient. In order for iontophoresis techniques to be utilized, the fixative or other drug within the balloon chamber 27 requires specific characteristics. Ideally, such fixative or

other drug should have an ionic nature or have other ionic molecules bound to the fixative or the active components of the drug to promote the iontophoretic movement or transport across the balloon wall 26. An electrical current for the iontophoretic process of Figure 6 is produced between the electrodes 28 and 31 by an external power source 30 through the electrical leads 29 and 33, respectively.

During operation of the device of Figure 6, the balloon 26 is first positioned across the stenotic lesion in the manner described above. The balloon interior 27 is then inflated with the fixative through the lumen 23. This is followed by activating the power supply 30, thereby creating a current between the electrode 28 and the electrode 31 which passes through the balloon wall 26. This current drives or drags the fixative or other drug within the chamber 27 across the wall and into contact with the surrounding vessel wall 15 and vascular tissue. The structure of Figure 6 utilizes both pressure and iontophoresis as the driving force, although, it is contemplated that iontophoresis could be utilized alone.

It is contemplated that iontophoresis by itself, or in combination with a solvent like DMSO as a carrier, could yield fixative or drug transport into or through a vessel wall at pressures less than about 20 mm Hg above normal ambient vessel wall pressure and preferably at less than about 5 mm Hg, thereby avoiding substantial damage to the vessel wall known to occur at higher pressures.

The polarity of the iontophoretic electrodes may be reversed in order to recapture excess fixative or drug delivered to or through the vessel wall.

A further embodiment of a drug delivery apparatus in accordance with the present invention is illustrated in Figure 7. Figure 7 illustrates a further modified catheter balloon design which includes a double

lobed balloon having a pair of spaced inflatable lobes 34 and 35. These lobes 34 and 35 are connected to a common interior chamber 38 which is in turn connected to a balloon lumen 40 extending to the proximal end of the catheter. The structure of Figure 7 also includes a drug supply lumen 39 extending to the proximal end of the catheter and in communication with an area 36 formed between the balloon lobes 34 and 35.

During use of the structure of Figure 7, the balloon is introduced into the vessel as described above in its deflated condition. After it has been positioned in that portion 41 of the vessel to which a drug is desired to be administered, the balloon lobes 34 and 35 are inflated by introducing an inflation medium through the lumen 40 and into the interior chamber 38. This inflation causes the lobes 34 and 35 to expand as illustrated so that their outer peripheral portions engage the inner surfaces of the vessel walls 15. Such engagement defines a drug treatment zone between the lobes 34 and 35. A desired drug is then introduced into the chamber 36 through the lumen 39 so that such drug is in direct contact with the vessel wall 15.

A still further embodiment of a drug delivery apparatus in accordance with the present invention is illustrated in Figure 8. This embodiment would be useful for delivery of a fixative, but would be particularly useful for delivery of antitumor drugs. Figure 8 illustrates a modified catheter balloon design having a balloon 44 positioned on catheter body 11 near its distal end. One delivery lumen or passageway 45 extends along the catheter body 11 to the proximal end of the body 11 and a recovery lumen or passageway 46 also extends along the catheter body 11 to the proximal end, said delivery lumen 45 and recovery lumen 46 useful for circulating solution containing a fixative or drug to and from the catheter balloon. The outlets 47 and 48 may be positioned in the balloon to achieve optimal

circulation within the balloon. This embodiment may be most useful in delivering antitumor drugs which are difficult to dissolve where the delivery solution accordingly is very low in concentration of the antitumor drug and easily depleted of such drug. Circulation in this case would be important for continuous delivery over long time periods. This embodiment may be combined with reversing the polarity of the electrodes of iontophoresis in order to remove excess drug after treatment.

In addition to the embodiment of Figure 8, the embodiments of Figures 1-7, illustrated principally for delivery of a fixative to a vessel wall, can also be useful in delivering any drug to or through a vessel wall. In particular, each of the above embodiments of Figures 1-8 may be used for such drug delivery and each embodiment would be useful for delivering an antitumor, antihyperplastic or other agent through a vessel wall to a nearby or adjacent tumor or other internal body tissue. For example, a drug may be delivered substantially transversely to the longitudinal axis of a body passageway in order to treat a localized region of tissue located adjacent to the passageway. This is illustrated by using iontophoresis to drive, or DMSO to carry, through the passageway wall and into the surrounding or adjacent tissue. Any of the foregoing alternative embodiments of the apparatus as seen in Figures 1-8 may also be used for such drug delivery.

In particular, tumors may be treated by delivering certain drugs through blood vessels or the intestinal tract or whatever to adjacent tumor sites. Without limiting the invention, the following table discloses certain drugs well suited for such delivery to the described tumors. Further, the present invention is well suited to delivery of sensitizer and immunomodulator drugs.

TABLE 1

| Drug | Major Indications |
|---|---|
| Mechlorethamine | Hodgkin's and non-Hodgkin's lymphomas, topical solution in mycosis fungoides, sclerosing agent for malignant pleural effusions |
| Cyclophosphamide | Hodgkin's and non-Hodgkin's lymphoma, multiple myeloma, neuroblastoma, Ewing's sarcoma, small cell carcinoma of lung, breast cancer, ovarian cancer, testicular cancer |
| Chlorambucil (Leukeran) | Chronic lymphocytic leukemia, Hodgkin's and non-Hodgkin's lymphomas, carcinomas of the breast and ovary, choriocarcinoma |
| Melphalan (Alkeran) | Multiple myeloma, polycythemia vera, carcinomas of the ovary and breast |
| Busulfan (Myleran) | Chronic myelogenous leukemia, polycythemia vera |
| Dacarbazine (DTIC) | Hodgkin's and non-Hodgkin's lymphomas, sarcomas, melanoma |
| Cisplatin (Platinol) | Testicular, ovarian, head and neck, and gastric carcinomas |
| Methotrexate | Acute lymphoblastic leukemia, carcinomas of the head and neck, ovary, breast, testis, small cell carcinoma of the lung, choriocarcinoma, osteosarcoma, mycosis fungoides |
| 6-Mercaptopurine 6-MP | Acute leukemias |
| Thioguanin 6-TG | Acute leukemias |
| 5-Fluorouacil (5-FU) | Carcinomas of the gastrointestinal tract, breast, and ovary |

| | |
|---|---|
| Vinblastine (Velban) | Hodgkin's and non-Hodgkin's lymphomas, acute lymphoblastic leukemia, carcinomas of the breast and testes, Wilms' tumor, neuroblastoma |
| Dactinomycin | Wilms' tumor, neuroblastoma, embryonal rhabdomyosarcoma, Ewing's sarcoma, choriocarcinoma, carcinoma of the testes, carcinoid tumors |
| Doxorubicin | Acute leukemias; sarcomas; Hodgkin's and non-Hodgkin's lymphomas; carcinomas of the breast, ovary, head, neck and thyroid; Ewing's sarcoma; small cell carcinoma of the lung |
| Daunorubicin | Acute leukemias |
| Mitomycin (Mutamycin) | Carcinomas of gastrointestinal tract, breast, head, and neck |
| Diethylstilbestrol | Carcinomas of the prostate and breast |
| Retinoic acid and analogues | Dermal hyperplasia |

For the purposes of primary or adjuvant treatment or other circumstances where drug delivery to a specific local or regional internal body tissue site such as a solid tumor, abscess, regional lymph nodes or the like is desired, further embodiments of the present invention as shown in Figures 9 and 10 are preferred. The tissue delivery system shown in Figures 9 and 10 includes a drug delivery apparatus 60 that is positioned into a specific tissue, such as a tumor.

As seen in Figure 9, a preferred drug delivery apparatus 60 for treating an internal body tissue includes a flexible catheter body 11' and drug delivery component 69 having a drug delivery passageway 64 including an outer wall 66, and an outer selectively permeable membrane portion 67 proximate the distal end 61. The outer selectively permeable membrane 67

prevents escape of the drug from passageway 64 and drug delivery component 69 until the desired time of delivery. It is to be understood that the selectively permeable membrane 67 also controls the rate of release of the drug. The drug is then driven across membrane 67 by a pressure gradient and/or voltage gradient (iontophoresis), or other force. In a preferred embodiment for iontophoresis, selectively permeable membrane 67 material is a dialysis membrane, nylon, or polysulfone. Drug delivery passageway 64 of drug delivery component 69 extends from proximal end 63 to distal end 61 of apparatus 60. As seen in Figures 9 and 10, preferably, drug delivery component 69 is coaxially aligned about catheter body 11'. It is to be appreciated that drug delivery component 69 can be connected with catheter body 11' by a variety of adjacent configurations by one of skill in the art.

The embodiment seen in Figure 9 illustrates selectively permeable membrane 67 affixed to a portion of outer wall 66 having at least one opening 68 that facilitate fluid transfer through outer wall 66 of passageway 64 to membrane 67. Alternatively, as seen in Figure 10, selectively permeable membrane 67 can form an integral portion of outer wall 66. As seen in both Figures 9 and 10, to position apparatus 60 over the shaft of an introducer such as a probe, needle or trocar (not shown) introducer lumen 65 through the center of catheter body 11' is provided. It is to be understood that apparatus 60 can range in size from very large (trocar) to very small (tenths of mm), depending on the type and location of internal body tissue to be treated.

The embodiments of apparatus 60 in Figures 9 and 10 utilize iontophoresis to assist in driving the drug across selectively permeable membrane 67. To deliver a drug to a target area of an internal body tissue, iontophoresis is preferred because it facilitates both transport of a fixative or drug across

the selectively permeable membrane 62 and enhances tissue penetration. If iontophoresis is used, then similarly to the structure seen in Figure 6, one electrode 28' with lead wire 29 (Figure 9); 29' (Figure 10), the catheter electrode, is located on or within catheter body 11', while the other electrode (31) is located on the body surface of the patient. The other electrode may in certain applications be positioned at other regions of the patient including appropriate internal areas.

As an alternative to the embodiments seen in Figures 9 and 10 using iontophoresis to deliver a drug to a target area, the tissue delivery system of the present invention can use pressure as the force to transport a drug to a target area of internal body tissue. For this purpose, regulation means known to those skilled in the art (e.g., compressor, regulator or syringe pump) can be used to apply sufficient pressure to deliver the drug to the target area. Those of skill in the art will recognize that the pressure applied will be adequate to drive the drug across selectively permeable membrane 67 to the target area without further traumatization of the internal body tissue to be treated.

As described earlier with respect to the embodiments shown in Figures 1-5, other transport forces can be used either with or in lieu of pressure to enhance or otherwise control the speed of drug transport to an internal body tissue according to the present invention. For example, one of skill in the art could utilize DMSO, propylene glycol, azone, or various surfactants as a carrier to transport the drug through selectively permeable membrane portion 67 to the target area of internal body tissue.

For treatment of an internal body tissue according to the present invention, the introducer (not shown) is placed into the target area, which may be a

tumor or the like, after identification of the position of the lesion mechanically, radiographically, thermally, ultrasonically, or through some other like methodology. The trocar/probe can be designed for steerability to facilitate positioning into the tumor. This can be accomplished by simply placing a bend in the trocar or by other mechanical design techniques known to those skilled in the art.

The active apparatus 60 is then passed through or over the introducing element directly over the inducer or through the void left in the intervening tissue by the withdrawal of the introducer. After apparatus 60 is in place, as confirmed by one of the foregoing methods, the active compound is delivered through passageway 64 into drug compartment 69 and across membrane 67 into the local or regional tissue. Using an embodiment of apparatus 60 of the type seen in of Figures 9 or 10, the delivery is accomplished iontophoretically. The active compounds delivered to an internal body tissue using apparatus 60 include, but are not limited to, antitumor agents such as the vinca alkaloids, anthracycline antibiotics, platinum analogs, antimetabolites (e.g., methotrexate); antibiotics; sensitizers or other compounds such as those exemplified in Table 1, herein.

The advantage of this method is that it allows delivery of the drug into the interstitial fluid and into the cells of the target area themselves even if the vasculature of the area is severely compromised and the cells do not preferentially take up the drug. These phenomena are a well-known attribute of solid tumors and constitute one of the most significant barriers to the treatment of such cancers.

In addition to delivery of antitumor agents to internal tissues, the usefulness of the present apparatus and method for the treatment of other diseases

of internal tissue will be appreciated by those skilled in the art.

In the case of both the vascular delivery embodiment (Figs. 1-8) and tissue delivery embodiment (Figs. 9 and 10) described herein phonophoresis (sometimes referred to as sonophoresis) can be used as an alternative transport force. Phonophoresis is the use of ultrasonic or high frequency sound waves to transport drugs. As used in the present invention, phonophoresis can be used to transport drugs through the selectively permeable membrane and into the surrounding tissue. For certain therapeutic procedures, phonophoresis has several advantages over iontophoresis, including the ability to achieve greater penetration and to more readily deliver an entire molecule, rather than an ionically charged form of the drug. All prior applications of phonophoresis have been limited to transdermal delivery of drugs. It has primarily been used to deliver anti-inflammatory agents and local anesthetics through the skin in treating epicondylitis, tendonitis, bursitis and osteoarthritis. It is also well-suited for driving fixatives or drugs across the catheter of this invention to localized body passageways or internal tissues because it facilitates both transport of a fixative or drug across the selectively permeable membrane and enhances tissue penetration. In addition to drug delivery, ultrasound may be advantageously used with the catheter of the present invention based on the increased tissue temperature, tissue hyperemia and increased capillary permeability associated with ultrasound. These actions can enhance intra-tissue drug transport and cellular uptake as well as cause vasodilation/relaxation which may be beneficial in vascular drug applications using catheter embodiments of the type described herein.

When phonophoresis is used with either the vascular delivery embodiment or tissue delivery

embodiment of the catheter of the present invention, the cathode electrode 28 of Figure 6 is replaced by an ultrasonic piezoelectric transducer (barium titanate, lead zirconate titanate, or the like), which is connected to the external power source 30 and placed within the catheter opposite the drug delivery wall. The ultrasonic transducer is activated to enhance transport of drugs or fixatives into tissue surrounding the catheter. The diffusion rate of drugs delivered by phonophoresis depends upon the intensity and frequency of the ultrasonic field. Prior transdermal applications of phonophoresis use intensities of .1 to 6 watts/cm and involve direct correlation between the amount of drug diffused and the intensity of the ultrasonic field. Internal applications (not requiring transdermal delivery) of phonophoresis with the catheter embodiments of the present invention are envisioned to require significantly less intensity to deliver an equal amount of drug. Various frequencies can be used. A frequency of about 1 MHz has been optimally used in transdermal phonophoresis. It is envisioned that approximately 1 MHz or less can be used for internal applications of the catheter embodiments described herein.

Although the description of the preferred embodiment and method have been quite specific, it is contemplated that various modifications could be made without deviating from the spirit of the present invention. For example, a fixative or other drugs may be delivered to the walls of an artery, perhaps already dilated, through a catheter balloon wall which is perforated. An antitumor drug may be similarly delivered through a perforated balloon wall for delivery through a vessel wall to an adjacent tumor. Such perforated balloon may be combined with iontophoresis or phonophoresis to drive the drug into or through the vessel wall. Further, a drug can be delivered to an internal body tissue through a selectively permeable

membrane portion of a drug delivery component connected to a catheter. When the catheter and connected drug delivery component are directed to a body tissue target area over a rigid probe or trocar the amount of drug delivered to the tissue to be treated is maximized and the leakage of drug back along the catheter and away from the target area is minimized. Accordingly, it is intended that the scope of the present invention be dictated by the appended claims, rather than by the description of the preferred embodiment and method.

WE CLAIM:

1. A drug delivery apparatus for local delivery of a drug to internal body tissue comprising:
   (a) an elongated member for insertion into a target area of internal tissue; and
   (b) a drug delivery means connected with said member for delivering a drug to said target area, said drug delivery means having a fluid delivery passageway, an outer wall and a selectively permeable outer membrane portion.

2. The drug delivery apparatus of claim 1 wherein said drug delivery means further comprises conduit means providing fluid transfer through said outer wall of said passageway to said membrane portion.

3. The drug delivery apparatus of claim 1 wherein said drug delivery apparatus has a distal end and a proximal end with said selectively permeable membrane portion forming a portion of said outer wall proximate said distal end.

4. The drug delivery apparatus of claim 1 wherein said elongated member defines an introducer cavity.

5. The drug delivery apparatus of claim 1 wherein said drug delivery means is coaxially aligned about and in contact with said elongated member.

6. The drug delivery apparatus of claim 1 wherein said apparatus further comprises drug delivery regulation means for drug delivery to said target area at a pressure sufficient to deliver said drug to said target without damaging tissue surrounding said target area.

7. The drug delivery apparatus of claim 1 further comprising an electrode means for iontophoretically assisting the transport of said drug across said selectively permeable outer membrane.

8. The drug delivery apparatus of claim 1 further comprising an ultrasonic transducer means for phonophoretically assisting the transport of said drug across said selectively permeable outer membrane.

9. The drug delivery apparatus of claim 1 including means for exerting pressure on the drug in said fluid delivery passageway to cause transport of said drug across said selectively permeable outer membrane.

10. A drug delivery apparatus having a distal end and a proximal end for local delivery of a drug to internal body tissue comprising:
    (a) a flexible catheter body and a drug delivery component connected to said catheter, said drug delivery component having a fluid delivery passageway, an outer wall and a selectively permeable outer membrane portion proximate said distal end of said drug delivery apparatus.

11. The drug delivery apparatus of claim 10 wherein said outer wall of said drug delivery component has one or more openings to provide fluid communication from said passageway to said outer membrane portion.

12. The drug delivery apparatus of claim 10 wherein said drug delivery component is coaxially aligned about said catheter body.

13. A drug delivery apparatus according to claim 10 wherein said catheter body includes an integral introducer.

14. A drug delivery apparatus according to claim 10 further comprising an electrode located in said catheter body.

15. A drug delivery apparatus according to claim 10 further comprising an ultrasonic transducer located in said catheter body.

16. A drug delivery apparatus for local delivery of a drug to internal body tissue comprising:
    (a) a flexible catheter body having proximal and distal ends and defining an introducer lumen therethrough;
    (b) a drug delivery component having a drug delivery passageway, an outer wall having an outer selectively permeable membrane portion proximate said distal end, said drug delivery component being coaxially aligned about and in contact with said catheter body, extending from said distal end to said proximal end.

17. A method of locally delivering a drug to internal body tissue comprising:
    (a) positioning a drug delivery component including a drug delivery passageway and a selectively permeable outer membrane portion at an internal body tissue target area; and
    (b) transporting a selected drug across said selectively permeable outer membrane and into said internal body tissue target area.

18. The method of claim 17 including transporting said selected drug across said drug transport wall by iontophoresis.

19. The method of claim 17 including transporting said selected drug across said drug transport wall by phonophoresis.

20. A drug delivery apparatus for local delivery of a drug to an internal body passageway having an elongated passageway wall comprising:
    (a) a flexible catheter having a distal end and a proximal end; and
    (b) drug delivery means connected to said catheter for delivery of a drug to said passageway wall, said drug delivery means including an expandable balloon near the distal end of the flexible catheter for engagement with said local area of said passageway wall, said balloon having an outer wall with a selectively permeable drug transport portion and a drug delivery chamber, and a drug delivery lumen extending from said drug delivery chamber to said proximal end of said flexible member.

21. The drug delivery apparatus of claim 20 wherein said apparatus further comprises drug delivery regulation means for drug delivery to said local area of said passageway wall at a pressure less than about 760 mm Hg above the ambient normal vessel wall pressure.

22. The drug delivery apparatus of claim 21 wherein said pressure is less than about 5 mm Hg above the ambient normal vessel wall pressure.

23. The drug delivery apparatus of claim 20 wherein said drug delivery means further includes a drug recovery lumen extending from said drug chamber to the proximal end of said flexible member.

24. The drug delivery apparatus of claim 20 wherein said transport wall includes a semipermeable membrane permitting the selective transport of said drug.

25. The drug delivery apparatus of claim 20 including means for exerting a pressure force on the drug within said drug chamber to cause the transport of said drug across said drug transport wall and into said local area of said passageway wall.

26. The drug delivery apparatus of claim 20 including means for iontophoretically assisting the transport of the drug within said drug delivery chamber across said drug transport wall.

27. The drug delivery apparatus of claim 20 including means for phonophoretically assisting the transport of the drug within said drug delivery chamber across said drug transport wall.

28. The drug delivery apparatus of claim 20 wherein said transport wall includes a perforated membrane permitting the selective transport of said drug.

29. The drug delivery apparatus of claim 28 including means for iontophoretically assisting the transport of the drug within said drug delivery chamber across said drug transport wall.

30. The drug delivery apparatus of claim 28 including means for phonophoretically assisting the transport

of the drug within said drug delivery chamber across said drug transport wall.

31. A method of locally delivering a drug to internal body tissue comprising:
(a) positioning a drug delivery member having a drug transport wall and a drug delivery chamber in a body passageway;
(b) engaging said body passageway with the drug transport wall of said drug delivery member to define a local drug delivery area of said body passageway; and
(c) transporting a selected drug from said drug delivery chamber, across said drug transport wall and into said local drug delivery area of said passageway.

32. The method of claim 31 wherein said drug is transported to said local drug delivery area of said passageway at a pressure less than about 760 mm Hg above the ambient normal passageway wall pressure.

33. The method of claim 31 wherein said pressure is less than about 5 mm Hg above the ambient normal passageway wall pressure.

34. The method of claim 31 wherein said drug delivery member includes an expandable balloon and said method includes engaging said body passageway by expanding said balloon.

35. The method of claim 31 including inflating said balloon with a solution containing said selected drug or combination of drugs.

36. The method of claim 31 including transporting said selected drug across said drug transport wall by exerting pressure on the selected drug in said drug delivery chamber.

37. The method of claim 31 including transporting said selected drug across said drug transport wall by iontophoresis.

38. The method of claim 31 including transporting said selected drug across said drug transport wall by phonophoresis.

39. The method of claim 31 including transporting said selected drug across said transport wall by diffusion of a carrier solution containing said drug.

40. The method of claim 39 wherein said carrier solution includes DMSO.

41. The method of claim 31 wherein the internal body tissue being treated is a vessel.

42. The method of claim 41 wherein said vessel is an arterial lumen.

43. The method of claim 31 wherein said body passageway is the urethra.

44. The method of claim 31 wherein the internal body tissue being treated is a tumor or tissue adjacent to said passageway.

45. A method of treating a vessel lumen comprising:
    (a) positioning a drug delivery member having a drug transport wall and a drug delivery chamber in a vessel lumen;
    (b) engaging said vessel lumen with the drug transport wall of said drug delivery member to define a local drug delivery area of said vessel lumen; and
    (c) transporting a therapeutic compound from said drug delivery chamber, across said drug transport wall and into said local drug delivery area of said vessel.

46. The method of claim 45 wherein said therapeutic compound is a fixative and the method further includes the step of exposing said vessel wall of said lumen to a fixative for a period of time effective to harden and fix the tissue portions of the vessel wall being treated.

47. The method of claim 46 wherein said fixative is glutaraldehyde.

48. The method of claim 46 wherein said fixative is formaldehyde.

FIG. 1

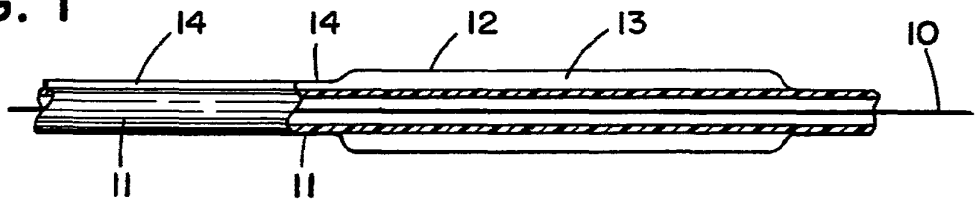



FIG. 2

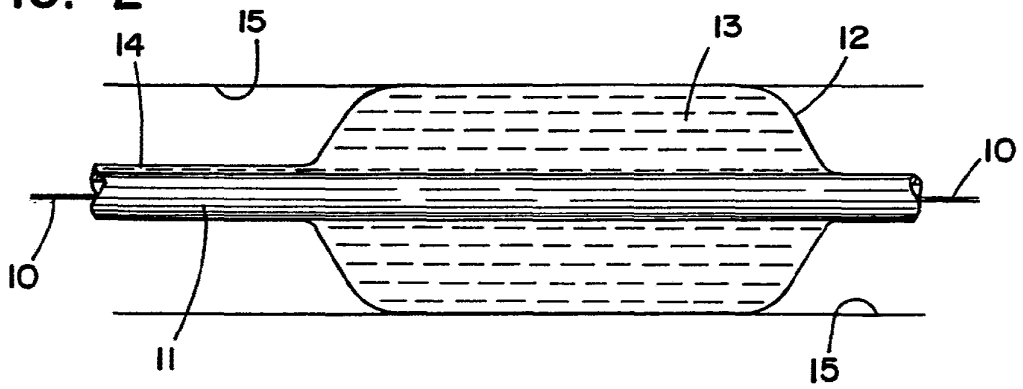



FIG. 3

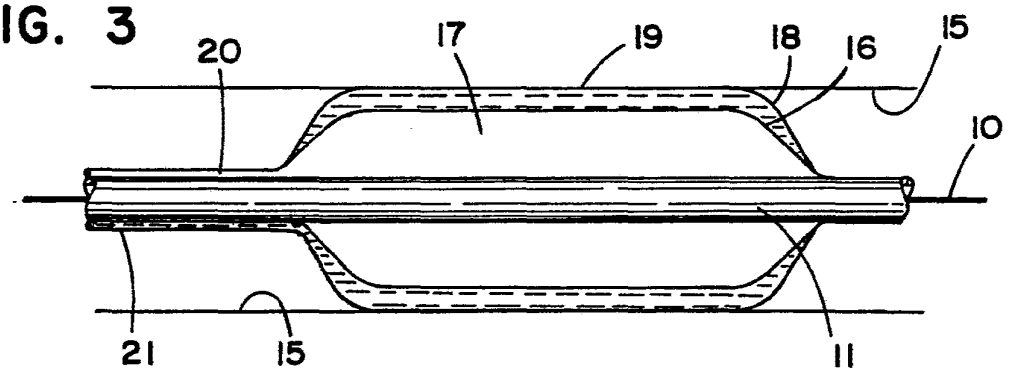
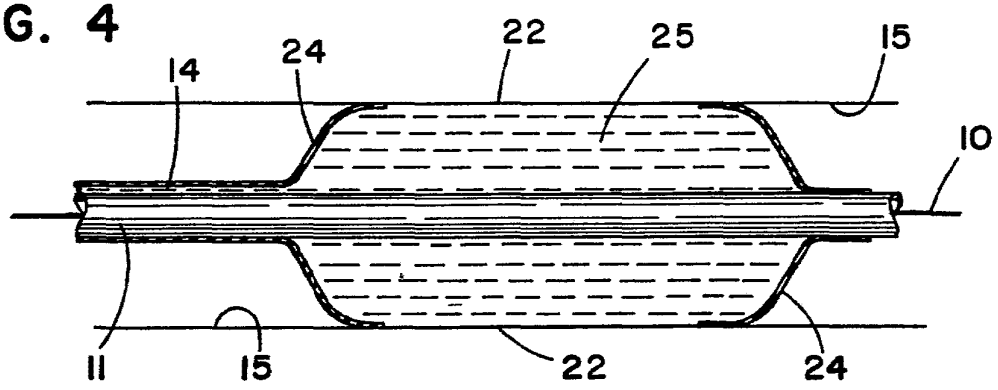



FIG. 4



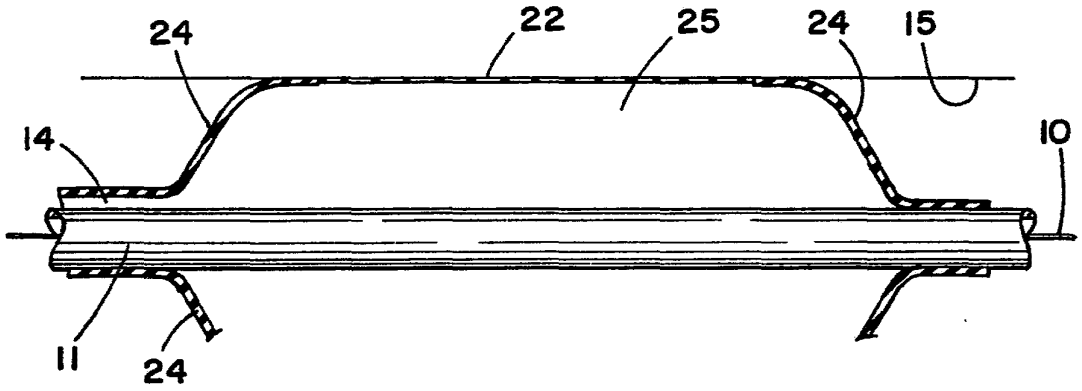



FIG. 5

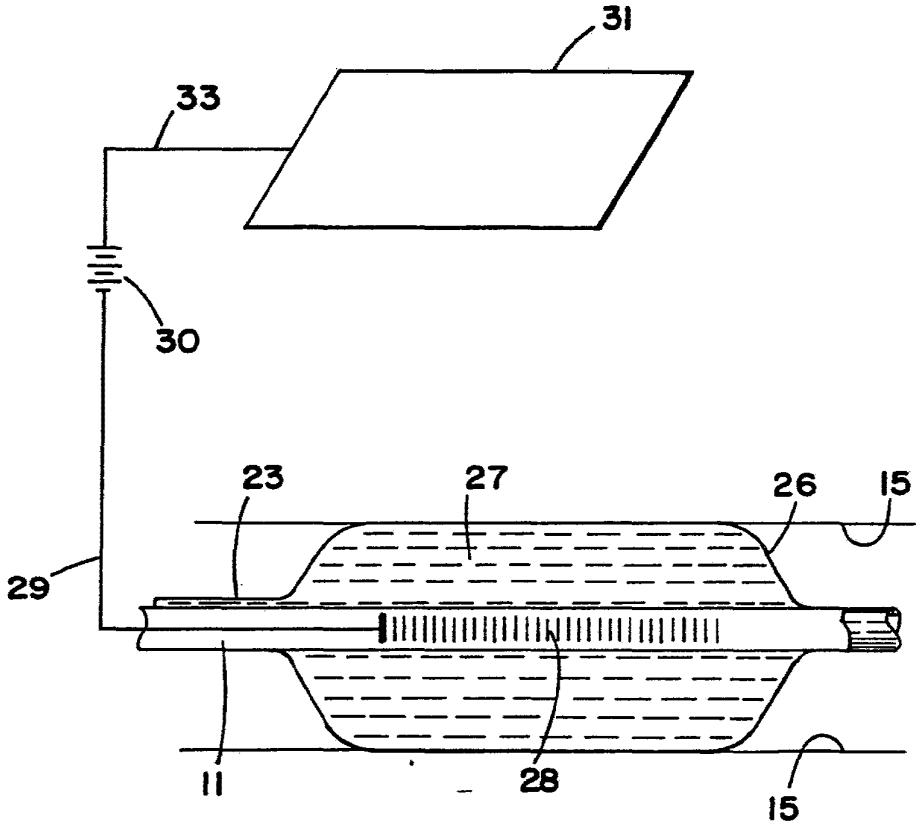



FIG. 6

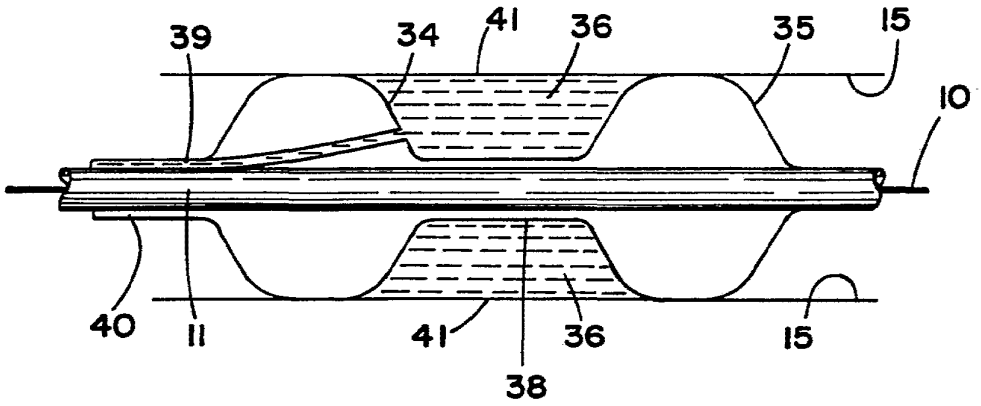



FIG. 7

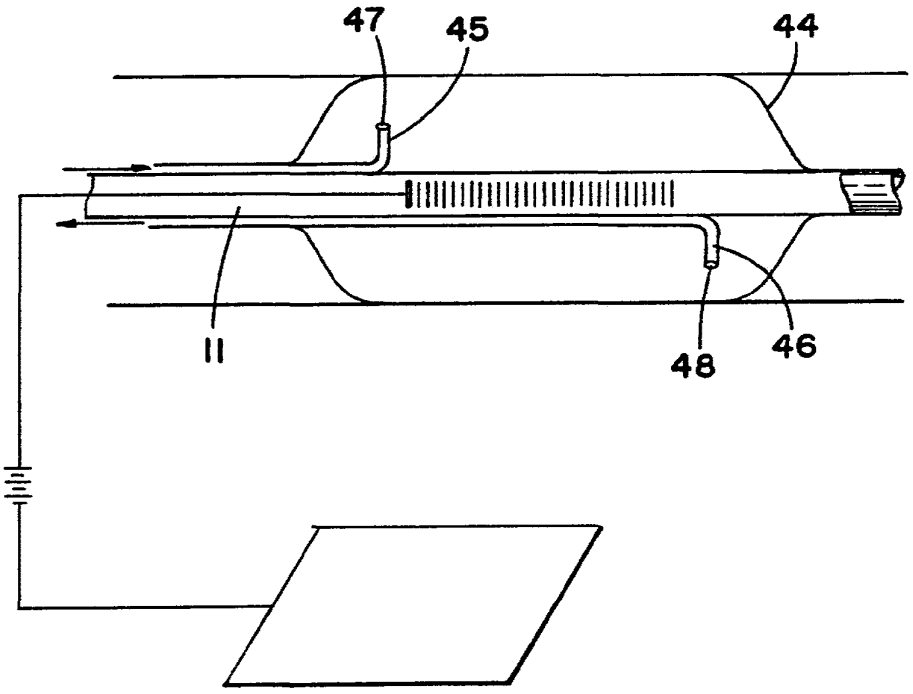



FIG. 8

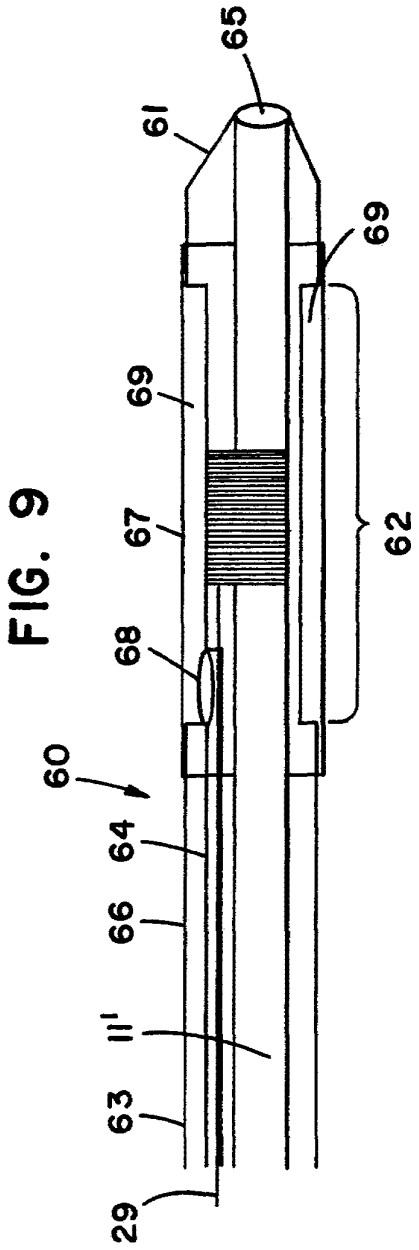

65
61
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69
67
62
68
60
64
66
11'
63
29

FIG. 9

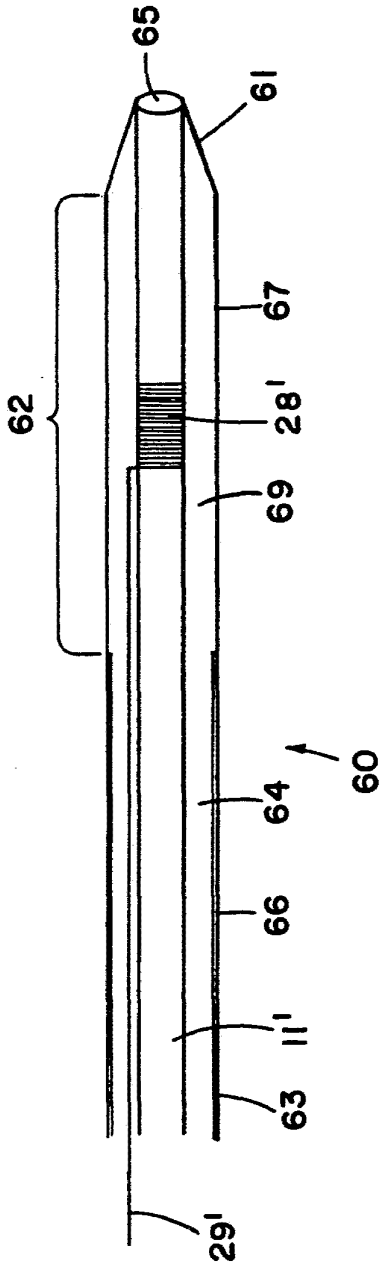

65
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67
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28'
69
60
64
66
11'
63
29'

FIG. 10

# INTERNATIONAL SEARCH REPORT

International Application No PCT/US 91/04288

## I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all)[6]

According to International Patent Classification (IPC) or to both National Classification and IPC

Int.Cl.5 A 61 M 29/02

## II. FIELDS SEARCHED

**Minimum Documentation Searched[7]**

| Classification System | Classification Symbols |
|---|---|
| Int.Cl.5 | A 61 M |

**Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched[8]**

## III. DOCUMENTS CONSIDERED TO BE RELEVANT[9]

| Category ° | Citation of Document, [11] with indication, where appropriate, of the relevant passages [12] | Relevant to Claim No.[13] |
|---|---|---|
| X | DE,C,3915636 (SASS) 26 April 1990, see the whole document | 1-7,9-14,16-18,20-22,24-26,28-29,31-37,39-48 |
| X | --- | |
| X | WO,A,8912478 (JUST) 28 December 1989, see abstract; claims; figures | 1-6,9-13,16-17,20-22,24-25,28,31-36,39-48 |
| X | --- -/- | |

° Special categories of cited documents : [10]

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

## IV. CERTIFICATION

| Date of the Actual Completion of the International Search | Date of Mailing of this International Search Report |
|---|---|
| 25-09-1991 | 24 OCT 1991 |
| **International Searching Authority** | **Signature of Authorized Officer** |
| EUROPEAN PATENT OFFICE | Mme N. KUIPER |

Form PCT/ISA/210 (second sheet) (January 1985)

III. DOCUMENTS CONSIDERED TO BE RELEVANT (CONTINUED FROM THE SECOND SHEET)

| Category ° | Citation of Document, with indication, where appropriate, of the relevant passages | Relevant to Claim No. |
|---|---|---|
| X | US,A,4423725 (BARAN et al.) 3 January 1984, see abstract; figures | 1-6,9-13,16,17,20-22,24-25,28,31-36, |
| X | US,A,4423725 | 39-48 |
| A | US,A,4411648 (DAVIS et al.) 25 October 1983, see abstract | 7,14,18,26,29,37-44 |
| A | Soviet Inventions Illustrated, Section P,Q, Week 8810, no. 88-069276/10, 20 April 1988, Derwent Publications Ltd., (London, GB), & SU 1326270 (TOMSK HEALTH RESORT), 30 July 1987 | 8,15,19,27,30,38 |

# ANNEX TO THE INTERNATIONAL SEARCH REPORT ON INTERNATIONAL PATENT APPLICATION NO. US 9104288 SA 48810

This annex lists the patent family members relating to the patent documents cited in the above-mentioned international search report. The members are as contained in the European Patent Office EDP file on 16/10/91
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| Patent document cited in search report | Publication date | Patent family member(s) | Publication date |
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| DE-C- 3915636 | 26-04-90 | EP-A- 0396945 | 14-11-90 |
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| US-A- 4411648 | 25-10-83 | None | |

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(54) Title: TREATMENT OF MAMMALIAN PHYSIOLOGICAL REACTION OF IgE ANTIBODIES PRESENT IN SAID MAMMAL UPON CONTACT WITH THE CORRESPONDING ANTIGEN

(57) Abstract: A method is disclosed for blocking or reducing physiological reaction in a mammal to the interaction of IgE antibodies present in said mammal upon contact with the corresponding antigen, by the administration to said mammal of a therapeutically effective amount of a neurotoxin (CnT) derived from Clostridia sp.

# TREATMENT OF MAMMALIAN PHYSIOLOGICAL REACTION OF IgE ANTIBODIES PRESENT IN SAID MAMMAL UPON CONTACT WITH THE CORRESPONDING ANTIGEN.

## FIELD OF THE INVENTION

A method is disclosed for blocking or reducing physiological reaction in a mammal to the interaction of IgE antibodies present in said mammal upon contact with the corresponding antigen, by the administration to said mammal of a therapeutically effective amount of a neurotoxin (CnT) derived from Clostridia sp.

## BACKGROUND OF THE INVENTION

Throughout this application various publications are referred to within parentheses or by footnote. The contents of these publications are hereby incorporated by reference in their entirety.

### Introduction

The physiological reaction in a mammal to the interaction of IgE antibodies present in said mammal upon contact with the corresponding antigen is generally referred to as allergy. It is believed that the allergic response evolved to combat infections with parasites. As parasitic infections are rare in industrialized countries this mechanism becomes pathologic in certain susceptible (atopic) individuals. Characteristic of allergies is that the antigen, also called the allergen, is normally innocuous, and the body's reaction is inappropriate.

Allergic reactions can involve all body tissues but are most prominent in the boundaries with the external environment: the airway, eye, gastrointestinal tract and skin. The conditions are known as allergic rhinitis in the nose (hay fever), allergic asthma in the lungs, food allergies in the GI tract and allergic hypersensitivity (hives) or dermatitis in the skin. Anaphylaxis refers to the systemic reaction that occurs when an allergen is introduced directly into the circulation, such as occurs with injection of drugs and insect stings. A massive early phase reaction occurs throughout the body. Symptoms include diffuse airway swelling and hypotension which can be life threatening.

Each year more than 50 million Americans suffer from allergic diseases, costing the health care system $18 billion annually (American Academy of Allergy,

Asthma and Immunology (AAAAI). The Allergy Report: Science Based Findings on the Diagnosis & Treatment of Allergic Disorders, 1996-2001)

Alarmingly, the prevalence and severity of allergic disorders has rapidly increased in the United States over the past twenty years, so there is a need for new therapies for these conditions.

In 1998, an estimated 15 million Americans, or 6.4 percent of the population, had asthma, with 5 million being children. Children account for 4.8 million of Americans with asthma. Each year, 1.8 million emergency room visits are for asthma, nearly 500,000 Americans are hospitalized and more than 5,000 die from the disease. Although asthma deaths are infrequent, they have increased significantly during the last two decades. From 1975-1979, the death rate was 8.2 per 100,000 people. That rate jumped in 1993-1995 to 17.9 per 100,000. Asthma cost the U.S. economy an estimated $10.7 billion in 1994, including a direct health care cost of $6.1 billion and indirect costs, such as lost workdays, of $4.6 billion.

Approximately 16.7 million office visits to health care providers each year are attributed to allergic rhinitis alone (CDC. Fast Stats A-Z, Vital and Health Statistics, Series 10, no. 13. 1999

A related condition, chronic sinusitis, is the most commonly reported chronic disease, affecting 12.6 percent of people (approximately 38 million) in the United States in 1996. Another related condition, serous otitis media, is the most common condition in children requiring an office visit to a health care provider.

Atopic dermatitis is one of the most common skin diseases, particularly in infants and children. The estimated prevalence in the United States is 9 percent[1] Rudikoff D and Lebwohl M. "Atopic dermatitis." Lancet 351(9117): 1715-21. 1998[i]

Experts estimate that food allergy occurs in 8 percent of children 6 years of age or under, and in 1 to 2 percent of adults Sampson HA. In Allergy, Principles and Practice, 5th Ed., E. Middleton et al, ed. Mosby, St. Louis, p. 1162. 1998[ii].

**Pathophysiology of allergy**

Allergy is an ailment that affects millions of individuals worldwide. Attempts to desensitize an individual against a material that causes an allergic response (hereafter designated as an "allergen") by injection of measured dosages of the allergen heretofore has failed to achieve complete relief of allergy symptoms reproducibly in all allergic individuals. An allergic response is a term of art and has a well-defined meaning. Within the context of the present invention, an allergic or reagenic response includes, in particular, at least one of the features of 1.) production of an abnormally high level of IgE in an individual's serum, 2.) immunologic interaction between an allergen, an individual's IgE and leukocytes resulting in release of histamines, 3.) production of hives, rashes, wheal and flare and similar dermatological manifestation of hypersensitivity, and 4.) anaphylaxis.

An allergic response is a state of hypersensitivity in which an exaggerated immune response is induced by the exposure to a particular antigen or allergen. Hypersensitivity reactions can be classified as immediate or delayed. Immediate or type I hypersensitivity (or anaphylactic response) is an allergic reaction which develops very quickly, i.e., within seconds or minutes of exposure of the patient to the causative allergen, and it is mediated by IgE antibodies produced by B lymphocytes. In non-allergic patients, there is no IgE antibody of clinical relevance. However, in a person suffering with allergic diseases, IgE antibody mediates immediate hypersensitivity by sensitizing mast cells which are abundant in the skin, membranes of the eye, nose and mouth, and in the respiratory tract and intestines.

IgE secreted from activated B cells can attach to Fc receptors located on the surface of mast cells and basophil granulocytes, which contain numerous cytoplasmic granules packed with chemical mediators e.g. histamine (J. Klein, "Immunology", Blackwell Sci. Pub., London, 1990; E. Benjamini & S. Leskowitz, "Immunology", Wiley-Liss, N.Y. 1991). This receptor binds circulating IgE with very high affinity and retains it at the mast cell surface for extended periods of time. Activation is accomplished through the binding of an allergen simultaneously to more than one polyvalent molecule of Fc receptor-bound IgE. This "cross linking" of at least two surface-bound IgE molecules brings Fc receptor proteins into close association with one another in the plane of the mast cell plasma membrane. When the bound IgE is contacted by the appropriate allergen, the mast cell becomes

activated. Kinases associated with these receptors become activated as a result of this proximity. They initiate the second messenger cascade, which results in the fusion of the granules with the cell surface membrane, leading to the exocytosis of the granule contents, such as histamine, cytokines, and leukotrienes into the surrounding tissue, and the concomitant induction of allergic symptoms. It is the activity of these substances which is responsible for the clinical symptoms typical of immediate hypersensitivity. These include contraction of smooth muscle in the airways or the intestine, the dilation of small blood vessels and the increase in their permeability to water and plasma proteins, the secretion of thick sticky mucus, and in the skin, , swelling and the stimulation of nerve endings that results in itching.

Delayed type hypersensitivity (DTH) reactions are mediated by T-cells and macrophages and become evident only after 1 to 2 days and persist from several days to a few weeks. DTH is also referred to as cell-mediated hypersensitivity (i.e., T-cell mediated) and is part of a larger group of reactions called cell-mediated immunity.

Anaphylaxis, or anaphylactic shock, is an acute systemic (whole body) type of allergic reaction, It occurs when a person has become sensitized to a certain substance or allergen (that is, the immune system has been abnormally triggered to recognize that allergen as a threat to the body). On the second or subsequent exposure to the substance, an allergic reaction occurs. This reaction is sudden, severe, and involves the whole body. Anaphylaxis is life-threatening and can occur at any time.

Therapeutically, many agents are used to try to prevent the release of mediators from mast cells and basophils and/or to treat the downstream events by blocking or ameliorating the effects of the mediators on target tissues. Therapeutic agents commonly employed fall under the following main groups.

Antihistamines block and mop up the released histamine, i.e. the major mediator of the allergic response.

01 02 agonists, e.g., Epinephrine, Salbutamol overcome indirectly the downstream effects on vasculature and smooth muscle.

Chromoglycate is useful for primary prevention of mast cells/basophil degranulation.

This prophylactic must be taken continuously. It does not prevent the cross-linking of IgE but it somehow interferes with subsequent events. Theophylline and other phosphodiesterase inhibitors again influence downstream biochemical events particularly associated with cyclic nucleotides. Steroids have multiple sites of activities against the allergic response. They are either administered locally and/or systematically/ systernically.

None of the above treatments are ideal for the modulation of allergic responses because each has specific problems such as side effects including drowsiness, they also lack specificity in the immune system leading to global immuno-suppression. Also many of these therapeutic agents need to be administered continuously. Therefore, new improved treatments are constantly being sought to control the allergic response prophylactically and/or therapeutically without the above-mentioned limitations.

Individuals who wish to become desensitized against an allergen often must submit himself/herself to injections of measured doses of the allergen, first administered at weekly or biweekly intervals, then gradually decreases to bimonthly or monthly intervals throughout the year. Such injections generally commence with a small dose of the allergen and then gradually increasing the dosage until a maximally-tolerated maintenance dose is achieved. The individual is then kept on a maintenance dose of the allergen for long periods of time or until the individual no longer exhibits an allergic reaction to the allergen.

Other treatment regimes have been devised to reduce or eliminate an allergic response.

Allergen injection therapy (allergen immunotherapy also known as subcutaneous immunotherapy (SCIT) is known to reduce the severity of allergic rhinitis. This treatment is theorized to involve the production of a different form of antibody, a protective antibody which is termed a "blocking antibody" (Cooke, RA et al., Serologic Evidence of Immunity with Coexisting Sensitization in a Type of Human Allergy, Exp. Med. 1935; 62:733). Chemical agents have been developed which inhibit the interactions between the IgE and its receptor (Cheng et al., U.S. Patent No. 5,965,605 and Ra et al., U.S. Patent No. 6,090,034). IgE antagonists have also been used to treat allergic disease (Presta et al., U.S. Patent No 5,965709) and compounds that exhibit immunosuppressive activity and inhibits the release of

histamine (Bycroft et al., U.S. Patent No. 5,969,158). St. Remy et al., U.S. Patent No. 4,740,371, discloses an immune complex of an allergen for treating allergies involving a combination of the specific allergen and the corresponding antibody to that allergen. The injection of the complex into a patient is said to reduce a patient's allergic reaction to that specific allergen. Others have suggested that certain human proteins can neutralize IgE by blocking it from interacting with the mast cells, but this has not been established clearly as a clinically effective therapy (Stanworth, et al., Allergy Treatment with a Peptide Vaccine, Lancet 1990; 336:1279-81). Patterson et al., U.S. Patent No. 5,314,690 disclosed a method and preparations for reducing IgE antibodies to allergens in allergic subjects wherein substance P (a neuropeptide) and an allergen or fragments of allergens or haptens acting as allergens are administered together to the allergic subjects through a non-oral route.

Cholera Toxin and B Subunit as Adjuvants Cholera toxin (CT) and the closely related heat-labile toxin (LT) from Escherichia coli are known as exceptionally potent immunoadjuvants when co-administered with antigens by various mucosal routes (Elson et al., J. humunol. 1984; 133:2892-2897; Hohngren et al., Vaccine 1973; 1 1: 1 179-1184; Lycke et al, Eur. J. Immunol. 1992; 22:2277-228 1. Both CT and LT are recognized as "AB" toxins in that they are composed of two distinct structural and functional components: a single toxic-active A subunit component and a non-toxic cell-binding B subunit. The latter is a honiopentamer component with strong binding affinity for GMI ganglioside receptors (Holingren et al., Nature 19 8 1; 292:413 -417). Such receptors are known to be present on most mammalian cells, e.g., on skin and other epithelial cells, on all known antigen-presenting cells including dendritic cells (DC) and Langerhan's cells (LC), as well as on B and T lymphocytes. Recently, Gleim et al., U.S. Patent No. 5,980,898 disclosed a system for transcutaneous immunization that induces an immune response (e.g., humoral and/or cellular effectors) in an animal or human. The system provides a simple application to intact skin of both rodents and humans of a formulation comprised of antigen and an adjuvant that was whole cholera toxin.

Common to allergies is the involvement of the IgE class of antibody. Individuals are not born with allergies; rather they acquire them by exposure to allergens. The steps of the IgE allergic reaction are sensitization upon first exposure to the allergen, and then the allergic response to subsequent exposures. The allergic response consists of an immediate and delayed response referred to as the early

and late phase responses respectively. In atopic individuals, those prone to allergies, the initial exposure to an antigen results in the production of IgE antibodies that specifically recognize that allergen. This process is called sensitization.

The early phase response (ERP) is the immediate reaction that occurs within minutes of exposure to an allergen. IgE are bound to the surface of a neuroimmune cell called the mast cell (in the circulation these cells are called basophils). Sufficient numbers of bound IgE antibodies that react with an allergen causes the mast cell to release its content of secretory vesicles, a process known as degranulation. The secretory vesicles contain histamine and other stored substances such as nerve growth factor (NGF). In addition the mast cell and T cells immediately begin manufacturing leukotrienes, cytokines, enzymes and substances that activate blood platelets and attract secondary cells such as eosinophils. Symptoms vary depending on the site, but common reactions are smooth muscle contraction, mucus secretion, vascular permeability, and sensory nerve stimulation.

The late phase response (LPR) develops over hours to days of exposure as eosinophils and other cells are attracted to the area. Eosinophils produce major basic protein, eosinophil cationic protein, leukotrienes and nerve growth factor. TH2 lymphocytes release cytokines that promote further IgE production and eosinophil chemo attraction, and increased numbers of mast cells.

**Nerve involvement in allergy**

The sensory nerve stimulation causes reflexes that are designed to aid in defending the tissue. These reflexes are often a larger problem then the local allergic response. Reflexes can range from large gross motor actions to regional afferent and efferent arcs or even local axon-axonal reflexes involving a single neuron.

Some reflexes recruit major motor actions that are well recognized. In the nose sneezing is a reflex attempt to expel unwanted material and coughing is the equivalent response in the lungs.

Regional reflex arcs involve the sensing of the stimulus by the sensory neuron, the transfer of the message to the ganglia and the central nervous system and an efferent response via autonomic neurons. Reflex excitation by the autonomic nervous system directly causes mast cell to degranulate, thereby spreading the reaction. In addition these reflexes control a variety of other functions. In the nose

these reflexes cause increased mucus production, increased cilia movement, nasal congestion and sneezing. In the lungs reflexes cause bronchospasm, increased mucosal congestion, production of airway secretions and coughing. In the GI tract reflexes cause dysmotility, mucosal congestion and secretions. In the skin the reflexes cause swelling and itching.

Finally there are local axon-axonal reflexes in sensory nociceptive nerve fibers. Allergic stimulation of a single neuron causes release of mediators from other axons of the same neuron. (Barnes P et al. 1991 Neuropeptides in the respiratory tract. Am Rev Resp Dis 144:1187-1198, 1391-1399)

In chronic allergic stimulation the mast cells and eosinophils releases nerve growth factor which causes growth of the nerves in the region. Thereby allowing for increased neural responses and hyper reactivity. This hyper reactivity is not limited to allergic reactions but extends to non-allergic conditions such as respiratory tract infections including viral and bacterial infections. Specifically viral rhinitis, viral and bacterial sinusitis, suppurative otitis media, bronchitis and pneumonia. Therefore individuals become more susceptible to these conditions and have more frequent and severe infections.

Furthermore the repeated allergic reactions cause changes in the qualitative response of the neural reflexes such that they are inappropriately activated. This negatively effects non-allergic conditions, such as bronchospasm mucus production and coughing in non-allergic lung conditions such as bronchitis and emphysema.

**Allergic reactions differ from inflammatory reactions**

Allergic reactions differ from inflammation. Allergies represent the body's inappropriate response to what is in essence a harmless antigen. It is believed that the IgE allergic reactions evolved to combat parasitic infections which are now rare in industrialized societies. In contrast, inflammation is the body's response to actual tissue damage or infection. Inflammation is clinically distinguished by the classical symptoms of calor, rubor and dolor: heat, redness and pain. Inflammation is a process that triggers a cascade of mediators with wide effects, both locally and systemically. Local reactions include pain, vasodilation and migration of macrophages and neutrophils. Systemic reactions include fever. Certain conditions, such as rhinitis or asthma, can be triggered by allergies, infections, irritating

chemicals or may be entirely neurogenic, the result of nerve activity without prior inflammatory or allergic stimulation.

**Specific Allergic Conditions**

**Rhinitis**

**Allergic rhinitis**

The inner lining of the nose is a mucosa that contains serous and mucus glands and large numbers of mast cells. This mucosa extends to the openings leading to the sinuses as well as the Eustachian tube where it is continuous with the mucosa of the sinuses and middle ear, respectively. The EPR of the nasal mucosa causes mast cell degranulation. The release of histamine, heparin and neuropeptides provokes vasodilation and acute swelling of the mucosa and has some minor direct stimulatory effect on the mucus secreting glands. Reflex excitation causes reflex sneezing, congestion and neural stimulation of the seromucinous glands and further congestion. LPR attracts eosinophils and prolongs the reaction.

Allergic reactions can also be chronic, a condition known as perennial rhinitis. In these cases airborne allergens are constantly in the environment. Chronic low-level allergic reactions cause a thickening of the nasal mucosa due to edema and hypertrophy of glandular elements. As a result the primary symptoms of perennial rhinitis are nasal congestion, and postnasal drip. After each allergic reaction the mucosa swells; repeated allergic reactions enlarges the mucosa permanently and may form polyps. Thickening of the mucosa can cause obstruction of the small openings that allow drainage from the sinus. Obstruction of these openings allows nasal secretions to collect and become infected, thereby causing sinusitis.

Topical treatment of allergic rhinitis includes steroid sprays and chromalyn sodium (Nasocrom®) a chemical that blocks mast cell degranulation, and/or nasal decongestants (Neosynephrine). Systemic treatment includes oral anti-histamines and non-sedating antihistamines (Allegra®, Zyrtec®, Claritin®). Long-term therapy requires immune desensitization to the allergen by progressive intradermal injections of the allergen over months to years. rhinitis can lead

Allergic rhinitis can lead to pulmonary disease, including but not limited to asthma and emphysema, suitably asthma caused by hyperreactivity and/or the

symptoms of bronchoconstriction, mucosal edema, increased secretions and cough. These can be treated by the application of CnT to the nasal cavity of patients with allergic rhinitis. It is well known in the art that allergic conditions of the nose can cause reflex changes in the lung that mimic or exacerbate asthma. (McCusker C et al 2002, Site-specific sensitization in a murine model of allergic rhinitis: Role of the upper airway in lower airway disease, J Allergy Clin Immunol, 110:891-898)

**Perennial allergic rhinitis**

Perenial rhinitis is a chronic condition and certain symptoms, such as nasal congestion, are more prominent then others such as sneezing. Therefore therapy for this condition needs to be over more prolonged period, if not indefinitely. Although the same treatments as disclosed for seasonal allergic rhinitis can be used repeatedly, certain method of treatment asre disclosed here that are more efficient and convenient for longer term therapy.

Parasympathetic neurons do not extend from the central nervous system to their target organs in the nose. Instead parasympathetic preganglionic neurons have their cell bodies in the brain stem and have an axon that extends partway and synapses on the cell body of a second neuron called the postganglionic neuron. The axons of the postganglionic neurons extend into nose and sinuses and modulate many of the biological responses seen during allergic reactions. The cell body of the post ganglionic parasympathetic neuron also receives collateral afferent synapses from sensory neurons that are stimulated during allergic reactions. Therefore much of the neuronal circuit involved in the allergic reaction converges onto the cell body of the postganglionic neuron.

All of the postganglionic neuron cell bodies are concentrated in small structure called the sphenopalatine ganglion. Moreover all afferent synaptic connections on these neurons is cholinergic, the neurotransmitter most sensitive to BoNT. Therefore application of CnT to the sphenopalatine ganglion is the most efficient way of blocking the allergic neural reaction.

The sphenopalatine ganglion is accessible to needle injection via the sphenopalatine canal. This canal passes though the hard palate and is accesible about one centimeter medial to the the second molar. Injections of anesthetic and

vasoconstrictor agents are commonly performed by clinicians skilled ion the art of nasal surgery.

**Infectious rhinitis**

Although they share some of the same symptoms, allergic rhinitis differs from infectious rhinitis. The most common cause of infectious rhinitis is a viral infection, known as the common cold. Bacterial and fungal infections of the nose occur also but these are comparatively rare as primary events. During viral infections the epithelial cells release secretions that trigger an inflammatory response. The classic signs of caldor, rubor and dolor; heat, redness, and pain characterize inflammation. White blood cells such as macrophages and neutrophils migrate from small blood vessels in the area to the infected mucosa. These cells in turn release a variety of chemical mediators that increase the inflammation. Infectious rhinitis is characterized by a purulent or pus like postnasal drip, and nasal congestion. In many viral infections there are systemic symptoms such as fever. Treatment of viral infectious is symptomatic with topical and systemic decongestants, and antipyretic and anti-inflammatory drugs.

**Vasomotor and other causes of rhinitis**

Vasomotor rhinitis is strictly a neural hyper stimulation of the serous secretory glands of the nose. This condition is characterized by a watery nasal discharge with a very small content of mucus. Vasomotor rhinitis results directly from neural stimulation of temperature changes or while eating, and associated other symptoms such as congestion, and sneezing are not prominent. US 5,766, 605 discloses a method of blocking the symptom of rhinorrhea in vasomotor rhinitis using clostridia neurotoxins.

**Serous otitis media**

Direct reaction of the middle ear mucosa to allergens, or indirect effects by blockage of the Eustachian tube, leads to serous otitis media. In this condition the middle ear fills with fluid and hearing is impaired. As this condition most often affects young children they are risk of learning disabilities due to the decreased hearing acuity.

**Sinusitis, a complication of rhinitis**

Sinusitis is an infection of the sinuses. The sinuses are air filled cavities surrounding and opening into the nasal cavity via small openings called ostia. The maxillary sinuses compose the mass of the cheeks and the ostia are between the inferior and middle turbinate. The frontal sinuses are above the brow underneath the skin of the forehead, they open into the nasal cavity via a duct that enters beneath the middle turbinate. The sphenoid sinuses are in the nasopharynx and have ostia on their anterior surface. The ethmoid sinuses are located between the eyes and are composed of numerous small air cells. The anterior and posterior cells drain independently. The anterior ethmoid region is especially important due to the confluence of drainage ostia. The area is called the infundibulum, and a small amount of obstruction can cause widespread sinus infections.

Sinus infections are either acute or chronic. In acute sinusitis a bacterial infection follows a viral infection of the upper respiratory tract. However, sinusitis can also occur from obstruction of the draining ostia of the sinuses by inflammation or mass lesion. Topical nasal decongestants and systemic antibiotics are used to treat acute sinusitis. Severe or complicated infections may require surgical drainage of the involved sinus. Chronic sinusitis is a low-grade ongoing or recurrent infection of the sinuses. In these cases the mucosa of the sinuses has become thickened and enlarged due to edema and increased secretory glandular elements. In these cases small abscess may persist and relatively mild inflammatory stimuli may cause obstruction of the narrowed sinus ostia. Treatment of chronic sinusitis includes topical steroid sprays, systemic anti histamines and decongestants, and/or surgical removal of diseased mucosa with enlargement of the ostia.

**Asthma**

Asthma is a general term given to a similar constellation of symptoms: bronchospasm, mucosal swelling and increased secretions. Allergic stimulation, infections, irritating chemicals, cold air or exercise can trigger asthma.

Allergic asthma is a specific subset of asthma that is initiated by allergens and involves the IgE mediated reaction. Local and organ reactions include bronchial smooth muscle constriction, mucosal swelling and increased secretions.

**Other Allergic conditions**

Other allergic conditions include food allergies, and allergic dermatitis.

**Clostridia neurotoxins (CnT)**

Clostridium (C.) botulinum and the closely related species C. butyricum and beratti produce an extremely powerful neurotoxin that causes the paralytic condition known as botulism. The botulinum neurotoxin (BoNT) protein consists of a light and heavy chain that together weigh approximately 150 kD. In botulism the primary target is the synapse of the motor neuron with the muscle fiber. Here BoNT is taken up by the membrane of the motor neuron and is internalized. The effect of BoNT is to inhibit the release of neurotransmitters and neuropeptides by neurons. In clinical use each serotype appears to differ in its potency in blocking different classes of neurons.

BoNT works by a two-stage mechanism, uptake and molecular action. Peripheral nerve terminals take up BoNT. After translocation across the cell membrane BoNT interferes with the molecular mechanism of neurosecretion. Specifically, BoNT cleaves the proteins involved in synaptic vesicle docking and release called the SNARE complex. The result is to block neural signals.

C. tetani produce tetanus neurotoxin (TeNT). TeNT is similar to the BoNTs in that it interferes with vesicle release by cleaving VAMP, one of the SNARE family of proteins. However the in vivo biological activity of TeNT is usually quite different from BoNT. The systemic disorder tetanus results from TnT produced at a wound site and disseminated throughout the body via the blood stream. The TeNT is taken up by peripheral motor neurons and transported to the central nervous system. The TeNT then preferentially blocks inhibitory neurons connecting to the motor neuron, thereby allowing unopposed excitatory input. However, at higher doses TeNT and when introduced directly into the neuron also blocks all neurons in the same manner as BoNT. In this application it is assumed that the when BoNT is discussed is includes the TeNT when used at higher blocking doses.

At present seven immunologically distinct serotypes of the BoNT are known, named A, B, C, D, E, F and G. The type C serotype is now known to be divided into three different toxins with distinct biological effects. Only C1 is a neurotoxin, whereas C2 and C3 are not. C2 is distinctive for blocking actin formation, which can prevent mast cell degranulation. Although all BoNT serotypes interfere with proteins that

cause the release of synaptic vesicles from cells they each interfere with different proteins, or different parts of the same protein:

BoNT A & E cleave SNAP-25 (synapse associated protein)

BoNT C cleaves SNAP-25 and syntaxin

BoNT B, D, F & G (and TeNT) cleave VAMP (vesicle associated membrane protein)

Most if not all cell types use the vesicle system for secretion, although the molecules within these vesicles differ for each type of cell. If experimentally introduced into any cell BoNT appears capable of blocking its vesicle release. However, in nature BoNT appears to be internalized into neurons, particularly the efferent neurons. The vesicles within neurons contain classical neurotransmitters (acetylcholine, epinephrine, nor epinephrine, dopamine, serotonin, glutamate, GABA and others) and/or neuropeptides (substance P, neurokinin A, calcitonin gene related peptide (CGRP), neuropeptide Y, interleukins, growth factors and others). Although the highest affinity of BoNT is for cholinergic neurons, in various preparations BoNT has been shown to block secretion of all these molecules.

**The clinical effects of botulinum toxin on different classes of neurons**

**Voluntary motor nerves**

The first and still primary use of BoNT is to block motor nerve communication with muscle fibers. BT is injected within the target muscle. The BoNT is then internalized into motor neurons where it decreases or stops the release of the neurotransmitter acetylcholine (AChE), thereby causing paresis or paralysis of the muscle. Scott introduced the concept of localized muscular injections of BoNT in the specific condition of strabismus (squint, crossed eyes). Later BoNT was found to be particularly useful for movement disorders such as tics, spasms, contractures, cramps and tremors. More recently, the injection of BoNT into facial muscles has been found to ameliorate skin wrinkling and lines related to aging. Another recent application of BoNT injections is to decrease the pain accompanying muscle tension in conditions such as headache and temporo-mandibular joint syndrome.

**Autonomic motor neurons**

Effector neurons of the autonomic system innervate and control the contraction of smooth muscles using AChE as the neurotransmitter. Injections of BoNT have been used to decrease tone in the smooth muscles of the lower esophageal sphincter, esophagus, stomach wall, and pyloric sphincter, sphincter of Odi, anal sphincter, and urinary bladder.

**Autonomic secretory neurons**

Effector neurons of the autonomic system control or modulate the secretion of various water and mucoid fluids throughout the body. BoNT injections have been used to decrease sweating, salivary gland flow, gastric secretions including acid production, nasal and other respiratory secretions, and tearing.

**Sensory neurons**

Sensory neurons release a wide variety of neuropeptides, cytokines, growth factors and other substances that effect parenchymal cells, blood vessels and immune cells. Notable is that these substances can activate mast cells directly thereby extending the allergic reaction. Except for nitrous oxide these substances are released via the SNARE mechanism and can be blocked by CnT.

## SUMMARY OF THE INVENTION

As used herein 'local administration' includes but is not limited to injection by needle and in-dwelling catheter (including pressure jet injectors), topical administration in lyophilized powder, liquid solutions, creams, ointments, aerosolized or introduced by liposomal (niosomes) vectors, or as nucleic acid introduced by viral or other vectors. The CnT may also be embedded in biopolymers or delivered by implanted pumps to release the CnT into solution over prolonged periods.

By "therapeutically effective amount" it is meant of purposes of this invention that the CnT is administered in a non-toxic amount sufficient to cause reduction in the occurrence or magnitude of the symptoms being targeted.

By "unit" it is meant the biological equivalent of the current unit measure used for botulinum toxin A marketed as Botox. At present BoNT is measured by biological assay; a unit of BoNT is the amount that causes death to 50% of mice when injected intraperitoneally. BoNT-A is marketed as Botox by Allergan Corp, Irvine Ca, and as Dysport by Ipsen Ltd, Berks United Kingdom. Although the biological assay is done the same way the in vivo effect of Botox and Dysport vary. BoNT-B is marketed as Myobloc by Elan Pharmaceuticals, Dublin, Ireland. TeNT is not commercially available but other assays have compared the potency of the blocking effect of TeNT to BoNT. All serotypes of BoNT as well as TeNT are commercially available from List Biological laboratories). A therapeutically effective amount of BoNT will vary depending on the organ to be treated, how much of the organ will be treated, the method of application and the exact preparation of BoNT used. A therapeutically effective amount will vary from a fraction of a unit to hundreds of units as is it currently does with intramuscular injections. The exact dosage will not require undo experimentation by those skilled in the art.

Where solutions or suspensions of BoNT or CnT are referred to, unless indicated to the contrary, this means the designated number of units in 1 ml of Normal saline.

By "CnT" it is meant that any biological substance having essentially the same biological effect within cells as the wild types of clostridia neurotoxins. Specifically, to block or decrease the activity of the SNARE family of proteins involvled in secretion of allergy related neurohumors. Numerous substitutions for the major parts of the CnT have been disclosed and these are all included in this specification. This would include fragments, altered forms, and recombinant forms of CnT. Also included are chimeras, hybrids and conjugates. Also included are the use of DNA and RNA sequences that are directly applied and translated in the allergic sites. Also included are "vectors", various compositions that deliver a botulinum or tetanus toxin light chain or its equivalent such as Protease A across cell membranes. These vectors include but are not limited to viruses, liposomes, noisomes, and protein transduction domains (US Provisional Application 60/449,107).

Allergic "neurohumors" are neurotransmitters, neuropeptides and cytokines that participate in allergic reactions and whose secretion or action can be blocked by CnT. They include acetylcholine, noradrenaline, neuropeptide Y, substance P,

calcitonin gene reactive protein (CGRP), histamine, nerve growth factor, and interleukins.

The invention is directed to a method of blocking or reducing physiological reaction in a mammal, suitably but not limited to H. sapiens, .to the interaction of IgE antibodies present in said mammal upon contact with the corresponding antigen. This blocking is achieved by the administration to said mammal of a therapeutically effective amount of a neurotoxin (CnT) derived from Clostridia sp. Suitably, the CnT is derived from a species of Clostridia selected from the group consisting of C. botulinum, C. butyricum, C. beratti, C. tetani . The neurotoxins (BoNT), derived from C. botulinum, are derived from serotypes A, B, C1, D, E, F and G, while neurotoxin (TeNT), is derived from C.tetani

BoNT/A is marketed as Botox® by Allergan Inc and as Dysport® by Ipsen Ltd as a lyophilized powder that is reconstituted with preservative free normal saline prior to use. BoNT/B is marketed as Myobloc® by Elan Pharmaceuticals in normal saline solution. The light chains and holotoxins for each BoNT serotypes and TeNT can be obtained from List Biological Labs and/or Metabologics Inc.

CnT compositions of the present inventions are prepared in a variety of forms depending on whether the composition is injected or implanted, topically applied to respiratory mucosa of the nasal cavity or lungs, gastrointestinal mucosa, or to skin.

For all injectable CnT compositions fluid dosage forms are prepared utilizing the compound and a pyrogen-free sterile vehicle. The compound, depending on the vehicle and concentration used, can be either dissolved or suspended in the vehicle. In preparing solutions the compound can be dissolved in the vehicle, the solution being made isotonic if necessary by addition of sodium chloride and sterilized by filtration through a sterile filter using aseptic techniques before filling into suitable sterile vials or ampoules and sealing. Alternatively, if solution stability is adequate, the solution in its sealed containers may be sterilized by autoclaving. Advantageously additives such as buffering, solubilizing, stabilizing, preservative or bactericidal, suspending or emulsifying agents and/or local anaesthetic agents may be dissolved in the vehicle.

Dry powders, which are dissolved or suspended in a suitable vehicle prior to

use, may be prepared by filling pre-sterilized drug substance and other ingredients into a sterile container using aseptic technique in a sterile area. Alternatively the drug and other ingredients may be dissolved into suitable containers using aseptic technique in a sterile area. The product is then freeze-dried and the containers are sealed aseptically.

In the respiratory and gastrointestinal systems, CnT binds to mucosal epithelial cells and is actively transcytosed across the mucosa. Compositions suitable for administration to the respiratory tract include aerosols, nebulisable solutions or micro-fine powders for insufflation. In the latter case, particle size of less than 50 microns, especially less than I 0 microns, is preferred.

Compositions suitable for topical mucosal application include normal saline solutions as described above for injections. Other suitable compositions include gels and creams.

The skin presents a formidable barrier to the application of CnT. CnT may be mechanically propelled across the dermal barier with air or water pressure injectors or in association with micro-pellets . Other suitable forms of transdermal delivery include iontophoresis .CnT may be encapsulated into liposomes or niosomes to form suitable trans-dermal compositions.

The method of administration may take many forms, including topical, intra-dermal, sub-cutaneous, trans-cutaneous, intra cavital and by inhalation of the CnT in a suitable carrier. Examples of such administration include, but are not limited to contact with absorbant pledgets having CnT absorbed thereon, contact with biodegradable micropellets having CnT embedded therein. Also included is injection, for example, injection to the nasal mucosa or injection into the pterygoplatine space through the palate, or injection into affected areas of the surface skin. More invasively, by myringotomy and injection into the middle ear space. tympanic membranes. Alternatively less invasive methods include by drops into the inner eyelid and inhalation of an aqueous mist containing same.

The physiological reaction reactions dealt with herein include but are not limited to conditions such as allergic rhinitis, Infectious rhinitis, vasomotor rhinitis, serous otitis media, sinusitis, asthma, food allergies and allergic dermatitis.

The amount of CnT administered per administration may be, but is not limited to between about 0.1 and about 1000 units, suitably between about 1 and about 100 units per administration, preferably between about 1 and about 20 units.

The invention is also directed to use of a neurotoxin (CnT) derived from Clostridia sp for the production of a medicament for blocking or reducing physiological reaction in a mammal to the interaction of IgE antibodies present in said mammal upon contact with the corresponding antigen. The formulations of CnT, including BoNT and TeNT, which are suitable for the purposes designated herein are well known, but have not previously been designated for this purpose.

There is a great need for an effective treatment for allergic disorders. It has long been thought that the allergic reaction involved only histamine release by mast cells. Therefore first line therapy for allergy was antihistamines, or more recently the non-sedating antihistamines. Other therapies are directed to block the effects of the mast cell secretions with adrenergic agonists. It is not obvious to those skilled in the art that a central role in allergic disorders involves the autonomic nervous system and that this nerve activity can be blocked by CnT for a beneficial effect.

It is an object of the invention to provide a treatment for allergic conditions. Included particularly are allergy related rhinitis, asthma, gastroenteritis, serous otitis, sinusitis and dermatitis) and their related conditions (such as sinusitis and serous otitis media that occur secondary to allergy induced mucosal swelling). Treatment is by local application of therapeutically effective amounts of CnTs to the body structure and/or the nerves and nerve ganglia supplying these structures. CnT interfere with the allergic process by:

1) Directly blocking neuroimmune secretions by the mast cell or other immune cell types including but not limited to eosinophils ()

2) Block the release of neurohumors by mast cells induced by autonomic nerve activity.

3) Decrease neurohumoral release during axonal reflexes.

4) Decrease the parasympathetic effector arm of reflex allergic responses

5) Decrease the increased tonic activity of the autonomic systemic that is related to prior allergic reactions.

6) Decrease the enlargement and hypersensitivity of sensory nerves induced by nerve growth factor and other neurohumors released during allergic reactions.

7) Reverse certain complications of allergic reactions such as mucosal thickening by decreasing autonomic nerve activity.

The beneficial effect of this treatment in the:

1) Nasal area, is to decrease the symptoms of sneezing, itching, nasal congestion and post nasal drip, as well as related conditions including nasal polyps and mucosal thickening, and complications such as sinusitis and serous otitis.

2) Lungs, is to decrease coughing and wheezing (bronchoconstriction, edema) and the non-specific sensory hypersensitivity related to chronic allegic reactions.

3) Eye, is to decrease itching, tearing and redness.

4) Skin, is to decrease itching and swelling.

5) Gastrointestinal tract, is to decrease gastrointestinal dysmotility.

## Examples

### Example 1. Seasonal allergic rhinitis

1a) A 30-year-old male has seasonal allergic rhinitis. In May, prior to pollen formation, 30 units of BoNT topically applied in each nostril. Specifically, the nasal cavity is sprayed with a solution of 1% lidocaine and ½% neosynephrine to anesthetize and decongest the nasal mucosa, respectively. Then 1 cc of normal saline containing 30 units of BoNT is sprayed into each nasal cavity. This method of delivery, although commonly used for application of nasal medication, is inherently inefficient as a significant percentage of a sprayed medication will exit the posterior nasal cavity and be exhaled or swallowed.

1b) In another embodiment, the patient is treated by placing 1 x 3 $cm^2$ cotton pledgets impregnated with 20 units of BoNT onto the medial surface of the turbinates and left for one hour, then removed by the physician. This delivery method is more efficient then a spray, however a significant percentage of the BoNT will not diffuse from the pledgets to the mucosa.

1c) Alternatively, the patient has topical anesthesia applied only to a localized area, preferably the anterior end of the inferior turbinate. Then, patient has a 1$cm^2$ cotton pledget impregnated with 10 units of BoNT placed onto the mucosa of the anterior turbinate for one hour and then removed. Within the nasal cavity a mucociliary blanket transports fluids and particles posteriorly, thereby distributing the BoNT. This is an example of applying a BoNT to a localized region of the nasal cavity and using the normal physiology of the nasal cavity for distribution. The routes of mucociliary clearance of the nose and sinus cavities are known so that other variations of this method are apparent to those skilled in the art.

1d) In another embodiment, using a topical biodegradable depot to deliver BoNT over an extended time period to nasal mucosa is used for treating the patient. Various biodegradable compounds are known in the art that vary in consistency and rate of dissolution.

An example is oxidized cellulose (marketed as Surgicel® by Johnson & Johnson, New Brunswick, NJ). The oxidized cellulose can be manufactured with BoNT as an integral component, or the BoNT can be added to the oxidized cellulose before its clinical use. Surgicel is available in the form of a thin flexible sheet that is

often cut to fit the area of the body to which it will be applied. For intranasal use the size may vary from a few square millimeters to a 4 by 8 $cm^2$ sheet that could contact the entire exposed mucosa of the nasal cavity. BoNT can be added to the Surgicel as a lyophilized powder or after reconstitution into solution. If added as a powder it can homogeneously applied onto one side of the Surgicel and the material can be folded. The material is then moistened with normal saline to bind the material together and immobilize the BoNT prior to clinical use. In contrast the BoNT can first be constituted into solution and then absorbed into the material.

As an example a 2 x 6 $cm^2$ piece of oxidized cellulose is saturated with 1 cc of normal saline containing a total of 10 units of BoNT. Using a nasal speculum the nostril is dilated and the nasal cavity is visualized and the saturated cellulose place therein. The cellulose will gradually dissolve over hours while releasing a small continual dose of BoNT directly onto the nasal mucosa.

Alternatively the patient is of 0.5 cc. of normal saline containing 5 units of BoNTis applied to the oxidized cellulose which is grasped with bayonet forceps and placed flat onto the medial surface of the anterior end of the inferior turbinate of each nasal cavity. As disclosed above the mucociliary action of the nasal mucosa transports liquids and particles from the anterior to posterior nasal cavity.

1e) In another embodiment the patient is injected with BoNT solution directly into the nasal mucosa. After anesthetizing and decongesting the mucosa, 5 units of BoNT in 1 cc of saline are injected beneath the mucosa throughout the length of the inferior turbinate with a 25 gauge spinal needle coupled to a 1 cc syringe.

1f) Alternatively the patient can be treated with TeNT.

Compositions of TeNT for intranasal administration, can range in dose from .1 to 1000 units in 0.1cc to 10 cc of solution. One preferable composition is 10 units of TeNT in 1 cc of normal saline.

As an example the same patient is treated by spraying each nostril with 1 cc of normal saline solution containing 10 units of TeNT.

Alternatively, if only decongestion is desired 10 units of TeNT can be topically applied.

In another embodiment, 1 unit of recombinant DNA coding for TeNT is pressure injected across the nasal mucosa to transfect mucosal cells. These cells then express the TeNT for months.

**Example 2. Perennial allergic rhinitis**

2a) Direct injection of the sphenopalatine ganglia.

A 40-year-old female has chronic nasal congestion due to perennial rhinitis. Skin testing demonstrates that she is allergic to numerous environmental antigens and intranasal examination shows enlarged turbinate mucosa and nasal polyps. Testing of nasal secretions shows eosinophilia. An injection of 20 units of BoNT in a 1cc solution of normal saline is made through the sphenopalatine canal into the area of the sphenopalatine ganglia.

In another embodiment, 100 units of BoNT embedded in 0.1 micron biodegradable pellets suspended in solution is injected into the mucosa of each turbinate to slowly release its contents over 6 months.

Alternatively a biodegradable carrier containing 5 units of BoNT is placed intranasally in the most superior and posterior aspect of the lateral nasal wall. This permits the BoNT to diffuse across the nasal wall to the underlying sphenopalatine ganglia.

**Example 3. Serous otitis media**

A 3-year male has a history of serous otitis media. Under general anesthesia a myringotomy is made into the tympanic membranes and 2 units of BoNT in .5 cc of normal saline is injected.

**Example 4. Sinusitis**

A fifty-year-old male has a history of allergic rhinitis and recurrent sinusitis. Ten units of BoNT are injected through the palate into the pterygopalatine space to block the sphenopalatine ganglion.

**Example 5. Allergic dermatitis.**

A seventy-year-old male has severe allergic dermatitis of the forearm skin. Each forearm is injected with 10 injections of 0.3 units BoNT in 0.1 cc of normal saline. Each injection is made intradermally at 3 cm intervals.

**Example 6. Allergic asthma**

A 13-year-old boy has severe allergic asthma. He is treated by bimonthly inhalation therapy of an aerosilized solution of 5 units of botulinum toxin in 5 cc of normal saline.

Alternatively the same botulinum solution can be injected directly into the trachea and bronchi. After injecting local anesthesia into the skin overlying the cricothyroid membrane a needle is passed directly through the skin and cricothyroid membrane and the BoNT solution is sprayed into the trachea. The solution drips down to reach the bronchial mucosa where it is topically absorbed. and is absorbed

**Example 7 Allergic rhinitis**

A 40 year old male has allergic rhinitis and an associated reflex chronic cough. Application of CnT to the nasal cavity as described above or alternatively injected or aerosilized topical application of BoNT to the lungs is used to treat the cough.

**Example 8. Food allergies**

A 10-year-old boy with food allergies manifested by bloating and diarrhea is treated with a rectal suppository containing 50 units of BoNT. The suppository is composed of biocompatible material designed to be solid at room temperature but to dissolve at body temperature. Sufficient materials for the composition are coacoa butter, glycerinated gelatin, hydrogenated vegetable oils, polyethylene glycols of various molecular weights and fatty esters of polyethylene glycol.

**Example 9. Infectious rhinitis**

Chronic allergic exposure causes the nervous system to become hyper responsive to non-allergic stimulation such as that caused by viral infections.

A patient with rhinitis is given 10 units of BoNT and 5 units of TeNT prior to spring.

I Claim

1. A method of blocking or reducing physiological reaction in a mammal to the interaction of IgE antibodies present in said mammal upon contact with the corresponding antigen, by the administration to said mammal of a therapeutically effective amount of a neurotoxin (CnT) derived from Clostridia sp.

2. The method of claim 1 wherein the mammal is a member of H. sapiens.

3. The method of claim 2 wherein the neurotoxin is derived from a species of Clostridia selected from the group consisting of C. botulinum, C. butyricum, C. beratti, C. tetani .

4. The method of claim 3 wherein the neurotoxins (BoNT), derived from C. botulinum, are derived from serotypes A, B, C1, D, E, F and G

5. The method of claim 3 wherein the neurotoxin (TeNT) is derived from C.tetani.

6. The method of claim 1 wherein CnT is administered by contact with absorbant pledgets having CnT absorbed thereon.

7. The method of claim 1 wherein CnT is administered by contact with biodegradable carrier containing CnT .

8. The method of claim 1 wherein CnT is administered by injection.

9. The method of claim 1 wherein CnT is administered by myringotomy into tympanic membranes.

10. The method of claim 1 wherein CnT is administered by injection into the pterygoplatine space through the palate.

11. The method of claim 7 wherein CnT is administered to pass through the nasal wall to the sphenopalatine ganglia .

12. The method of claim 1 wherein CnT is administered by inhalation of an aqueous mist containing same.

13. The method of claim 1 wherein CnT is administered by injection to the nasal mucosa.

14. The method of claim 1 wherein CnT is administered by application of a suppository containing same.

15. The method of claim 1 wherein the physiological reaction is manifested by a condition or symptoms selected from the group consisting of allergic rhinitis, infectious rhinitis, serous otitis media, sinusitis, pulmonary disease, food allergies, allergic dermatitis, and sneezing, coughing, itching and excess mucous secretion related to allergic reactions.

16. The method of claim 15 wherein the pulmonary disease is selected from the group consisting of bronchitis, emphysema and hypereactive asthma.

17. The method of claim 1 wherein CnT is adminstered by contact with absorbant pledgets having CnT absorbed thereon.

18. The method of claim 1 wherein the amount of CnT administered per administration is between about 0.1 and about 1000 units per administration.

19. The method of claim 1 wherein the amount of CnT administered per administration is between about 1 and about 100 units per administration.

20. The method of claim 1 wherein the amount of CnT administered per administration is between about 1 and about 20 units per administration.

21. The use of a neurotoxin (CnT) derived from Clostridia sp for the production of a medicament for blocking or reducing physiological reaction in a mammal to the interaction of IgE antibodies present in said mammal upon contact with the corresponding antigen.

22. The use of claim 21 wherein the physiological reaction is manifested by a condition selected from the group consisting of allergic rhinitis, infectious rhinitis, serous otitis media, sinusitis, pulmonary disease, food allergies , allergic

dermatitis and sneezing, coughing, itching and excess mucous secretion related to allergic reactions.

23. The use of claim 22 wherein the pulmonary disease is selected from the group consisting of asthma and/or the symptoms of broncho-constriction, bronchitis, mucosal edema, emphysema increased secretions and cough,

24. A medicament for blocking or reducing physiological reaction in a mammal to the interaction of IgE antibodies present in said mammal upon contact with the corresponding antigen comprising a neurotoxin (CnT) derived from Clostridia sp and a pharmacologically acceptable carrier.

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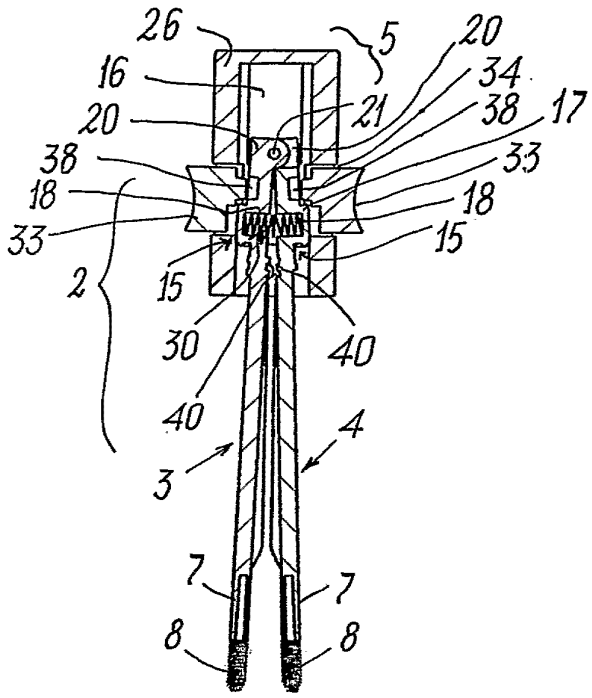
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(54) Title: MASCARA APPLICATOR WITH MOVABLE ARMS




(57) Abstract: A mascara applicator comprises a wand (2) presenting two side-by-side arms (3, 4) movable relative to each other, at least one of said arms (3, 4) carrying an element (8) for interacting with the eyelashes and a part for applying the mascara to the eyelashes. The arms (3, 4) are connected together and can be made to elastically approach each other, said arms being partially contained within a retaining member (5), this latter presenting members (6) for controlling the movement of said arms (3, 4), enabling them to be closed together so that they can interact with the eyelashes.

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"MASCARA APPLICATOR WITH MOVABLE ARMS"

The present invention relates to a mascara applicator in accordance with the introduction to the main claim.

Mascara applicators substantially of tweezer form have been known for some time, they presenting two adjacent arms movable relative to each other, one of these arms carrying an element or brush for depositing the cosmetic product on the user's eyelashes. The second of these brushes can support a curved element for curling the eyelashes, or another element for their surface treatment.

These known arrangements present the most disparate configurations: for example they can comprise a one-piece V-shaped wand defined by the aforesaid arms joined together (integrally) at their free end; or they can present a scissor configuration with the said arms forming ends of substantially straight parts hinged together as scissor arms. In another embodiment, these known arrangements comprise pairs of V-shaped arms carrying eyelash support elements and mascara applicators at their ends.

These known arrangements present various drawbacks: for example, they are of large dimensions and hence

difficult to use and to deposit in a compartment of a small case or, as in the case of one-piece V-shaped applicators, the user can make contact with the cosmetic product during its application, with obvious inconvenience.

An object of the present invention is to provide a mascara applicator which is of improved construction and use compared with known arrangements.

Another object is to provide a mascara applicator of the stated type which enables the user to easily move the adjacent arms while making it difficult for the user to make contact with the mascara while depositing it on the eyelashes.

These and other objects which will be apparent to the expert of the art are attained by a mascara applicator in accordance with the accompanying claims.

The present invention will be better understood from the accompanying drawing, which is provided by way of non-limiting example and in which:

Figure 1 is a perspective view of a first applicator according to the invention, taken from below;

Figure 2 is a side perspective view of the applicator

of Figure 1;

Figure 3 is a side perspective view of the applicator of Figure 1, but in a different utilization position;

Figure 4 is a section on the line 4-4 of Figure 2;

Figure 5 is a section on the line 5-5 of Figure 2;

Figure 6 is an exploded perspective view of the applicator of Figure 1;

Figures 7-9 are longitudinal sections showing the various steps in using a mascara provided with a container and an applicator according to the invention; and

Figures 10-13 show different elements which can be associated with the applicator of Figure 1;

Figure 14 is a perspective view of a second applicator of the invention, seen from below;

Figure 15 is an exploded side perspective view of the applicator of Figure 14;

Figure 16 is a longitudinal side section through the applicator of Figure 14;

Figure 17 is a longitudinal section through a mascara provided with a container and the applicator of Figure 14;

Figures 18-20 are longitudinal sections showing the

various steps in using the mascara of Figure 17;

Figure 21 is a perspective view of a third applicator according to the invention; and

Figures 22 and 23 are longitudinal sections through the applicator of Figure 21 in two different utilization positions.

With reference to Figures from 1 to 13, a mascara applicator is indicated overall by 1. It comprises a wand 2 presenting elongate arms 3 and 4 positioned side by side and movable relative to each other. These arms are associated with a retaining member 5 provided with manipulator means 6 for their manipulation, said arms carrying at a first end 7 an interacting element 8 able to interact with the eyelashes to deposit mascara thereon or to provide a mechanical curling or combing action. These interacting elements 8 comprise (see Figures 10-13) brushes 10, a small comb 11, an arcuate element 12 or an element 13 with a helical surface projection; the elements 11-13 are generally associated with one of said arms 3, 4, the other arm carrying the brush 10. The elements 10-13 are associated with a seat 14 provided in the first end 7.

Each arm 3, 4 presents a second end 15 inserted into a cavity 16 of the retaining member 5. Said second end comprises a widened part 17 external to the arm, presenting an inner cavity 18 and a terminal part 20 provided with a through hole 21. The terminal part 20 of the arm 3 is flat and is inserted into the terminal part 20 of the arm 4 which instead is fork-shaped. Both said terminal parts 20 can evidently be fork-shaped or flat, similar to the part 20 of the arm 3 visible in Figure 6.

The retaining member 5 presents a jacket 26 defining its cavity 16. In this jacket, in opposing positions on the same axis K, there are provided two through holes 27 to receive a pin 28. This latter is inserted into the through holes 21 in the terminal parts 20 of the arms 3 and 4 when these have been fitted together such that their holes lie coaxial with said axis K. The pin 28 acts as a mutual fixing element for the arms 3 and 4 and enables them to be moved away from and towards each other about the pin, against the action of a spring 30 inserted into the inner cavities 18 of the externally widened parts 17 of said arms when fitted together.

To enable the arms to be moved towards each other against the spring 30, manipulator means 6 are provided. These comprise pushbuttons 33 movably inserted into lateral cavities 34 in the jacket 26 of the retaining member 5 communicating with the inner cavity 16 in this latter. These pushbuttons 33 present a part 35 which is external to the jacket 36 of the retaining member, and a part 36 arranged to cooperate with the terminal part 20 of the arms 3 and 4; the part 36 has a projecting shape able to engage a seat 38 provided in said part 20 of said arms 3 and 4, so becoming rigid with said part 20.

Each arm 3 and 4 also presents in proximity to the widened part 17 a series of transverse recesses 40 to receive corresponding transverse projections 41 of the other arm 4 and 3 when the two arms are closed for their insertion into a mascara container 42. This latter is shown in Figures 7-9 and comprises a hollow body 43 provided with an aperture 44 where a usual scraper 45 is positioned through which the mascara applicator 1 is inserted with its arms closed. They are closed (arrows F of Figure 8) by pressing the pushbuttons 33 towards the retaining member

(arrows G of Figure 8). On releasing the pushbuttons 33, the spring 30 forces the arms apart so that they open (arrows K1 of Figure 9).

The arms 3 and 4 may be opened and closed several times in applying mascara to a user's eyelashes and possibly in subjecting them to mechanical curling or other action depending on the interacting element 8 carried by one of the arms.

Reference will now be made to Figures 14-20. In these the mascara applicator is indicated overall by 100. It comprises a wand 102 presenting elongate arms 103 and 104 positioned side by side and movable relative to each other. These arms are associated with a cup-shaped retaining member 105 provided with manipulator means 106 for their manipulation, said arms carrying, in any known manner, at a first end 107 an interacting element 108 able to interact with the eyelashes to deposit mascara thereon or to provide a mechanical curling or combing action. These interacting elements 108 comprise, for example, brushes, a small comb, an arcuate element or other similar element. The elements 108 are connected to said arms 103, 104 for example by a

part

Each arm 103, 104 presents a second end 115 inserted into a cavity 116 provided in the retaining member 105 and closed by an upper plug 111. Said second end of each arm forms one piece with an interconnection element 113 which hence connects said two arms together. These latter, together with the element 113, hence define a single member partially inserted into said cavity 116.

Said second end 115 of each arm 103, 104 presents a widened part 117 external to the arm. This part 117 penetrates into a lateral cavity 118 provided in the jacket of the part 105 where movable elements 120 are present acting as pushbuttons for manipulating the arms 103 and 104 and defining the aforesaid means 106.

By pressing on the elements 120 towards the interior of the cavity 116 (arrows E of Figure 18) these act on the parts 117 to elastically urge the ends 107 of the arms 103 and 104 together (arrows M of Figure 18), to enable the mascara to be applied to the eyelashes while maintaining then elements 120 pressed.

The element 113 is externally threaded at 124 (Figure

15) and cooperates with an internal thread 125 provided in the cavity 116. A lower end 129 of the part 105 is internally threaded to cooperate with a thread 126 provided on the open terminal part 127 of a container 128 for the mascara where a scraper 129 with two apertures 130 for the arms 103 and 104 is positioned. The thread on the lower end 124 is opposite to that provided in the cavity 116 so that on screwing the part 105 onto the container 128, the arms 103 and 104 remain at rest, while moving relative to, i.e. translate upwards within, the cavity 16 of this part (so that the element 13 moves close to the upper plug 111, arrow L of Figure 20).

The arms 103 and 104 may be opened and closed several times in applying mascara to a user's eyelashes and possibly in subjecting them to mechanical curling or other action depending on the interacting element 108 carried by one of these arms.

With reference to Figures 21, 22 and 23, these show a mascara applicator 200 comprising a wand 202 presenting arms 203 and 204 positioned side by side and movable relative to each other. These arms are associated with a

cup-shaped retaining member 205 provided with manipulator means 206 for their manipulation, said arms carrying at a first end 207 an interacting element 208 able to interact with the eyelashes to deposit mascara thereon or to provide a mechanical curling or combing action. These interacting elements 208 are similar to the elements 8 and 108 already described in relation to the preceding figures and will therefore not be further described.

Each arm 203, 204 presents a second end 215 inserted into a cavity 216 provided in the retaining member 205 (for example of cup shape). The second ends 215 of the arms 203, 204 are connected together by a spring 230 having a first end 231 mounted about a projection 232 on the first arm 203 and a second end 234 inserted into a recess 235 in the second arm 204. This latter is associated with (or, as in the figures, integral with) a pushbutton movable within an aperture 236 of the retaining member 205. The pushbutton and the second arm 204 move against the action of the springs 230 towards the first arm 203, which is itself fixed to the retaining member 205.

In this manner, by acting on said pushbutton, the arms

203 and 204 can be elastically closed together to apply the mascara.

Specific embodiments of the invention have been described. Others are however possible in the light of the preceding description: for example the expert of the art can provide a different configuration of the manipulator means 6, 106, 206 such that they do not project from the member 5, 105, 205 or that they take the form of a pushbutton movable towards the arms (3, 103, 203; 4, 104, 204).

These embodiments are also to be considered as falling within the scope of the present document as defined by the accompanying claims.

CLAIMS

1. A mascara applicator comprising a wand (2, 102, 202) presenting two side-by-side arms (3, 4: 103, 104: 203, 204) movable relative to each other, at least one of said arms (3, 4: 103, 104: 203, 204) carrying an element (8, 108, 208) for interacting with the eyelashes and a part for applying the mascara to the eyelashes, characterised in that said arms (3, 4: 103, 104: 203, 204) are connected together and can be made to elastically approach each other, said arms (3, 4: 103, 104: 203, 204) being partially contained within a retaining member (5, 105, 205) acting as a lid for a mascara container (28, 128), said retaining member (5, 105, 205) presenting means (6, 106, 206) for controlling the movement of said arms (3, 4: 103, 104: 203, 204), enabling them to be closed together so that they can interact with the eyelashes and to apply mascara thereto.

2. A mascara applicator as claimed in claim 1, characterised in that each arm (3, 4: 103, 104: 203, 204) presents a first end (7, 107, 207) carrying the element (8, 108, 208) for interacting with the eyelashes and a second end (15, 115, 215) inserted into a cavity (16, 116, 216) of

the retaining member, said second ends (15) of said movable arms (3, 4) being hinged together and moving against the action of elastic means (30) contained in the retaining member (5).

3. A mascara applicator as claimed in claim 2, characterised in that the second ends (15) of the movable arms (3, 4) present through holes (21) arranged to lie coaxially with each other and with at least one hole (27) provided in the retaining member, in these holes (21, 27) there being inserted a pin (28) acting as a hinge for the movement of the movable arms (3, 4).

4. A mascara applicator as claimed in claim 3, characterised in that the pin (28) joins the movable arms (3, 4) to the retaining member (5).

5. A mascara applicator as claimed in claim 2, characterised in that the second end (15) of one of said movable arms (3, 4) comprises a fork-shaped terminal part (20) arranged to receive a flat terminal part (20) of the other movable arm (4, 3).

6. A mascara applicator as claimed in claim 2, characterised in that the elastic means (30) are positioned

between the movable arms (3, 4).

7. A mascara applicator as claimed in claim 6, characterised in that said elastic means (30) are a spring positioned between seats (18) provided in parts (17) of said arms (3, 4), said seats (18) being opposing.

8. A mascara applicator as claimed in claim 1, characterised in that each arm (103, 104) presents a first end (107) carrying the element (108) for interacting with the eyelashes and a second end (115) inserted into a cavity (116) of the retaining member, said second end (115) of said movable arms (1031, 104) being integral with an interconnection element (113) located in said cavity.

9. A mascara applicator as claimed in claim 8, characterised in that the interconnection element (113) is movable within the cavity (116) of the retaining member (105).

10. A mascara applicator as claimed in claim 9, characterised in that the interconnection element (113) is threaded (at 124) and cooperates with a thread (1125) provided in the cavity (116) of the retaining member (105).

11. A mascara applicator as claimed in claim 1,

characterised in that the each arm (203, 204) presents a first end (207) carrying the element (208) for interacting with the eyelashes and a second end (215) inserted into a cavity (216) of the retaining member (105), a first (203) of said arms being rigid with said part (205) and the second (204) of said arms being movable relative to the first against the action of elastic means (230) interposed between the second ends (215) of said arms (203, 204).

12. A mascara applicator as claimed in claim 11, characterised in that the elastic means (230) are a spring having a first end (231) rigid with the first arm (203) and a second end (232) rigid with the second arm and movable therewith.

13. A mascara applicator as claimed in claim 11, characterised in that the second arm (204) is rigid with the control means (6).

14. A mascara applicator as claimed in claim 1, characterised in that the control means (6, 106, 206) are at least one pushbutton (33, 120).

15. A mascara applicator as claimed in claim 14, characterised in that the control means (6) are pushbuttons

(33, 120) movably inserted into lateral cavities (34, 118, 236) of the retaining member (5, 105, 205).

16. A mascara applicator as claimed in claim 15, characterised in that each pushbutton (33) engages a seat (38) provided in a corresponding movable arm (3, 4).

17. A mascara applicator as claimed in claim 15, characterised in that each pushbutton projects from the retaining member (5, 105, 205).

18. A mascara applicator as claimed in claim 15, characterised in that each pushbutton is coplanar between a free end surface with the outer surface of the retaining member (5, 105, 205)

19. A mascara applicator as claimed in claim 14, characterised in that the is only one pushbutton, this moving axially on the retaining member.

20. A mascara applicator as claimed in claim 1, characterised in that the retaining member (105) presents a threaded end (129) cooperating, by screwing, with a threaded free end (127) of a container (128), said threaded free end (127) supporting a scraper (129).

21. A mascara applicator as claimed in claim 5,

characterised in that the scraper (129) presents separate apertures (130) for the movable arms (103, 104), said arms being torsionally immovable when screwing the retaining member (105) onto the container.

22. A mascara applicator as claimed in claim 1, characterised in that the element (8, 108, 208) for interacting with the eyelashes comprises a brush (10).

23. A mascara applicator as claimed in claim 1, characterised in that the element (8, 108, 208) for interacting with the eyelashes comprises an eyelash curler (12).

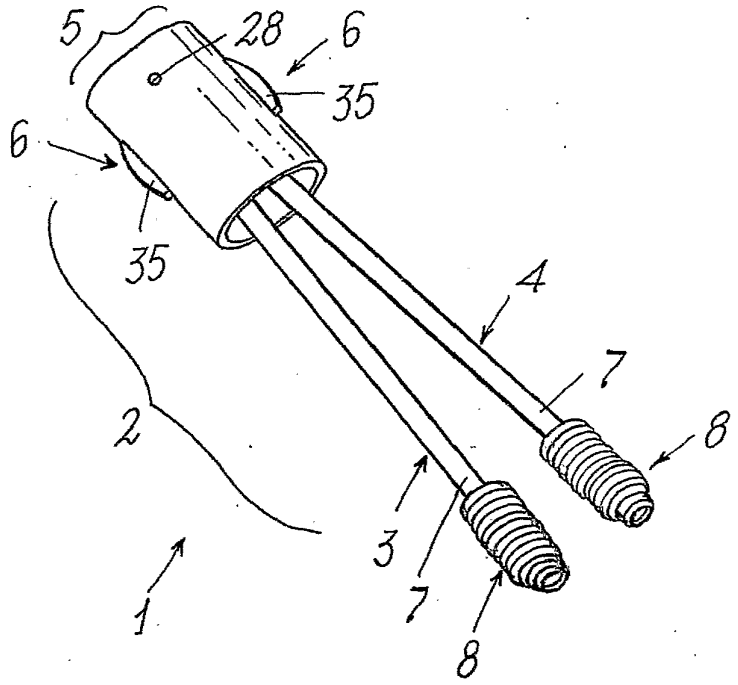



FIG. 1

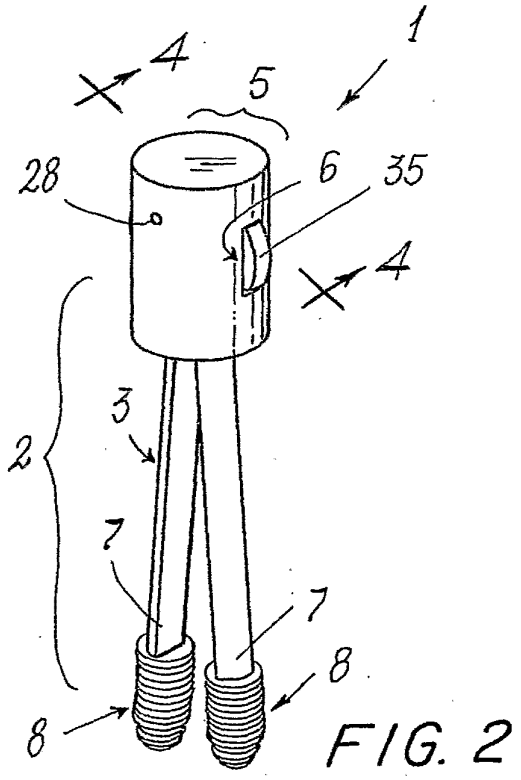



FIG. 2

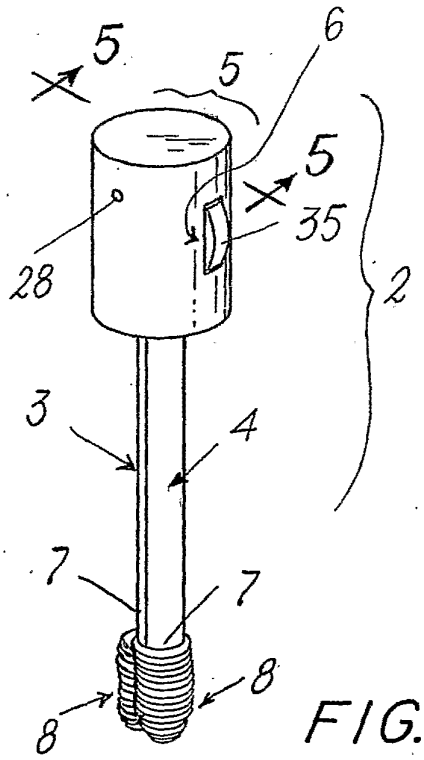



FIG. 3

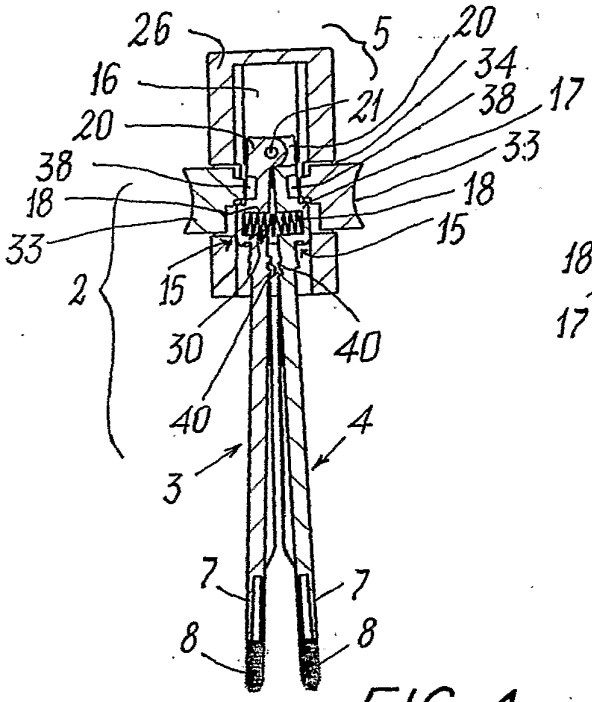



FIG. 4

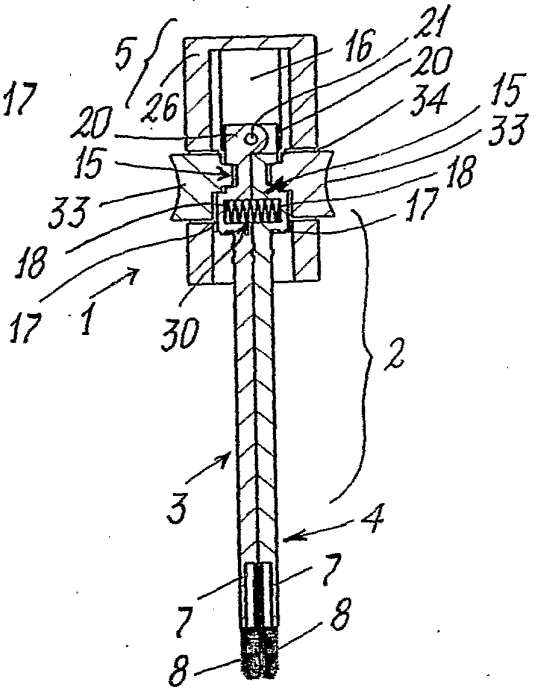



FIG. 5

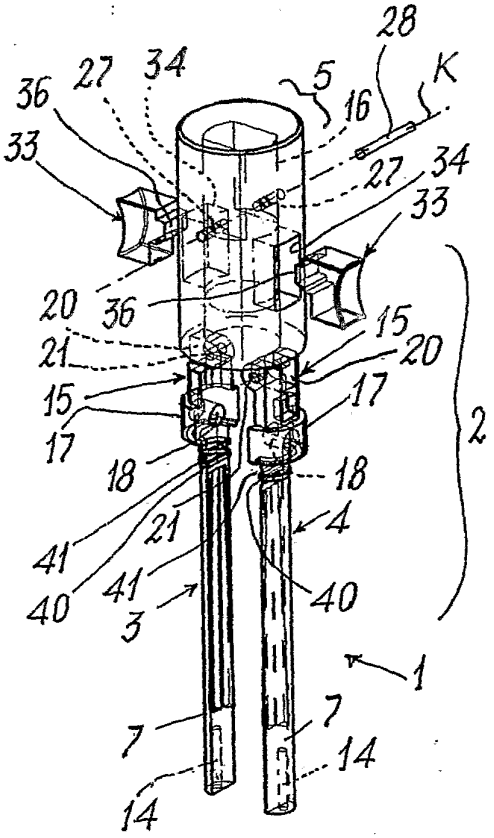



FIG. 6

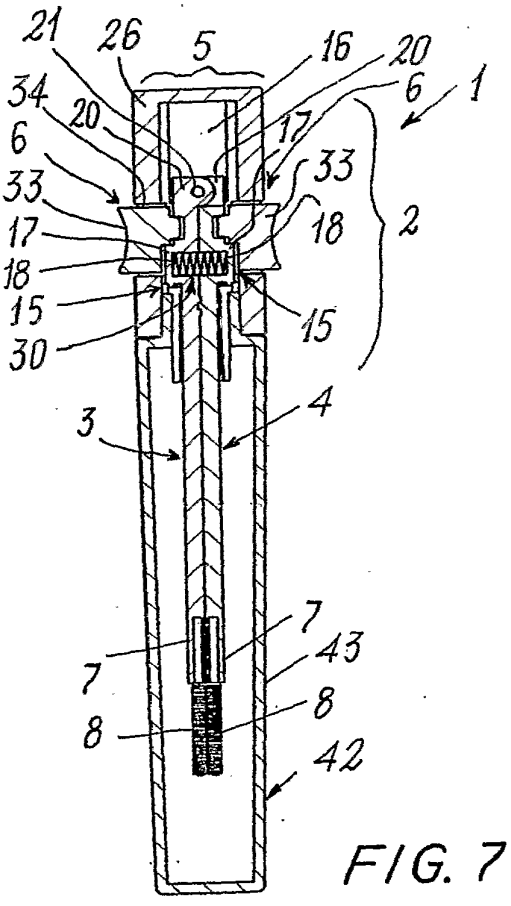
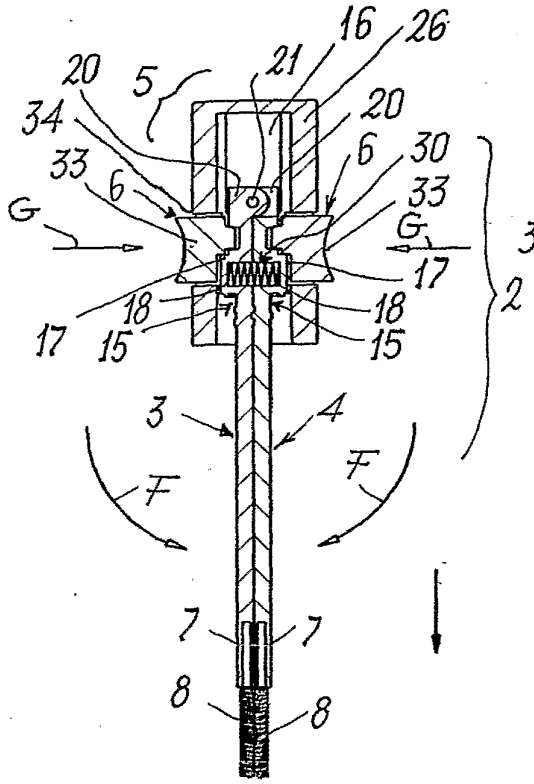



FIG. 7



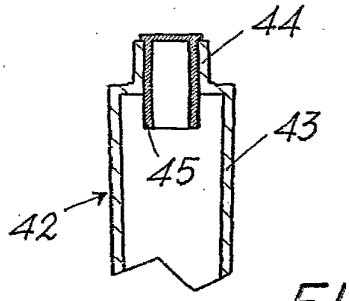
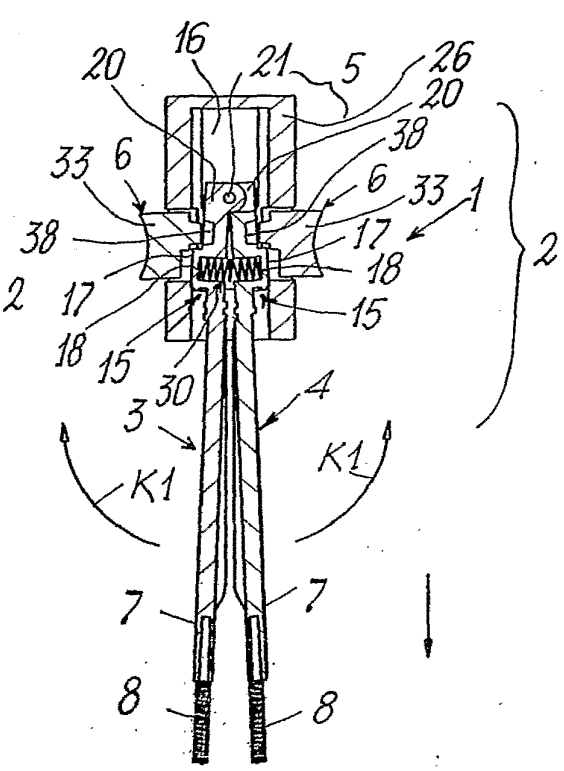




FIG. 8



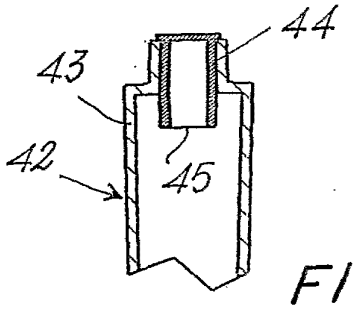




FIG. 9

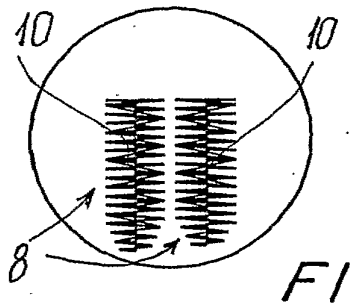



FIG. 10

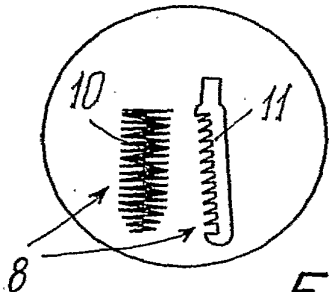



FIG. 11

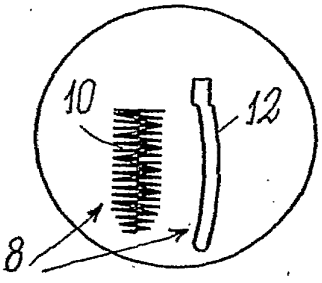



FIG. 12

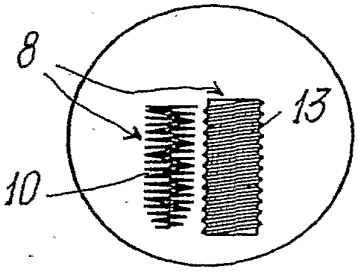



FIG. 13

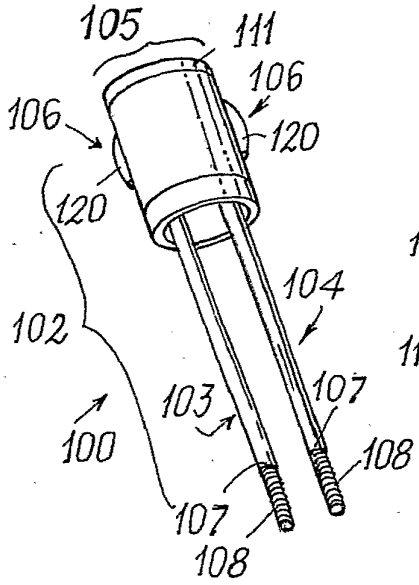



FIG. 14

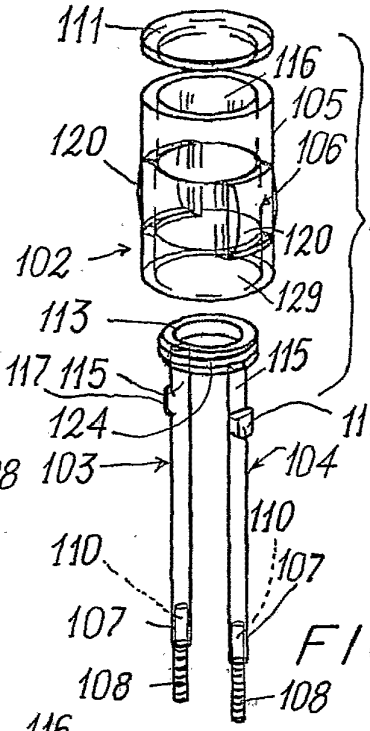



FIG. 15

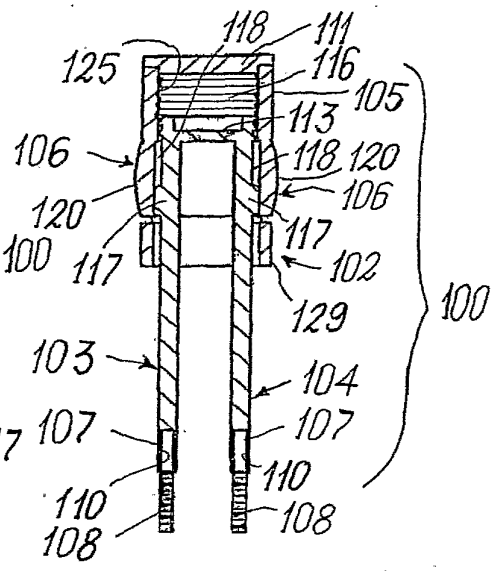



FIG. 16

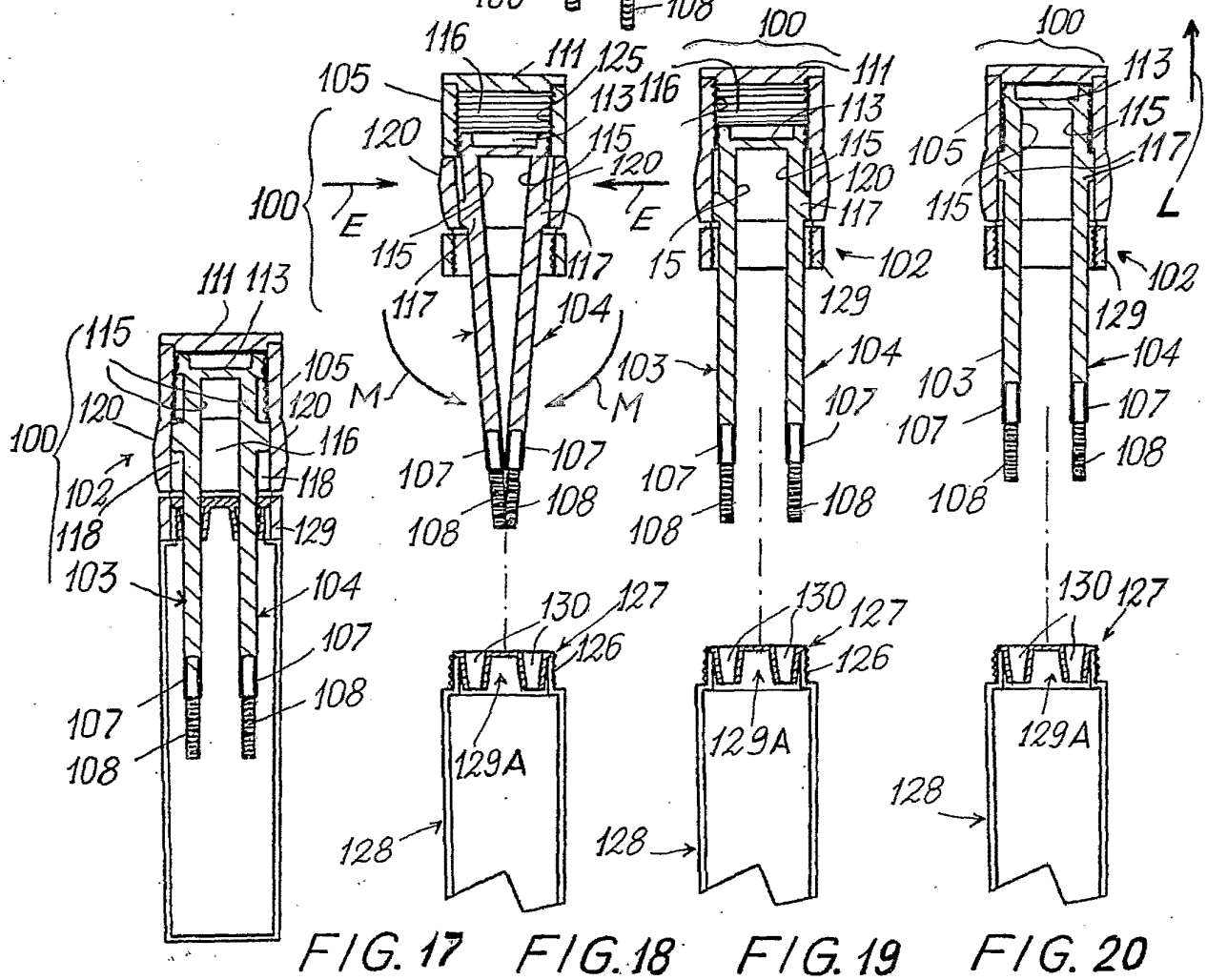



FIG. 17 FIG. 18 FIG. 19 FIG. 20

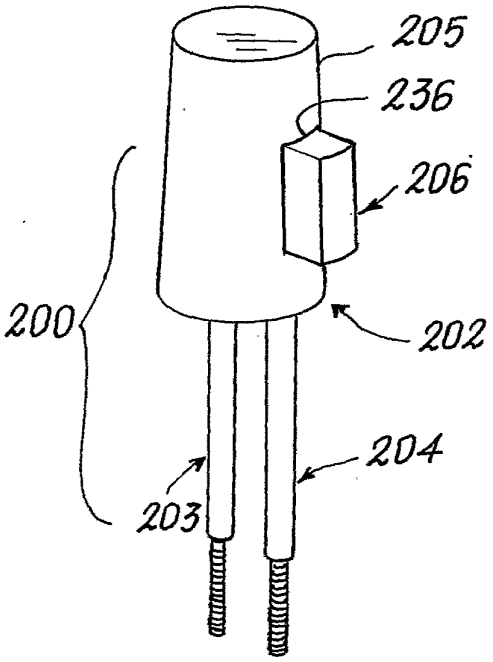



FIG.21

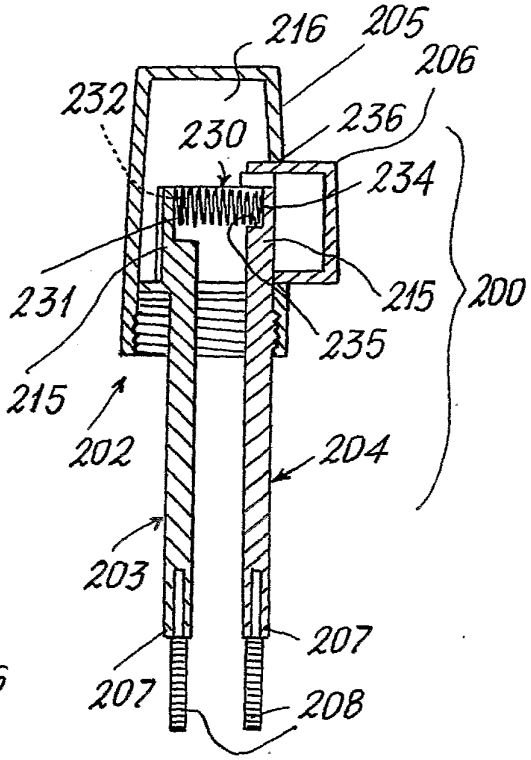



FIG. 22

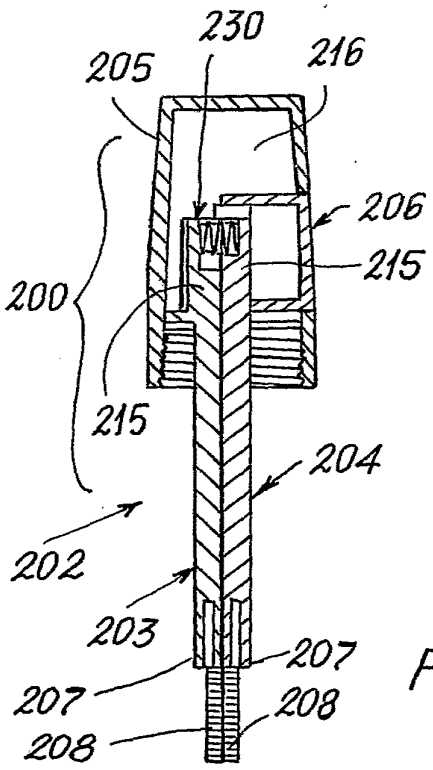



FIG. 23

# INTERNATIONAL SEARCH REPORT

International Application No
PCT/IB2004/000794

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A45D40/26 A45D2/48

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A45D A46B

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, WPI Data, PAJ

C. DOCUMENTS CONSIDERED TO BE RELEVANT

| Category ° | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|---|---|---|
| X | US 2 022 896 A (NATHANS ROBERT R)<br>3 December 1935 (1935-12-03)<br>page 1, column 2, line 26 -page 2, column 2, line 27; claims; figures 1-4 | 1,2,6,7 |
| X | GB 526 272 A (CHARLES WILLIAM STICKEL;KURLASH COMPANY INC; WILLIAM RAYMOND TUTTLE)<br>13 September 1940 (1940-09-13)<br>page 1, line 55 -page 2, line 104; claims; figures | 1,2,8, 22,23 |
| X | DE 820 792 C (HEROLD WILFRIED)<br>12 November 1951 (1951-11-12)<br>page 2, line 28,29; claims; figures | 1,22 |

-/--

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

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| Date of the actual completion of the international search | Date of mailing of the international search report |
|---|---|
| 17 June 2004 | 30/06/2004 |

| Name and mailing address of the ISA | Authorized officer |
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| European Patent Office, P.B. 5818 Patentlaan 2<br>NL – 2280 HV Rijswijk<br>Tel. (+31–70) 340–2040, Tx. 31 651 epo nl,<br>Fax: (+31–70) 340–3016 | Herry, M |

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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

| Category ° | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
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| A | US 6 026 825 A (DE LAFORCADE VINCENT)<br>22 February 2000 (2000-02-22)<br>figures | 1 |
| A | DE 817 945 C (KEHDER OTTO)<br>22 October 1951 (1951-10-22)<br>figures | 1 |

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PCT/IB2004/000794

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| | | JP 3210910 B2 | 25-09-2001 |
| | | JP 11346827 A | 21-12-1999 |
| DE 817945 C | 22-10-1951 | NONE | |

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1 February 2007 (01.02.2007)

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*A61K 39/08* (2006.01) *A61K 36/47* (2006.01)

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(71) Applicant *(for all designated States except US)*: **THE FOUNDRY INC.** [US/US]; 199 Jefferson Drive, Menlo Park, California 94025 (US).

(72) Inventors; and
(75) Inventors/Applicants *(for US only)*: **DEEM, Mark, E.** [US/US]; 685 Sierra Avenue, Mountain View, California 94041 (US). **GIFFORD, Hanson, S.** [US/US]; 3180 Woodside Road, Woodside, California 94062 (US).

(74) Agents: **HESLIN, James, M.** et al.; Two Embarcadero Center, 8th Floor, San Francisco, California 94111-3834 (US).

(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LV, LY, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

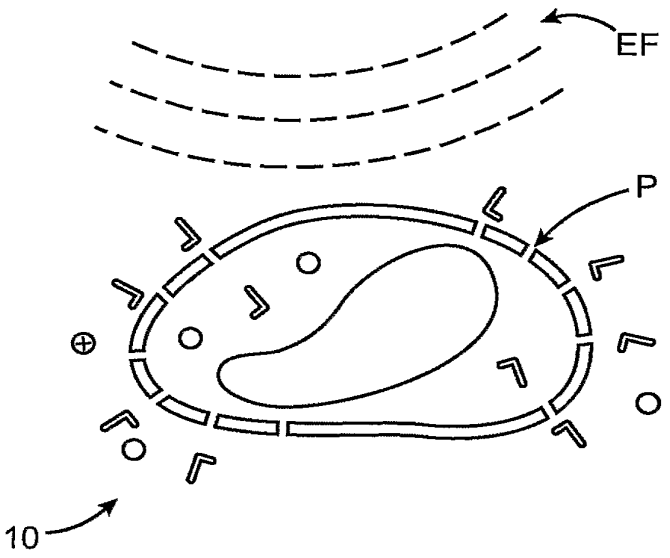
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**Published:**
— *without international search report and to be republished upon receipt of that report*

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(54) Title: SYSTEMS AND METHODS FOR DELIVERY OF A THERAPEUTIC AGENT




(57) Abstract: Methods and apparatus are provided for applying an fragment of a neurotoxin such as the active light chain (LC) of the botulinum toxin (BoNT), such as one of the serotype A, B, C, D, E, F or G botulinum toxins, via permeabilization of targeted cell membranes to enable translocation of the botulinum neurotoxin light chain (BoNT-LC) molecule across the targeted cell membrane to the cell cytosol where a therapeutic response is produced in a mammalian system. The methods and apparatus include use of catheter based delivery systems, non-invasive delivery systems, and transdermal delivery systems.

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# SYSTEMS AND METHODS FOR DELIVERY OF A THERAPEUTIC AGENT

## BACKGROUND OF THE INVENTION

**[0001]** 1. Field of the Invention. The present invention relates to methods and apparatus for the control of autonomic nerve function comprising delivery via permeabilization of targeted cell membranes a therapeutically effective amount of a portion or fragment of a neurotoxin such as botulinum toxin (BoNT), the active portion known as the light chain (LC), to cause a clinical benefit in various regions within the body.

**[0002]** First used for medical purposes over 20 years ago for treatment of blepharospasm and strabismus and other skeletal muscle abnormalities, certain neurotoxins have found widespread use in millions of patients worldwide for a variety of conditions.

**[0003]** Controlled injection of neurotoxins has become a common procedure to control skeletal muscle spasms. While the primary application of neurotoxins such as BOTOX®, commercially sold by Allergan, Inc. (Irvine, CA), has been focused on cosmetic applications, such as treatment of facial wrinkles, other uses for the compound are now common. Certain applications include treatment of cervical dystonia, tremor, headache (migraine), spasticity, torticollis, hemifacial spasm, blepharospasm, meige syndrome, spastic dysphonia, writers cramp, hyperhydrosis, hypersalivation, bladder dysfunction multiple sclerosis, spinal cord injury, cystic fibrosis, stroke paralysis, stuttering, and all types of pain.

**[0004]** *Clostridium botulinum* neurotoxins (BoNTs) block the release of acetylcholine from peripheral cholinergic nerve endings thereby disabling the release of neurotransmitters from the cells (Bigalke, H. and Shoer, L.F. (1999) *Clostridial Neurotoxins in Handbook of Experimental Pharmacology* 45, 407-443). This mechanism of action is well defined. Seven immunologically distinct serotypes of neurotoxin, designated types A through G, have been identified as discussed by Simpson, L.L., Schmidt, J.J. and Middlebrook, J.L. (1988) in *Methods Enzymol.* 165, 76-85. There are general structural and functional similarities among the various types of neurotoxins, but they all have preferred recipients, for example some favor use in humans and other in non-human species.

**[0005]** A frequently used neurotoxin for many applications in the human body is Botulinum Toxin Type A (BoNT\A), a protein produced by the bacterium Clostridium botulinum and sold commercially by Allergan, inc., as BOTOX®. Botulinum toxin blocks the release of neurotransmitter from the nerves that control the contraction of the target muscles. When used in medical settings, small doses of the toxin are injected into the affected muscles and block the release of a chemical acetylcholine that signals the muscle to contract. The toxin thus paralyzes or weakens the injected muscle.

**[0006]** In addition, use of neurotoxin for control of the following conditions has been proposed in United States Patents 6,063,768 to First, and 5,766,605 to Sanders, including: rhinorrhea, asthma, COPD, excessive stomach acid secretion, spastic colitis, otitus media, arthritis, tensoynovitis, lupus, connective tissue disease, inflammatory bowel disease, gout, tumors, musculo-skeletal abnormalities, reflex sympathetic dystrophies, tendonitis, bursitis, and peripheral neuropathy. Various other patents contemplate the use of a neurotoxin for additional applications such as, neuromuscular disorders (6,872,397), essential tremor (6,861,058), pancreatitis (6,843,998), muscle spasm (6,841,156), sinus headache (6,838,434), endocrine disorders (6,827,931), priapism (6,776,991), thyroiditis (6,773,711), cardiovascular disease (6,767,544), thyroid disorders (6,740,321), hypocalcemia (6,649,161), hypercalcemia (6,447,785), tardive dyskenesia (6,645,496), fibromyalgia (6,623,742), Parkinson's Disease (6,620,415) cerebral palsy (6,448,231), inner ear disorders (6,358,926), cancers (6,139,845), otic disorders (6,265,379), appetite reduction ((US2004/0253274), compulsive disorders (US2004/0213814, US2004/0213813), uterine disorders ((US2004/0175399), neuropsychiatric disorders (US2003/0211121), dermatological or transdermal applications (US2004/00091880), focal epilepsy (US2003/0202990) the contents of which are expressly incorporated herein by reference in their entirety.

**[0007]** The patent authors have further detailed devices and methods for treating asthma with local delivery of the intact botulinum toxin in United States Patent Application 10/437,882, filed on May 13, 2003, the contents of which are expressly incorporated by reference herein in its entirety.

**[0008]** Due to their extreme toxicity, neurotoxins are highly controlled and can have disastrous consequences if not used and controlled properly, especially when used *in vivo*. In addition, due to their toxicity, the body tends to build up a resistance to their use, resulting in

lower efficacy, the need for increased treatments, or the need to discontinue their use all together in certain patients.

**[0009]** In light of the foregoing, it would be desirable to provide methods and apparatus for delivering neurotoxins such as botulinum toxins non-toxically.

**[0010]** It would also be desirable to provide methods and apparatus for treating various conditions with a neurotoxin such as botulinum toxin fragments via *in vivo* cell permeabilization.

**[0011]** In would also be desirable to provide a system of devices, including catheters, trocars, needles, endoscopes, inhalers, nebulizers and aerosolizers and other mechanisms to deliver fragmented neurotoxins non-toxically.

**[0012]** Further, it would be desirable to couple energy delivery devices with the delivery of fragmented neurotoxins to deliver active neurotoxins, non-toxically, including catheter based energy systems, and non-invasive energy systems.

**[0013]** All publications and patents or patent applications mentioned in this specification are herein incorporated by reference to the same extent as if each individual publication, patent or patent application was specifically and individually so incorporated by reference.

## BRIEF SUMMARY OF THE INVENTION

**[0014]** According to the present invention, an active fragment (sometimes referred to as a catalytic portion) of a neurotoxin such as the botulinum neurotoxin (BoNT), preferably the light chain (LC) portion of BoNT, is delivered to target cells via cell membrane permeabilization. Such delivery provides a non-toxic delivery scheme for deriving a variety of clinical benefits. Although botulinum toxins are used broadly for a variety of clinical applications, the present invention provides enhanced methods of delivery and use of the isolated active fragments or portions of the toxin. Other neurotoxins which may be used in the methods and systems of the present invention include ricin and its active fragments, exotoxin A and its active fragments, diphtheria toxin and its active fragments, cholera toxin and its active fragments, tetanus toxin and its active fragments, and the like.

**[0015]** The present invention contemplates application to all of the conditions listed herein, collectively defined as "therapeutic target conditions", and any other conditions for which BoNT and other neurotoxins are known to or can be shown to provide a therapeutic benefit.

Certain examples have been detailed below for specific applications, but it is within the scope of the present invention that the methods and devices detailed herein have specific applications to many or all of the conditions wherein the intact neurotoxins have shown or proposed to show a therapeutic benefit or effect.

**[0016]** In one aspect of the present invention, BoNT-LC or other active neurotoxin fragment is delivered with the application of energy to achieve cell membrane permeabilization.

**[0017]** In another aspect of the present invention methods and apparatus are provided for altering autonomic nerve function by utilizing an electric field or ultrasonic energy generated by a pulse or pulses of a designated duration and amplitude to alter tissue at the cellular level via permeabilization of the cell membrane to facilitate the translocation of the BoNT-LC or other active neurotoxin fragment to the cell cytosol.

**[0018]** A further aspect of the invention is to provide methods and apparatus for treating or inhibiting a variety of diseases or syndromes that have an underlying neurogenic component, by disrupting the neurogenic activities of the promoters or mediators of the disease or syndrome. Such disruption is facilitated by delivering an active fragment of botulinum toxin, such as the light chain portion of botulinum toxin serotype A (BoNT-LC/A), in the presence of an electric field or ultrasonic energy applied to permeabilize the wall of targeted cell under conditions which induce reversible poration of the cellular membrane and efficient passage of the BoNT-LC fragment to the cell cytosol, its catalytic environment.

**[0019]** In addition to the methods described thus far, the present invention further provides systems for delivering toxins to target cells in a mammalian host. The target cells may be in any of the target regions described above or in any other target region which may benefit from the specific and enhanced delivery of a neurotoxin to cells within the region. Systems comprise catheter or other structure adapted to introduce the toxin or toxin fragment to a region adjacent the target cells. The systems further comprise an energy applicator for applying energy to the target cells under condition which cause poration of the cell membranes to enhance delivery of the toxins and/or their active fragments. The systems still further comprise a source of the toxin or active fragments suitable for introduction from the catheter or other delivery structure.

**[0020]** The energy applicator will typically be adapted to selectively apply energy to target cells within the region where the toxin is to be introduced, e.g., by focusing energy

distribution to the particular target cells or regions which are rich with the target cells. Alternatively, the energy applicator may be adapted to apply energy non-selectively within the target region where both target cells and other cell types may receive the energy.

**[0021]** In some instances, the toxin may comprise an intact toxin, but more usually will comprise an active toxin fragment as defined elsewhere in this application. In the exemplary embodiments, the active toxin fragment is the light chain fragment of the botulinum toxin (BoNT-LC). The light chain fragment may be derived from any one of at least botulinum toxins A, B, C, D, E, F, and G.

**[0022]** The energy applicators of the systems of the present invention may be adapted to apply electric energy, typically pulses between 1 V and 500 V to the targeted region. The electric energy may be radiofrequency (RF) energy, where the energy may be pulsed for durations between 5 microseconds to 100 milliseconds. Alternatively, the electrical energy can be direct current (DC), alternating current (AC), or combinations thereof.

**[0023]** In addition to electrical energy, the energy applicator may be adapted to deliver ultrasonic energy, X-ray beam energy, microwave energy, or any other energy type which can achieve a reversible poration of the target cell walls.

**[0024]** There are at least two general power categories of medical ultrasound waves which may be utilized in the present invention. One category of medical ultrasound wave is high acoustic pressure ultrasound. Another category of medical ultrasound wave is low acoustic pressure ultrasound. Acoustic power is expressed in a variety of ways by those skilled in the art. One method of estimating the acoustic power of an acoustic wave on tissue is the Mechanical Index. The Mechanical Index (MI) is a standard measure of the acoustic output in an ultrasound system. High acoustic pressure ultrasound systems generally have a MI greater than 10. Low acoustic pressure systems generally have a MI lower than 5. For example, diagnostic ultrasound systems are limited by law to a Mechanical Index not to exceed 1.9. Another measurement used by those skilled in the art is the spatial peak, peak average intensity (Isppa). The intensity of an ultrasound beam is greater at the center of its cross section than at the periphery. Similarly, the intensity varies over a given pulse of ultrasound energy. Isppa is measured at the location where intensity is maximum averaged over the pulse duration. Isppa for high acoustic pressure or high intensity focused ultrasound (HIFU) applications ranges from approximately 1500W/cm2. to 9000 $W/cm_2$. Diagnostic ultrasound equipment, for instance, will generally have, and an Isppa less than 700 $W/cm_2$.

Yet another way in which ultrasound waves can be characterized is by the amplitude of their peak negative pressure. High acoustic pressure or HIFU applications employ waves with peak amplitudes in excess of 10MPa. Low acoustic pressure ultrasound will generally have peak negative pressures in the range of 0.01 to 5.0 MPa . Diagnostic ultrasound equipment, for example, will generally have a peak amplitude less than 3.0MPa. Both high and low acoustic pressure ultrasound systems generally operate within the frequency range of 20KHz – 10.0 MHz Interventional applications (such as in blood vessels) operate clinically up to about 50 MHz. Also opthalmologic applications up to about 15 MHz. Diagnostic imaging typically uses frequencies of about 3 to about 10 MHz. Physical therapy ultrasound systems generally operate at frequencies of either 1.0MHz or 3.3MHz. High acoustic pressure ultrasound or high intensity focused ultrasound has been used for tissue disruption, for example for direct tumor destruction. High intensity focused ultrasound using high acoustic pressure ultrasound is most commonly focused at a point in order to concentrate the energy from the generated acoustic waves in a relatively small focus of tissue.

**[0025]** Systems and methods for permeabilization of target tissue cell membranes according to the present invention may employ either high acoustic pressure or low acoustic pressure ultrasound. Some embodiments may preferably employ relatively low acoustic pressure, for example the systems described herein where the transducers are mounted on the delivery devices and operate inside the body. Other systems may operate at interim acoustic pressure ranges. For example, systems described herein which employ an external ultrasound generator and transducer and which conduct the ultrasound to the target tissues through the use of a wave guide. In these systems, losses due to transduction through the wave guide can be compensated for by increasing the input power to the wave guide until adequate power is delivered to the target tissue. Finally, some systems described herein may employ focused or partially focused higher pressure ultrasound, for example the systems which employ an external mask to conduct the ultrasonic power through the tissues to the target tissues. It should be appreciated that combinations of high and low acoustic pressure systems may also be employed.

**[0026]** The catheter or other structure may be adapted to introduce the toxin to the target cells in a variety of ways. For example, catheters may comprise a needle for injecting the toxin, optionally a needle which is deployable axially or radially from the catheter body.

Alternatively or additionally, catheters may be provided with nozzles or other ports for aerosolizing the toxin, particularly within regions of the lung as described herein. Still further alternatively or additionally, the catheters may comprise balloons or other expandable elements for deflecting an end of the catheter to engage one or more ports on the catheter against the tissue where the toxin fragments are released through the port(s). In a specific embodiment, the ports may be in the balloon itself where the toxin fragments are released through the ports in the balloon as the balloon is inflated with the medium containing the fragments. With such balloon embodiments, the electrodes or other energy transducers will typically be located within the balloon for applying the poration energy to the target tissue. Further optionally, the energy applicators may be mounted directly on the catheters, for example in the form of acoustic transducers, RF or other electrical electrodes, or the like. Alternatively, the energy applicator may be provided separately from the toxin delivery catheter or other source, typically being an external source, such as an external high intensity focused ultrasound (HIFU) source or an external electrode array for delivering radiofrequency or other electroporation energy.

**[0027]** In a further aspect of the invention, it may be desirable to provide methods and devices that utilize a non-toxic delivery mechanism to target cells to reduce the potential for an immunogenic response to the delivered toxin over time.

**[0028]** In a further aspect of the invention, it may be desirable to deliver the therapeutic neurotoxin fragment and energy via a catheter.

**[0029]** In a further aspect of the invention, it may be desirable to deliver the therapeutic neurotoxin fragment via an aerosolizer or nebulizer.

**[0030]** In a further aspect of the invention, it may be desirable to deliver the therapeutic neurotoxin fragment via an inhaler.

**[0031]** In a further aspect of the invention, it may be desirable to deliver the therapeutic neurotoxin fragment and membrane transport energy transdermally.

**[0032]** In a further aspect of the invention, it may be desirable to deliver the therapeutic neurotoxin fragment via a catheter, or aerosolizer or inhaler, and the energy via a catheter placed in the vicinity of the targeted cell.

**[0033]** In a further aspect of the invention, it may be desirable to delivery the therapeutic neurotoxin fragment and the membrane transport energy via an implantable generator and drug delivery pump.

**[0034]** In a further aspect of the invention, it may be desirable to deliver the therapeutic neurotoxin fragment via a catheter, or aerosolizer (nebulizer) or inhaler, and the energy via an external energy source adapted to target the applied energy in the vicinity of the targeted cell.

## BRIEF DESCRIPTION OF THE DRAWINGS

**[0035]** Further features of the invention, its nature and various advantages will be more apparent from the accompanying drawings and the following detailed description, in which:

**[0036]** Figure 1 – depicts a schematic of the creation of neurotoxin Botulinum Toxin Type A (BoNT/A), including the light chain (LC) fragment or portion.

**[0037]** Figure 2A – depicts a schematic of a target cell, including the cell membrane, and inner cellular matrices.

**[0038]** Figure 2B – depicts a schematic of the target cell wherein LC molecule has been introduced.

**[0039]** Figure 3A-3B – depicts a the target cell of Figure 2 showing application of an energy field (EF) to produce permeabilization or pores (P) in the cell membrane, and introduction of the LC fragment therethrough.

**[0040]** Figure 4 – depicts a schematic of a cell wherein the energy field has been discontinued, and neurotransmission of the cell has been effectively blocked.

**[0041]** Figures 5, 5A-5B – depicts various embodiments of a delivery device of the present invention utilizing multiple energy transmission elements and an energy transmission system.

**[0042]** Figures 6A-D, 6AA, and 6CC – depict various electrode catheter configurations adapted to deliver energy or energy and therapeutic agents to target tissue.

**[0043]** Figure 7 – depicts an alternative embodiment of the present invention wherein one of the multiple energy transmission elements is placed at the targeted cell site, and the other in a location remote therefrom.

**[0044]** Figure 8 - depicts an embodiment of the present invention utilizing an ultrasound element on a catheter device.

**[0045]** Figure 9 - depicts an embodiment of the present invention utilizing an inhaler with an *in vivo* energy delivery source.

**[0046]** Figure 10 - depicts an interstitial method of use of the present invention.

**[0047]** Figure 11 – depicts an embodiment of the present invention utilizing an aerosolizing element.

**[0048]** Figure 12 – depicts a fully implantable pulse generator, lead and agent delivery pump of the present invention.

**[0049]** Figure 13 – depicts an embodiment of the present invention utilizing an external energy delivery source applied to the therapeutic agent applied in the vicinity of a targeted cell.

**[0050]** Figure 14 – depicts an embodiment of the present invention wherein the energy and therapeutic agent are delivered transdermally.

**[0051]** Figure 15 – depicts a method of use of a noninvasive agent delivery device coupled with a non-invasive energy source for treating a lumen or tract of the respiratory system.

**[0052]** Figures 15A and 15B – depict use of a balloon for delivering toxin fragments in a lung.

**[0053]** Figures 16A and 16B – depict use of a deflected catheter tip for delivering toxin fragments in a lung.

## DETAILED DESCRIPTION OF THE INVENTION

**[0054]** The present invention is directed to methods and apparatus for targeting the non-toxic delivery of a fragment of a neurotoxin, while still maintaining the catalytic or toxic effect of the neurotoxin fragment once it is non-toxically delivered to its targeted cell. For purposes of this specification, the term "non-toxic", "non-toxically" and the like refer to the state of the fragment molecule prior to delivery to a target location. In this description, the fragment neurotoxin is intended to retain its toxic effect once delivered to its catalytic environment; the intracellular matrix or cytosol of the targeted cell.

**[0055]** Devices and methods of the present invention may be directed to suitable "targeted regions" such as muscle cells in various regions of the body related to the various "therapeutic target conditions" or syndromes to be treated, as detailed in this specification

above. Some particular examples include targeting mucosal and muscular lining of the lung, cholinergic cells in the region of tumors, myofacial regions, vascular smooth muscle cells, musculoskeletal regions and the like.

**[0056]** According to the present invention, energy fields (EF) may be applied to target regions in conjunction with the delivery of a fragmented neurotoxin such as BoNT-LC to facilitate the transfer of the neurotoxin fragment into the targeted cell, non-toxically via *in vivo* target cell permeabilization.

**[0057]** Use of Isolated Light Chain of Botulinum Neurotoxins. Generally, the BoNT molecule is synthesized as a single polypeptide chain of 150kD molecular weight. The neurotoxin is then exposed to enzymes, either during cultivation of the *Clostridium botulinum* organism or subsequent to purification of the toxin, wherein specific peptide bonds are cleaved or "nicked" resulting in the formation of a dichain molecule referred to as BoNT. As shown in Figure 1, dichain neurotoxin is composed of a light chain (LC) region 50kD molecular weight linked by disulfide bonds to a heavy chain (HC) 100kD molecular weight (Kistner, A., Habermann, E. (1992) *Naunyn Schmiedebergs Arch. Pharmacol.* 345, 227-334). When the light chain is separated from the heavy chains of botulinum toxin, neither chain is capable of blocking neurotransmitter release, however, the light chain alone is capable of blocking acetylcholine release if transported directly into the cell cytosol. (Ahnert-Hilger, G., Bader, M.F., Bhakdi, S., Gratzl, M. (1989) *J. Neurochem.* 52, 1751-1758 and Simpson, L.L. (1981) *Pharmacol. Rev.* 33, 155-188.) Focusing on the light chain, the isolation or separation process essentially renders the light chain "non-toxic" in a general environment, while still maintaining its effect or toxicity, once it is transported through the target cell membrane.

**[0058]** Over the past several years, the separation and purification of the light chain and heavy chain of BoNT has seen significant development activity. In the case of the heavy chain (HC), researchers are interested in its ability to bond with a target cell and deliver certain molecules into that cell. For example, various drug delivery applications have been suggested, for example, using the HC to bind to tPA so that a patient could inhale the HC-bound tPA allowing it to cross the membrane of the lungs and be transported into the bloodstream for anticoagulation. Of particular interest to the present invention are the efforts to isolate and purify the light chain (LC) of the botulinum molecule. In its isolated and purified form, all HC elements are removed, rendering the LC incapable of crossing the cell

membrane without assistance. Thus, the LC is non-toxic until delivered to the target cell cytosol by the delivery protocols of the present invention.

**[0059]** Various groups have been active in the area of isolation and purification. For example, companies such as Metabiologics, a group affiliated with the University of Wisconsin, the Center for Applied Microbiology and Research (CAMR), a division of the UK Health Protection Agency, List Biological Laboratories, Inc. of California, and other research groups throughout the world. Many of these companies provide purified preparations of botulinum neurotoxins from *Clostridium botulinum* types A and B. List Laboratories in particular provides recombinantly produced light chains from both types A, B, C, D and E.

**[0060]** According to the present invention, the therapeutic use and delivery of the light chain only may significantly improve the safety profile of certain applications of therapies utilizing BoNT. BoNT are some of the most lethal toxins known to man. All concerns about migration of the neurotoxin into unintended regions, and harm or toxicity to the patient or physician are eliminated by storing, handling, injecting and metabolizing the light chain only. In the absence of a specific membrane binding technology, the LC is completely non-toxic. In certain applications, such as the treatment of asthma, this is of critical import. In using BoNT to treat asthma, a large quantity of the purified LC substance may be introduced directly into the lung, and then specifically transported to target cells in the exact location and only during the period of use of application of the membrane transport technology, such as cell membrane permeabilization by energy. Once the membrane transport technology has been removed, turned off or otherwise inactivated, the remaining LC which has not been transported into target cells can simply be removed from the body by standard biologic processes for expelling foreign materials, e.g. coughing, immune system or lymphatic system transport and the like.

**[0061]** In addition, therapeutic use of only the LC of the neurotoxin BoNT may reduce the likelihood of the body developing an immunogenic response to the therapy that is seen with delivery of the intact toxin. This could be a major advantage in light of the repetitive application or injection of the toxin that is required to maintain a therapeutic effect.

**[0062]** Non-Toxic Membrane Transport Mechanisms. To date, the main application of purified or isolated light chain has been the study of its mechanism of action. To further this research, literature has reported the use of certain detergent based permeabilization

techniques to deliver fragment BoNT (Bittner MA, DasGupta BR, Holz RW. Isolated light chains of botulinum neurotoxins inhibit exocytosis. Studies in digitonin-permeabilized chromaffin cells. J Biol Chem 1989 Jun 25; 264(18):10354–10360.) Further reference to the mechanism of permeability of cell membranes to deliver botulinum toxin are mentioned in United States Patent 6,063,768 to First, and United States Patent No. 6,632,440 to Quinn, Chaddock, et al "Expression and Purification of Catalytically Active Non-Toxic Endopeptidase Derivatives of Clostridium botulinum toxin type A", *Protein Expression and Purification*, 25 (2002) 219-228, contemplating the insertion of the light chain of BoNT into a target cell without the heavy chain for purposes of deriving vaccines or in bench top studies of cell mechanisms of action. The contents of these references are expressly incorporated by reference in their entirety. None of the teachings contemplate a delivery of a fragment of neurotoxin using a clinically acceptable permeabilization technique *in vivo* for therapeutic uses as is contemplated by the present invention.

**[0063]** For purposes of this specification, the term "poration" includes various forms of electroporation, such as the use of pulsed electric fields (PEFs) , nanosecond pulsed electric fields (nsPEFs), ionophoreseis, electrophoresis, electropermeabilization, as well as other energy mediated permeabilization, including sonoporation (mediated by ultrasonic or other acoustic energy), and/or combinations thereof, to create temporary pores in a targeted cell membrane. Similarly, the term "electrode" or "energy source" used herein, encompasses the use of various types of energy producing devices, including x-ray, radiofrequency (RF), DC current, AC current, microwave, ultrasound, adapted and applied in ranges to produce membrane permeabilization in the targeted cell.

**[0064]** Reversible electroporation, first observed in the early 1970's, has been used extensively in medicine and biology to transfer chemicals, drugs, genes and other molecules into targeted cells for a variety of purposes such as electrochemotherapy, gene transfer, transdermal drug delivery, vaccines, and the like.

**[0065]** In general, electroporation may be achieved utilizing a device adapted to activate an electrode set or series of electrodes to produce an electric field. Such a field can be generated in a bipolar or monopolar electrode configuration. When applied to cells, depending on the duration and strength of the applied pulses, this field operates to increase the permeabilization of the cell membrane and reversibly open the cell membrane for a short period of time by causing pores to form in the cell lipid bilayer allowing entry of various therapeutic elements

or molecules, after which, when energy application ceases, the pores spontaneously close without killing the cell after a certain time delay. As characterized by Weaver, *Electroporation: A General Phenomenon for Manipulating Cells and* Tissues Journal of Cellular Biochemistry, 51:426-435 (1993), short(1-100μs) and longer (1-10ms) pulses have induced electroporation in a variety of cell types. In a single cell model, most cells will exhibit electroporation in the range of 1-1.5V applied across the cell (membrane potential).

**[0066]** In addition, it is known in the art that macromolecules can be made to cross reversibly created pores at voltages of 120V or less applied to cells for durations of 20 microseconds to many milliseconds. For applications of electroporation to cell volumes, ranges of 10 V/cm to 10,000 V/cm and pulse durations ranging from 1 nanosecond to 0.1 seconds can be applied. In one example, a relatively narrow (μsec) high voltage (200V)pulse can be followed by a longer (>msec) lower voltage pulse (<100V). The first pulse or series of pulses open the pores and the second pulse or series of pulses assist in the movement of the BoNT-LC across the cell membrane and into the cell.

**[0067]** Certain factors affect how a delivered electric field will affect a targeted cell, including cell size, cell shape, cell orientation with respect to the applied electric field, cell temperature, distance between cells (cell-cell separation), cell type, tissue heterogeneity, properties of the cellular membrane and the like.

**[0068]** Various waveforms or shapes of pulses may be applied to achieve electroporation, including sinusoidal AC pulses, DC pulses, square wave pulses, exponentially decaying waveforms or other pulse shapes such as combined AC/DC pulses, or DC shifted RF signals such as those described by Chang in *Cell Poration and Cell Fusion using and Oscillating Electric Field*, Biophysical Journal October 1989, Volume 56 pgs 641-652, depending on the pulse generator used or the effect desired. The parameters of applied energy may be varied, including all or some of the following: waveform shape, amplitude, pulse duration, interval between pulses, number of pulses, combination of waveforms and the like.

**[0069]** A schematic example of the methods of the present invention are shown in Figures 2-4 in a simplified single cell model. A targeted cell 10 is shown in Figure 2A. Fragmented neurotoxin such as BoNT-LC (LC) is introduced into the vicinity of the targeted cell as depicted in Figure 2B. An energy field (EF) is applied in accordance with the present invention resulting in the transfer of the BoNT-LC through pores P to the intracellular matrix (cytosol) as shown in Figures 3A and 3B. Once this transfer has occurred, the release of

neurotransmitters of the target cell are then blocked or disrupted, and once energy application is discontinued, the pores P in the cell membrane recover or close as depicted in Figure 4.

**[0070]** Of particular interest for application in certain therapeutic target conditions is the developing field of sonoporation. Just as pulses of high voltage electricity can open transient pores in the cell membrane, ultrasonic energy can do the same. See for example Guzman et al. "Equilibrium Loading of Cells with Macromolecules by Ultrasound: Effects of Molecular Sizing and Acoustic Energy," *Journal of Pharmaceutical Sciences*, 91:7, 1693-1701, which examines the viability of ultrasound to deliver molecules of a variety of sizes into target cells. In addition, techniques for nebulizing fluids and aqueous drugs are well known in the art, and as such, devices of the present invention may be adapted to introduce a BoNT-LC solution to a target region, such as the lung and then effect selective membrane transport of the BoNT-LC into the cell using sonoporation.

**[0071]** For example, United States Patent 6,601,581 to Babaev, hereby incorporated by reference in its entirety, describes certain techniques for delivering therapeutic agents using ultrasound for pulmonary delivery via an aerosolizing technique. Further, Guzman, et al, depicts delivery of molecules from a low of 62Da up to 464 kDa (a range of 0.6-18.5nm radius). Since the LC of the botulinum toxin is in the 50kDa range, the LC would be very susceptible to sonoporetic delivery. Furthermore, Guzman, et al also showed that for all size ranges tested, levels of macromolecule within the cell reached thermodynamic equilibrium with the extracellular environment, and the cell uptake also depended on the energy delivered, as expressed in $J/cm^2$. As such, the sonoporetic delivery of LC to the targeted regions may be controlled by adjusting the concentration of the LC exposed to the target region (e.g. wall or membrane of the lung), the energy delivered to the target region, or both.

**[0072]** Catheter Devices. To achieve the goals of the present invention, it may be desirable to employ methods and apparatus for achieving cell membrane permeabilization via the application of an energy source, either from a catheter located directly in the vicinity of the targeted cells, or an externally focused energy system. For purposes of this specification, the term "catheter" may be used to refer to an elongate element, hollow or solid, flexible or rigid and capable of percutaneous introduction to a body (either by itself, or through a separately created incision or puncture), such as a sheath, a trocar, a needle, a lead. Further descriptions of certain electroporation catheters are described in United States Patent Application

60/701,747 (Attorney Docket No. 020979-003500US), filed on July 22, 2005, the full disclosure of which is expressly incorporated herein by reference.

**[0073]** Figures 5 and 5A-5B depict a system 20 utilizing an electroporation catheter 22 for selective electroporation of targeted cells. In certain configurations of the present invention, voltages may be applied via the electroporation catheter 22 to induce reversible electroporation at the same time as the catheter delivers the fragmented neurotoxin to the targeted region.

**[0074]** Referring to Figure 5, electroporation catheter system 20 further comprises a pulse generator 24 such as those generators available from Cytopulse Sciences, Inc. (Columbia, MD) or the Gene Pulser Xcell (Bio-Rad, Inc.), or IGEA (Carpi, Italy), electrically connected to a catheter having a proximal end and a distal end and adapted for minimally invasive insertion into the desired region of the body as described herein. The catheter further comprises an electroporation element 26 at a distal 28 end thereof. The electroporation element may include for example a first and second electrode 30 and 32 operatively connected to the pulse generator for delivering the desired number, duration, amplitude and frequency of pulses to affect the targeted cells. These parameters can be modified either by the system or the user, depending on the location of the catheter within the body (intervening tissues or structures), and the timing and duration of reversible cell poration desired. Figure 5A depicts an arrangement of electrodes 30 and 32 that produces an electric field concentrated in a lateral direction from the catheter body whereas, Figure 5B shows a device constructed to create a more uniform electric field about the shaft of the catheter body.

**[0075]** Further catheter device and electrode configurations are shown in Figures 6A-6D. Figure 6A depicts an elongate catheter 40 having first and second electrodes 42 and 44 near the distal tip thereof, and including a monitoring or stimulation electrode 46 in the vicinity of the active porating electrodes for localizing the treatment area. In some embodiments, the monitoring or stimulating function may be performed by one or more of the treatment electrodes. The catheter device may have an optional sharp tip 48 to facilitate percutaneous introduction. Cross-sectional view Figure 6AA shows various lumens provided for neurotoxin fragment delivery and other purposes.

**[0076]** Figure 6B is a similar catheter device 50 having electrodes 52, 54, and 56, but is further adapted to be steerable, or articulate at a region 53 near the distal end of the device, e.g., including a pull wire for deflecting the tip. Such steering ability enables the operator to

introduce the device into tight or tortuous spaces (such as the bronchial passages or cardiovascular vessels) so that optimal placement of the device at the target location may be achieved.

**[0077]** Figure 6C depicts a catheter device 60 having a needle 62 or other injection element to allow for the injection of a therapeutic agent such as a fragmented neurotoxin before, during or after the application of the pulsed energy or electroporation. The catheter 60 further includes electrodes 64 and 66 or other poration components as discussed herein. The injection element may be a needle 62 as shown in Figure 6C, an infusion port, or other infusion means. Needle 62 may also be used as an electrode in addition to an injection port. Electrode 68 comprises a monitoring or stimulating electrode. Figure 10 depicts the use of a catheter of Figure 6C to treat bronchial tissue in the lung for a variety of respiratory ailments such as asthma. Figure 6CC is a cross-sectional view taken along line 6CC-6CC in Figure 6, showing a co-axial sleeve design.

**[0078]** Figure 6D depicts a catheter device 70 having electrode elements 72 and 74 that are adapted to extend laterally from the main catheter body, and in some cases, penetrate the surrounding tissue prior to application of energy. In doing so the depth and direction of the energy field created by the electroporative process, may be further controlled. A monitoring/stimulating electrode 76 will usually also be provided. Elements 72 and 74 may also be used as injection ports for introduction of toxin or toxin fragments.

**[0079]** Figure 7 depicts the use of a catheter device 80 of the present invention for treatment of a respiratory tract, by positioning at least one electrode (82) at the target region, and a second electrode (84) remote from the target region, the target region being positioned between 82 and 84, such that activation of the electrodes produces an energy field (EF) therebetween, the size and intensity of which can be controlled by the placement of the electrodes relative to each other and the targeted region.

**[0080]** Figure 8 depicts catheter 90 constructed in accordance with the principles of the present invention utilizing an ultrasonic element 92 that may be particularly useful in delivery of the BoNT-LC to bronchial tissue (lung) that provides a broad but targeted transport of the LC across the target cell walls, for example, epithelial and goblet cell walls. In this device, ultrasound energy is delivered to the distal end of the catheter device via an ultrasonic waveguide 94 that is operatively connected to an ultrasound energy source (U/SES). The LC fragment would be delivered from a receptacle 96 via the same lumen as the waveguide via a

lumen provided the distal tip of the device. In operation, the ultrasonic energy would cause the LC solution to be nebulized, forming a mist or aerosol 98 within the lung, as shown in Figure 11. The aerosol 98 itself, in the appropriate concentrations, may act as an ultrasound coupler, conveying the ultrasonic energy to the wall of the lung or other targeted cellular structures, causing sonoporation of the targeted cells whereby the LC fragment is transmitted across the cell membranes to become an effective neurotransmitter blocker. In an alternative embodiment, an ultrasonic transducer may be located directly at the tip of the delivery device, eliminating the need for a wave guide. Various catheters useful for delivering vibrational energy to tissue are described in United States Patent 6,361,554 and 6,464,680 to Brisken, the contents of which are expressly incorporated herein by reference in their entirety, for various therapeutic effects, such as enhancing cellular absorption of a substance.

**[0081]** Since air is a very effective insulator against transmission of ultrasonic energy, the treatment area in the lung may be more precisely controlled by the concentration of the LC mist and the intensity of the ultrasonic energy. A fairly steep drop off in energy delivery would occur as mist concentration diffused, effectively protecting areas outside the predetermined radius surrounding the distal end of the delivery device. According to the present invention, since no functional neurotoxin exists without an effective membrane transport technology, terminating the energy application leaves a harmless mist that is then coughed up (if resident in the lungs) or otherwise metabolized and excreted by the body.

**[0082]** Any of the catheter devices described herein, or described in the contemporaneously filed United States Patent Application 60/701,747 (Attorney Docket No. 020979-003500US), previously incorporated by reference in its entirety, may be adapted to include an energy delivery element such as those described herein for purposes of providing a membrane transport system for delivery of a fragment of neurotoxin. In addition, certain catheter devices and methods such as those set forth in United States Patents 5,964,223 and 6,526,976 to Baran may be adapted to include energy transmission elements capable of producing a porative effect at the cellular level, including electrodes, ultrasonic elements and the like, for treatment in the respiratory tract.

**[0083]** Furthermore, any of the foregoing systems may include electrodes or other monitoring systems either located on the treatment catheter, or external to the patient, to determine the degree of treatment to the region, including, thermocouple, ultrasound transducers, fiberoptics, sensing or stimulating electrodes. Further, it may be desirable to

incorporate multiple pairs of electrodes that may be activated in pairs, in groups, or in a sequential manner in order to maximize the desired shape of the energy field (EF) while minimizing the field strength requirements.

**[0084]** Implantable Devices. Just as energy may be delivered to a targeted region to facilitate the delivery of fragmented neurotoxin via a catheter system, it is also within the scope of the present invention to deliver neurotoxins via an implantable system, including a pulse generator, lead and drug pump as depicted in Figures 12. A neuromodulation system 200 may be fully implantable, having a pulse generator and a power supply or battery and be operatively connected to a programmable drug delivery pump all housed within a module 202, including a reservoir in which the BoNT-LC is stored for delivery over time using the principles of the present invention and technology of the programmable drug pump. A catheter 204 can be adapted to deliver the drug and poration energy to a desired target location in the patient's body.

**[0085]** Examples of useful implantable devices of the present invention are, devices such as those set forth in United States Patent 5,820,589 to Torgerson et al, the entire contents of which are hereby incorporated by reference, the SynchroMed® programmable pump available from Medtronic, Inc. (Minneapolis, MN), and the neurostimulation units such as the RESTORE® or SynergyPlus® available from Medtronic, Inc., modified if necessary to delivery the desired voltage range for cell membrane permeabilization. Implantation of the neurostimulation device is further described in US Patent 6,847,849, incorporated herein by reference in its entirety.

**[0086]** The non-toxic nature of the BoNT in the absence of applied energy makes it possible to contemplate placing a bolus of neurotoxin in the body of a patient in what might otherwise be a toxic amount. This is particularly advantageous, since the traditional treatment regime using neurotoxins, is typically repeat injections of the toxins every 3 to 6 months and sometimes more frequently depending on the application. Certainly in more chronic conditions such as chronic pain, tremor, spasm, palsy and the like, such a fully implantable system may be highly desirable.

**[0087]** Non-Invasive Devices. It is within the scope of the invention to deliver either the energy or the therapeutic BoNT-LC non-invasively, or both. For example, Figure 13 depicts delivery of the BoNT-LC via a catheter 100 placed in the bronchial passageway with the energy field (EF) delivered from outside the patient in the form of an energy system 102 such

as focused ultrasound (HIFU), stereotactic x-ray beams, magnetic resonance transmission, and the like. As detailed in United States Patents 6,626,855 and 6,719,694 to Weng, the contents of which are expressly incorporated herein by reference in their entirety, an ultrasound beam can be controlled from outside the patient to focus the ultrasound beam in the desired location and intensity. For use in the present invention, it may be desirable to pulse or otherwise attenuate the ultrasound beam to achieve reversible cellular poration at the targeted site. Further, due to its non-toxic state, the BoNT-LC may be inhaled by the patient using a standard inhaler device such as those using pressurized aerosols known as metered does inhalers (MDI) available from Cardinal Health (Somerset, NJ), the OPTIHALER® available from National Allergy Supply Incorporated (Georgia, USA), or a nebulizer breathing machine such as a Pari DURANEB 3000 portable nebulizer available from Medinfinity, Co. (Fountain Valley, CA). In addition, certain technology currently under development employing thermal aerosols, such as a the STACCATO™ vaporization technology from Alexza Molecular Delivery (Palo Alto, CA) may also be useful within the scope of the present invention. Such devices 110 may be used as depicted in Figure 9 for treating a respiratory ailment such as asthma. Optionally, the drug can be delivered with the catheter 22 (as shown) or with the external sources of Fig. 13.

**[0088]** A combination of these non-invasive approaches may also be advantageous as shown in Figure 15, wherein an non-invasive inhaler 110 is used to deliver the BoNT-LC to the target region (such as the lung), and the energy is delivered to the target region by the non-invasive source 102 such as the focused ultrasound (HIFU), stereotactic x-ray, or magnetic resonance transmission as previously described. Due to its non-invasive technique, this approach may have broad appeal to a large patient population, including pediatric use, on an outpatient basis in a clinic designated for the treatment of specific respiratory ailments.

**[0089]** In a further aspect of the present invention, the fragmented molecule BoNT-LC may be delivered intravenously to a patient to achieve a systemic affect. A non-invasive energy application device, such as those described above, may then be targeted at the area of interest to porate the target area, thereby locally delivering the BoNT-LC to the region sufficiently porated by the applied energy.

**[0090]** Cosmetic and Myofacial Applications. For some conditions, it may be desirable to apply the energy field from the surface of the skin to produce a porative effect, while injecting the BoNT-LC fragment into the targeted facial muscles as shown in Figure 14. In

operation, an injection device 220 places the BoNT-LC in the muscle to be treated (target region), and an energy transmission device such as an ultrasonic pen 222 with a single, or a series of ultrasonic elements located on the distal end and coupled to an energy transmission system 224, follows along the target region to controllably discharge the BoNT-LC fragments to the targeted cells leaving a highly controlled treated region. In some instances for treatments around the eye, it may be desirable to limit the penetration of the BoNT-LC to dermal or subdermal layers. In these applications, BoNT-LC may be applied transdermally with ultrasound assistance using techniques similar to those set forth in US Patent 4,767,402 to Kost the contents of which is expressly incorporated herein in its entirety or through transdermal electroporation.

**[0091]** Intraluminal Devices. It may further be advantageous to position catheters of the present invention through vessels in the body to direct them to various regions to affect neurotransmitters in the cardiovascular system. Intraluminal catheters such as those shown in United States Patent Applications 2001/0044596 to Jaafar and 2002/0198512 to Seward, hereby incorporated by reference in their entirety, may be used in this application of the present invention.

**[0092]** Treatment Enhancements. In some applications of the present invention, it may be desirable to asses the appropriate location for the therapy prior to treatment, the therapeutic effect as it is delivered, and ultimately the resulting effect. To achieve this, once the treatment device is in place adjacent the tissue to be treated, the energy generator may be activated, causing an energized field to be generated in the target area. Prior to activation of therapeutic voltages and agent, stimulation using one or more electrodes may be used to elicit a nerve response or reflex. By observing the nerve response, a target treatment location can be confirmed. Similarly, once the therapy has been delivered, a similar stimulation response may be sought, to determine presence or lack of neurogenic response.

**[0093]** In operation, effects of electroporation and delivery of a therapeutic does of BoNT-LC may be selective due to the cellular structure and orientation of the targeted cells. For example, targeted cells may be preferentially affected due to size, avoiding smaller or cross-oriented tissue cells.

**[0094]** In a further aspect of the present invention, the method of delivering the LC fragment of the BoNT molecule may include the use of a media that contains microspheres or microbubbles, such as Optison™ sold by GE Healthcare (www.amershamhealth-

us.com/optison/). Delivery of an ultrasound energy (or other form of energy, for example, laser, RF, thermal, energy) to the media causes the microspheres to rupture, which causes a release of energy toward the targeted region. Such a technique may assist in the desired porative effect by reducing the amount of applied energy required to create poration in the targeted cell membrane. *Bioeffects Caused by Changes in Acoustic Cavitation Bubble Density and Cell Concentration: A Unified Explanation Based on Cell-to-Bubble Ratio and Blast Radius*, Guzman, et al. Ultrasound in Med. & Biol., Vol. 29, No. 8, pp. 1211-1222 (2003). In an alternative embodiment, the LC fragment may actually be contained or encapsulated within a microsphere to assist in delivery. Such enhancing elements may be delivered prior to energy application or during energy application.

**[0095]** In a further aspect of the present invention, it may be advantageous to heat the targeted cells or surrounding tissue by either applying thermal energy directly to the region, or directing a heated fluid, such as saline to the region through an injection element, to aid the cell poration process. Other substances may also be injected to aid in the transmission of the BoNT-LC into the intracellular membrane, such as amino acids, detergents or other agents that may facilitate the catalytic activity of the LC, in addition to the applied energy.

**[0096]** Referring now to Figs. 15A and 15B, a balloon catheter 300 may be delivered to a target site in the bronchus B of a lung (Fig. 15B). Typically, the catheter 300 will be delivered through an endoscope E, and the shaft 302 of the catheter will comprise at least one lumen for inflating the balloon 304. The inflation medium may carry the toxin fragment which is released through ports 306 formed in the balloon itself. Thus, inflation of the balloon both engages the ports against the wall of the bronchus B and provides the pressure necessary to infuse the neurotoxin fragments into the wall of the bronchus B. Usually, energy will be applied from electrodes 308 or other transducers located within the balloon 304.

**[0097]** Referring now Figs. 16A and 16B, the catheter 400 may also be delivered to a bronchus B of a lung through an endoscope E. Catheter shaft 402 terminates with a delivery port 404 near its distal end. A deflection balloon 406 (or other expandable element capable of pressing against the wall of the bronchus B to engage the port 404 against target tissue) is provided on a side of the catheter shaft 402 which is opposite to that of the port 404. Electrodes 408 are provided on either side of the port 404 in order to deliver the poration energy into the target tissue.

**[0098]** Although various illustrative embodiments of the present invention are described above, it will be evident to one skilled in the art that various changes and modifications may be made without departing from the scope of the invention. It will also be apparent that various changes and modifications may be made herein without departing from the invention. The appended claims are intended to cover all such changes and modifications that fall within the true spirit and scope of the invention.

WHAT IS CLAIMED IS:

1. A method for treating conditions affected by neurogenic function in a targeted region of mammalian cells, said method comprising:

delivering an active neurotoxin fragment to cells in the targeted region;

applying energy to the cells under conditions which cause a reversible poration in the cell membranes to permit delivery of the active fragment.

2. A method as in claim 1, wherein the active fragment is selected from the group consisting of botulinum toxin fragments, ricin fragments, exotoxin A fragments, diphtheria toxin fragments, cholera toxin fragments, and tetanus toxin fragments.

3. A method as in claim 2, wherein the active fragment comprises the botulinum light chain (BoNT-LC).

4. A method of claim 3, wherein the active fragment comprises an amount of BoNT-LC therapeutically effective to inhibit a neurogenic pathway associated with the neurogenic function.

5. A method of claim 4, wherein the active fragment is BoNT-LC derived from at least one of the botulinum toxins A, B, C, D, E, F or G.

6. A method of claim 1, wherein the neurogenic pathway is associated with and contributes to at least one symptom of asthma.

7. A method of claim 1, wherein delivering comprises advancing a catheter to said vicinity and releasing the active neurotoxin fragments from the catheter while applying energy from an applicator on the catheter.

8. A method of claim 7, wherein delivering comprises aerosolizing the fragment from the catheter.

9. A method as in claim 7, wherein delivering comprises injecting the fragment from a needle on the catheter.

10. A method as in claim 7, wherein delivery comprises engaging one or more ports on the catheter against tissue and releasing the fragments from the port(s).

11. A method as in claim 10, wherein engaging comprises inflating a balloon on the catheter to deflect the catheter.

12. A method of claim 1, wherein the delivering is achieved using an inhaler.

13. A method of claim 1, wherein the delivering is achieved transdermally

14. A method of claim 1, wherein the energy applied to the targeted region is an electric pulse.

15. A method of claim 14, wherein the electric pulse has a voltage between 1V and 500V.

16. A method of claim 14, wherein the electric pulse comprises radiofrequency energy.

17. A method of claim 16, wherein the radiofrequency energy is pulsed for durations between 5 microseconds to 100 milliseconds.

18. A method of claim 13, wherein the electric pulse comprises a direct current pulse.

19. A method of claim 13, wherein the electric pulse comprises an alternating current pulse.

20. A method of claim 1, wherein the energy applied to the targeted region comprises ultrasonic energy.

21. A method of claim 20, wherein the ultrasonic energy applied to the targeted region comprises focused ultrasound energy.

22. A method of claim 1, wherein the energy applied to the targeted region comprises an x-ray beam.

23. A method of claim 1, wherein the energy applied to the targeted region comprises microwave energy.

24. A method of claim 4, wherein the neurogenic pathway is associated with and contributes to at least one symptom of pain.

25. A method of treating a respiratory ailment, comprising the steps of:
providing a therapeutically effective amount of BoNT-LC, and
delivering the amount of BoNT-LC to a region of the respiratory system under conditions selected to permeabilize target cells within the region and allow entry of the BoNT-LC to enter the cells.

26. A system for delivering toxins to target cells in a mammalian target, said system comprising:
a catheter or other structure adapted to introduce a toxin to a region adjacent the target cells;
an energy applicator for applying energy to the target cells under conditions which cause poration of the cell membranes to enhance delivery of the toxin; and
a source of toxin suitable for introduction from the catheter.

27. A system as in claim 26, wherein the energy applicator is adapted to selectively apply energy to target cells within the region where toxin has been introduced.

28. A system as in claim 26, wherein the energy applicator is adapted to apply energy non-selectively within the region where toxin has been introduced.

29. A system as in claim 26, wherein the toxin comprises an intact toxin.

30. A system as in claim 29, wherein the toxin is an active toxin fragment.

31. A system as in claim 30, wherein the fragment is a light chain fragment.

32. A system as in claim 31, wherein the active fragment is selected from the group consisting of botulinum toxin fragments, ricin fragments, exotoxin A fragments, diphtheria toxin fragments, cholera toxin fragments, and tetanus toxin fragments.

33. A system as in claim 32, wherein the active fragment comprises the botulinum light chain (BoNT-LC).

34. A system as in claim 33, wherein the light chain fragment is derived from at least one of botulinum toxins A, B, C, D, E, F, and G.

35. A system as in claim 26, wherein the energy applicator is adapted to apply an electric pulse of between 1V and 500V to the target region.

36. A system as in claim 35, wherein the electric pulse is radiofrequency (RF) energy.

37. A system as in claim 35, wherein the RF energy is pulsed for durations between 5 microseconds to 100 milliseconds.

38. A system as in claim 35, wherein the electric pulse is produced by a DC power source.

39. A system as in claim 35, wherein the electric pulse is produced by an AC power source.

40. A system as in claim 26, wherein the energy applicator is adapted to apply ultrasonic energy to the targeted region.

41. A system as in claim 40, wherein the energy applicator is adapted to apply focused ultrasound to the targeted region.

42. A system as in claim 26, wherein the energy applicator is adapted to apply an x-ray beam to the targeted region.

43. A system as in claim 26, wherein the energy applicator is adapted to apply microwave to the targeted region.

44. A system as in claim 26, wherein the catheter comprises a needle for delivering the toxin.

45. A system as in claim 26, wherein the catheter comprises a port for aerosolizing the toxin.

46. A system as in claim 28, wherein the catheter comprises a balloon for deflecting one or more ports against target tissue.

47. A system as in claim 46, wherein the balloon comprises the one or more ports.

48. A system as in claim 26, wherein the energy applicator is on the catheter.

49. A system as in claim 48, wherein the energy applicator applies acoustic energy from a transducer on the catheter.

50. A system as in claim 48, wherein the energy applicator applies electrical energy from an electrode on the catheter.

51. A system as in claim 26, wherein the applicator applies energy from a source external to the patient.

52. A system as in claim 51, wherein the source is an acoustic energy transducer.

53. A system as in claim 52, wherein the acoustic energy transducer is focused ultrasound transducer.

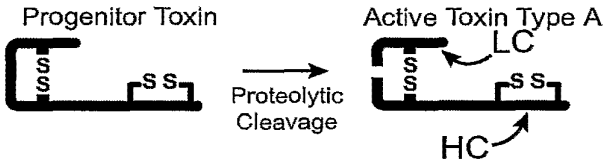

Progenitor Toxin
Active Toxin Type A
LC
HC
Proteolytic
Cleavage

FIG. 1

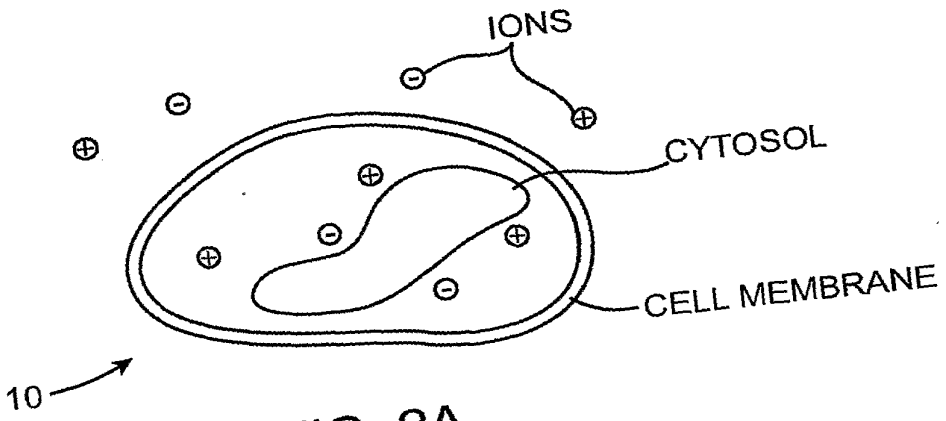



FIG. 2A

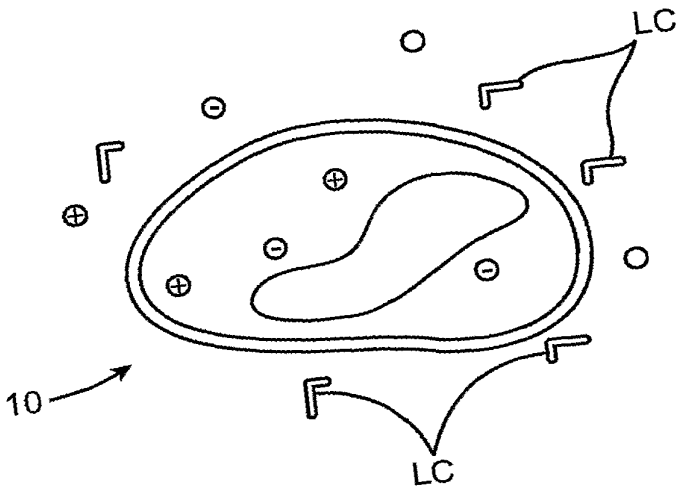



FIG. 2B

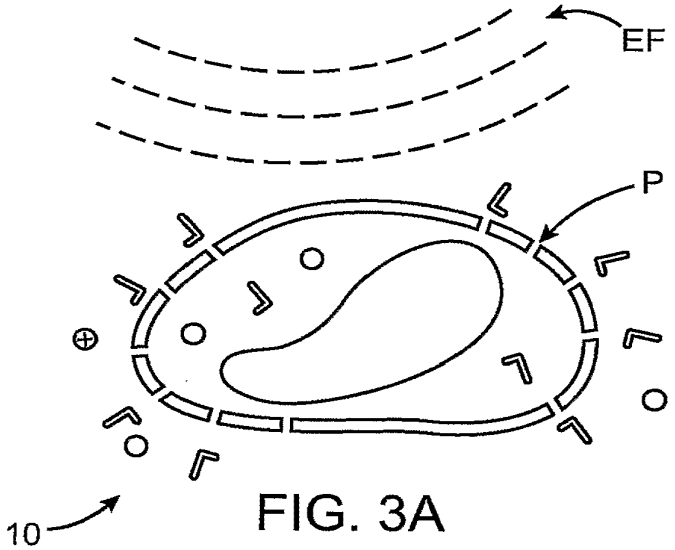



FIG. 3A

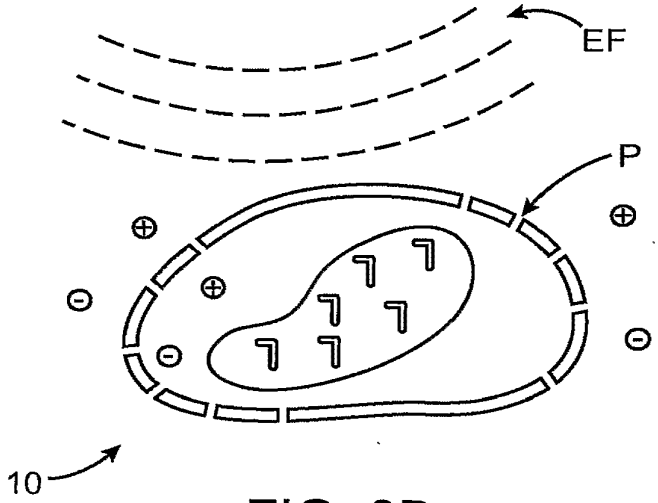



FIG. 3B

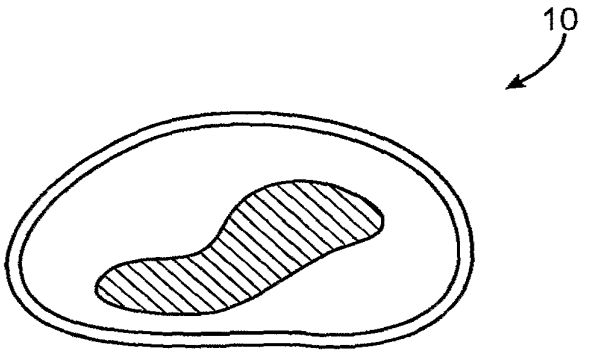



FIG. 4

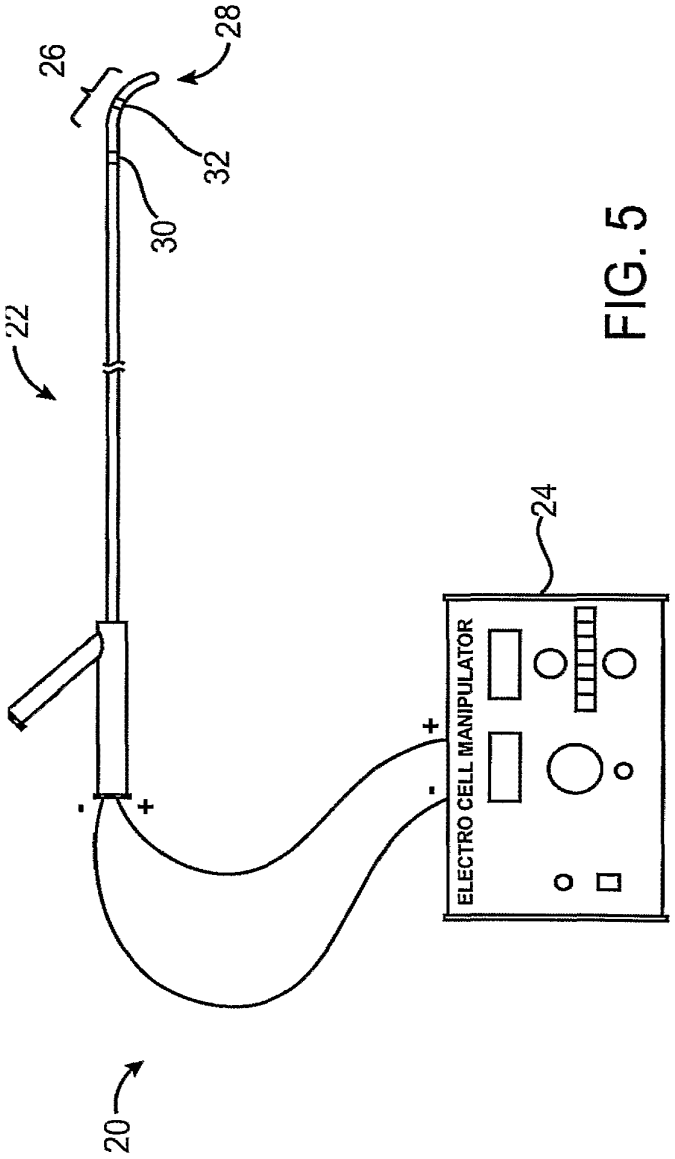



FIG. 5

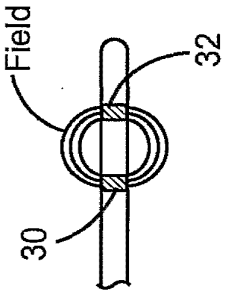



FIG. 5B

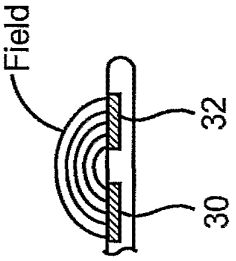



FIG. 5A

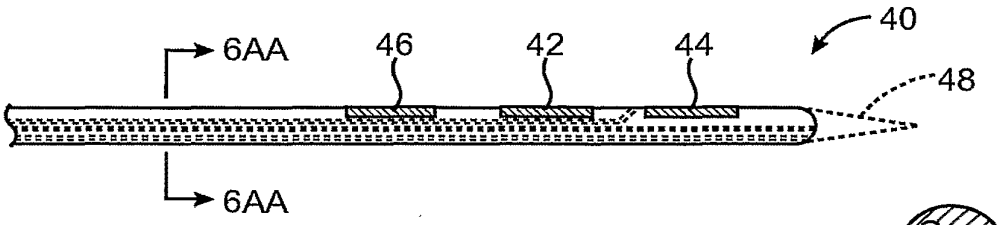



FIG. 6A

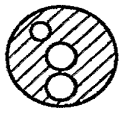


FIG. 6AA

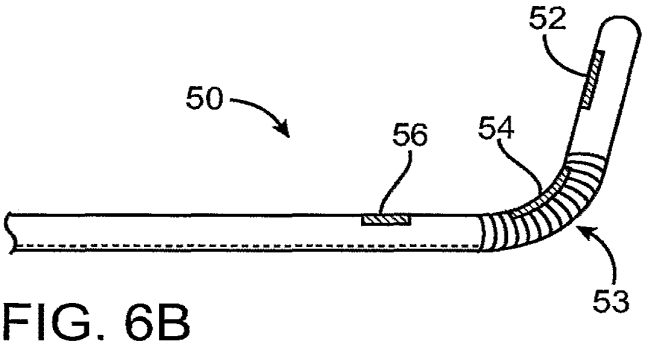



FIG. 6B

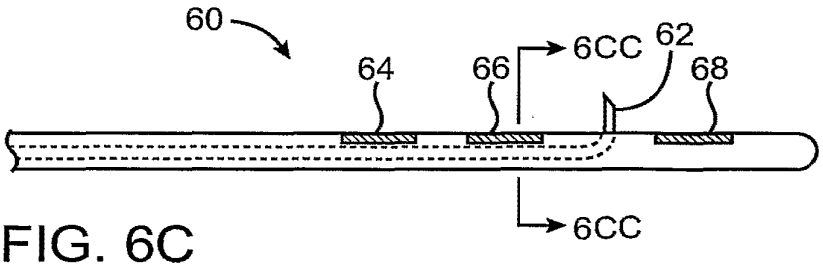



FIG. 6C



FIG. 6CC

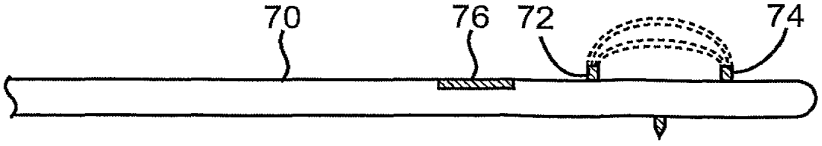



FIG. 6D

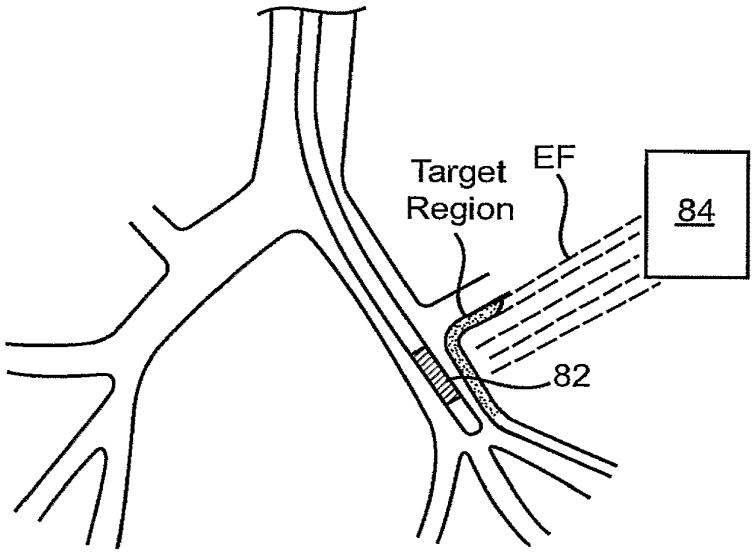



FIG. 7

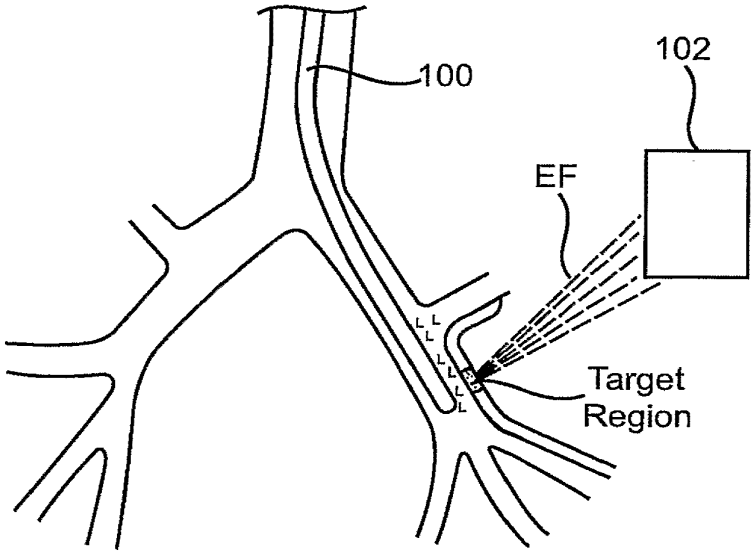



FIG. 13

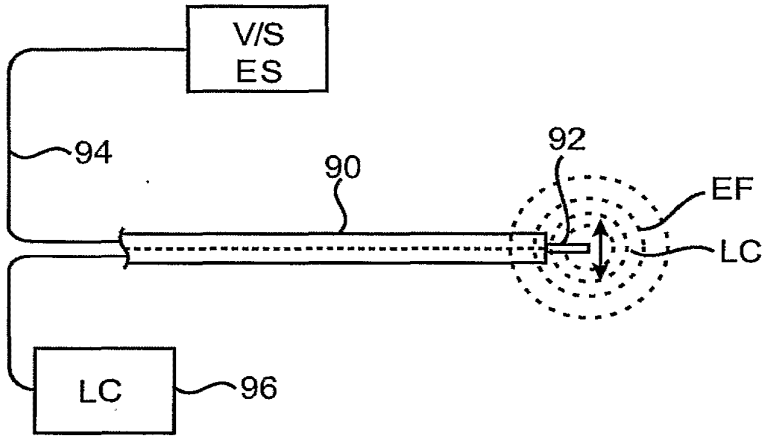



FIG. 8

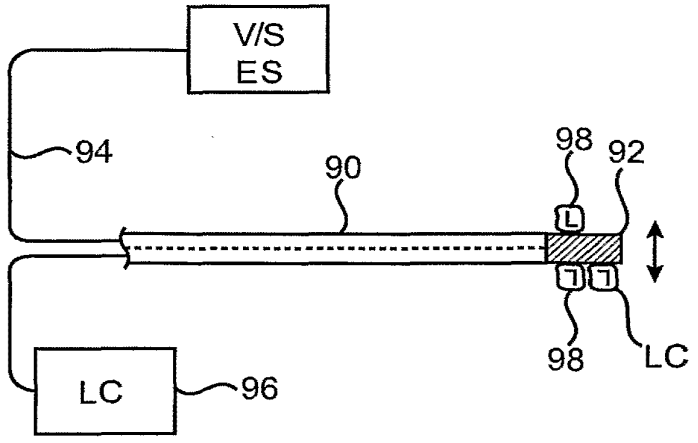



FIG. 11

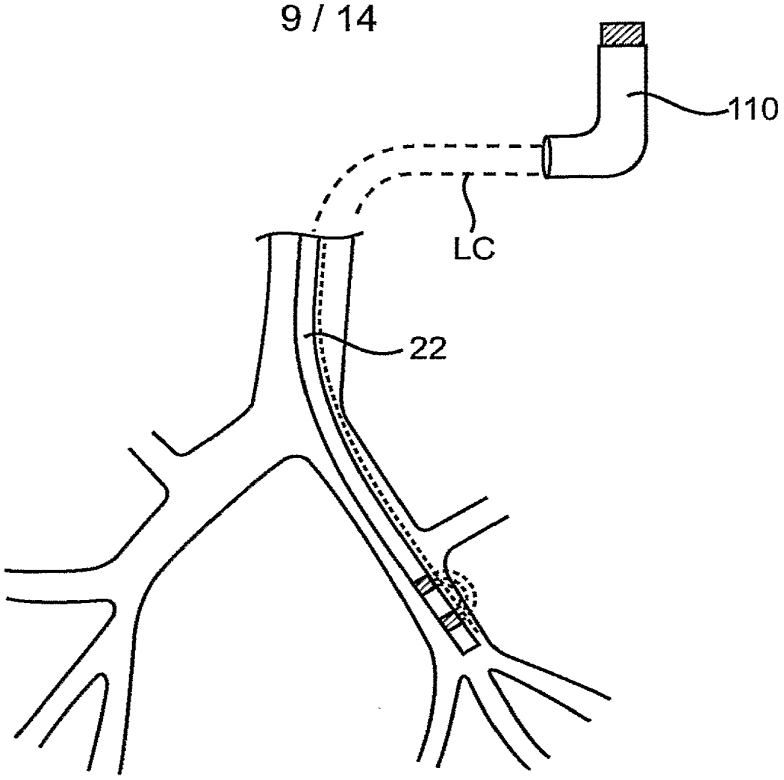



FIG. 9

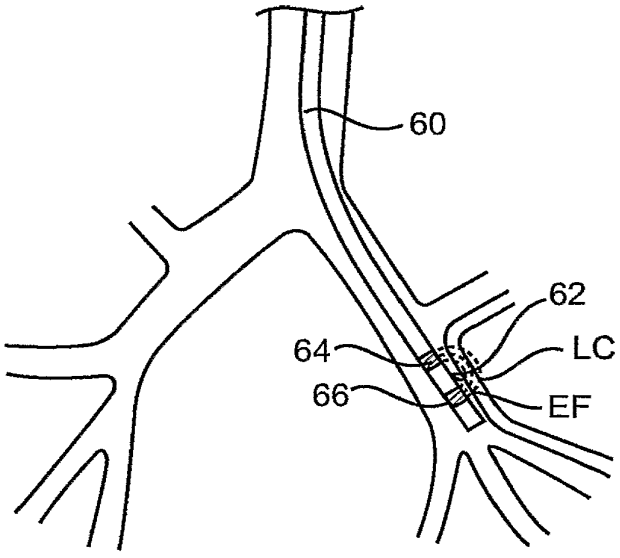



FIG. 10

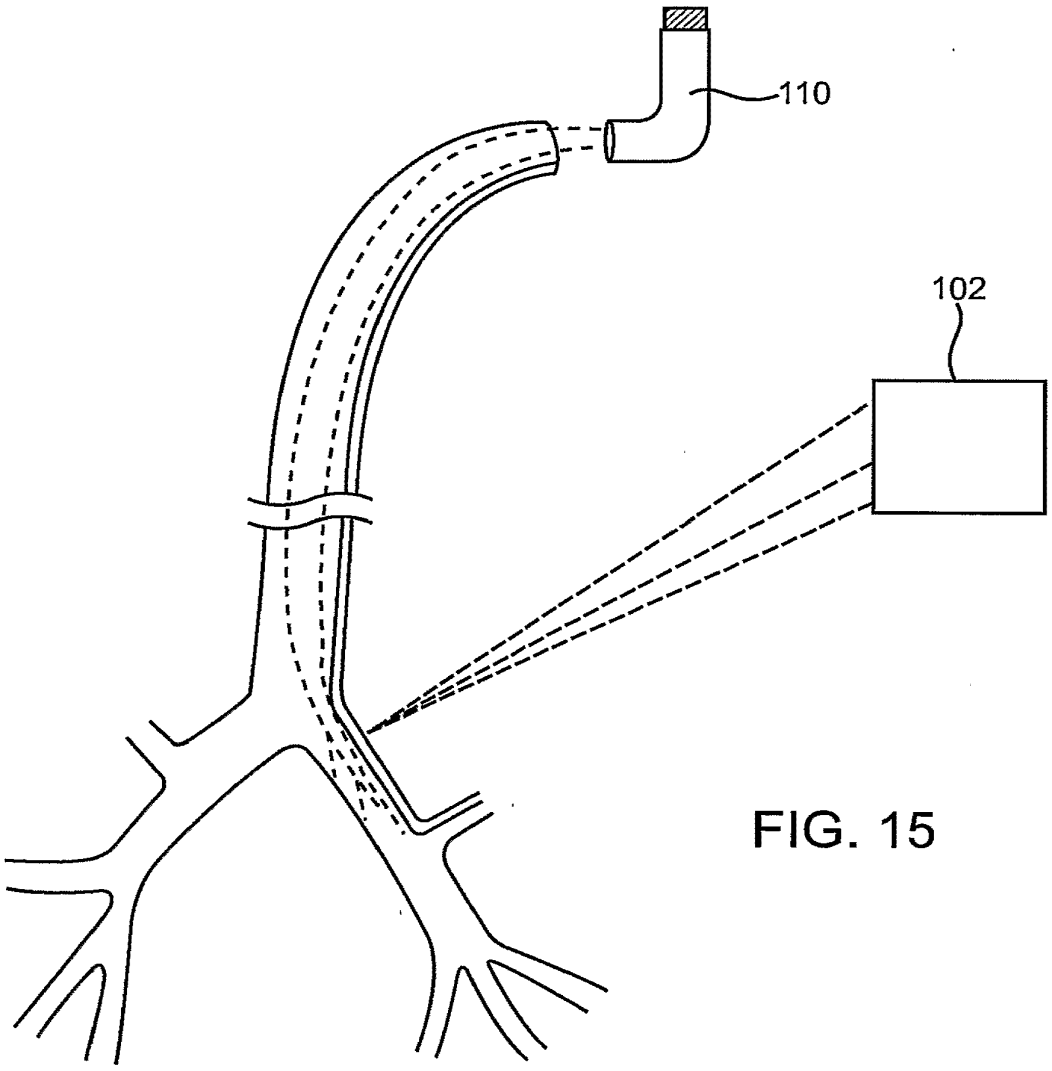



FIG. 15

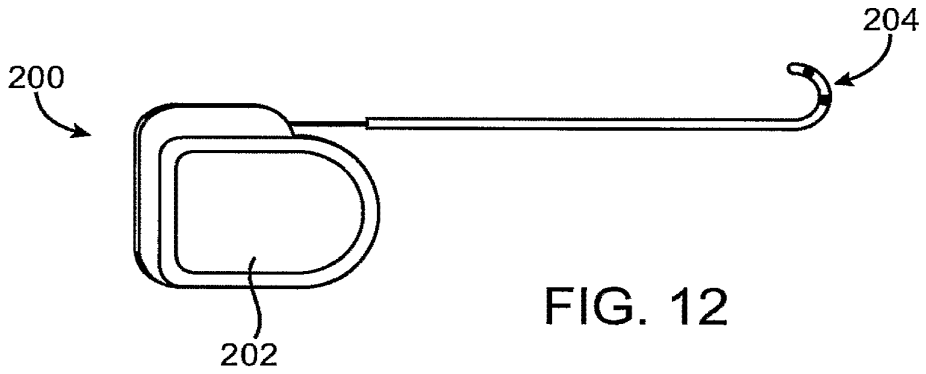



FIG. 12

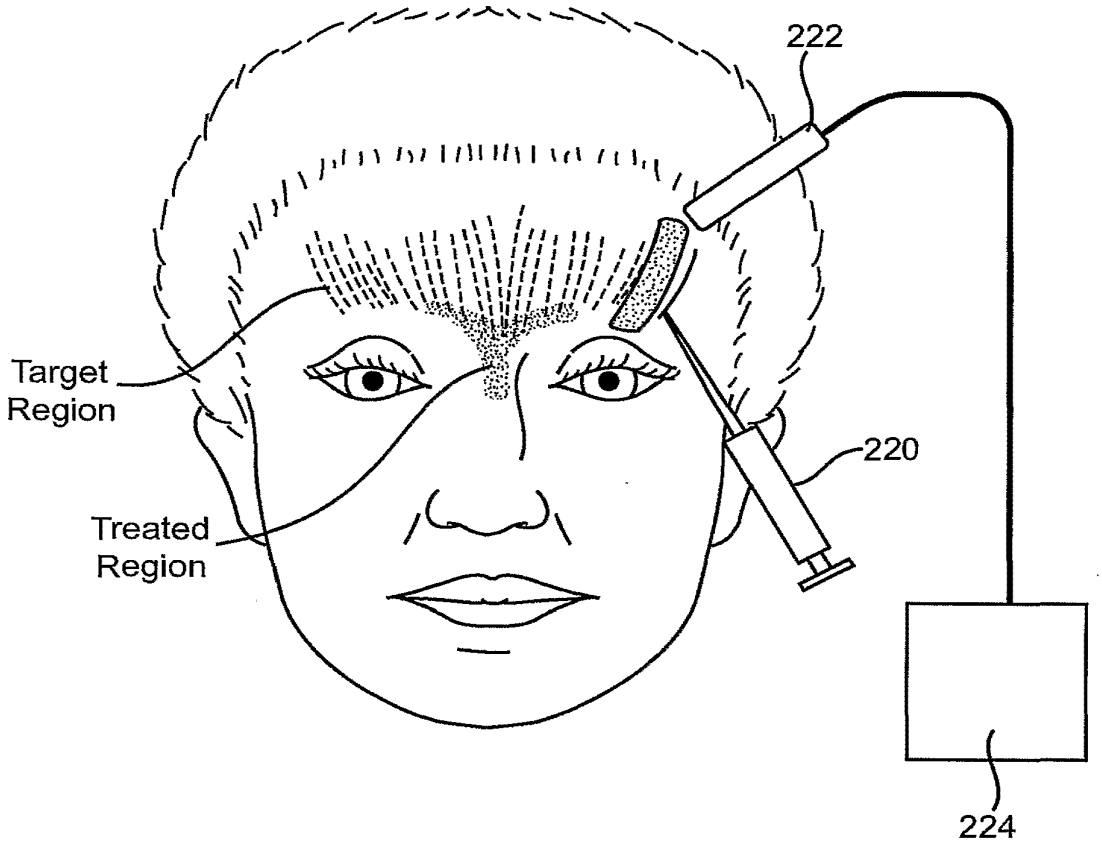



FIG. 14

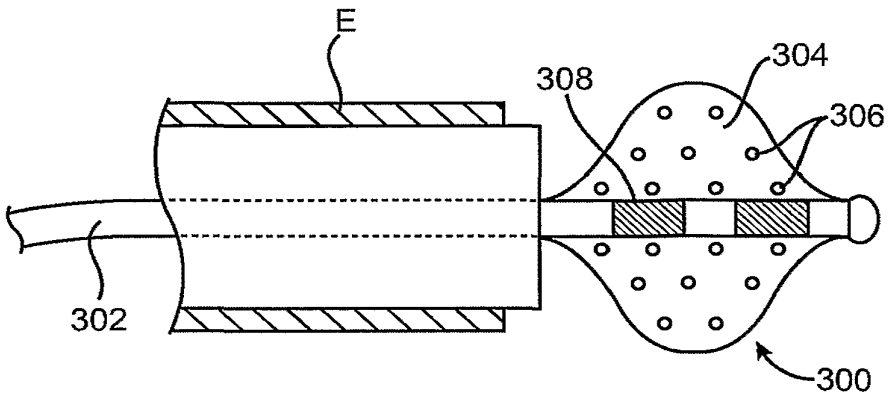



FIG. 15A

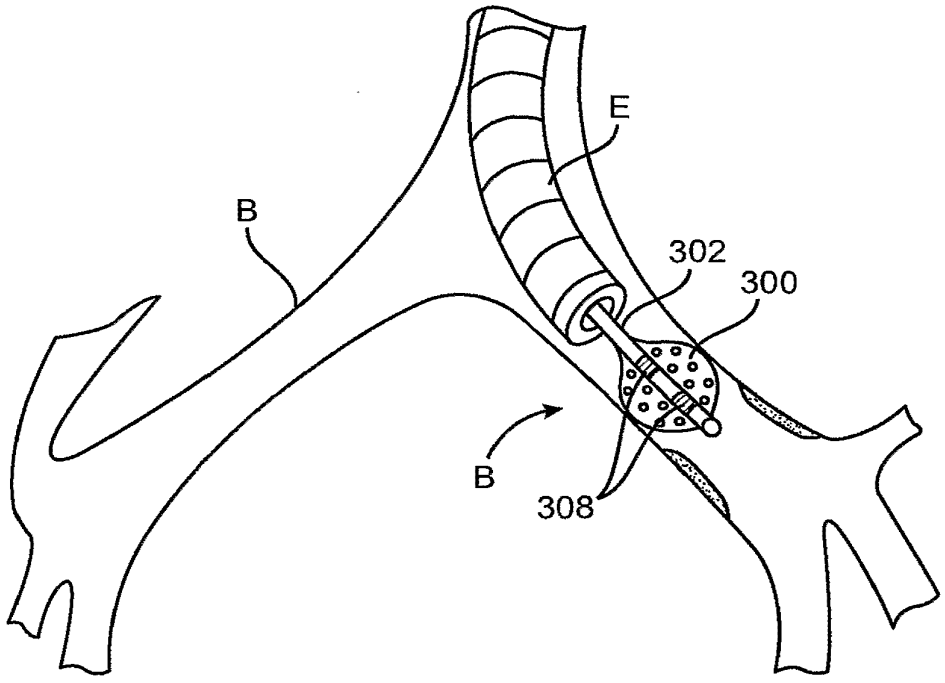



FIG. 15B

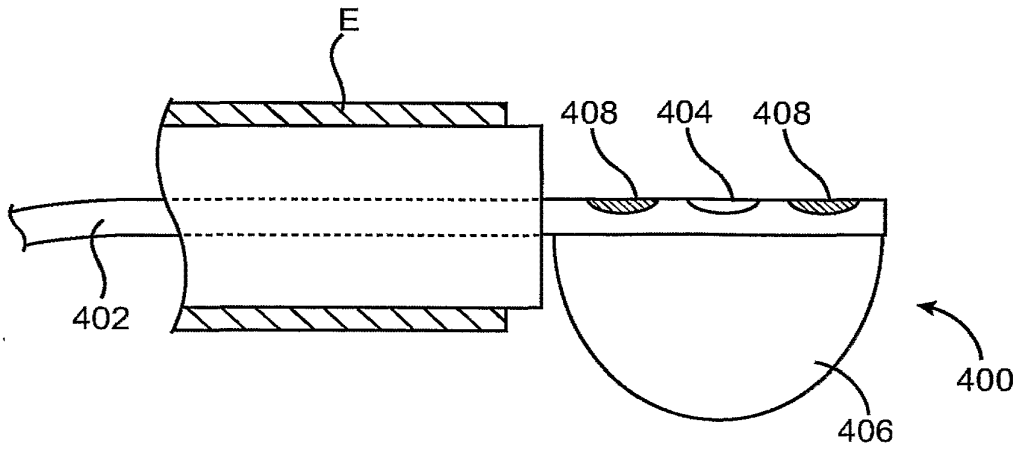



FIG. 16A

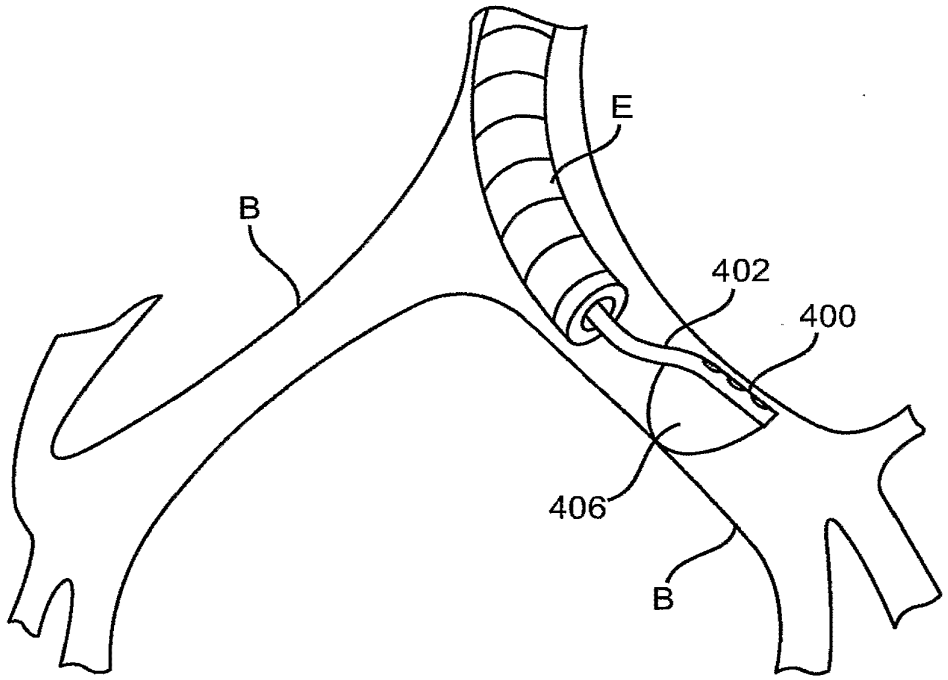



FIG. 16B

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

| | |
|---|---|
| In re the application of: | Attorney Docket No.: 5187.01US01AP |
| Deem et al. | Confirmation No.: 4259 |
| Application No.: 16/659,893 | Examiner: Albert Mark Navarro |
| Filed: October 22, 2019 | Group Art Unit: 1645 |

For: SYSTEMS AND METHODS FOR DELIVERY OF A THERAPEUTIC AGENT

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INFORMATION DISCLOSURE STATEMENT

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Alexandria, VA 22313-1450

Commissioner:

Pursuant to 37 CFR § 1.56, the attention of the Patent and Trademark Office is hereby directed to the references listed on the attached Form PTO-1449. It is respectfully requested that the information be expressly considered during the prosecution of the above-referenced application, and be made of record therein and appear among the "References Cited" on any patent to issue therefrom.

The listing of a reference herein is not an admission that the reference is prior art or is material to patentability. 37 CFR § 1.97(h). Applicant reserves the right to establish the patentability of any claimed invention over any of the information provided herewith, and/or prove that this information may not be prior art, and/or prove that this information may not be enabling for any aspect of the information provided herewith.

This Information Disclosure Statement is being filed without a certification or fee because this Information Disclosure Statement is being filed within three months of the U.S. filing date. No certification or fee is required. 37 CFR § 1.97(b)(1) and 37 CFR § 1.97(b)(2).

The Examiner's attention is directed to the applications or patents, if any, to which priority is claimed, as well as to any continuing applications which claim priority to the above-referenced application, and to applications, if any, that may be related by virtue of similar claimed subject matter as the above-referenced application (collectively, the "Related Case(s)"). The Related Case(s), or documents associated with the Related Case(s), are identified on the attached form PTO-1449 by serial number, publication number and/or patent number, along with a copy of the current prosecution history, downloaded from PAIR where available. The current prosecution history for the Related Case(s) is submitted as an NPL document for the convenience of the Examiner.

The prosecution history for any and all of these Related Case(s) may include information material to patentability of the above-referenced application including Office Actions, Responses, Office Communications or Notices of Allowance, all of which are readily accessible to the Examiner via PAIR/PALM. To promote consistency and full disclosure during the prosecution of the above-referenced application together with the prosecution of any of the Related Case(s) and to assist the Examiner in complying with the obligations of MPEP 609.02 and/or 2001.06(b), the Examiner is respectfully requested to review the prosecution history of each of the Related Case(s). **This request for review should be considered ongoing throughout the prosecution of the above-referenced application with an updated review via PAIR/PALM of the prosecution histories of any Related Case(s) being made prior to**

**issuance of any Notice of Allowance for the above-referenced application.** The identification of any of the Related Case(s) for purposes of this Information Disclosure Statement should not be construed as a waiver of secrecy, if applicable, as to such applications now or upon issuance of the above-referenced application as a patent. For purposes of the Related Case(s), it should be noted that all of the Related Case(s) are published or otherwise publicly available on PAIR.

Please note that copies of the references that were cited by or submitted to the Office in applications which are relied upon for an earlier filing date under 35 U.S.C. § 120 may be found in the appropriate records via PAIR/PALM. 37 CFR § 1.98(d).

Respectfully submitted,

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***Please grant any extension of time necessary for entry; charge any fee due to Deposit Account No. 16-0631.***

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(54) Title: TREATMENT OF MAMMALIAN PHYSIOLOGICAL REACTION OF IgE ANTIBODIES PRESENT IN SAID MAMMAL UPON CONTACT WITH THE CORRESPONDING ANTIGEN

(57) Abstract: A method is disclosed for blocking or reducing physiological reaction in a mammal to the interaction of IgE antibodies present in said mammal upon contact with the corresponding antigen, by the administration to said mammal of a therapeutically effective amount of a neurotoxin (CnT) derived from Clostridia sp.

# TREATMENT OF MAMMALIAN PHYSIOLOGICAL REACTION OF IgE ANTIBODIES PRESENT IN SAID MAMMAL UPON CONTACT WITH THE CORRESPONDING ANTIGEN.

## FIELD OF THE INVENTION

A method is disclosed for blocking or reducing physiological reaction in a mammal to the interaction of IgE antibodies present in said mammal upon contact with the corresponding antigen, by the administration to said mammal of a therapeutically effective amount of a neurotoxin (CnT) derived from Clostridia sp.

## BACKGROUND OF THE INVENTION

Throughout this application various publications are referred to within parentheses or by footnote. The contents of these publications are hereby incorporated by reference in their entirety.

### Introduction

The physiological reaction in a mammal to the interaction of IgE antibodies present in said mammal upon contact with the corresponding antigen is generally referred to as allergy. It is believed that the allergic response evolved to combat infections with parasites. As parasitic infections are rare in industrialized countries this mechanism becomes pathologic in certain susceptible (atopic) individuals. Characteristic of allergies is that the antigen, also called the allergen, is normally innocuous, and the body's reaction is inappropriate.

Allergic reactions can involve all body tissues but are most prominent in the boundaries with the external environment: the airway, eye, gastrointestinal tract and skin. The conditions are known as allergic rhinitis in the nose (hay fever), allergic asthma in the lungs, food allergies in the GI tract and allergic hypersensitivity (hives) or dermatitis in the skin. Anaphylaxis refers to the systemic reaction that occurs when an allergen is introduced directly into the circulation, such as occurs with injection of drugs and insect stings. A massive early phase reaction occurs throughout the body. Symptoms include diffuse airway swelling and hypotension which can be life threatening.

Each year more than 50 million Americans suffer from allergic diseases, costing the health care system $18 billion annually (American Academy of Allergy,

Asthma and Immunology (AAAAI). The Allergy Report: Science Based Findings on the Diagnosis & Treatment of Allergic Disorders, 1996-2001)

Alarmingly, the prevalence and severity of allergic disorders has rapidly increased in the United States over the past twenty years, so there is a need for new therapies for these conditions.

In 1998, an estimated 15 million Americans, or 6.4 percent of the population, had asthma, with 5 million being children. Children account for 4.8 million of Americans with asthma. Each year, 1.8 million emergency room visits are for asthma, nearly 500,000 Americans are hospitalized and more than 5,000 die from the disease. Although asthma deaths are infrequent, they have increased significantly during the last two decades. From 1975-1979, the death rate was 8.2 per 100,000 people. That rate jumped in 1993-1995 to 17.9 per 100,000. Asthma cost the U.S. economy an estimated $10.7 billion in 1994, including a direct health care cost of $6.1 billion and indirect costs, such as lost workdays, of $4.6 billion.

Approximately 16.7 million office visits to health care providers each year are attributed to allergic rhinitis alone (CDC. Fast Stats A-Z, Vital and Health Statistics, Series 10, no. 13. 1999

A related condition, chronic sinusitis, is the most commonly reported chronic disease, affecting 12.6 percent of people (approximately 38 million) in the United States in 1996. Another related condition, serous otitis media, is the most common condition in children requiring an office visit to a health care provider.

Atopic dermatitis is one of the most common skin diseases, particularly in infants and children. The estimated prevalence in the United States is 9 percent[1] Rudikoff D and Lebwohl M. "Atopic dermatitis." Lancet 351(9117): 1715-21. 1998[i]

Experts estimate that food allergy occurs in 8 percent of children 6 years of age or under, and in 1 to 2 percent of adults Sampson HA. In Allergy, Principles and Practice, 5th Ed., E. Middleton et al, ed. Mosby, St. Louis, p. 1162. 1998[ii].

**Pathophysiology of allergy**

Allergy is an ailment that affects millions of individuals worldwide. Attempts to desensitize an individual against a material that causes an allergic response (hereafter designated as an "allergen") by injection of measured dosages of the allergen heretofore has failed to achieve complete relief of allergy symptoms reproducibly in all allergic individuals. An allergic response is a term of art and has a well-defined meaning. Within the context of the present invention, an allergic or reagenic response includes, in particular, at least one of the features of 1.) production of an abnormally high level of IgE in an individual's serum, 2.) immunologic interaction between an allergen, an individual's IgE and leukocytes resulting in release of histamines, 3.) production of hives, rashes, wheal and flare and similar dermatological manifestation of hypersensitivity, and 4.) anaphylaxis.

An allergic response is a state of hypersensitivity in which an exaggerated immune response is induced by the exposure to a particular antigen or allergen. Hypersensitivity reactions can be classified as immediate or delayed. Immediate or type I hypersensitivity (or anaphylactic response) is an allergic reaction which develops very quickly, i.e., within seconds or minutes of exposure of the patient to the causative allergen, and it is mediated by IgE antibodies produced by B lymphocytes. In non-allergic patients, there is no IgE antibody of clinical relevance. However, in a person suffering with allergic diseases, IgE antibody mediates immediate hypersensitivity by sensitizing mast cells which are abundant in the skin, membranes of the eye, nose and mouth, and in the respiratory tract and intestines.

IgE secreted from activated B cells can attach to Fc receptors located on the surface of mast cells and basophil granulocytes, which contain numerous cytoplasmic granules packed with chemical mediators e.g. histamine (J. Klein, "Immunology", Blackwell Sci. Pub., London, 1990; E. Benjamini & S. Leskowitz, "Immunology", Wiley-Liss, N.Y. 1991). This receptor binds circulating IgE with very high affinity and retains it at the mast cell surface for extended periods of time. Activation is accomplished through the binding of an allergen simultaneously to more than one polyvalent molecule of Fc receptor-bound IgE. This "cross linking" of at least two surface-bound IgE molecules brings Fc receptor proteins into close association with one another in the plane of the mast cell plasma membrane. When the bound IgE is contacted by the appropriate allergen, the mast cell becomes

activated. Kinases associated with these receptors become activated as a result of this proximity. They initiate the second messenger cascade, which results in the fusion of the granules with the cell surface membrane, leading to the exocytosis of the granule contents, such as histamine, cytokines, and leukotrienes into the surrounding tissue, and the concomitant induction of allergic symptoms. It is the activity of these substances which is responsible for the clinical symptoms typical of immediate hypersensitivity. These include contraction of smooth muscle in the airways or the intestine, the dilation of small blood vessels and the increase in their permeability to water and plasma proteins, the secretion of thick sticky mucus, and in the skin, , swelling and the stimulation of nerve endings that results in itching.

Delayed type hypersensitivity (DTH) reactions are mediated by T-cells and macrophages and become evident only after 1 to 2 days and persist from several days to a few weeks. DTH is also referred to as cell-mediated hypersensitivity (i.e., T-cell mediated) and is part of a larger group of reactions called cell-mediated immunity.

Anaphylaxis, or anaphylactic shock, is an acute systemic (whole body) type of allergic reaction, It occurs when a person has become sensitized to a certain substance or allergen (that is, the immune system has been abnormally triggered to recognize that allergen as a threat to the body). On the second or subsequent exposure to the substance, an allergic reaction occurs. This reaction is sudden, severe, and involves the whole body. Anaphylaxis is life-threatening and can occur at any time.

Therapeutically, many agents are used to try to prevent the release of mediators from mast cells and basophils and/or to treat the downstream events by blocking or ameliorating the effects of the mediators on target tissues. Therapeutic agents commonly employed fall under the following main groups.

Antihistamines block and mop up the released histamine, i.e. the major mediator of the allergic response.

01 02 agonists, e.g., Epinephrine, Salbutamol overcome indirectly the downstream effects on vasculature and smooth muscle.

Chromoglycate is useful for primary prevention of mast cells/basophil degranulation.

This prophylactic must be taken continuously. It does not prevent the cross-linking of IgE but it somehow interferes with subsequent events. Theophylline and other phosphodiesterase inhibitors again influence downstream biochemical events particularly associated with cyclic nucleotides. Steroids have multiple sites of activities against the allergic response. They are either administered locally and/or systematically/ systernically.

None of the above treatments are ideal for the modulation of allergic responses because each has specific problems such as side effects including drowsiness, they also lack specificity in the immune system leading to global immuno-suppression. Also many of these therapeutic agents need to be administered continuously. Therefore, new improved treatments are constantly being sought to control the allergic response prophylactically and/or therapeutically without the above-mentioned limitations.

Individuals who wish to become desensitized against an allergen often must submit himself/herself to injections of measured doses of the allergen, first administered at weekly or biweekly intervals, then gradually decreases to bimonthly or monthly intervals throughout the year. Such injections generally commence with a small dose of the allergen and then gradually increasing the dosage until a maximally-tolerated maintenance dose is achieved. The individual is then kept on a maintenance dose of the allergen for long periods of time or until the individual no longer exhibits an allergic reaction to the allergen.

Other treatment regimes have been devised to reduce or eliminate an allergic response.

Allergen injection therapy (allergen immunotherapy also known as subcutaneous immunotherapy (SCIT) is known to reduce the severity of allergic rhinitis. This treatment is theorized to involve the production of a different form of antibody, a protective antibody which is termed a "blocking antibody" (Cooke, RA et al., Serologic Evidence of Immunity with Coexisting Sensitization in a Type of Human Allergy, Exp. Med. 1935; 62:733). Chemical agents have been developed which inhibit the interactions between the IgE and its receptor (Cheng et al., U.S. Patent No. 5,965,605 and Ra et al., U.S. Patent No. 6,090,034). IgE antagonists have also been used to treat allergic disease (Presta et al., U.S. Patent No 5,965709) and compounds that exhibit immunosuppressive activity and inhibits the release of

histamine (Bycroft et al., U.S. Patent No. 5,969,158). St. Remy et al., U.S. Patent No. 4,740,371, discloses an immune complex of an allergen for treating allergies involving a combination of the specific allergen and the corresponding antibody to that allergen. The injection of the complex into a patient is said to reduce a patient's allergic reaction to that specific allergen. Others have suggested that certain human proteins can neutralize IgE by blocking it from interacting with the mast cells, but this has not been established clearly as a clinically effective therapy (Stanworth, et al., Allergy Treatment with a Peptide Vaccine, Lancet 1990; 336:1279-81). Patterson et al., U.S. Patent No. 5,314,690 disclosed a method and preparations for reducing IgE antibodies to allergens in allergic subjects wherein substance P (a neuropeptide) and an allergen or fragments of allergens or haptens acting as allergens are administered together to the allergic subjects through a non-oral route.

Cholera Toxin and B Subunit as Adjuvants Cholera toxin (CT) and the closely related heat-labile toxin (LT) from Escherichia coli are known as exceptionally potent immunoadjuvants when co-administered with antigens by various mucosal routes (Elson et al., J. humunol. 1984; 133:2892-2897; Hohngren et al., Vaccine 1973; 1 1: 1 179-1184; Lycke et al, Eur. J. Immunol. 1992; 22:2277-228 1. Both CT and LT are recognized as "AB" toxins in that they are composed of two distinct structural and functional components: a single toxic-active A subunit component and a non-toxic cell-binding B subunit. The latter is a honiopentamer component with strong binding affinity for GMI ganglioside receptors (Holingren et al., Nature 19 8 1; 292:413 -417). Such receptors are known to be present on most mammalian cells, e.g., on skin and other epithelial cells, on all known antigen-presenting cells including dendritic cells (DC) and Langerhan's cells (LC), as well as on B and T lymphocytes. Recently, Gleim et al., U.S. Patent No. 5,980,898 disclosed a system for transcutaneous immunization that induces an immune response (e.g., humoral and/or cellular effectors) in an animal or human. The system provides a simple application to intact skin of both rodents and humans of a formulation comprised of antigen and an adjuvant that was whole cholera toxin.

Common to allergies is the involvement of the IgE class of antibody. Individuals are not born with allergies; rather they acquire them by exposure to allergens. The steps of the IgE allergic reaction are sensitization upon first exposure to the allergen, and then the allergic response to subsequent exposures. The allergic response consists of an immediate and delayed response referred to as the early

and late phase responses respectively. In atopic individuals, those prone to allergies, the initial exposure to an antigen results in the production of IgE antibodies that specifically recognize that allergen. This process is called sensitization.

The early phase response (ERP) is the immediate reaction that occurs within minutes of exposure to an allergen. IgE are bound to the surface of a neuroimmune cell called the mast cell (in the circulation these cells are called basophils). Sufficient numbers of bound IgE antibodies that react with an allergen causes the mast cell to release its content of secretory vesicles, a process known as degranulation. The secretory vesicles contain histamine and other stored substances such as nerve growth factor (NGF). In addition the mast cell and T cells immediately begin manufacturing leukotrienes, cytokines, enzymes and substances that activate blood platelets and attract secondary cells such as eosinophils. Symptoms vary depending on the site, but common reactions are smooth muscle contraction, mucus secretion, vascular permeability, and sensory nerve stimulation.

The late phase response (LPR) develops over hours to days of exposure as eosinophils and other cells are attracted to the area. Eosinophils produce major basic protein, eosinophil cationic protein, leukotrienes and nerve growth factor. TH2 lymphocytes release cytokines that promote further IgE production and eosinophil chemo attraction, and increased numbers of mast cells.

**Nerve involvement in allergy**

The sensory nerve stimulation causes reflexes that are designed to aid in defending the tissue. These reflexes are often a larger problem then the local allergic response. Reflexes can range from large gross motor actions to regional afferent and efferent arcs or even local axon-axonal reflexes involving a single neuron.

Some reflexes recruit major motor actions that are well recognized. In the nose sneezing is a reflex attempt to expel unwanted material and coughing is the equivalent response in the lungs.

Regional reflex arcs involve the sensing of the stimulus by the sensory neuron, the transfer of the message to the ganglia and the central nervous system and an efferent response via autonomic neurons. Reflex excitation by the autonomic nervous system directly causes mast cell to degranulate, thereby spreading the reaction. In addition these reflexes control a variety of other functions. In the nose

these reflexes cause increased mucus production, increased cilia movement, nasal congestion and sneezing. In the lungs reflexes cause bronchospasm, increased mucosal congestion, production of airway secretions and coughing. In the GI tract reflexes cause dysmotility, mucosal congestion and secretions. In the skin the reflexes cause swelling and itching.

Finally there are local axon-axonal reflexes in sensory nociceptive nerve fibers. Allergic stimulation of a single neuron causes release of mediators from other axons of the same neuron. (Barnes P et al. 1991 Neuropeptides in the respiratory tract. Am Rev Resp Dis 144:1187-1198, 1391-1399)

In chronic allergic stimulation the mast cells and eosinophils releases nerve growth factor which causes growth of the nerves in the region. Thereby allowing for increased neural responses and hyper reactivity. This hyper reactivity is not limited to allergic reactions but extends to non-allergic conditions such as respiratory tract infections including viral and bacterial infections. Specifically viral rhinitis, viral and bacterial sinusitis, suppurative otitis media, bronchitis and pneumonia. Therefore individuals become more susceptible to these conditions and have more frequent and severe infections.

Furthermore the repeated allergic reactions cause changes in the qualitative response of the neural reflexes such that they are inappropriately activated. This negatively effects non-allergic conditions, such as bronchospasm mucus production and coughing in non-allergic lung conditions such as bronchitis and emphysema.

**Allergic reactions differ from inflammatory reactions**

Allergic reactions differ from inflammation. Allergies represent the body's inappropriate response to what is in essence a harmless antigen. It is believed that the IgE allergic reactions evolved to combat parasitic infections which are now rare in industrialized societies. In contrast, inflammation is the body's response to actual tissue damage or infection. Inflammation is clinically distinguished by the classical symptoms of calor, rubor and dolor: heat, redness and pain. Inflammation is a process that triggers a cascade of mediators with wide effects, both locally and systemically. Local reactions include pain, vasodilation and migration of macrophages and neutrophils. Systemic reactions include fever. Certain conditions, such as rhinitis or asthma, can be triggered by allergies, infections, irritating

chemicals or may be entirely neurogenic, the result of nerve activity without prior inflammatory or allergic stimulation.

**Specific Allergic Conditions**

**Rhinitis**

**Allergic rhinitis**

The inner lining of the nose is a mucosa that contains serous and mucus glands and large numbers of mast cells. This mucosa extends to the openings leading to the sinuses as well as the Eustachian tube where it is continuous with the mucosa of the sinuses and middle ear, respectively. The EPR of the nasal mucosa causes mast cell degranulation. The release of histamine, heparin and neuropeptides provokes vasodilation and acute swelling of the mucosa and has some minor direct stimulatory effect on the mucus secreting glands. Reflex excitation causes reflex sneezing, congestion and neural stimulation of the seromucinous glands and further congestion. LPR attracts eosinophils and prolongs the reaction.

Allergic reactions can also be chronic, a condition known as perennial rhinitis. In these cases airborne allergens are constantly in the environment. Chronic low-level allergic reactions cause a thickening of the nasal mucosa due to edema and hypertrophy of glandular elements. As a result the primary symptoms of perennial rhinitis are nasal congestion, and postnasal drip. After each allergic reaction the mucosa swells; repeated allergic reactions enlarges the mucosa permanently and may form polyps. Thickening of the mucosa can cause obstruction of the small openings that allow drainage from the sinus. Obstruction of these openings allows nasal secretions to collect and become infected, thereby causing sinusitis.

Topical treatment of allergic rhinitis includes steroid sprays and chromalyn sodium (Nasocrom®) a chemical that blocks mast cell degranulation, and/or nasal decongestants (Neosynephrine). Systemic treatment includes oral anti-histamines and non-sedating antihistamines (Allegra®, Zyrtec®, Claritin®). Long-term therapy requires immune desensitization to the allergen by progressive intradermal injections of the allergen over months to years. rhinitis can lead

Allergic rhinitis can lead to pulmonary disease, including but not limited to asthma and emphysema, suitably asthma caused by hyperreactivity and/or the

symptoms of bronchoconstriction, mucosal edema, increased secretions and cough. These can be treated by the application of CnT to the nasal cavity of patients with allergic rhinitis. It is well known in the art that allergic conditions of the nose can cause reflex changes in the lung that mimic or exacerbate asthma. (McCusker C et al 2002, Site-specific sensitization in a murine model of allergic rhinitis: Role of the upper airway in lower airway disease, J Allergy Clin Immunol, 110:891-898)

**Perennial allergic rhinitis**

Perenial rhinitis is a chronic condition and certain symptoms, such as nasal congestion, are more prominent then others such as sneezing. Therefore therapy for this condition needs to be over more prolonged period, if not indefinitely. Although the same treatments as disclosed for seasonal allergic rhinitis can be used repeatedly, certain method of treatment asre disclosed here that are more efficient and convenient for longer term therapy.

Parasympathetic neurons do not extend from the central nervous system to their target organs in the nose. Instead parasympathetic preganglionic neurons have their cell bodies in the brain stem and have an axon that extends partway and synapses on the cell body of a second neuron called the postganglionic neuron. The axons of the postganglionic neurons extend into nose and sinuses and modulate many of the biological responses seen during allergic reactions. The cell body of the post ganglionic parasympathetic neuron also receives collateral afferent synapses from sensory neurons that are stimulated during allergic reactions. Therefore much of the neuronal circuit involved in the allergic reaction converges onto the cell body of the postganglionic neuron.

All of the postganglionic neuron cell bodies are concentrated in small structure called the sphenopalatine ganglion. Moreover all afferent synaptic connections on these neurons is cholinergic, the neurotransmitter most sensitive to BoNT. Therefore application of CnT to the sphenopalatine ganglion is the most efficient way of blocking the allergic neural reaction.

The sphenopalatine ganglion is accessible to needle injection via the sphenopalatine canal. This canal passes though the hard palate and is accesible about one centimeter medial to the the second molar. Injections of anesthetic and

vasoconstrictor agents are commonly performed by clinicians skilled ion the art of nasal surgery.

**Infectious rhinitis**

Although they share some of the same symptoms, allergic rhinitis differs from infectious rhinitis. The most common cause of infectious rhinitis is a viral infection, known as the common cold. Bacterial and fungal infections of the nose occur also but these are comparatively rare as primary events. During viral infections the epithelial cells release secretions that trigger an inflammatory response. The classic signs of caldor, rubor and dolor; heat, redness, and pain characterize inflammation. White blood cells such as macrophages and neutrophils migrate from small blood vessels in the area to the infected mucosa. These cells in turn release a variety of chemical mediators that increase the inflammation. Infectious rhinitis is characterized by a purulent or pus like postnasal drip, and nasal congestion. In many viral infections there are systemic symptoms such as fever. Treatment of viral infectious is symptomatic with topical and systemic decongestants, and antipyretic and anti-inflammatory drugs.

**Vasomotor and other causes of rhinitis**

Vasomotor rhinitis is strictly a neural hyper stimulation of the serous secretory glands of the nose. This condition is characterized by a watery nasal discharge with a very small content of mucus. Vasomotor rhinitis results directly from neural stimulation of temperature changes or while eating, and associated other symptoms such as congestion, and sneezing are not prominent. US 5,766, 605 discloses a method of blocking the symptom of rhinorrhea in vasomotor rhinitis using clostridia neurotoxins.

**Serous otitis media**

Direct reaction of the middle ear mucosa to allergens, or indirect effects by blockage of the Eustachian tube, leads to serous otitis media. In this condition the middle ear fills with fluid and hearing is impaired. As this condition most often affects young children they are risk of learning disabilities due to the decreased hearing acuity.

**Sinusitis, a complication of rhinitis**

Sinusitis is an infection of the sinuses. The sinuses are air filled cavities surrounding and opening into the nasal cavity via small openings called ostia. The maxillary sinuses compose the mass of the cheeks and the ostia are between the inferior and middle turbinate. The frontal sinuses are above the brow underneath the skin of the forehead, they open into the nasal cavity via a duct that enters beneath the middle turbinate. The sphenoid sinuses are in the nasopharynx and have ostia on their anterior surface. The ethmoid sinuses are located between the eyes and are composed of numerous small air cells. The anterior and posterior cells drain independently. The anterior ethmoid region is especially important due to the confluence of drainage ostia. The area is called the infundibulum, and a small amount of obstruction can cause widespread sinus infections.

Sinus infections are either acute or chronic. In acute sinusitis a bacterial infection follows a viral infection of the upper respiratory tract. However, sinusitis can also occur from obstruction of the draining ostia of the sinuses by inflammation or mass lesion. Topical nasal decongestants and systemic antibiotics are used to treat acute sinusitis. Severe or complicated infections may require surgical drainage of the involved sinus. Chronic sinusitis is a low-grade ongoing or recurrent infection of the sinuses. In these cases the mucosa of the sinuses has become thickened and enlarged due to edema and increased secretory glandular elements. In these cases small abscess may persist and relatively mild inflammatory stimuli may cause obstruction of the narrowed sinus ostia. Treatment of chronic sinusitis includes topical steroid sprays, systemic anti histamines and decongestants, and/or surgical removal of diseased mucosa with enlargement of the ostia.

**Asthma**

Asthma is a general term given to a similar constellation of symptoms: bronchospasm, mucosal swelling and increased secretions. Allergic stimulation, infections, irritating chemicals, cold air or exercise can trigger asthma.

Allergic asthma is a specific subset of asthma that is initiated by allergens and involves the IgE mediated reaction. Local and organ reactions include bronchial smooth muscle constriction, mucosal swelling and increased secretions.

**Other Allergic conditions**

Other allergic conditions include food allergies, and allergic dermatitis.

**Clostridia neurotoxins (CnT)**

Clostridium (C.) botulinum and the closely related species C. butyricum and beratti produce an extremely powerful neurotoxin that causes the paralytic condition known as botulism. The botulinum neurotoxin (BoNT) protein consists of a light and heavy chain that together weigh approximately 150 kD. In botulism the primary target is the synapse of the motor neuron with the muscle fiber. Here BoNT is taken up by the membrane of the motor neuron and is internalized. The effect of BoNT is to inhibit the release of neurotransmitters and neuropeptides by neurons. In clinical use each serotype appears to differ in its potency in blocking different classes of neurons.

BoNT works by a two-stage mechanism, uptake and molecular action. Peripheral nerve terminals take up BoNT. After translocation across the cell membrane BoNT interferes with the molecular mechanism of neurosecretion. Specifically, BoNT cleaves the proteins involved in synaptic vesicle docking and release called the SNARE complex. The result is to block neural signals.

C. tetani produce tetanus neurotoxin (TeNT). TeNT is similar to the BoNTs in that it interferes with vesicle release by cleaving VAMP, one of the SNARE family of proteins. However the in vivo biological activity of TeNT is usually quite different from BoNT. The systemic disorder tetanus results from TnT produced at a wound site and disseminated throughout the body via the blood stream. The TeNT is taken up by peripheral motor neurons and transported to the central nervous system. The TeNT then preferentially blocks inhibitory neurons connecting to the motor neuron, thereby allowing unopposed excitatory input. However, at higher doses TeNT and when introduced directly into the neuron also blocks all neurons in the same manner as BoNT. In this application it is assumed that the when BoNT is discussed is includes the TeNT when used at higher blocking doses.

At present seven immunologically distinct serotypes of the BoNT are known, named A, B, C, D, E, F and G. The type C serotype is now known to be divided into three different toxins with distinct biological effects. Only C1 is a neurotoxin, whereas C2 and C3 are not. C2 is distinctive for blocking actin formation, which can prevent mast cell degranulation. Although all BoNT serotypes interfere with proteins that

cause the release of synaptic vesicles from cells they each interfere with different proteins, or different parts of the same protein:

BoNT A & E cleave SNAP-25 (synapse associated protein)

BoNT C cleaves SNAP-25 and syntaxin

BoNT B, D, F & G (and TeNT) cleave VAMP (vesicle associated membrane protein)

Most if not all cell types use the vesicle system for secretion, although the molecules within these vesicles differ for each type of cell. If experimentally introduced into any cell BoNT appears capable of blocking its vesicle release. However, in nature BoNT appears to be internalized into neurons, particularly the efferent neurons. The vesicles within neurons contain classical neurotransmitters (acetylcholine, epinephrine, nor epinephrine, dopamine, serotonin, glutamate, GABA and others) and/or neuropeptides (substance P, neurokinin A, calcitonin gene related peptide (CGRP), neuropeptide Y, interleukins, growth factors and others). Although the highest affinity of BoNT is for cholinergic neurons, in various preparations BoNT has been shown to block secretion of all these molecules.

**The clinical effects of botulinum toxin on different classes of neurons**

**Voluntary motor nerves**

The first and still primary use of BoNT is to block motor nerve communication with muscle fibers. BT is injected within the target muscle. The BoNT is then internalized into motor neurons where it decreases or stops the release of the neurotransmitter acetylcholine (AChE), thereby causing paresis or paralysis of the muscle. Scott introduced the concept of localized muscular injections of BoNT in the specific condition of strabismus (squint, crossed eyes). Later BoNT was found to be particularly useful for movement disorders such as tics, spasms, contractures, cramps and tremors. More recently, the injection of BoNT into facial muscles has been found to ameliorate skin wrinkling and lines related to aging. Another recent application of BoNT injections is to decrease the pain accompanying muscle tension in conditions such as headache and temporo-mandibular joint syndrome.

**Autonomic motor neurons**

Effector neurons of the autonomic system innervate and control the contraction of smooth muscles using AChE as the neurotransmitter. Injections of BoNT have been used to decrease tone in the smooth muscles of the lower esophageal sphincter, esophagus, stomach wall, and pyloric sphincter, sphincter of Odi, anal sphincter, and urinary bladder.

**Autonomic secretory neurons**

Effector neurons of the autonomic system control or modulate the secretion of various water and mucoid fluids throughout the body. BoNT injections have been used to decrease sweating, salivary gland flow, gastric secretions including acid production, nasal and other respiratory secretions, and tearing.

**Sensory neurons**

Sensory neurons release a wide variety of neuropeptides, cytokines, growth factors and other substances that effect parenchymal cells, blood vessels and immune cells. Notable is that these substances can activate mast cells directly thereby extending the allergic reaction. Except for nitrous oxide these substances are released via the SNARE mechanism and can be blocked by CnT.

## SUMMARY OF THE INVENTION

As used herein 'local administration' includes but is not limited to injection by needle and in-dwelling catheter (including pressure jet injectors), topical administration in lyophilized powder, liquid solutions, creams, ointments, aerosolized or introduced by liposomal (niosomes) vectors, or as nucleic acid introduced by viral or other vectors. The CnT may also be embedded in biopolymers or delivered by implanted pumps to release the CnT into solution over prolonged periods.

By "therapeutically effective amount" it is meant of purposes of this invention that the CnT is administered in a non-toxic amount sufficient to cause reduction in the occurrence or magnitude of the symptoms being targeted.

By "unit" it is meant the biological equivalent of the current unit measure used for botulinum toxin A marketed as Botox. At present BoNT is measured by biological assay; a unit of BoNT is the amount that causes death to 50% of mice when injected intraperitoneally. BoNT-A is marketed as Botox by Allergan Corp, Irvine Ca, and as Dysport by Ipsen Ltd, Berks United Kingdom. Although the biological assay is done the same way the in vivo effect of Botox and Dysport vary. BoNT-B is marketed as Myobloc by Elan Pharmaceuticals, Dublin, Ireland. TeNT is not commercially available but other assays have compared the potency of the blocking effect of TeNT to BoNT. All serotypes of BoNT as well as TeNT are commercially available from List Biological laboratories). A therapeutically effective amount of BoNT will vary depending on the organ to be treated, how much of the organ will be treated, the method of application and the exact preparation of BoNT used. A therapeutically effective amount will vary from a fraction of a unit to hundreds of units as is it currently does with intramuscular injections. The exact dosage will not require undo experimentation by those skilled in the art.

Where solutions or suspensions of BoNT or CnT are referred to, unless indicated to the contrary, this means the designated number of units in 1 ml of Normal saline.

By "CnT" it is meant that any biological substance having essentially the same biological effect within cells as the wild types of clostridia neurotoxins. Specifically, to block or decrease the activity of the SNARE family of proteins involvled in secretion of allergy related neurohumors. Numerous substitutions for the major parts of the CnT have been disclosed and these are all included in this specification. This would include fragments, altered forms, and recombinant forms of CnT. Also included are chimeras, hybrids and conjugates. Also included are the use of DNA and RNA sequences that are directly applied and translated in the allergic sites. Also included are "vectors", various compositions that deliver a botulinum or tetanus toxin light chain or its equivalent such as Protease A across cell membranes. These vectors include but are not limited to viruses, liposomes, noisomes, and protein transduction domains (US Provisional Application 60/449,107).

Allergic "neurohumors" are neurotransmitters, neuropeptides and cytokines that participate in allergic reactions and whose secretion or action can be blocked by CnT. They include acetylcholine, noradrenaline, neuropeptide Y, substance P,

calcitonin gene reactive protein (CGRP), histamine, nerve growth factor, and interleukins.

The invention is directed to a method of blocking or reducing physiological reaction in a mammal, suitably but not limited to H. sapiens, .to the interaction of IgE antibodies present in said mammal upon contact with the corresponding antigen. This blocking is achieved by the administration to said mammal of a therapeutically effective amount of a neurotoxin (CnT) derived from Clostridia sp. Suitably, the CnT is derived from a species of Clostridia selected from the group consisting of C. botulinum, C. butyricum, C. beratti, C. tetani . The neurotoxins (BoNT), derived from C. botulinum, are derived from serotypes A, B, C1, D, E, F and G, while neurotoxin (TeNT), is derived from C.tetani

BoNT/A is marketed as Botox® by Allergan Inc and as Dysport® by Ipsen Ltd as a lyophilized powder that is reconstituted with preservative free normal saline prior to use. BoNT/B is marketed as Myobloc® by Elan Pharmaceuticals in normal saline solution. The light chains and holotoxins for each BoNT serotypes and TeNT can be obtained from List Biological Labs and/or Metabologics Inc.

CnT compositions of the present inventions are prepared in a variety of forms depending on whether the composition is injected or implanted, topically applied to respiratory mucosa of the nasal cavity or lungs, gastrointestinal mucosa, or to skin.

For all injectable CnT compositions fluid dosage forms are prepared utilizing the compound and a pyrogen-free sterile vehicle. The compound, depending on the vehicle and concentration used, can be either dissolved or suspended in the vehicle. In preparing solutions the compound can be dissolved in the vehicle, the solution being made isotonic if necessary by addition of sodium chloride and sterilized by filtration through a sterile filter using aseptic techniques before filling into suitable sterile vials or ampoules and sealing. Alternatively, if solution stability is adequate, the solution in its sealed containers may be sterilized by autoclaving. Advantageously additives such as buffering, solubilizing, stabilizing, preservative or bactericidal, suspending or emulsifying agents and/or local anaesthetic agents may be dissolved in the vehicle.

Dry powders, which are dissolved or suspended in a suitable vehicle prior to

use, may be prepared by filling pre-sterilized drug substance and other ingredients into a sterile container using aseptic technique in a sterile area. Alternatively the drug and other ingredients may be dissolved into suitable containers using aseptic technique in a sterile area. The product is then freeze-dried and the containers are sealed aseptically.

In the respiratory and gastrointestinal systems, CnT binds to mucosal epithelial cells and is actively transcytosed across the mucosa. Compositions suitable for administration to the respiratory tract include aerosols, nebulisable solutions or micro-fine powders for insufflation. In the latter case, particle size of less than 50 microns, especially less than I 0 microns, is preferred.

Compositions suitable for topical mucosal application include normal saline solutions as described above for injections. Other suitable compositions include gels and creams.

The skin presents a formidable barrier to the application of CnT. CnT may be mechanically propelled across the dermal barier with air or water pressure injectors or in association with micro-pellets . Other suitable forms of transdermal delivery include iontophoresis .CnT may be encapsulated into liposomes or niosomes to form suitable trans-dermal compositions.

The method of administration may take many forms, including topical, intra-dermal, sub-cutaneous, trans-cutaneous, intra cavital and by inhalation of the CnT in a suitable carrier. Examples of such administration include, but are not limited to contact with absorbant pledgets having CnT absorbed thereon, contact with biodegradable micropellets having CnT embedded therein. Also included is injection, for example, injection to the nasal mucosa or injection into the pterygoplatine space through the palate, or injection into affected areas of the surface skin. More invasively, by myringotomy and injection into the middle ear space. tympanic membranes. Alternatively less invasive methods include by drops into the inner eyelid and inhalation of an aqueous mist containing same.

The physiological reaction reactions dealt with herein include but are not limited to conditions such as allergic rhinitis, Infectious rhinitis, vasomotor rhinitis, serous otitis media, sinusitis, asthma, food allergies and allergic dermatitis.

The amount of CnT administered per administration may be, but is not limited to between about 0.1 and about 1000 units, suitably between about 1 and about 100 units per administration, preferably between about 1 and about 20 units.

The invention is also directed to use of a neurotoxin (CnT) derived from Clostridia sp for the production of a medicament for blocking or reducing physiological reaction in a mammal to the interaction of IgE antibodies present in said mammal upon contact with the corresponding antigen. The formulations of CnT, including BoNT and TeNT, which are suitable for the purposes designated herein are well known, but have not previously been designated for this purpose.

There is a great need for an effective treatment for allergic disorders. It has long been thought that the allergic reaction involved only histamine release by mast cells. Therefore first line therapy for allergy was antihistamines, or more recently the non-sedating antihistamines. Other therapies are directed to block the effects of the mast cell secretions with adrenergic agonists. It is not obvious to those skilled in the art that a central role in allergic disorders involves the autonomic nervous system and that this nerve activity can be blocked by CnT for a beneficial effect.

It is an object of the invention to provide a treatment for allergic conditions. Included particularly are allergy related rhinitis, asthma, gastroenterititis, serous otitis, sinusitis and dermatitis) and their related conditions (such as sinusitis and serous otitis media that occur secondary to allergy induced mucosal swelling). Treatment is by local application of therapeutically effective amounts of CnTs to the body structure and/or the nerves and nerve ganglia supplying these structures. CnT interfere with the allergic process by:

1) Directly blocking neuroimmune secretions by the mast cell or other immune cell types including but not limited to eosinophils ()

2) Block the release of neurohumors by mast cells induced by autonomic nerve activity.

3) Decrease neurohumoral release during axonal reflexes.

4) Decrease the parasympathetic effector arm of reflex allergic responses

5) Decrease the increased tonic activity of the autonomic systemic that is related to prior allergic reactions.

6) Decrease the enlargement and hypersensitivity of sensory nerves induced by nerve growth factor and other neurohumors released during allergic reactions.

7) Reverse certain complications of allergic reactions such as mucosal thickening by decreasing autonomic nerve activity.

The beneficial effect of this treatment in the:

1) Nasal area, is to decrease the symptoms of sneezing, itching, nasal congestion and post nasal drip, as well as related conditions including nasal polyps and mucosal thickening, and complications such as sinusitis and serous otitis.

2) Lungs, is to decrease coughing and wheezing (bronchoconstriction, edema) and the non-specific sensory hypersensitivity related to chronic allegic reactions.

3) Eye, is to decrease itching, tearing and redness.

4) Skin, is to decrease itching and swelling.

5) Gastrointestinal tract, is to decrease gastrointestinal dysmotility.

## Examples

### Example 1. Seasonal allergic rhinitis

1a) A 30-year-old male has seasonal allergic rhinitis. In May, prior to pollen formation, 30 units of BoNT topically applied in each nostril. Specifically, the nasal cavity is sprayed with a solution of 1% lidocaine and ½% neosynephrine to anesthetize and decongest the nasal mucosa, respectively. Then 1 cc of normal saline containing 30 units of BoNT is sprayed into each nasal cavity. This method of delivery, although commonly used for application of nasal medication, is inherently inefficient as a significant percentage of a sprayed medication will exit the posterior nasal cavity and be exhaled or swallowed.

1b) In another embodiment, the patient is treated by placing 1 x 3 $cm^2$ cotton pledgets impregnated with 20 units of BoNT onto the medial surface of the turbinates and left for one hour, then removed by the physician. This delivery method is more efficient then a spray, however a significant percentage of the BoNT will not diffuse from the pledgets to the mucosa.

1c) Alternatively, the patient has topical anesthesia applied only to a localized area, preferably the anterior end of the inferior turbinate. Then, patient has a 1$cm^2$ cotton pledget impregnated with 10 units of BoNT placed onto the mucosa of the anterior turbinate for one hour and then removed. Within the nasal cavity a mucociliary blanket transports fluids and particles posteriorly, thereby distributing the BoNT. This is an example of applying a BoNT to a localized region of the nasal cavity and using the normal physiology of the nasal cavity for distribution. The routes of mucociliary clearance of the nose and sinus cavities are known so that other variations of this method are apparent to those skilled in the art.

1d) In another embodiment, using a topical biodegradable depot to deliver BoNT over an extended time period to nasal mucosa is used for treating the patient. Various biodegradable compounds are known in the art that vary in consistency and rate of dissolution.

An example is oxidized cellulose (marketed as Surgicel® by Johnson & Johnson, New Brunswick, NJ). The oxidized cellulose can be manufactured with BoNT as an integral component, or the BoNT can be added to the oxidized cellulose before its clinical use. Surgicel is available in the form of a thin flexible sheet that is

often cut to fit the area of the body to which it will be applied. For intranasal use the size may vary from a few square millimeters to a 4 by 8 $cm^2$ sheet that could contact the entire exposed mucosa of the nasal cavity. BoNT can be added to the Surgicel as a lyophilized powder or after reconstitution into solution. If added as a powder it can homogeneously applied onto one side of the Surgicel and the material can be folded. The material is then moistened with normal saline to bind the material together and immobilize the BoNT prior to clinical use. In contrast the BoNT can first be constituted into solution and then absorbed into the material.

As an example a 2 x 6 $cm^2$ piece of oxidized cellulose is saturated with 1 cc of normal saline containing a total of 10 units of BoNT. Using a nasal speculum the nostril is dilated and the nasal cavity is visualized and the saturated cellulose place therein. The cellulose will gradually dissolve over hours while releasing a small continual dose of BoNT directly onto the nasal mucosa.

Alternatively the patient is of 0.5 cc. of normal saline containing 5 units of BoNTis applied to the oxidized cellulose which is grasped with bayonet forceps and placed flat onto the medial surface of the anterior end of the inferior turbinate of each nasal cavity. As disclosed above the mucociliary action of the nasal mucosa transports liquids and particles from the anterior to posterior nasal cavity.

1e) In another embodiment the patient is injected with BoNT solution directly into the nasal mucosa. After anesthetizing and decongesting the mucosa, 5 units of BoNT in 1 cc of saline are injected beneath the mucosa throughout the length of the inferior turbinate with a 25 gauge spinal needle coupled to a 1 cc syringe.

1f) Alternatively the patient can be treated with TeNT.

Compositions of TeNT for intranasal administration, can range in dose from .1 to 1000 units in 0.1cc to 10 cc of solution. One preferable composition is 10 units of TeNT in 1 cc of normal saline.

As an example the same patient is treated by spraying each nostril with 1 cc of normal saline solution containing 10 units of TeNT.

Alternatively, if only decongestion is desired 10 units of TeNT can be topically applied.

In another embodiment, 1 unit of recombinant DNA coding for TeNT is pressure injected across the nasal mucosa to transfect mucosal cells. These cells then express the TeNT for months.

**Example 2. Perennial allergic rhinitis**

2a) Direct injection of the sphenopalatine ganglia.

A 40-year-old female has chronic nasal congestion due to perennial rhinitis. Skin testing demonstrates that she is allergic to numerous environmental antigens and intranasal examination shows enlarged turbinate mucosa and nasal polyps. Testing of nasal secretions shows eosinophilia. An injection of 20 units of BoNT in a 1cc solution of normal saline is made through the sphenopalatine canal into the area of the sphenopalatine ganglia.

In another embodiment, 100 units of BoNT embedded in 0.1 micron biodegradable pellets suspended in solution is injected into the mucosa of each turbinate to slowly release its contents over 6 months.

Alternatively a biodegradable carrier containing 5 units of BoNT is placed intranasally in the most superior and posterior aspect of the lateral nasal wall. This permits the BoNT to diffuse across the nasal wall to the underlying sphenopalatine ganglia.

**Example 3. Serous otitis media**

A 3-year male has a history of serous otitis media. Under general anesthesia a myringotomy is made into the tympanic membranes and 2 units of BoNT in .5 cc of normal saline is injected.

**Example 4. Sinusitis**

A fifty-year-old male has a history of allergic rhinitis and recurrent sinusitis. Ten units of BoNT are injected through the palate into the pterygopalatine space to block the sphenopalatine ganglion.

**Example 5. Allergic dermatitis.**

A seventy-year-old male has severe allergic dermatitis of the forearm skin. Each forearm is injected with 10 injections of 0.3 units BoNT in 0.1 cc of normal saline. Each injection is made intradermally at 3 cm intervals.

**Example 6. Allergic asthma**

A 13-year-old boy has severe allergic asthma. He is treated by bimonthly inhalation therapy of an aerosilized solution of 5 units of botulinum toxin in 5 cc of normal saline.

Alternatively the same botulinum solution can be injected directly into the trachea and bronchi. After injecting local anesthesia into the skin overlying the cricothyroid membrane a needle is passed directly through the skin and cricothyroid membrane and the BoNT solution is sprayed into the trachea. The solution drips down to reach the bronchial mucosa where it is topically absorbed. and is absorbed

**Example 7 Allergic rhinitis**

A 40 year old male has allergic rhinitis and an associated reflex chronic cough. Application of CnT to the nasal cavity as described above or alternatively injected or aerosilized topical application of BoNT to the lungs is used to treat the cough.

**Example 8. Food allergies**

A 10-year-old boy with food allergies manifested by bloating and diarrhea is treated with a rectal suppository containing 50 units of BoNT. The suppository is composed of biocompatible material designed to be solid at room temperature but to dissolve at body temperature. Sufficient materials for the composition are coacoa butter, glycerinated gelatin, hydrogenated vegetable oils, polyethylene glycols of various molecular weights and fatty esters of polyethylene glycol.

**Example 9. Infectious rhinitis**

Chronic allergic exposure causes the nervous system to become hyper responsive to non-allergic stimulation such as that caused by viral infections.

A patient with rhinitis is given 10 units of BoNT and 5 units of TeNT prior to spring.

I Claim

1. A method of blocking or reducing physiological reaction in a mammal to the interaction of IgE antibodies present in said mammal upon contact with the corresponding antigen, by the administration to said mammal of a therapeutically effective amount of a neurotoxin (CnT) derived from Clostridia sp.

2. The method of claim 1 wherein the mammal is a member of H. sapiens.

3. The method of claim 2 wherein the neurotoxin is derived from a species of Clostridia selected from the group consisting of C. botulinum, C. butyricum, C. beratti, C. tetani .

4. The method of claim 3 wherein the neurotoxins (BoNT), derived from C. botulinum, are derived from serotypes A, B, C1, D, E, F and G

5. The method of claim 3 wherein the neurotoxin (TeNT) is derived from C.tetani.

6. The method of claim 1 wherein CnT is administered by contact with absorbant pledgets having CnT absorbed thereon.

7. The method of claim 1 wherein CnT is administered by contact with biodegradable carrier containing CnT .

8. The method of claim 1 wherein CnT is administered by injection.

9. The method of claim 1 wherein CnT is administered by myringotomy into tympanic membranes.

10. The method of claim 1 wherein CnT is administered by injection into the pterygoplatine space through the palate.

11. The method of claim 7 wherein CnT is administered to pass through the nasal wall to the sphenopalatine ganglia .

12. The method of claim 1 wherein CnT is administered by inhalation of an aqueous mist containing same.

13. The method of claim 1 wherein CnT is administered by injection to the nasal mucosa.

14. The method of claim 1 wherein CnT is administered by application of a suppository containing same.

15. The method of claim 1 wherein the physiological reaction is manifested by a condition or symptoms selected from the group consisting of allergic rhinitis, infectious rhinitis, serous otitis media, sinusitis, pulmonary disease, food allergies, allergic dermatitis, and sneezing, coughing, itching and excess mucous secretion related to allergic reactions.

16. The method of claim 15 wherein the pulmonary disease is selected from the group consisting of bronchitis, emphysema and hypereactive asthma.

17. The method of claim 1 wherein CnT is adminstered by contact with absorbant pledgets having CnT absorbed thereon.

18. The method of claim 1 wherein the amount of CnT administered per administration is between about 0.1 and about 1000 units per administration.

19. The method of claim 1 wherein the amount of CnT administered per administration is between about 1 and about 100 units per administration.

20. The method of claim 1 wherein the amount of CnT administered per administration is between about 1 and about 20 units per administration.

21. The use of a neurotoxin (CnT) derived from Clostridia sp for the production of a medicament for blocking or reducing physiological reaction in a mammal to the interaction of IgE antibodies present in said mammal upon contact with the corresponding antigen.

22. The use of claim 21 wherein the physiological reaction is manifested by a condition selected from the group consisting of allergic rhinitis, infectious rhinitis, serous otitis media, sinusitis, pulmonary disease, food allergies , allergic

dermatitis and sneezing, coughing, itching and excess mucous secretion related to allergic reactions.

23. The use of claim 22 wherein the pulmonary disease is selected from the group consisting of asthma and/or the symptoms of broncho-constriction, bronchitis, mucosal edema, emphysema increased secretions and cough,

24. A medicament for blocking or reducing physiological reaction in a mammal to the interaction of IgE antibodies present in said mammal upon contact with the corresponding antigen comprising a neurotoxin (CnT) derived from Clostridia sp and a pharmacologically acceptable carrier.

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Declaration under Rule 4.17:
— *of inventorship (Rule 4.17(iv)) for US only*

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(54) Title: TREATMENT OF MAMMALIAN REACTION TO IGE INTERACTIONS

(57) Abstract: A method is disclosed for blocking or reducing physiological reaction in a mammal to the interaction of IgE antibodies present in said mammal upon contact with the corresponding antigen, by the administration to said mammal of a therapeutically effective amount of a neurotoxin (CnT) derived from Clostridia sp.

WO 2004/048519 A3

# INTERNATIONAL SEARCH REPORT

International application No.
PCT/US03/37286

**A. CLASSIFICATION OF SUBJECT MATTER**

IPC(7) : A61K 39/00, 39/395, 39/02, 39/08, 38/00; C07K 1/00
US CL : 424/236.1, 234.1, 239.1, 247.1, 810, 805; 530/825, 350; 514/2, 826, 886, 849

According to International Patent Classification (IPC) or to both national classification and IPC

**B. FIELDS SEARCHED**

Minimum documentation searched (classification system followed by classification symbols)
U.S. : 424/236.1, 234.1, 239.1, 247.1, 810, 805; 530/825, 350; 514/2, 826, 886, 849

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
Please See Continuation Sheet

**C. DOCUMENTS CONSIDERED TO BE RELEVANT**

| Category * | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|---|---|---|
| X<br>---<br>Y | WO 95/28171 A1 (MOUNT SINAI SCHOOL OF MEDICINE OF THE CITY UNIVERSITY OF NEW YORK) 26 Octobrer 1995 (26.10.1995), claims; Examples; and Summary of the invention | 1-4, 6-15, 17-22 and 24<br>---<br>5, 16 and 23 |
| X<br>---<br>Y | SHAARI, C.M. et al. Rhinorrhea is decreased in dogs after nasal application of botulinum toxin. Otolaryngology-Head and Neck Surgery. April 1995, Vol. 112, No. 4, 566-571, entire document. | 1-4, 11-13, 15 and 24<br>---<br>5-10, 14, 16-23 |

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" carlier application or patent published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search
14 April 2004 (14.04.2004)

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Form PCT/ISA/210 (second sheet) (July 1998)

# INTERNATIONAL SEARCH REPORT

International application No.
PCT/US03/37286

**Box I Observations where certain claims were found unsearchable (Continuation of Item 1 of first sheet)**

This international report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claim Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claim Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claim Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

**Box II Observations where unity of invention is lacking (Continuation of Item 2 of first sheet)**

This International Searching Authority found multiple inventions in this international application, as follows:
Please See Continuation Sheet

1. ☒ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

**Remark on Protest**

☐ The additional search fees were accompanied by the applicant's protest.
☐ No protest accompanied the payment of additional search fees.

Form PCT/ISA/210 (continuation of first sheet(1)) (July 1998)

# INTERNATIONAL SEARCH REPORT

**Continuation of Item 4 of the first sheet:**
The title shall be short and precise, PCT Rule 4.3, suggested new title follows: "TREATMENT OF MAMMALIAN REACTION TO IGE INTERACTIONS"

## BOX II. OBSERVATIONS WHERE UNITY OF INVENTION IS LACKING

This application contains the following inventions or groups of inventions which are not so linked as to form a single general inventive concept under PCT Rule 13.1. In order for all inventions to be examined, the appropriate additional examination fees must be paid.

Group I, claims 1-20, drawn to a method of blocking physiological reaction to the interaction of IgE with the corresponding antigen in a mammal by administering a clsotridial neurotoxin.
Group II, claims 21-23, drawn to the use of a clostridial neurotoxin for the production of a medicament.
Group III, claim 24, drawn to a medicament comprising a clostridial neurotoxin and a pharmaceutically acceptable carrier.

The inventions listed as Groups I-III do not relate to a single general inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, they lack the same or corresponding special technical features for the following reasons:

The special technical feature of invention I is a method of blocking physiological reaction to the interaction of IgE with the corresponding antigen in a mammal by administering a clsotridial neurotoxin.
However, such a method is already disclosed in the prior art, for example, by Shaari *et al.* (*Otolaryngology-Head and Neck Surgery* 112 (4): April 1995. See abstract; Methods; Results; and Discussion. The special technical features of inventions II and III respectively are the use of a clostridial neurotoxin for the production of a medicament, and a medicament comprising a clostridial neurotoxin. These are also disclosed in the prior art, for example, by MOUNT SINAI SCHOOL OF MEDICINE OF THE CITY UNIVERSITY OF NEW YORK (WO 9528171). The special technical features do not define over the prior art.

**Continuation of B. FIELDS SEARCHED Item 3:**
DIALOG, WEST, MEDLINE, TOXLINE, BIOSIS, EMBASE, DERWENT
clostrid?, neurotoxin?, BOTOX, IgE, allerg?, rhinitis, otitis, sinusitis, dermatitis, sneez?, cough?, itch?

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**Published:**
— *without international search report and to be republished upon receipt of that report*

*For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.*

(54) Title: APPARATUS AND METHODS FOR TREATING ASTHMA USING NEUROTOXIN

(57) Abstract: Apparatus providing intrabronchial delivery of neurotoxin to control the effects of asthma comprises a shaft having proximal and distal ends and a neurotoxin applicator assembly disposed on the distal end, wherein the neurotoxin applicator assembly comprises a deployable needle assembly, a rotating needle assembly, a needle-less injection assembly, a nebulizer assembly or a microporous tip. Further embodiments involve apparatus comprising drug-eluting bioabsorbable stents having one or more layers of asthma-fighting drugs.

WO 2004/101028 A2

# APPARATUS AND METHODS FOR TREATING ASTHMA USING NEUROTOXIN

## Field of the Invention

**[0001]** The present invention relates to apparatus for treating asthma by controlled delivery of neurotoxin using a neurotoxin applicator assembly.

## Background of the Invention

**[0002]** The lung is made up of progressively smaller bronchial bifurcations stemming downward from the trachea. The trachea and proximal bronchi are lumens consisting of an outer layer of fascia surrounding a U-shaped inner cartilaginous layer, wherein the open portion of the U is spanned by smooth muscle. Inside the cartilaginous layer are a collagenous elastic layer and an innermost epithelial layer. Mucus secreting goblet cells and transport cilial cells are interspersed within these inner layers.

**[0003]** As the bronchi branch and get smaller, the cartilaginous layer changes from a U-shape to irregular and helical shapes. In addition, the smooth muscle layer becomes helical bands surrounding the entire circumference of the bronchi, the goblet cells gradually decrease in numbers and the ciliated cells get smaller

and fewer in number. In the most distal bronchi, the outer cartilaginous layer disappears completely, the smooth muscle layer becomes the outermost layer and goblet cells and ciliated cells disappear completely.

[0004] Asthma is a complex disease of the bronchial tree, characterized by airway hyperresponsiveness to allergens, stress and environmental triggers. Environmental triggers include irritants such as pollutants and non-allergenic triggers such as exposure to cold air. Airway hyperresponsiveness results in acute narrowing of the entire bronchial tree reducing airflow through the lungs, compromising respiration and limiting gas exchange in the alveoli. The narrowing of the bronchial tree is a result of three basic characteristic physiologic responses: (1) smooth muscle contraction; (2) increased mucus production; and (3) edema caused by arterial dilatation and increased arterial permeability. The triggering mechanisms for these physiologic responses are part of the body's inflammatory response system.

[0005] Chronic uncontrolled asthma can result in structural changes to the bronchial wall itself. Smooth muscle hyperplasia results in thickening of the smooth muscle components of the bronchial wall. Thickening of the subepithelial collagen layer that lies between the airway epithelium and the smooth muscle layer results in progressive stiffening of the wall of the bronchi. Studies have shown that stiffening of the airway wall results in more profound narrowing of the airway for a given asthma attack. This is due to changes in the ability of the mucosal layer to fold in response to the smooth muscle layer contraction.

[0006] Recently, the controlled injection of neurotoxin has become a common procedure for controlling

skeletal muscle spasms. A frequently used neurotoxin for this procedure is the botulinum toxin, serotype A, sold commercially by Allergan, Inc. as Botox™. Botulinum toxin blocks the release of neurotransmitter from the nerves that control the contraction of the target muscles. Many applications for botulinum toxin have been proposed and/or clinically tested, including cervical dystonia, cosmetic relief of frown lines and tremor associated with cerebral palsy. Recently, botulinum toxin has become the subject of clinical study for the relief of hyperhidrosis (profuse sweating) and hypersalivation. These studies indicate that botulinum toxin can be used to control the action of cholinergic parasympathetic nerves as well as large skeletal muscle groups. The recent findings open the possibility of using neurotoxins such as botulinum toxin to control some of the main mechanisms of airway narrowing in asthmatic attacks, specifically smooth muscle contraction and hypersecretion of mucus from the goblet cells. Additionally, there is evidence that some part of the inflammatory response of asthma is stimulated by the release of the neurotransmitters that botulinum toxin inhibits. This opens the possibility that botulinum toxin also may work to mitigate the inflammatory cycle itself.

**[0007]** The use of neurotoxin for the control of asthma is described in U.S. Patent No. 6,063,768 to First, wherein asthma is included in a list of neurogenic inflammatory disorders that may be controlled through the action of neurotoxins such as botulinum toxin but does not describe the methods or devices used to do so. An earlier patent, U.S. Patent No. 5,766,605 to Sanders, et.al., describes the use of botulinum toxin to treat

asthma and COPD. That patent also describes that botulinum toxin could be aerosolized and introduced into the lungs. Further mention of botulinum toxin in connection with asthma is provided in a press release dated February 7, 2003 by the University of Alberta in describing the work of Dr. Redwan Moqbel. The release mentions that Dr. Moqbel and others are researching the possible use of neurotoxins such as tetanus and botulinum toxin to prevent eosinophils from activating and starting the inflammatory cascade that results in an asthma attack.

**[0008]** While it may be possible to simply aerosolize neurotoxins for introduction into the lungs, introducing it into the patient through traditional inhalation means would expose the mouth, tongue, epiglottis, vocal cords, etc. to the actions of the neurotoxin, with obvious deleterious results. Much more controlled and direct application of the neurotoxin to the desired tissue is required for safe and effective therapy.

**[0009]** Accordingly, it would be desirable to provide apparatus that enables controlled delivery of a neurotoxin to target treatment areas within a patient's bronchial airways.

**[0010]** It also would be desirable to provide an apparatus permitting the controlled injection of neurotoxin into the bronchial wall of a patient.

**[0011]** It would further be desirable to provide a needle-less injection apparatus to eliminate potential complications related to the presence of needles within a patient's bronchial airways.

**[0012]** Additionally, it would be desirable to provide an apparatus permitting the application of neurotoxin

onto a target treatment area within a patient's bronchial airways.

**[0013]** In addition, implantable drug eluting devices for treating various diseases also have been developed. Examples include drug eluting coronary stents such as those under clinical investigation and commercial sale from such companies as Boston Scientific and Cordis Corporation. Bioabsorbable devices for drug delivery have likewise been contemplated, such as those under development by Synecor, Inc. (recently acquired by Guidant), and by numerous university and hospital-based development efforts. Examples of such efforts are provided in Blindt, et al., *Development of a New Biodegradable Intravascular Polymer Stent with Simultaneous Incorporation of Bioactive Substances*, Int'l J. Artif. Organs, 22(12):843-853 (1998) and Tsuji, et al., *Biodegradable Stents as a Platform to Drug Loading*, Int'l J. Cardio. Interv., 13-16 (2003).

**[0014]** Other uses for biodegradable stents include restoring patency of the urethra following treatment of prostatic hyperplasia and maintaining the patency of bronchial airways after impingement by lung tumors. Biodegradable and non-biodegradable implants for the controlled release of neurotoxin for the treatment of various diseases is described in U.S. Patent Nos. 6,306,423, 6,506,399 and 6,383,509. Further, U.S. Patent No. 5,766,605 describes the use of neurotoxin to treat autonomic nerve dysfunction, including specific claims involving treating asthma and chronic obstructive pulmonary disease (COPD). Additionally, U.S. Patent Publication No. 2002/0082197 describes the use of neurotoxin for treating mucus secreting disease, such as asthma and COPD, as does WO 00/10598.

[0015] It further would be desirable to provide implantable apparatus that provides a sustained or periodic dosage of asthma-fighting drugs to a target treatment area within a patient's bronchial airways.

Summary of the Invention

[0016] In view of the foregoing, it is an object of the present invention to provide apparatus that enables the controlled delivery of a neurotoxin to target treatment areas within a patient's bronchial airways.

[0017] It is a further object of the present invention to provide an apparatus permitting the controlled injection of neurotoxin into the bronchial wall of a patient.

[0018] It is an additional object of the present invention to provide a needle-less injection apparatus to eliminate potential complications related to the presence of needles within a patient's bronchial airways.

[0019] It is another object of the present invention to provide an apparatus permitting the application of neurotoxin onto a target treatment area within a patient's bronchial airways.

[0020] It still further is an object of this invention to provide implantable apparatus that provides a sustained or periodic dosage of asthma-fighting drugs to a target treatment area within a patient's bronchial airways.

[0021] These and other objects of the present invention are accomplished by providing an intrabronchial neurotoxin delivery system for controlled delivery of neurotoxin to a target treatment area within a patient's bronchial airways to lessen the effects of asthma. The introduction of neurotoxin into the bronchial airways

disables the hyperresponsive smooth muscle layer and controls the hypersecretion of mucus.

**[0022]** In accordance with a first aspect of the present invention, the intrabronchial neurotoxin delivery system comprises neurotoxin applicator assembly. The distal end of the neurotoxin applicator assembly may comprise a needle tip, a rotating needle assembly, a needle-less injection assembly, a nebulizer, or a micro-porous tip. This and all following applicator embodiments may be designed to work through or in concert with a standard bronchoscope, or may be incorporated into a stand-alone system for accessing and treating the airways.

**[0023]** In accordance with this aspect of the invention, the neurotoxin applicator assembly comprises an elongated shaft having a lumen in fluid communication with a source of liquid neurotoxin. The distal end of the shaft includes one or more needles that are preformed to contract radially when disposed within a lumen of the bronchoscope, but may be extended to penetrate and inject small doses of neurotoxin into the bronchial wall of a patient.

**[0024]** Alternatively, the distal end of the neurotoxin applicator assembly may carry a rotating needle assembly including plural needles disposed along the circumference of a wheel, so that the wheel may be rolled across a target treatment area. Optionally, the rotating needle assembly may include a fender to protect a portion of the bronchial wall substantially opposite the target treatment area.

**[0025]** In another alternative embodiment, the distal end of the neurotoxin applicator assembly may comprise a needle-less injection assembly that may be used to inject

neurotoxin into the bronchial wall without needle penetration. An inflatable balloon optionally may be provided to help position a port of the needle-less injection assembly adjacent to the target treatment area.

**[0026]** In a further alternative embodiment, the distal end of the neurotoxin applicator assembly comprises a nebulizer assembly having an atomizer that converts the liquid neurotoxin into a fine spray or mist that is directed onto the target treatment area. The particle size of the mist can be controlled using injection pressure or atomizer head design to access specific portions of the lung adjacent to or downstream of the treatment device. An inflatable balloon optionally may be provided to facilitate positioning the atomizer adjacent the target treatment area, and further serves to isolate the lung segment downstream of the device to prevent reflux of the mist into undesired portions of the airway. In addition, lumens optionally may be disposed between the balloon and atomizer to provide a ventilation system that allows pressure control of the treatment area to prevent over-inflation of the lung, mixing of the atomized fluid, and evacuation of remaining mist at termination of therapy, prior to balloon deflation.

**[0027]** In a still further embodiment, the distal end of the neurotoxin applicator assembly may comprises an articulable region of the shaft including a micro-porous tip that mediates flow of asthma-fighting solution through the lumen and out of the distal tip.

**[0028]** In accordance with another aspect of the present invention, the intrabronchial neurotoxin delivery system comprises a drug-eluting bioabsorbable stent comprising one or more layers of asthma-fighting drugs.

Brief Description of the Drawings

**[0029]** The above and other objects and advantages of the present invention will be apparent upon consideration of the following detailed description, taken in conjunction with the accompanying drawings, in which like reference characters refer to like parts throughout, and in which:

**[0030]** FIG. 1 is a side view of an intrabronchial neurotoxin delivery system of the present invention;

**[0031]** FIG. 2 is a perspective view of an illustrative embodiment of a neurotoxin applicator assembly of the present invention;

**[0032]** FIGS. 3A and 3B are cross-sectional views of the neurotoxin applicator assembly of FIG. 2 in retracted and extended positions, respectively;

**[0033]** FIG. 4 is a perspective view of an alternative embodiment of a neurotoxin applicator assembly of the present invention;

**[0034]** FIGS. 5A and 5B are partial cross-sectional views of the neurotoxin applicator assembly of FIG. 4 in retracted and extended positions, respectively;

**[0035]** FIG. 6 is a perspective view of another alternative embodiment of a neurotoxin applicator assembly of the present invention;

**[0036]** FIG. 7A and 7B are partial cross-sectional views of the neurotoxin applicator assembly of FIG. 6 in retracted and extended positions, respectively;

**[0037]** FIG. 8 is a perspective view of a yet further alternative embodiment of a neurotoxin applicator assembly of the present invention;

**[0038]** FIGS. 9A and 9B are partial cross-sectional views of the neurotoxin applicator assembly of FIG. 8 in retracted and extended positions, respectively;

[0039] FIG. 10 is a side view of a distal end of a neurotoxin applicator assembly for topically applying an asthma-fighting solution to a patient's bronchi;

[0040] FIGS. 11A-11C are side views of the applicator of FIG. 10 depicting the curved distal segment in different configurations;

[0041] FIG. 12 is a perspective view of a syringe that is employed to provide pressurization at the proximal end of the applicator of FIG. 10;

[0042] FIG. 13 is a perspective view of an alternative syringe that is employed to provide pressurization at the proximal end of the applicator of FIG. 10;

[0043] FIG. 14 is a side view of a drug-eluting bioabsorbable stent of the present invention;

[0044] FIG. 15 is a side view of another drug-eluting bioabsorbable stent of the present invention;

[0045] FIG. 16 is a cross-sectional view of the drug-eluting bioabsorbable stent of FIG. 14;

[0046] FIG. 17 is a perspective view depicting the delivery of drug-eluting bioabsorbable stents within a patient's bronchi;

[0047] FIG. 18 is a perspective view depicting the delivery of alternative drug-eluting bioabsorbable stents within a patient's bronchi; and

[0048] FIG. 19 is a perspective view depicting the delivery of further alternative drug-eluting bioabsorbable stents within a patient's bronchi.

Detailed Description of the Invention

[0049] Referring to FIG. 1, apparatus for controlled delivery of neurotoxin to a target treatment area within a patient's bronchial airways to lessen the effects of asthma is described. Preferably, the apparatus comprises bronchoscope 10 and neurotoxin applicator assembly 20.

Bronchoscope 10 has proximal end 12, distal end 13, and lumen 14. As is conventional, bronchoscope 10 also includes a light source for illuminating the interior of a patient's lung and optics, such as a miniature camera, that enables the physician to view the interior of the patient's lung. Alternatively, bronchoscope 10 may omit the light source and optics, and instead comprise an outer sheath. In this latter case, device 10 and neurotoxin applicator 20 would be observed using a separate conventional bronchoscope or through a light source and optics that are built into the neurotoxin applicator 20.

**[0050]** In accordance with the principles of the present invention, neurotoxin applicator assembly 20, of which various illustrative embodiments are described hereinbelow, enables the physician to selectively administer controlled doses of neurotoxin to or within selected treatment sites in the patient's lung. More specifically, neurotoxin applicator assembly 20 may be selectively advanced through lumen 14 of bronchoscope 10 to deliver a neurotoxin, such as botulinum toxin, serotype A, to a target treatment area.

**[0051]** Neurotoxin applicator assembly 20 includes shaft 21 coupled to at its proximal end to handle 22, distal end 23 having neurotoxin applicator 24, and lumen 25. Lumen 25 provides fluid communication between proximal end and handle 22 and applicator 24. Syringe 26 having plunger 27 is coupled to a port on proximal end 22. Syringe 26 is filled with neurotoxin in liquid form, and applies the neurotoxin to applicator 24 via lumen 25 when plunger 27 is actuated.

**[0052]** Handle 22 enables the physician to extend and retract applicator 24 from within lumen 14 of

bronchoscope 10, and to manipulate distal end 23 of neurotoxin applicator assembly 20 under direct visual observation using the optics of bronchoscope 10. The neurotoxin applicator assembly preferably remains retracted within lumen 14 of the bronchoscope during insertion of the catheter into the patient's bronchial airways, and is deployed once the applicator is in a desired position. Alternatively, applicator 20 may be housed inside of a retaining sheath, and both units can be advanced through lumen 14 together.

**[0053]** Referring now to FIGS. 2-3, a first illustrative embodiment of applicator 24 of neurotoxin applicator assembly 20 constructed in accordance with the principles of the present invention is described. Applicator 24 comprises needle assembly 28 having at least one needle 30 with lumen 31 in fluid communication with lumen 25. The needles are configured to penetrate the airway epithelium and directly inject small amounts of neurotoxin from the syringe into the collagenous and smooth muscle layers of bronchial wall **B**.

**[0054]** In FIG. 3A, needle assembly 28 is depicted retracted with lumen 14 of bronchoscope 10. Alternatively, device 10 may comprise an outer sheath that is dimensioned to be slidably accept neurotoxin applicator assembly 20, and which is selectively retractable to expose needle assembly 28. Again, in the case where device 10 is an outer sheath, visualization could be achieved through a separate bronchoscope or through built-in optics. In a further embodiment, a retaining sheath housed within lumen 14 and covering applicator 20 is selectably retractable to expose needle assembly 28. As depicted in FIG. 3B, needles 30 comprise a material capable of retaining a preformed shape, such

as nickel-titanium, and are preformed to deflect radially outward when extended beyond distal end 13 of bronchoscope 10 (or the distal end of the outer sheath, if present). Each needle 30 optionally includes hilt 36 disposed a pre-selected distance from the distal end of the needle to control the depth of penetration of the needle tip into the bronchial wall.

**[0055]** When needle assembly 30 is deployed, as illustrated in FIGS. 2 and 3B, needles 30 penetrate target treatment area **T** of bronchial wall **B** so that neurotoxin may be injected in the bronchial wall. Syringe 26 may include graduations that enable the physician to inject a pre-determined amount of neurotoxin at each target treatment area.

**[0056]** Referring now to FIGS. 4 and 5, an alternative embodiment of applicator 24 of neurotoxin applicator assembly 20 is described. Applicator 24 in this embodiment comprises rotating needle assembly 38, including wheel 39 mounted to rotate about hub 40. While wheel 39 illustratively is round, it alternatively may comprise a ellipse or hexagon or other polygonal shape. Plurality of needles 41 is disposed around the circumference of the wheel, each needle 41 having lumen 42 in fluid communication with lumen 25 via a passageway in hub 40. Optional fender 45 protects a portion of the bronchial wall substantially opposite the target treatment area.

**[0057]** In FIG. 5A, rotating needle assembly 38 is shown retracted within outer sheath 37. Outer sheath 37 is dimensioned to fit within lumen 14 of bronchoscope 10, and may be selectively retracted to expose rotating needle assembly 38. Alternatively, rotating needle assembly 38 extends through lumen 14 and past the tip of

bronchoscope 10. In this embodiment, the wheel is covered by a retractable protection sheath which covers the wheel during insertion of the system. In FIGS. 4 and 5B, rotating needle assembly 38 is shown in the extended position. When so deployed, wheel 39 may be rolled across target treatment area **T**, so that as the wheel rotates needles 41 alternately penetrate and inject neurotoxin into bronchial wall **B**.

**[0058]** Suitable needles materials for needle assembly 28 of FIGS. 2-3 and rotating needle assembly 38 of FIGS. 4-5 include shape memory alloys such as nickel titanium alloys and spring tempered stainless steel alloys. Advantageously, either needle assembly permits direct injection of neurotoxin into the bronchial wall. This prevents the cilial transport system from trapping the neurotoxin and transporting it to other regions of the respiratory system, e.g., the oropharynx, where potentially unintended targets may be exposed to the neurotoxin, and prevents accidental exhalation of aerosolized neurotoxin.

**[0059]** Referring now to FIGS. 6 and 7, another alternative embodiment of applicator 24 of the neurotoxin applicator assembly of the present invention is described. Applicator 24 of FIGS. 6-7 comprises a needle-less injection assembly 46, which uses pressurized injection to deliver neurotoxin from the proximal controller to target treatment area **T**. Advantageously, the needle-less injection assembly allows controlled introduction of neurotoxin across the airway epithelium without the potential complications of introducing needles proximate to the delicate bronchial tissues, and may allow a lower profile system.

[0060] Needle-less injection assembly 46 comprises shaft 47 including at least one port 48 in fluid communication with lumen 25. Inflatable balloon 49 optionally may be coupled to shaft 47, and used to position the shaft adjacent target treatment area **T**. Balloon 49 is inflated with a fluid introduced through a lumen of shaft 47. When the shaft is aligned with the target treatment area, pulses of pressurized gas may be employed to inject predetermined amounts of neurotoxin across the airway wall and into the collagenous and smooth muscle layers.

[0061] In FIG. 7A, needle-less injection assembly 46, with balloon 49 deflated, is depicted housed within the lumen 14 of bronchoscope 10 (or a separate outer sheath). FIGS. 6 and 7B depict needle-less injection assembly 46 with balloon 49 inflated to place ports 48 in apposition to target treatment area **T**. Once the physician has confirmed placement of needle-less injection assembly 46, e.g., by visualization using the optics of bronchoscope 10, x-ray, fluoroscopy or other suitable means, a controller attached to the proximal end of neurotoxin applicator assembly 20 (instead of syringe 26), may be activated to deliver the desired doses of neurotoxin to the bronchial wall. As an alternative to the balloon 49, the assembly may have 2 or more needle-less injectors arranged to position against opposite walls of the bronchial passage. For instance, they might be spring loaded to expand the sections away from the midline and contact the bronchial wall. As a further alternative, the shaft of the assembly may be pre-curved or actively curved with an activation mechanism to urge the injector against the wall of the bronchial passage. Yet another alternative includes lower-pressure injection of

neurotoxin through port(s) 48, creating a weeping-balloon applicator. In this case, transport of neurotoxin across the epithelial surface is achieved by cellular endocytosis of the neurotoxin.

**[0062]** With respect to FIGS. 8 and 9, a yet further alternative embodiment of applicator 24 of the neurotoxin applicator assembly constructed in accordance with the present invention is described. Applicator 24 comprises nebulizer assembly 50 having shaft 55 with atomizer 51 disposed at its distal end and in fluid communication with central lumen 25. Atomizer 51 converts the liquid neurotoxin from the syringe into a fine spray or mist. Particle size of the mist can be controlled through nebulizer head design or by varying injection pressure in order to control the depth of penetration of the mist into the target segment.

**[0063]** Nebulizer assembly 50 may also include optional inflatable balloon 52 disposed on shaft 55 proximal of atomizer 51. Selective inflation of balloon 52 allows positioning of atomizer 51 so that aerosolized neurotoxin may be directly sprayed onto target treatment area **T**. Balloon 52 also acts to isolate the treatment area from the rest of the lung, preventing reflux of mist into unintended areas. As for the embodiment of FIGS. 6-7, balloon 52 may be inflated using a fluid introduced through an auxiliary lumen in shaft 55.

**[0064]** In FIG. 9A, the nebulizer assembly, including deflated balloon 52, is disposed within lumen 14 of bronchoscope 10, or alternatively, in an outer sheath that is slidably received in lumen 14. Alternatively, the nebulizer assembly may be inserted within a separate delivery sheath, with the bronchoscope inserted separately or with the optics and/or steering mechanisms

built into the nebulizer assembly. In FIGS. 8 and 9B, nebulizer assembly 50 is depicted deployed from lumen 14 (or the outer sheath, if present), with balloon 52 inflated. Advantageously, nebulizer assembly 50 can be dimensioned to access very small bronchial passageways, and also may be used to deliver neurotoxin to upstream regions of the lung.

**[0065]** Still referring to FIGS. 9A and 9B, shaft 55 optionally also may include an additional auxiliary lumen or lumens coupled to inlet port 53 and outlet port 54 disposed between the balloon and the atomizer. Inlet port 53 allows the introduction of gas (such as fresh air) near the target treatment area, while outlet port 54 allows air or gas mixed with atomized neurotoxin to be removed. Inlet and outlet ports 53 and 54 therefore provide a ventilation system that shields tissue adjacent and proximal to target treatment area **T** from being inadvertently exposed to the atomized neurotoxin. Inlet and outlet ports 53 and 54 further serve to either actively inflate and deflate the isolated segment, or simply to normalize pressure within the lung near the target treatment area. A control unit may be connected to the proximal outlets of ports 53 & 54 to control the introduction and removal of gases from the lung without allowing escape of atomized neurotoxin to the environment or patient.

**[0066]** According to some embodiments, the nebulizer assembly may be built into a single, disposable fiberoptic unit having a unidirectional tip-deflection element having an integral isolation balloon and aerosolizing tip. A neurotoxin containing canister can also be provided integral with the nebulizer assembly. Advantageously, such an assembly permits a much lower

profile, user-friendly system suitable for trans-nasal introduction past the vocal cords and into the lung.

**[0067]** With respect to FIGS. 10-13, another alternative embodiment of a neurotoxin applicator of the present invention is described. In this embodiment, neurotoxins or other therapeutic drugs are delivered to the patient's bronchial tree via sub-selective topical application of toxin to the bronchial lining. The applicator assembly may be inserted through the working channel of a bronchoscope (as in FIG. 1) and used to paint a solution containing neurotoxins onto the epithelial surface of the airways of the lung.

**[0068]** Referring now to FIG. 10, neurotoxin applicator assembly 60 comprises proximal shaft 62, spring-reinforced distal segment 64, and beveled distal tip 66 comprising a micro-porous filter material that functions as a topical applicator for the asthma-fighting solution. Distal segment 64 preferably is bendable into an infinite number of configurations having various radii of curvature. Additionally, torsional rotation of distal tip 66 is provided in response to torque applied to proximal shaft 62. In the illustrated embodiment, neurotoxin applicator assembly 60 comprises a wire-braid reinforced tube that provides desirable characteristics of high burst strength and good torque response, and may be formed of a nickel-titanium alloy.

**[0069]** Referring to FIGS. 11A-11C, curved distal segment 64 of neurotoxin applicator assembly 60 extends out of the tip of bronchoscope 70. Neurotoxin applicator assembly 60 preferably may be rotated with respect to and in conjunction with bronchoscope 70. The variable curve of distal segment 64 and the beveled termination of distal tip 66 provide intimate contact of distal tip 66

against bronchial walls having different diameters. The beveled distal tip 66 allows for easy introduction through the working channel of the bronchoscope 70. Distal segment 64 preferably is spring-biased into a curved configuration to permit self-adjustment of the device to a wide range of inner bronchial diameters. FIGS. 11 demonstrate that the curved distal segment will remain in contact with the walls of very small bronchi having a diameter of 5 mm or less (FIG. 11A), average bronchi having a diameter of 5 mm to 15 mm (FIG. 11B), as well as very large bronchi having a diameter of 15 mm or more (FIG. 11C).

**[0070]** In operation, the asthma-fighting solution is induced to flow through a central lumen running through neurotoxin applicator assembly 60. According to some embodiments, the rotation of distal tip 66 using torque applied at the proximal end of proximal shaft 62, in addition to proximal end pressure, is used to control the flow of solution through distal tip 66. This flow control aspect, in combination with the variable curve of distal segment 64, allows a rotational "painting" onto the walls of the bronchi.

**[0071]** Referring to FIG. 12, syringe 72 is employed to provide pressurization at the proximal end of neurotoxin applicator assembly 60 for controlling the flow of asthma-fighting solution through the central lumen and distal tip of the device. Syringe 72 comprises syringe barrel 73 and threaded plunger 74, which terminates in finger slot 75. A proximal end of syringe barrel 73 terminates in an outwardly-projecting rim 76, whereas a distal end of syringe barrel 73 is fixedly attached to the proximal end of torque-responsive neurotoxin applicator assembly 60. Syringe 73 preferably further

comprises a threaded half-collar 77 adapted to slide into place over syringe barrel 73 and threaded plunger 74. Half-collar 77 preferably comprises internal threads corresponding to the threads on threaded plunger 74. Moreover, half-collar 77 preferably further comprises a recess that engages rim 76. When slid into place over syringe 72, threaded half-collar 77 locks the threaded plunger in place with respect to the barrel.

**[0072]** When collar 77 is in place, rotation of syringe barrel 73 (e.g., in a clockwise direction) results in a controlled deflection of plunger 74 relative to barrel 73. The deflection of plunger 74 increases the pressure within the central lumen of neurotoxin applicator assembly 60, thereby causing a controlled amount of solution to be dispensed from distal tip 66. By altering the pitch of the thread on the plunger and half-collar, the volume of fluid dispensed per revolution may be varied. Since syringe barrel 73 is fixedly attached to torque-responsive neurotoxin applicator assembly 60, rotation of syringe barrel 73 results in corresponding rotation of distal tip 66. The half-collar may be removed from the assembly to allow conventional syringe operation for rapid filling or emptying of syringe 72.

**[0073]** Referring to FIG. 13, standard syringe 80 is attached to the proximal end of torque-responsive neurotoxin applicator assembly 60, which is disposed within bronchoscope 85. Syringe comprises syringe barrel 82 and non-threaded plunger 83. In this embodiment, a collar is not provided, and flow control is provided by manually modulating the force applied to plunger 83. The force applied to plunger 83, in addition to the rotation of syringe 80 (which causes corresponding rotation of

neurotoxin applicator assembly 60) dispenses the asthma-fighting solution onto the patient's bronchial walls.

**[0074]** In accordance with another aspect of the present invention, implantable devices and methods for treating asthma are described with respect to FIGS. 14-19. The bioabsorbable implants are employed to controllably introduce one or more neurotoxins into the walls of a patient's bronchial tree, which control asthma by disabling the hyperresponsive smooth muscle layer and controlling hypersecretion of mucus.

**[0075]** More specifically, delivery of neurotoxins or other therapeutic drugs to the bronchial tree is achieved through drug elution from bioabsorbable implants placed within the bronchial passages. The implants preferably are bioabsorbable, but alternatively may comprise permanent devices with refillable reservoirs as well as elution devices that may be removed and replaced at periodic intervals, e.g., when drug supplies are determined be depleted.

**[0076]** In accordance with the principles of the present invention, a system for treating asthma comprises one or more drug-eluting bioabsorbable stents. Referring to FIG. 14, stent 102 comprises a single wire 104 including a plurality of turns 106. According to some embodiments, the stent system comprises one or more discrete-length coiled stents. Alternatively, the stent system comprises one or more custom-length coiled stents, which are deployed and cut to length at the end point of delivery by a cutting mechanism that is part of the stent delivery system. Bioabsorbable stent 102 preferably is loaded with neurotoxin and/or other asthma-fighting drugs. Gradual elution of the neurotoxin and/or other asthma-fighting drugs treats the underlying inflammatory

disease that causes the asthmatic response. Advantageously, stent 102 also lends mechanical reinforcement to the patient's bronchi.

**[0077]** Referring to FIG. 15, alternative drug-eluting bioabsorbable stent 108 is shown, and comprises a plurality of wires 110 that are intertwined to form a slotted or knitted tube. As will be appreciated by those of skill in the art, many other known stent designs may be used to deliver the asthma-fighting drugs without departing from the scope of the present invention. Suitable materials for stents 102, 108 include PEG, PLLA, collagen and copolymers of these materials. Appropriate drugs include the array of steroids and bronchodilators that are currently used systemically to treat asthmatic conditions. Examples of other suitable asthma-fighting drugs include corticosteroid and albuterol.

**[0078]** Additionally, a neurotoxin composition such as botulinum toxin or tetanus may be delivered using the stent. According to some embodiments, stents 102 encapsulate the neurotoxin, releasing it gradually onto the bronchial wall, thereby greatly extending the effective working life of the neurotoxin past its usual 3+ month active lifespan.

**[0079]** Since the effect of neurotoxin on the smooth muscle and inflammatory responses related to asthma are not permanent, it is desirable to provide doses of neurotoxin that are automatically delivered at predetermined intervals. FIG. 16 is a cross-sectional view of stent wire 104 of drug-eluting bioabsorbable stent 102. Wire 110 forming drug-eluting bioabsorbable stent 108 may comprises a substantially similar cross-section.

**[0080]** In the illustrated embodiment, stent wire comprises alternating layers of drug-loaded and non-drug-loaded resorbable materials. More particularly stent wire 104 comprises inner drug-eluting layer 114 that is substantially circular in cross-section and barrier layer 116 disposed around the perimeter of inner layer 114. Stent wire 104 further comprises outer drug-eluting layer 118 surrounding barrier layer 116, and protective outer coating 120 surrounding outer layer 118. In this manner, the drug is loaded into the implant in discrete dosing layers 114, 118 and delivered at predetermined intervals.

**[0081]** After the drug-eluting stent is implanted within a patient's bronchial airways, protective outer coating 20 dissolves, thereby exposing outer drug-eluting layer 118. The outer layer is slowly absorbed, thus providing a first dose of asthma-fighting drugs to a target treatment area within the patient's bronchi. After outer layer 118 is absorbed, barrier layer 116 dissolves within the bronchi over a predetermined amount of time. Then, inner layer 114 is slowly absorbed, thereby providing a second dose of asthma-fighting drugs to the target treatment area. Of course, as would be understood by those of ordinary skill in the art, additional drug-eluting layers (and barrier layers) may be employed to deliver additional doses of asthma-fighting drugs at predetermined intervals without departing from the scope of the present invention. In this manner, the first dose is administered shortly after implantation, and then subsequent doses are released at predetermined intervals, for example every 3 months.

**[0082]** Delivery of the drug-eluting stents of the present invention preferably is achieved through the working channel of a conventional bronchoscope, either

oral or nasal, or through a custom device specifically designed for placing the loaded stents. Referring to FIG. 17, one or more drug-eluting bioabsorbable stents 102 are delivered to target treatment area within a patient's bronchi **B** through the working channel of bronchoscope 122. Stent 102 is a continuous length of coiled drug-loaded wire 104 that is initially delivered at the distal end of a target bronchial passage. Then, stent 102 is unwound along the target bronchial passage to the desired proximal termination point. Manipulation of the bronchoscope during deployment allows the physician to avoid placing coils across side branches of the bronchial tree. When the proximal termination point is reached, a cutting mechanism is used to cut the implant coil.

**[0083]** Alternatively, as depicted with respect to FIGS. 18 and 19, one or more discrete length drug-eluting bioabsorbable coiled stents 108, 130, may be deployed within the patient's bronchi **B**. Stents 108 and 130 are formed of wire segments that preferably include alternating layers of drug-loaded and non-drug-loaded materials, such as described with respect to FIG. 16. Stents 108 and 130 preferably are delivered through the working channel of a bronchoscope or through another delivery device. As would be understood by those of skill in the art, stents 108 and 130 may comprise any number of different sizes and configurations without departing from the scope of the present invention.

**[0084]** Deployment of the inventive stents described hereinabove may be accomplished using conventional stent delivery catheters and procedures, via either self-expansion or balloon expansion of the stents, by heating and setting a final size with a purpose-built delivery

system, or any other suitable procedure. Delivery may be achieved one stent at a time, or multiple implants may be placed from a single multi-stent delivery system.

**[0085]** Although preferred illustrative embodiments of the present invention are described above, it will be evident to one skilled in the art that various changes and modifications may be made without departing from the invention. It is intended in the appended claims to cover all such changes and modifications that fall within the true spirit and scope of the invention.

What is claimed is:

1. Apparatus for intrabronchial delivery of medication to treat lung disease, the apparatus comprising:

a shaft having a proximal end including at least one inlet port, a distal end and a lumen extending between the inlet ports and the distal end; and

a medication applicator disposed on the distal end of the shaft in fluid communication with the lumen.

2. The apparatus of claim 1, wherein the medication is a neurotoxin.

3. The apparatus of claim 1, further comprising a bronchoscope having proximal and distal ends, and a lumen extending therebetween, and wherein the shaft is dimensioned to slidably pass through the lumen of the bronchoscope.

4. The apparatus of claim 1, wherein the neurotoxin applicator includes a needle assembly.

5. The apparatus of claim 4, wherein the needle assembly has a retracted delivery position and a deployed position wherein at least one needle extends radially outward from the shaft to penetrate bronchial tissue.

6. The apparatus of claim 4, wherein the needle assembly comprises a wheel having a circumference and a plurality of needles disposed around the

circumference, wherein the plurality of needles are in fluid communication with the lumen of the shaft.

7. The apparatus of claim 6, wherein the wheel further comprises a hub that forms an axis of rotation for the wheel.

8. The apparatus of claim 6, wherein the wheel is adapted to be rolled across a target treatment area within a patient's bronchial airways.

9. The apparatus of claim 8, wherein the needle assembly further comprises a fender that protects an area of the patient's bronchial airways opposite the target treatment area.

10. The apparatus of claim 2, wherein the neurotoxin is a serotype of botulinum toxin.

11. The apparatus of claim 10, wherein the serotype of botulinum toxin is selected from the group consisting of serotype A and serotype B.

12. The apparatus of claim 2, wherein the neurotoxin is tetanus or a tetanus derivative.

13. The apparatus of claim 1, wherein the applicator uses pressurized fluid to inject neurotoxin into a target treatment area.

14. The apparatus of claim 13, wherein the shaft includes a portion defining a port in fluid communication with the lumen.

15. The apparatus of claim 13, further comprising a deflection means disposed on the shaft to position the port adjacent to the target treatment area.

16. The apparatus of claim 15, wherein the deflection means is an inflatable balloon.

17. The apparatus of claim 13, wherein the applicator further comprises an atomizer in fluid communication with the lumen.

18. The apparatus of claim 17, further comprising an inflatable balloon disposed proximal to the atomizer.

19. The apparatus of claim 18, further comprising at least one lumen disposed between the balloon and the atomizer to ventilate tissue adjacent the target treatment area.

20. The apparatus of claim 1 wherein the medication applicator comprises a micro-porous filter material.

21. The apparatus of claim 1 wherein the shaft is selectively bendable.

22. The apparatus of claim 1 wherein the shaft is steerable.

23. The apparatus of claim 1 further comprising an optical component disposed in operative relation to the medication applicator.

24. The apparatus of claim 20 further comprising a syringe coupled to the proximal end of the shaft for controlling the flow of medication.

25. Apparatus for treating lung disease by intrabronchial delivery of medication, the apparatus comprising:

an elongate shaft having a proximal end including at least one inlet port, a distal end and a lumen extending between the inlet port and the distal end; and

a medication applicator disposed on the distal end of the shaft in fluid communication with the lumen, the medication applicator having a contracted delivery position, and a deployed position adapted to deliver medication to a target tissue area of a patient's bronchial wall.

26. The apparatus of claim 25, wherein the neurotoxin applicator includes a needle assembly.

27. The apparatus of claim 25, wherein the needle assembly comprises at least one needle that extend radially outward from the shaft to penetrate bronchial tissue.

28. The apparatus of claim 25, wherein the needle assembly comprises a wheel having a circumference and a plurality of needles disposed around the circumference, wherein the plurality of needles are in fluid communication with the lumen of the shaft.

29. The apparatus of claim 28, wherein the needle assembly further comprises a fender that protects an area of the patient's bronchial airways opposite the target treatment area.

30. The apparatus of claim 25, wherein the neurotoxin is botulinum toxin.

31. The apparatus of claim 25, wherein the applicator uses pressurized fluid to inject neurotoxin into a target treatment area.

32. The apparatus of claim 31, wherein the shaft includes a portion defining at least one port in fluid communication with the lumen.

33. The apparatus of claim 25, wherein the applicator further comprises an atomizer in fluid communication with the lumen.

34. The apparatus of claim 25 wherein the medication applicator comprises a micro-porous filter material.

35. The apparatus of claim 25 wherein a distal portion of the elongated shaft is selectively bendable.

36. The apparatus of claim 25 further comprising a syringe coupled to the proximal end of the shaft for controlling the flow of medication.

37. Apparatus for intrabronchial delivery of medication to treat asthma, the apparatus comprising:

a drug-eluting bioabsorbable stent comprising one or more layers of asthma-fighting drugs.

38. The apparatus of claim 37, wherein the stent comprises a single wire including a plurality of turns.

39. The apparatus of claim 37, wherein the stent comprises a plurality of wires that are intertwined to form a slotted or knitted tube.

40. The apparatus of claim 37, wherein the asthma-fighting drug is a neurotoxin.

41. The apparatus of claim 40, wherein the neurotoxin is botulinum toxin

42. The apparatus of claim 40, wherein the neurotoxin is tetanus.

43. The apparatus of claim 37, wherein the asthma-fighting drug is a steroid or bronchodilator.

44. The apparatus of claim 37, wherein the stent comprises alternating layers of drug-loaded and non-drug-loaded resorbable materials.

45. The apparatus of claim 44, wherein the material for the non-drug-loaded resorbable materials is chosen from the group consisting of PLLA, collagen and copolymers of these materials.

46. The apparatus of claim 44, wherein the non-drug-loaded resorbable materials encapsulate the drug-loaded resorbable materials such that the asthma-fighting drug is released gradually into the bronchial airways.

47. The apparatus of claim 37, wherein the stent comprises:

an inner drug-eluting layer; and

a barrier layer disposed around the perimeter of the inner layer.

48. The apparatus of claim 47, further comprising:

an outer drug-eluting layer surrounding the barrier layer; and

a protective outer coating surrounding the outer layer.

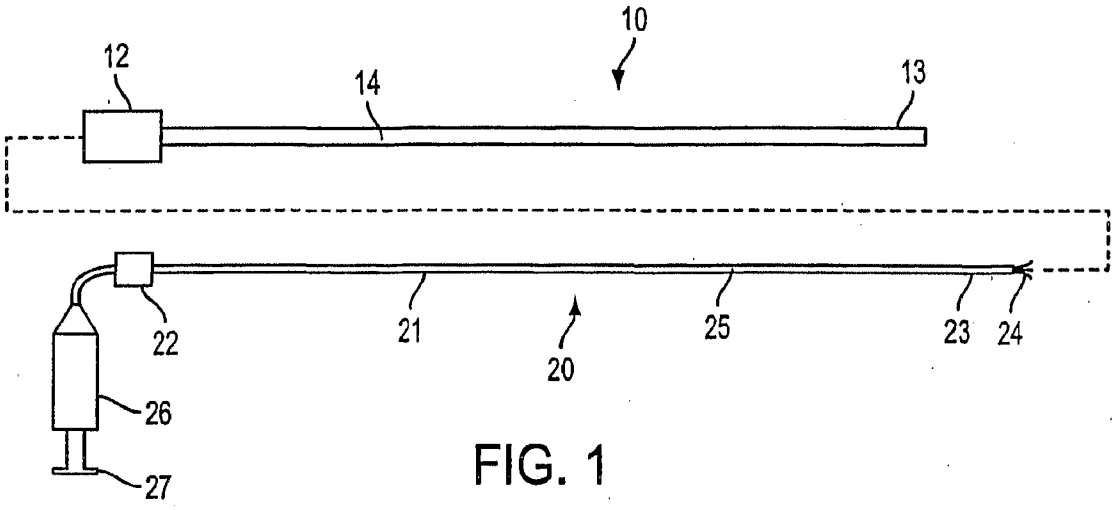



FIG. 1

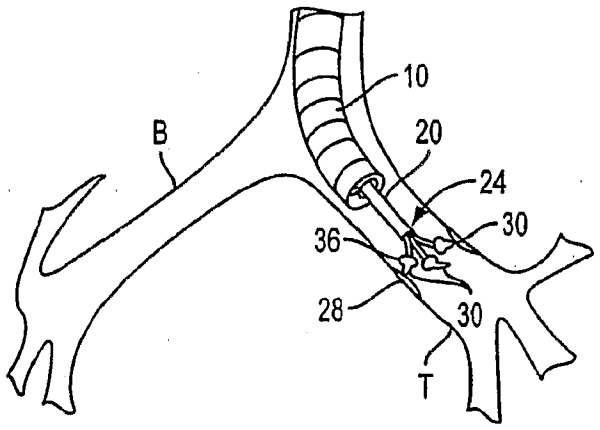



FIG. 2

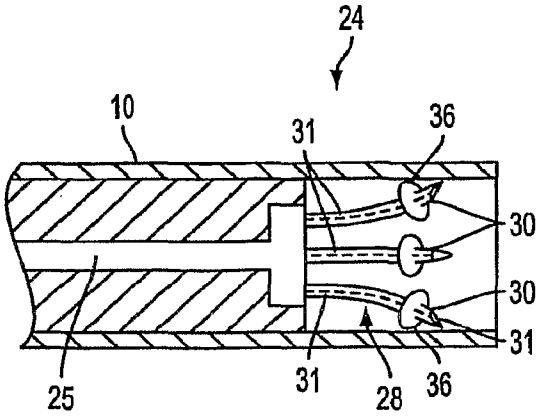



FIG. 3A

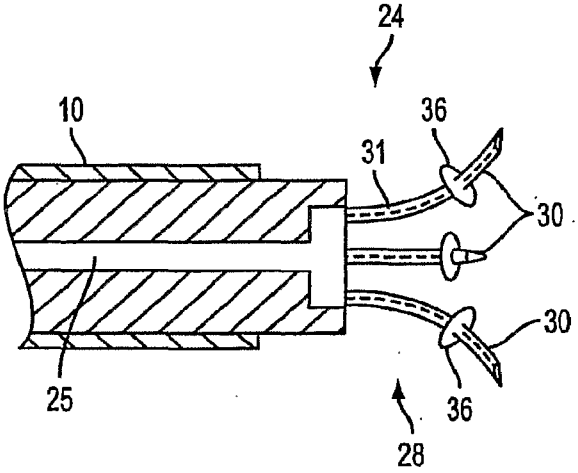



FIG. 3B

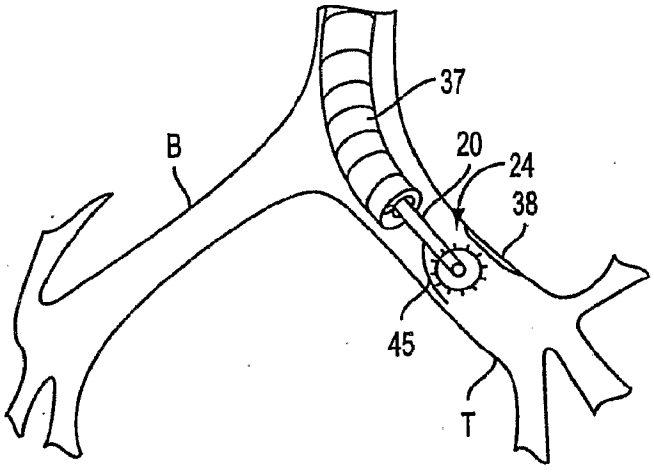



FIG. 4

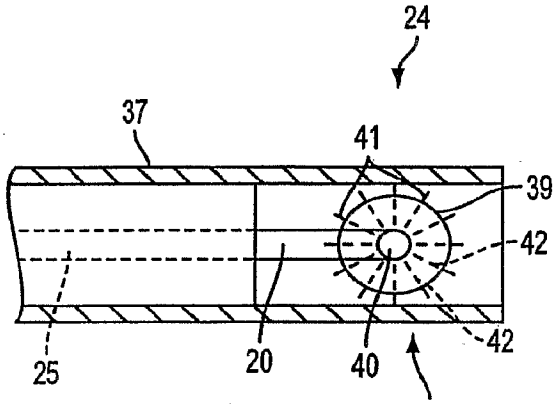



FIG. 5A

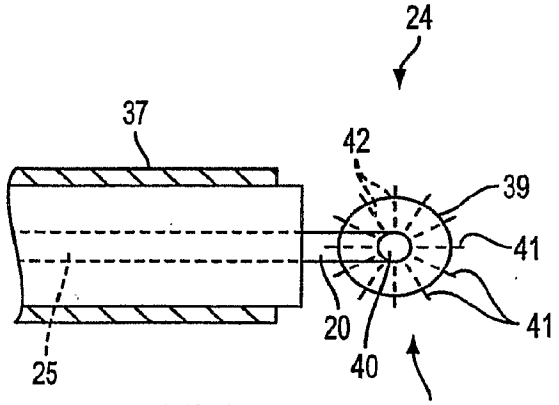



FIG. 5B

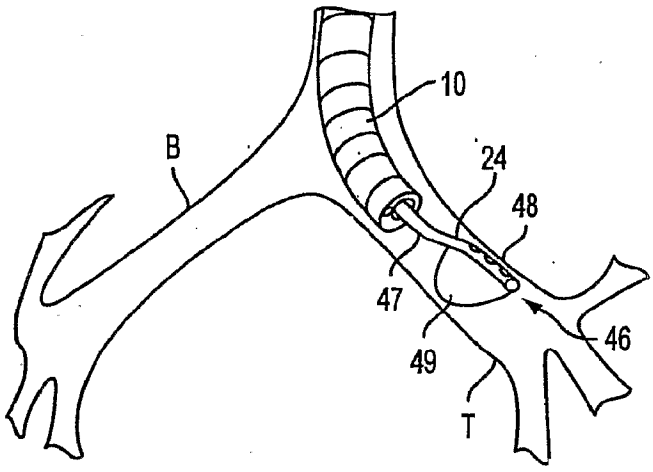



FIG. 6

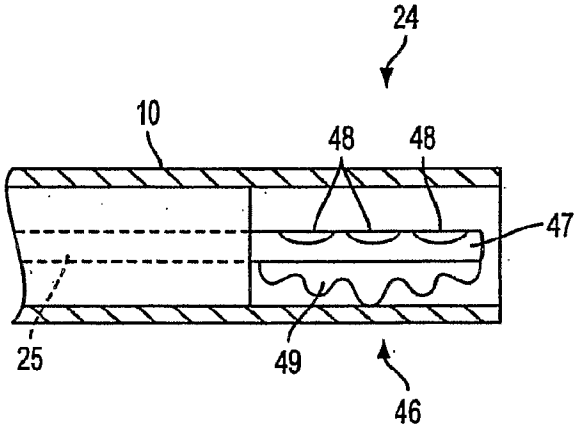



FIG. 7A

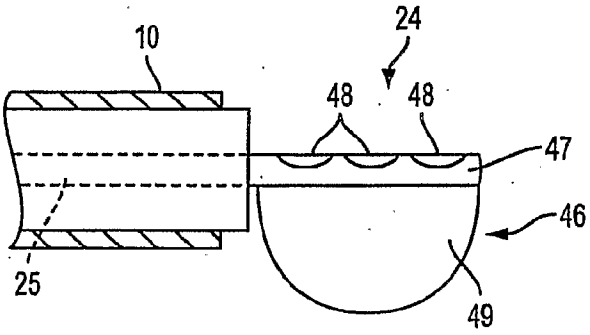



FIG. 7B

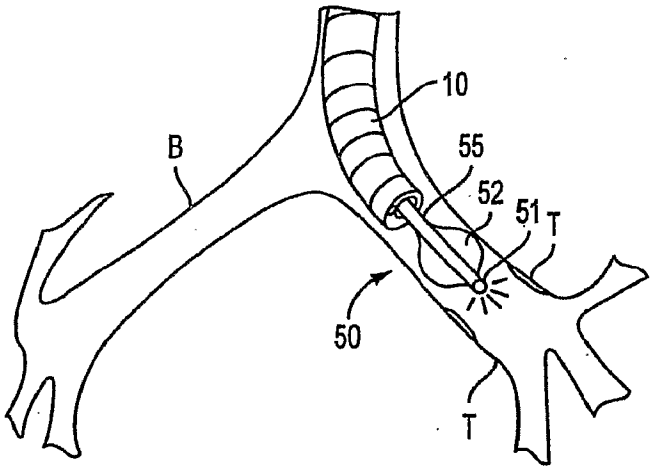



FIG. 8

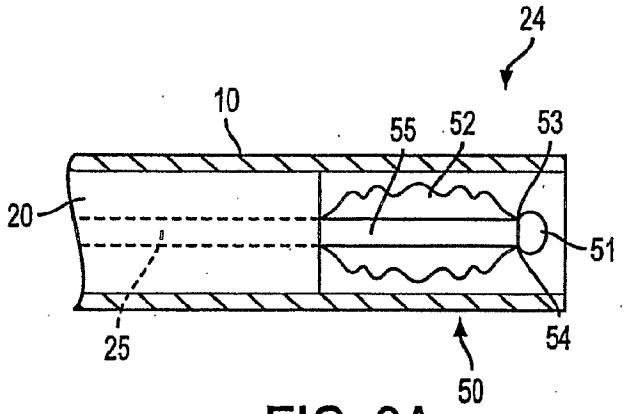



FIG. 9A

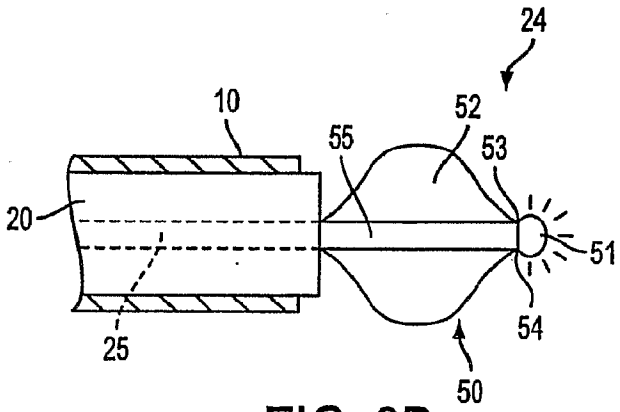



FIG. 9B

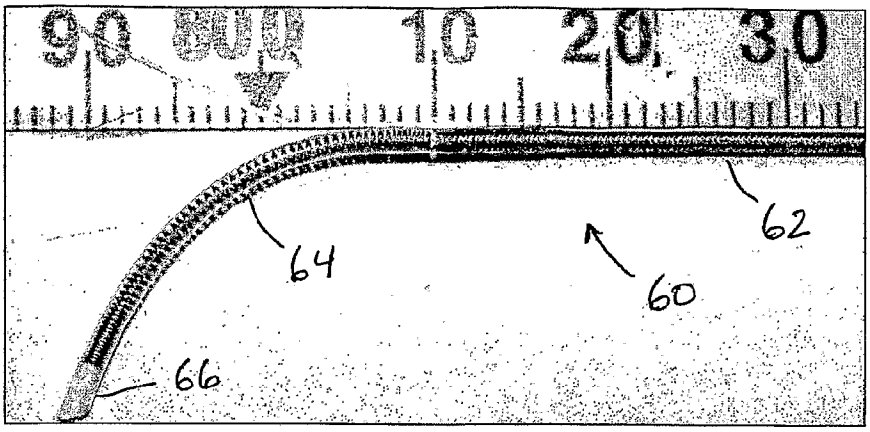



FIG. 10

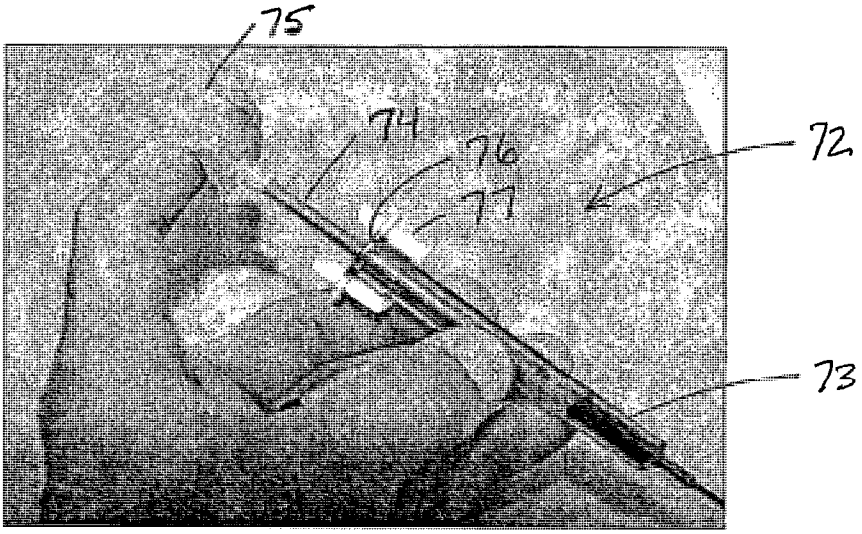



FIG. 12

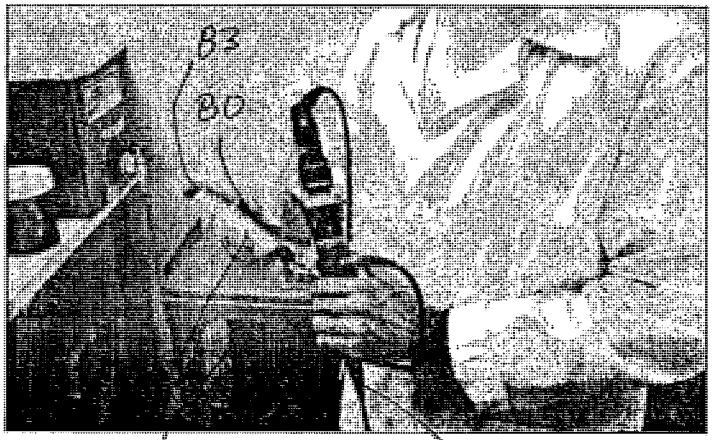



FIG. 13

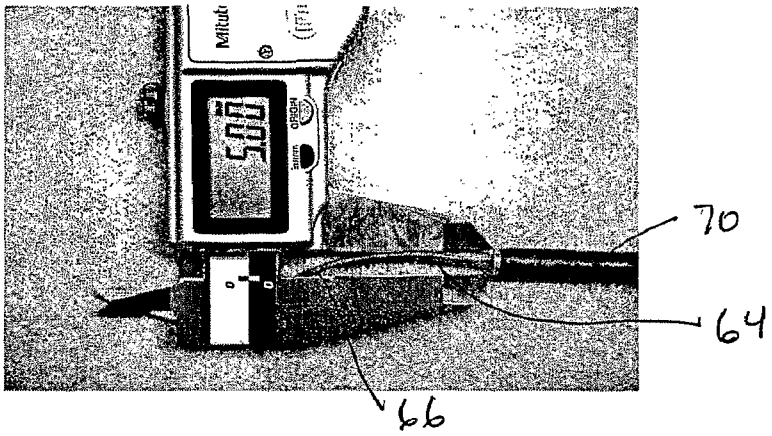



FIG. 11A

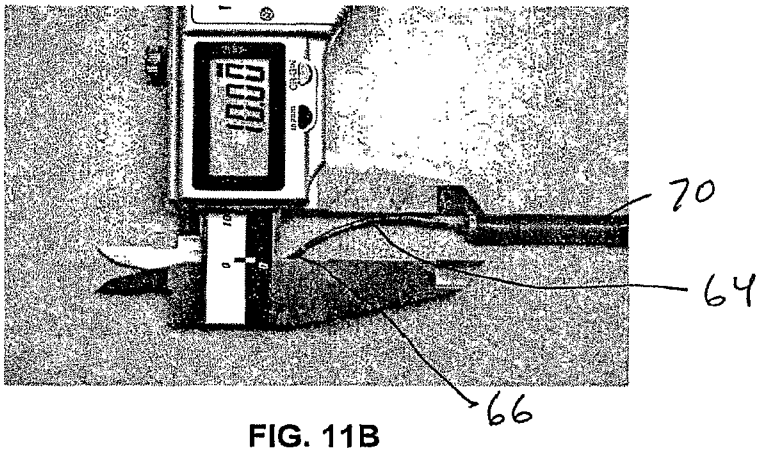



FIG. 11B

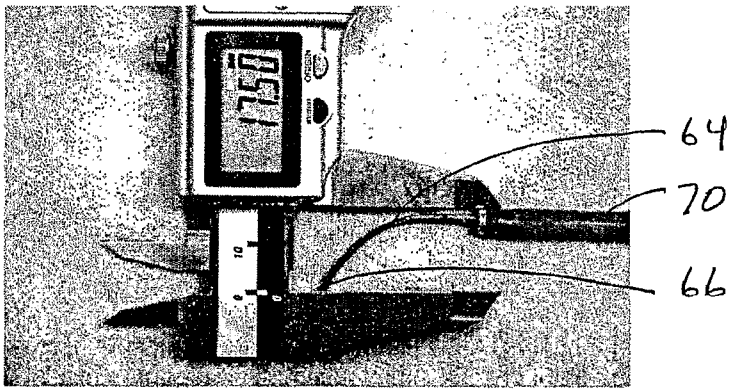



FIG. 11C

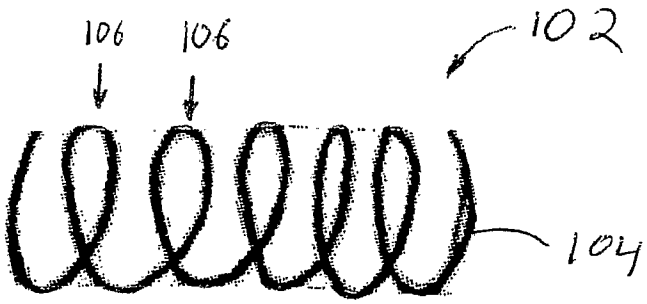



FIG. 14

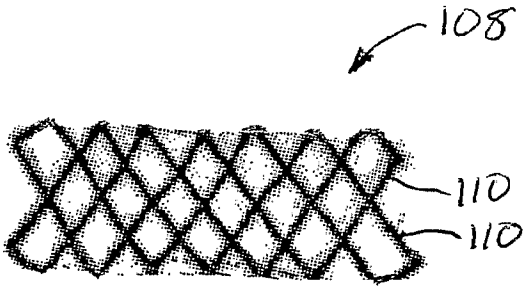



FIG. 15

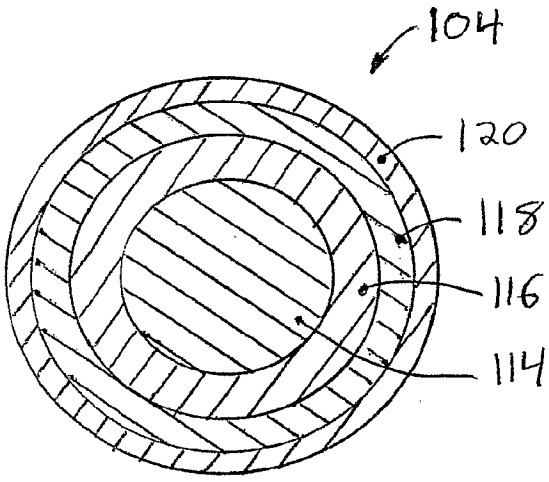



FIG. 16

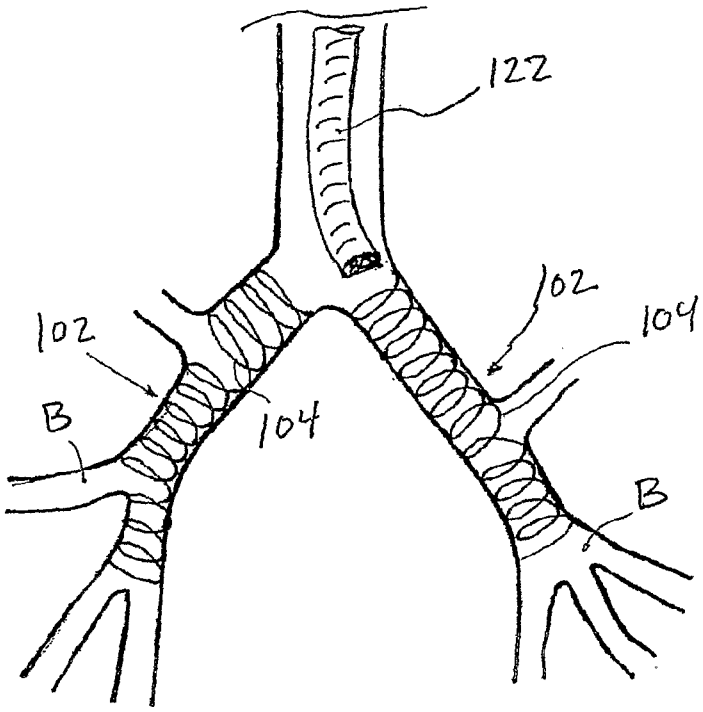



FIG. 17

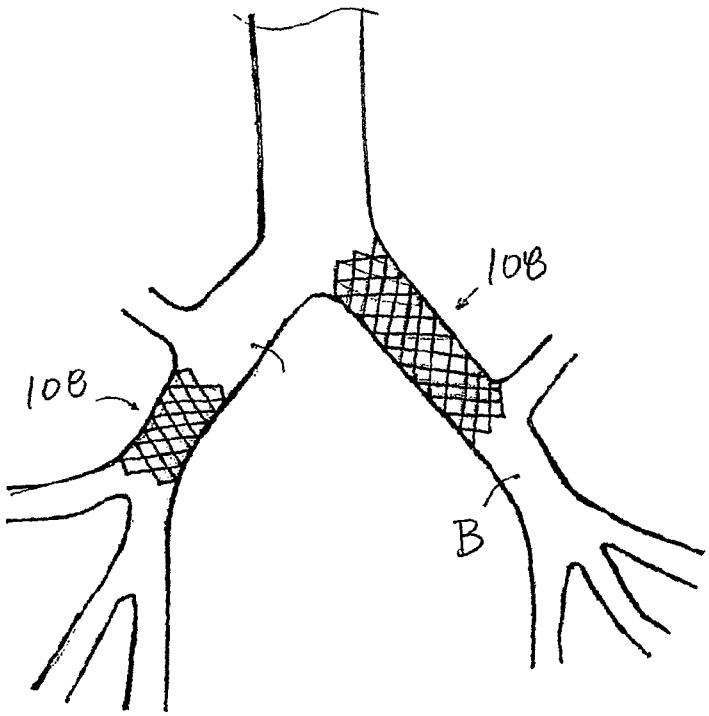



FIG. 18

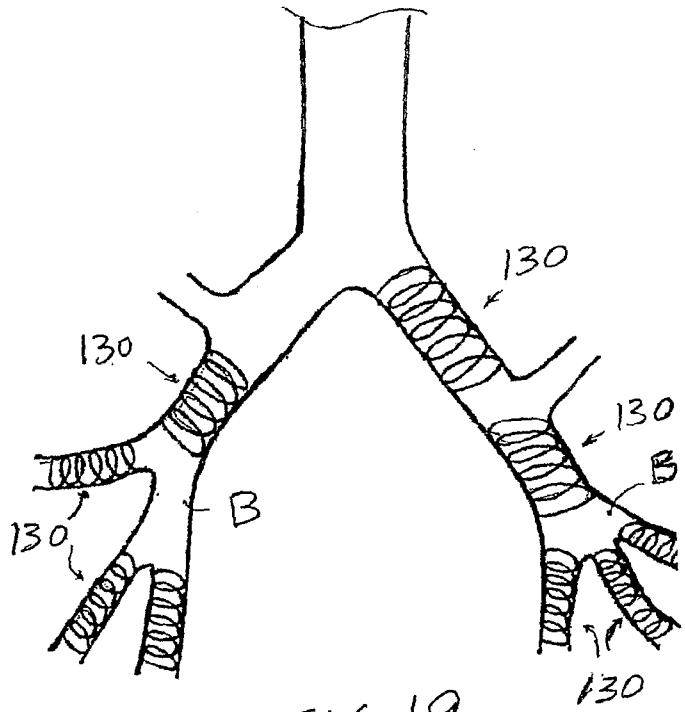



FIG. 19

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10/437,882 13 May 2003 (13.05.2003) US

(71) Applicant *(for all designated States except US)*: **THE FOUNDRY, INC.** [US/US]; 199 Jefferson Drive, Menlo Park, CA 94025 (US).

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(74) Agents: **HESLIN, James** et al.; Townsend and Townsend and Crew LLP, Two Embarcadero Center, 8th Floor, San Francisco, CA 94111-3834 (US).

(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.

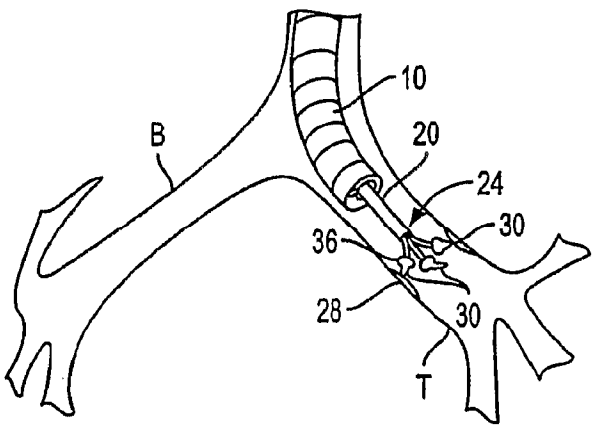
(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

**Published:**
— *with international search report*
— *before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments*

(88) Date of publication of the international search report:
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(54) Title: APPARATUS AND METHODS FOR TREATING ASTHMA USING NEUROTOXIN




(57) Abstract: Apparatus providing intrabronchial delivery of neurotoxin to control the effects of asthma comprises a shaft having proximal and distal ends and a neurotoxin applicator assembly disposed on the distal end, wherein the neurotoxin applicator assembly comprises a deployable needle assembly, a rotating needle assembly, a needle-less injection assembly, a nebulizer assembly or a microporous tip. Further embodiments involve apparatus comprising drug-eluting bioabsorbable stents having one or more layers of asthma-fighting drugs.

WO 2004/101028 A3

# INTERNATIONAL SEARCH REPORT

International application No.
PCT/US04/15222

**A. CLASSIFICATION OF SUBJECT MATTER**
IPC: **A61M 16/00**( 2006.01)

USPC: 128/207.14
According to International Patent Classification (IPC) or to both national classification and IPC

**B. FIELDS SEARCHED**

Minimum documentation searched (classification system followed by classification symbols)
U.S. : 128/207.14, 207.15, 207.16, 200.14, 200.21, 200.18, 200.24

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

**C. DOCUMENTS CONSIDERED TO BE RELEVANT**

| Category * | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|---|---|---|
| X<br>---<br>Y | US 5,964,223 (BARAN) 12 October 1999 (12.10.1999), See Figures. | 1, 3, 25 |
| Y | US 5,766,605 A (SANDERS et al) 16 June 1998 (16.06.1998), column 7, lines 10-13 & column 10, lines 46-50. | 2, 4, 10-24, 26, 30-36 |
| A | US 6,546,932 B1 (NAHON et al) 15 April 2003 (15.04.2003), Figure 10. | 1-36 |
| A | US 2002/0111620 A1 (COOPER et al) 15 August 2002 (15.08.2002), Figure 5J. | 1-36 |

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

| Date of the actual completion of the international search | Date of mailing of the international search report |
|---|---|
| 06 April 2006 (06.04.2006) | 05 OCT 2006 |
| Name and mailing address of the ISA/US<br>Mail Stop PCT, Attn: ISA/US<br>Commissioner of Patents<br>P.O. Box 1450<br>Alexandria, Virginia 22313-1450<br>Facsimile No. (571) 273-3201 | Authorized officer<br>For Henry Bennett<br>Telephone No. (571) 272-0000 |

Form PCT/ISA/210 (second sheet) (July 1998)

# INTERNATIONAL SEARCH REPORT

International application No.
PCT/US04/15222

## Box I Observations where certain claims were found unsearchable (Continuation of Item 1 of first sheet)

This international report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claim Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claim Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claim Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

## Box II Observations where unity of invention is lacking (Continuation of Item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:
Please See Continuation Sheet

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☒ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.: 1-36

**Remark on Protest**

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.

Form PCT/ISA/210 (continuation of first sheet(1)) (July 1998)

**BOX II. OBSERVATIONS WHERE UNITY OF INVENTION IS LACKING**

This application contains claims directed to more than one species of the generic invention. These species are deemed to lack unity of invention because they are not so linked as to form a single general inventive concept under PCT Rule 13.1.

In order for more than one species to be examined, the appropriate additional examination fees must be paid. The species are as follows:

Group I, claim(s) 1-36, drawn to an apparatus for intrabronchial delivery of a medication using a medication applicator disposed on the distal end of a shaft.

Group II, claim(s) 37-48, drawn to an apparatus for intrabronchial delivery of medication using a drug-eluting bioabsorbable stent comprising one or more layers of drugs.

The species listed above do not relate to a single general inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, the species lack the same or corresponding special technical features for the following reasons: each group corresponds to a distinctly different means for intrabronchial delivery of medication.

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*A61K 39/08* (2006.01) *A61K 36/47* (2006.01)

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60/747,771 19 May 2006 (19.05.2006) US

(71) Applicant *(for all designated States except US)*: **THE FOUNDRY INC.** [US/US]; 199 Jefferson Drive, Menlo Park, California 94025 (US).

(72) Inventors; and
(75) Inventors/Applicants *(for US only)*: **DEEM, Mark, E.** [US/US]; 685 Sierra Avenue, Mountain View, California 94041 (US). **GIFFORD, Hanson, S.** [US/US]; 3180 Woodside Road, Woodside, California 94062 (US).

(74) Agents: **HESLIN, James, M.** et al.; Two Embarcadero Center, 8th Floor, San Francisco, California 94111-3834 (US).

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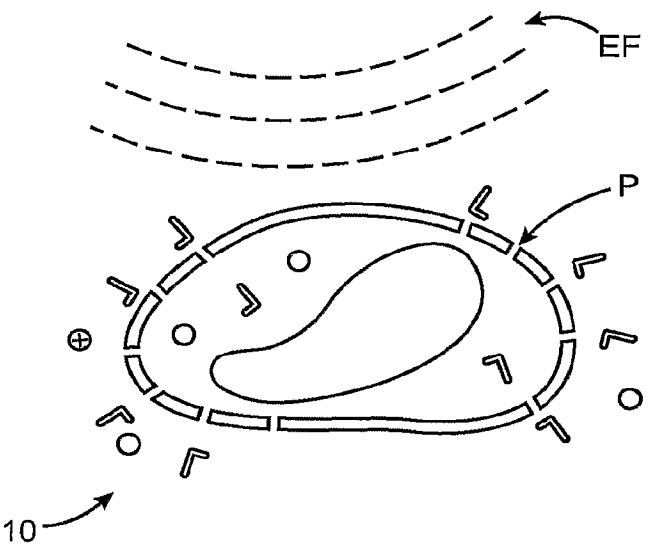
(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, LV, MC, NL, PL, PT, RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

**Declaration under Rule 4.17:**
— *as to applicant's entitlement to apply for and be granted a patent (Rule 4.17(ii))*

**Published:**
— *without international search report and to be republished upon receipt of that report*

*For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.*

(54) Title: SYSTEMS AND METHODS FOR DELIVERY OF A THERAPEUTIC AGENT




(57) Abstract: Methods and apparatus are provided for applying an fragment of a neurotoxin such as the active light chain (LC) of the botulinum toxin (BoNT), such as one of the serotype A, B, C, D, E, F or G botulinum toxins, via permeabilization of targeted cell membranes to enable translocation of the botulinum neurotoxin light chain (BoNT-LC) molecule across the targeted cell membrane to the cell cytosol where a therapeutic response is produced in a mammalian system. The methods and apparatus include use of catheter based delivery systems, non-invasive delivery systems, and transdermal delivery systems.

WO 2007/014003 A2

# SYSTEMS AND METHODS FOR DELIVERY OF A THERAPEUTIC AGENT

## BACKGROUND OF THE INVENTION

**[0001]** 1. Field of the Invention. The present invention relates to methods and apparatus for the control of autonomic nerve function comprising delivery via permeabilization of targeted cell membranes a therapeutically effective amount of a portion or fragment of a neurotoxin such as botulinum toxin (BoNT), the active portion known as the light chain (LC), to cause a clinical benefit in various regions within the body.

**[0002]** First used for medical purposes over 20 years ago for treatment of blepharospasm and strabismus and other skeletal muscle abnormalities, certain neurotoxins have found widespread use in millions of patients worldwide for a variety of conditions.

**[0003]** Controlled injection of neurotoxins has become a common procedure to control skeletal muscle spasms. While the primary application of neurotoxins such as BOTOX®, commercially sold by Allergan, Inc. (Irvine, CA), has been focused on cosmetic applications, such as treatment of facial wrinkles, other uses for the compound are now common. Certain applications include treatment of cervical dystonia, tremor, headache (migraine), spasticity, torticollis, hemifacial spasm, blepharospasm, meige syndrome, spastic dysphonia, writers cramp, hyperhydrosis, hypersalivation, bladder dysfunction multiple sclerosis, spinal cord injury, cystic fibrosis, stroke paralysis, stuttering, and all types of pain.

**[0004]** *Clostridium botulinum* neurotoxins (BoNTs) block the release of acetylcholine from peripheral cholinergic nerve endings thereby disabling the release of neurotransmitters from the cells (Bigalke, H. and Shoer, L.F. (1999) *Clostridial Neurotoxins in Handbook of Experimental Pharmacology* 45, 407-443). This mechanism of action is well defined. Seven immunologically distinct serotypes of neurotoxin, designated types A through G, have been identified as discussed by Simpson, L.L., Schmidt, J.J. and Middlebrook, J.L. (1988) in *Methods Enzymol.* 165, 76-85. There are general structural and functional similarities among the various types of neurotoxins, but they all have preferred recipients, for example some favor use in humans and other in non-human species.

**[0005]** A frequently used neurotoxin for many applications in the human body is Botulinum Toxin Type A (BoNT\A), a protein produced by the bacterium Clostridium botulinum and sold commercially by Allergan, inc., as BOTOX®. Botulinum toxin blocks the release of neurotransmitter from the nerves that control the contraction of the target muscles. When used in medical settings, small doses of the toxin are injected into the affected muscles and block the release of a chemical acetylcholine that signals the muscle to contract. The toxin thus paralyzes or weakens the injected muscle.

**[0006]** In addition, use of neurotoxin for control of the following conditions has been proposed in United States Patents 6,063,768 to First, and 5,766,605 to Sanders, including: rhinorrhea, asthma, COPD, excessive stomach acid secretion, spastic colitis, otitus media, arthritis, tensoynovitis, lupus, connective tissue disease, inflammatory bowel disease, gout, tumors, musculo-skeletal abnormalities, reflex sympathetic dystrophies, tendonitis, bursitis, and peripheral neuropathy. Various other patents contemplate the use of a neurotoxin for additional applications such as, neuromuscular disorders (6,872,397), essential tremor (6,861,058), pancreatitis (6,843,998), muscle spasm (6,841,156), sinus headache (6,838,434), endocrine disorders (6,827,931), priapism (6,776,991), thyroiditis (6,773,711), cardiovascular disease (6,767,544), thyroid disorders (6,740,321), hypocalcemia (6,649,161), hypercalcemia (6,447,785), tardive dyskenesia (6,645,496), fibromyalgia (6,623,742), Parkinson's Disease (6,620,415) cerebral palsy (6,448,231), inner ear disorders (6,358,926), cancers (6,139,845), otic disorders (6,265,379), appetite reduction ((US2004/0253274), compulsive disorders (US2004/0213814, US2004/0213813), uterine disorders ((US2004/0175399), neuropsychiatric disorders (US2003/0211121), dermatological or transdermal applications (US2004/00091880), focal epilepsy (US2003/0202990) the contents of which are expressly incorporated herein by reference in their entirety.

**[0007]** The patent authors have further detailed devices and methods for treating asthma with local delivery of the intact botulinum toxin in United States Patent Application 10/437,882, filed on May 13, 2003, the contents of which are expressly incorporated by reference herein in its entirety.

**[0008]** Due to their extreme toxicity, neurotoxins are highly controlled and can have disastrous consequences if not used and controlled properly, especially when used *in vivo*. In addition, due to their toxicity, the body tends to build up a resistance to their use, resulting in

lower efficacy, the need for increased treatments, or the need to discontinue their use all together in certain patients.

**[0009]** In light of the foregoing, it would be desirable to provide methods and apparatus for delivering neurotoxins such as botulinum toxins non-toxically.

**[0010]** It would also be desirable to provide methods and apparatus for treating various conditions with a neurotoxin such as botulinum toxin fragments via *in vivo* cell permeabilization.

**[0011]** In would also be desirable to provide a system of devices, including catheters, trocars, needles, endoscopes, inhalers, nebulizers and aerosolizers and other mechanisms to deliver fragmented neurotoxins non-toxically.

**[0012]** Further, it would be desirable to couple energy delivery devices with the delivery of fragmented neurotoxins to deliver active neurotoxins, non-toxically, including catheter based energy systems, and non-invasive energy systems.

**[0013]** All publications and patents or patent applications mentioned in this specification are herein incorporated by reference to the same extent as if each individual publication, patent or patent application was specifically and individually so incorporated by reference.

## BRIEF SUMMARY OF THE INVENTION

**[0014]** According to the present invention, an active fragment (sometimes referred to as a catalytic portion) of a neurotoxin such as the botulinum neurotoxin (BoNT), preferably the light chain (LC) portion of BoNT, is delivered to target cells via cell membrane permeabilization. Such delivery provides a non-toxic delivery scheme for deriving a variety of clinical benefits. Although botulinum toxins are used broadly for a variety of clinical applications, the present invention provides enhanced methods of delivery and use of the isolated active fragments or portions of the toxin. Other neurotoxins which may be used in the methods and systems of the present invention include ricin and its active fragments, exotoxin A and its active fragments, diphtheria toxin and its active fragments, cholera toxin and its active fragments, tetanus toxin and its active fragments, and the like.

**[0015]** The present invention contemplates application to all of the conditions listed herein, collectively defined as "therapeutic target conditions", and any other conditions for which BoNT and other neurotoxins are known to or can be shown to provide a therapeutic benefit.

Certain examples have been detailed below for specific applications, but it is within the scope of the present invention that the methods and devices detailed herein have specific applications to many or all of the conditions wherein the intact neurotoxins have shown or proposed to show a therapeutic benefit or effect.

**[0016]** In one aspect of the present invention, BoNT-LC or other active neurotoxin fragment is delivered with the application of energy to achieve cell membrane permeabilization.

**[0017]** In another aspect of the present invention methods and apparatus are provided for altering autonomic nerve function by utilizing an electric field or ultrasonic energy generated by a pulse or pulses of a designated duration and amplitude to alter tissue at the cellular level via permeabilization of the cell membrane to facilitate the translocation of the BoNT-LC or other active neurotoxin fragment to the cell cytosol.

**[0018]** A further aspect of the invention is to provide methods and apparatus for treating or inhibiting a variety of diseases or syndromes that have an underlying neurogenic component, by disrupting the neurogenic activities of the promoters or mediators of the disease or syndrome. Such disruption is facilitated by delivering an active fragment of botulinum toxin, such as the light chain portion of botulinum toxin serotype A (BoNT-LC/A), in the presence of an electric field or ultrasonic energy applied to permeabilize the wall of targeted cell under conditions which induce reversible poration of the cellular membrane and efficient passage of the BoNT-LC fragment to the cell cytosol, its catalytic environment.

**[0019]** In addition to the methods described thus far, the present invention further provides systems for delivering toxins to target cells in a mammalian host. The target cells may be in any of the target regions described above or in any other target region which may benefit from the specific and enhanced delivery of a neurotoxin to cells within the region. Systems comprise catheter or other structure adapted to introduce the toxin or toxin fragment to a region adjacent the target cells. The systems further comprise an energy applicator for applying energy to the target cells under condition which cause poration of the cell membranes to enhance delivery of the toxins and/or their active fragments. The systems still further comprise a source of the toxin or active fragments suitable for introduction from the catheter or other delivery structure.

**[0020]** The energy applicator will typically be adapted to selectively apply energy to target cells within the region where the toxin is to be introduced, e.g., by focusing energy

distribution to the particular target cells or regions which are rich with the target cells. Alternatively, the energy applicator may be adapted to apply energy non-selectively within the target region where both target cells and other cell types may receive the energy.

**[0021]** In some instances, the toxin may comprise an intact toxin, but more usually will comprise an active toxin fragment as defined elsewhere in this application. In the exemplary embodiments, the active toxin fragment is the light chain fragment of the botulinum toxin (BoNT-LC). The light chain fragment may be derived from any one of at least botulinum toxins A, B, C, D, E, F, and G.

**[0022]** The energy applicators of the systems of the present invention may be adapted to apply electric energy, typically pulses between 1 V and 500 V to the targeted region. The electric energy may be radiofrequency (RF) energy, where the energy may be pulsed for durations between 5 microseconds to 100 milliseconds. Alternatively, the electrical energy can be direct current (DC), alternating current (AC), or combinations thereof.

**[0023]** In addition to electrical energy, the energy applicator may be adapted to deliver ultrasonic energy, X-ray beam energy, microwave energy, or any other energy type which can achieve a reversible poration of the target cell walls.

**[0024]** There are at least two general power categories of medical ultrasound waves which may be utilized in the present invention. One category of medical ultrasound wave is high acoustic pressure ultrasound. Another category of medical ultrasound wave is low acoustic pressure ultrasound. Acoustic power is expressed in a variety of ways by those skilled in the art. One method of estimating the acoustic power of an acoustic wave on tissue is the Mechanical Index. The Mechanical Index (MI) is a standard measure of the acoustic output in an ultrasound system. High acoustic pressure ultrasound systems generally have a MI greater than 10. Low acoustic pressure systems generally have a MI lower than 5. For example, diagnostic ultrasound systems are limited by law to a Mechanical Index not to exceed 1.9. Another measurement used by those skilled in the art is the spatial peak, peak average intensity (Isppa). The intensity of an ultrasound beam is greater at the center of its cross section than at the periphery. Similarly, the intensity varies over a given pulse of ultrasound energy. Isppa is measured at the location where intensity is maximum averaged over the pulse duration. Isppa for high acoustic pressure or high intensity focused ultrasound (HIFU) applications ranges from approximately 1500W/cm2. to 9000 $W/cm_2$. Diagnostic ultrasound equipment, for instance, will generally have, and an Isppa less than 700 $W/cm_2$.

Yet another way in which ultrasound waves can be characterized is by the amplitude of their peak negative pressure. High acoustic pressure or HIFU applications employ waves with peak amplitudes in excess of 10MPa. Low acoustic pressure ultrasound will generally have peak negative pressures in the range of 0.01 to 5.0 MPa . Diagnostic ultrasound equipment, for example, will generally have a peak amplitude less than 3.0MPa. Both high and low acoustic pressure ultrasound systems generally operate within the frequency range of 20KHz – 10.0 MHz Interventional applications (such as in blood vessels) operate clinically up to about 50 MHz. Also opthalmologic applications up to about 15 MHz. Diagnostic imaging typically uses frequencies of about 3 to about 10 MHz. Physical therapy ultrasound systems generally operate at frequencies of either 1.0MHz or 3.3MHz. High acoustic pressure ultrasound or high intensity focused ultrasound has been used for tissue disruption, for example for direct tumor destruction. High intensity focused ultrasound using high acoustic pressure ultrasound is most commonly focused at a point in order to concentrate the energy from the generated acoustic waves in a relatively small focus of tissue.

**[0025]** Systems and methods for permeabilization of target tissue cell membranes according to the present invention may employ either high acoustic pressure or low acoustic pressure ultrasound. Some embodiments may preferably employ relatively low acoustic pressure, for example the systems described herein where the transducers are mounted on the delivery devices and operate inside the body. Other systems may operate at interim acoustic pressure ranges. For example, systems described herein which employ an external ultrasound generator and transducer and which conduct the ultrasound to the target tissues through the use of a wave guide. In these systems, losses due to transduction through the wave guide can be compensated for by increasing the input power to the wave guide until adequate power is delivered to the target tissue. Finally, some systems described herein may employ focused or partially focused higher pressure ultrasound, for example the systems which employ an external mask to conduct the ultrasonic power through the tissues to the target tissues. It should be appreciated that combinations of high and low acoustic pressure systems may also be employed.

**[0026]** The catheter or other structure may be adapted to introduce the toxin to the target cells in a variety of ways. For example, catheters may comprise a needle for injecting the toxin, optionally a needle which is deployable axially or radially from the catheter body.

Alternatively or additionally, catheters may be provided with nozzles or other ports for aerosolizing the toxin, particularly within regions of the lung as described herein. Still further alternatively or additionally, the catheters may comprise balloons or other expandable elements for deflecting an end of the catheter to engage one or more ports on the catheter against the tissue where the toxin fragments are released through the port(s). In a specific embodiment, the ports may be in the balloon itself where the toxin fragments are released through the ports in the balloon as the balloon is inflated with the medium containing the fragments. With such balloon embodiments, the electrodes or other energy transducers will typically be located within the balloon for applying the poration energy to the target tissue. Further optionally, the energy applicators may be mounted directly on the catheters, for example in the form of acoustic transducers, RF or other electrical electrodes, or the like. Alternatively, the energy applicator may be provided separately from the toxin delivery catheter or other source, typically being an external source, such as an external high intensity focused ultrasound (HIFU) source or an external electrode array for delivering radiofrequency or other electroporation energy.

**[0027]** In a further aspect of the invention, it may be desirable to provide methods and devices that utilize a non-toxic delivery mechanism to target cells to reduce the potential for an immunogenic response to the delivered toxin over time.

**[0028]** In a further aspect of the invention, it may be desirable to deliver the therapeutic neurotoxin fragment and energy via a catheter.

**[0029]** In a further aspect of the invention, it may be desirable to deliver the therapeutic neurotoxin fragment via an aerosolizer or nebulizer.

**[0030]** In a further aspect of the invention, it may be desirable to deliver the therapeutic neurotoxin fragment via an inhaler.

**[0031]** In a further aspect of the invention, it may be desirable to deliver the therapeutic neurotoxin fragment and membrane transport energy transdermally.

**[0032]** In a further aspect of the invention, it may be desirable to deliver the therapeutic neurotoxin fragment via a catheter, or aerosolizer or inhaler, and the energy via a catheter placed in the vicinity of the targeted cell.

**[0033]** In a further aspect of the invention, it may be desirable to delivery the therapeutic neurotoxin fragment and the membrane transport energy via an implantable generator and drug delivery pump.

**[0034]** In a further aspect of the invention, it may be desirable to deliver the therapeutic neurotoxin fragment via a catheter, or aerosolizer (nebulizer) or inhaler, and the energy via an external energy source adapted to target the applied energy in the vicinity of the targeted cell.

## BRIEF DESCRIPTION OF THE DRAWINGS

**[0035]** Further features of the invention, its nature and various advantages will be more apparent from the accompanying drawings and the following detailed description, in which:

**[0036]** Figure 1 – depicts a schematic of the creation of neurotoxin Botulinum Toxin Type A (BoNT/A), including the light chain (LC) fragment or portion.

**[0037]** Figure 2A – depicts a schematic of a target cell, including the cell membrane, and inner cellular matrices.

**[0038]** Figure 2B – depicts a schematic of the target cell wherein LC molecule has been introduced.

**[0039]** Figure 3A-3B – depicts a the target cell of Figure 2 showing application of an energy field (EF) to produce permeabilization or pores (P) in the cell membrane, and introduction of the LC fragment therethrough.

**[0040]** Figure 4 – depicts a schematic of a cell wherein the energy field has been discontinued, and neurotransmission of the cell has been effectively blocked.

**[0041]** Figures 5, 5A-5B – depicts various embodiments of a delivery device of the present invention utilizing multiple energy transmission elements and an energy transmission system.

**[0042]** Figures 6A-D, 6AA, and 6CC – depict various electrode catheter configurations adapted to deliver energy or energy and therapeutic agents to target tissue.

**[0043]** Figure 7 – depicts an alternative embodiment of the present invention wherein one of the multiple energy transmission elements is placed at the targeted cell site, and the other in a location remote therefrom.

**[0044]** Figure 8 - depicts an embodiment of the present invention utilizing an ultrasound element on a catheter device.

**[0045]** Figure 9 - depicts an embodiment of the present invention utilizing an inhaler with an *in vivo* energy delivery source.

**[0046]** Figure 10 - depicts an interstitial method of use of the present invention.

**[0047]** Figure 11 – depicts an embodiment of the present invention utilizing an aerosolizing element.

**[0048]** Figure 12 – depicts a fully implantable pulse generator, lead and agent delivery pump of the present invention.

**[0049]** Figure 13 – depicts an embodiment of the present invention utilizing an external energy delivery source applied to the therapeutic agent applied in the vicinity of a targeted cell.

**[0050]** Figure 14 – depicts an embodiment of the present invention wherein the energy and therapeutic agent are delivered transdermally.

**[0051]** Figure 15 – depicts a method of use of a noninvasive agent delivery device coupled with a non-invasive energy source for treating a lumen or tract of the respiratory system.

**[0052]** Figures 15A and 15B – depict use of a balloon for delivering toxin fragments in a lung.

**[0053]** Figures 16A and 16B – depict use of a deflected catheter tip for delivering toxin fragments in a lung.

## DETAILED DESCRIPTION OF THE INVENTION

**[0054]** The present invention is directed to methods and apparatus for targeting the non-toxic delivery of a fragment of a neurotoxin, while still maintaining the catalytic or toxic effect of the neurotoxin fragment once it is non-toxically delivered to its targeted cell. For purposes of this specification, the term "non-toxic", "non-toxically" and the like refer to the state of the fragment molecule prior to delivery to a target location. In this description, the fragment neurotoxin is intended to retain its toxic effect once delivered to its catalytic environment; the intracellular matrix or cytosol of the targeted cell.

**[0055]** Devices and methods of the present invention may be directed to suitable "targeted regions" such as muscle cells in various regions of the body related to the various "therapeutic target conditions" or syndromes to be treated, as detailed in this specification

above. Some particular examples include targeting mucosal and muscular lining of the lung, cholinergic cells in the region of tumors, myofacial regions, vascular smooth muscle cells, musculoskeletal regions and the like.

**[0056]** According to the present invention, energy fields (EF) may be applied to target regions in conjunction with the delivery of a fragmented neurotoxin such as BoNT-LC to facilitate the transfer of the neurotoxin fragment into the targeted cell, non-toxically via *in vivo* target cell permeabilization.

**[0057]** Use of Isolated Light Chain of Botulinum Neurotoxins. Generally, the BoNT molecule is synthesized as a single polypeptide chain of 150kD molecular weight. The neurotoxin is then exposed to enzymes, either during cultivation of the *Clostridium botulinum* organism or subsequent to purification of the toxin, wherein specific peptide bonds are cleaved or "nicked" resulting in the formation of a dichain molecule referred to as BoNT. As shown in Figure 1, dichain neurotoxin is composed of a light chain (LC) region 50kD molecular weight linked by disulfide bonds to a heavy chain (HC) 100kD molecular weight (Kistner, A., Habermann, E. (1992) *Naunyn Schmiedebergs Arch. Pharmacol.* 345, 227-334). When the light chain is separated from the heavy chains of botulinum toxin, neither chain is capable of blocking neurotransmitter release, however, the light chain alone is capable of blocking acetylcholine release if transported directly into the cell cytosol. (Ahnert-Hilger, G., Bader, M.F., Bhakdi, S., Gratzl, M. (1989) *J. Neurochem.* 52, 1751-1758 and Simpson, L.L. (1981) *Pharmacol. Rev.* 33, 155-188.) Focusing on the light chain, the isolation or separation process essentially renders the light chain "non-toxic" in a general environment, while still maintaining its effect or toxicity, once it is transported through the target cell membrane.

**[0058]** Over the past several years, the separation and purification of the light chain and heavy chain of BoNT has seen significant development activity. In the case of the heavy chain (HC), researchers are interested in its ability to bond with a target cell and deliver certain molecules into that cell. For example, various drug delivery applications have been suggested, for example, using the HC to bind to tPA so that a patient could inhale the HC-bound tPA allowing it to cross the membrane of the lungs and be transported into the bloodstream for anticoagulation. Of particular interest to the present invention are the efforts to isolate and purify the light chain (LC) of the botulinum molecule. In its isolated and purified form, all HC elements are removed, rendering the LC incapable of crossing the cell

membrane without assistance. Thus, the LC is non-toxic until delivered to the target cell cytosol by the delivery protocols of the present invention.

**[0059]** Various groups have been active in the area of isolation and purification. For example, companies such as Metabiologics, a group affiliated with the University of Wisconsin, the Center for Applied Microbiology and Research (CAMR), a division of the UK Health Protection Agency, List Biological Laboratories, Inc. of California, and other research groups throughout the world. Many of these companies provide purified preparations of botulinum neurotoxins from *Clostridium botulinum* types A and B. List Laboratories in particular provides recombinantly produced light chains from both types A, B, C, D and E.

**[0060]** According to the present invention, the therapeutic use and delivery of the light chain only may significantly improve the safety profile of certain applications of therapies utilizing BoNT. BoNT are some of the most lethal toxins known to man. All concerns about migration of the neurotoxin into unintended regions, and harm or toxicity to the patient or physician are eliminated by storing, handling, injecting and metabolizing the light chain only. In the absence of a specific membrane binding technology, the LC is completely non-toxic. In certain applications, such as the treatment of asthma, this is of critical import. In using BoNT to treat asthma, a large quantity of the purified LC substance may be introduced directly into the lung, and then specifically transported to target cells in the exact location and only during the period of use of application of the membrane transport technology, such as cell membrane permeabilization by energy. Once the membrane transport technology has been removed, turned off or otherwise inactivated, the remaining LC which has not been transported into target cells can simply be removed from the body by standard biologic processes for expelling foreign materials, e.g. coughing, immune system or lymphatic system transport and the like.

**[0061]** In addition, therapeutic use of only the LC of the neurotoxin BoNT may reduce the likelihood of the body developing an immunogenic response to the therapy that is seen with delivery of the intact toxin. This could be a major advantage in light of the repetitive application or injection of the toxin that is required to maintain a therapeutic effect.

**[0062]** Non-Toxic Membrane Transport Mechanisms. To date, the main application of purified or isolated light chain has been the study of its mechanism of action. To further this research, literature has reported the use of certain detergent based permeabilization

techniques to deliver fragment BoNT (Bittner MA, DasGupta BR, Holz RW. Isolated light chains of botulinum neurotoxins inhibit exocytosis. Studies in digitonin-permeabilized chromaffin cells. J Biol Chem 1989 Jun 25; 264(18):10354–10360.) Further reference to the mechanism of permeability of cell membranes to deliver botulinum toxin are mentioned in United States Patent 6,063,768 to First, and United States Patent No. 6,632,440 to Quinn, Chaddock, et al "Expression and Purification of Catalytically Active Non-Toxic Endopeptidase Derivatives of Clostridium botulinum toxin type A", *Protein Expression and Purification*, 25 (2002) 219-228, contemplating the insertion of the light chain of BoNT into a target cell without the heavy chain for purposes of deriving vaccines or in bench top studies of cell mechanisms of action. The contents of these references are expressly incorporated by reference in their entirety. None of the teachings contemplate a delivery of a fragment of neurotoxin using a clinically acceptable permeabilization technique *in vivo* for therapeutic uses as is contemplated by the present invention.

**[0063]** For purposes of this specification, the term "poration" includes various forms of electroporation, such as the use of pulsed electric fields (PEFs) , nanosecond pulsed electric fields (nsPEFs), ionophoreseis, electrophoresis, electropermeabilization, as well as other energy mediated permeabilization, including sonoporation (mediated by ultrasonic or other acoustic energy), and/or combinations thereof, to create temporary pores in a targeted cell membrane. Similarly, the term "electrode" or "energy source" used herein, encompasses the use of various types of energy producing devices, including x-ray, radiofrequency (RF), DC current, AC current, microwave, ultrasound, adapted and applied in ranges to produce membrane permeabilization in the targeted cell.

**[0064]** Reversible electroporation, first observed in the early 1970's, has been used extensively in medicine and biology to transfer chemicals, drugs, genes and other molecules into targeted cells for a variety of purposes such as electrochemotherapy, gene transfer, transdermal drug delivery, vaccines, and the like.

**[0065]** In general, electroporation may be achieved utilizing a device adapted to activate an electrode set or series of electrodes to produce an electric field. Such a field can be generated in a bipolar or monopolar electrode configuration. When applied to cells, depending on the duration and strength of the applied pulses, this field operates to increase the permeabilization of the cell membrane and reversibly open the cell membrane for a short period of time by causing pores to form in the cell lipid bilayer allowing entry of various therapeutic elements

or molecules, after which, when energy application ceases, the pores spontaneously close without killing the cell after a certain time delay. As characterized by Weaver, *Electroporation: A General Phenomenon for Manipulating Cells and* Tissues Journal of Cellular Biochemistry, 51:426-435 (1993), short(1-100μs) and longer (1-10ms) pulses have induced electroporation in a variety of cell types. In a single cell model, most cells will exhibit electroporation in the range of 1-1.5V applied across the cell (membrane potential).

**[0066]** In addition, it is known in the art that macromolecules can be made to cross reversibly created pores at voltages of 120V or less applied to cells for durations of 20 microseconds to many milliseconds. For applications of electroporation to cell volumes, ranges of 10 V/cm to 10,000 V/cm and pulse durations ranging from 1 nanosecond to 0.1 seconds can be applied. In one example, a relatively narrow (μsec) high voltage (200V)pulse can be followed by a longer (>msec) lower voltage pulse (<100V). The first pulse or series of pulses open the pores and the second pulse or series of pulses assist in the movement of the BoNT-LC across the cell membrane and into the cell.

**[0067]** Certain factors affect how a delivered electric field will affect a targeted cell, including cell size, cell shape, cell orientation with respect to the applied electric field, cell temperature, distance between cells (cell-cell separation), cell type, tissue heterogeneity, properties of the cellular membrane and the like.

**[0068]** Various waveforms or shapes of pulses may be applied to achieve electroporation, including sinusoidal AC pulses, DC pulses, square wave pulses, exponentially decaying waveforms or other pulse shapes such as combined AC/DC pulses, or DC shifted RF signals such as those described by Chang in *Cell Poration and Cell Fusion using and Oscillating Electric Field*, Biophysical Journal October 1989, Volume 56 pgs 641-652, depending on the pulse generator used or the effect desired. The parameters of applied energy may be varied, including all or some of the following: waveform shape, amplitude, pulse duration, interval between pulses, number of pulses, combination of waveforms and the like.

**[0069]** A schematic example of the methods of the present invention are shown in Figures 2-4 in a simplified single cell model. A targeted cell 10 is shown in Figure 2A. Fragmented neurotoxin such as BoNT-LC (LC) is introduced into the vicinity of the targeted cell as depicted in Figure 2B. An energy field (EF) is applied in accordance with the present invention resulting in the transfer of the BoNT-LC through pores P to the intracellular matrix (cytosol) as shown in Figures 3A and 3B. Once this transfer has occurred, the release of

neurotransmitters of the target cell are then blocked or disrupted, and once energy application is discontinued, the pores P in the cell membrane recover or close as depicted in Figure 4.

**[0070]** Of particular interest for application in certain therapeutic target conditions is the developing field of sonoporation. Just as pulses of high voltage electricity can open transient pores in the cell membrane, ultrasonic energy can do the same. See for example Guzman et al. "Equilibrium Loading of Cells with Macromolecules by Ultrasound: Effects of Molecular Sizing and Acoustic Energy," *Journal of Pharmaceutical Sciences*, 91:7, 1693-1701, which examines the viability of ultrasound to deliver molecules of a variety of sizes into target cells. In addition, techniques for nebulizing fluids and aqueous drugs are well known in the art, and as such, devices of the present invention may be adapted to introduce a BoNT-LC solution to a target region, such as the lung and then effect selective membrane transport of the BoNT-LC into the cell using sonoporation.

**[0071]** For example, United States Patent 6,601,581 to Babaev, hereby incorporated by reference in its entirety, describes certain techniques for delivering therapeutic agents using ultrasound for pulmonary delivery via an aerosolizing technique. Further, Guzman, et al, depicts delivery of molecules from a low of 62Da up to 464 kDa (a range of 0.6-18.5nm radius). Since the LC of the botulinum toxin is in the 50kDa range, the LC would be very susceptible to sonoporetic delivery. Furthermore, Guzman, et al also showed that for all size ranges tested, levels of macromolecule within the cell reached thermodynamic equilibrium with the extracellular environment, and the cell uptake also depended on the energy delivered, as expressed in $J/cm^2$. As such, the sonoporetic delivery of LC to the targeted regions may be controlled by adjusting the concentration of the LC exposed to the target region (e.g. wall or membrane of the lung), the energy delivered to the target region, or both.

**[0072]** Catheter Devices. To achieve the goals of the present invention, it may be desirable to employ methods and apparatus for achieving cell membrane permeabilization via the application of an energy source, either from a catheter located directly in the vicinity of the targeted cells, or an externally focused energy system. For purposes of this specification, the term "catheter" may be used to refer to an elongate element, hollow or solid, flexible or rigid and capable of percutaneous introduction to a body (either by itself, or through a separately created incision or puncture), such as a sheath, a trocar, a needle, a lead. Further descriptions of certain electroporation catheters are described in United States Patent Application

60/701,747 (Attorney Docket No. 020979-003500US), filed on July 22, 2005, the full disclosure of which is expressly incorporated herein by reference.

**[0073]** Figures 5 and 5A-5B depict a system 20 utilizing an electroporation catheter 22 for selective electroporation of targeted cells. In certain configurations of the present invention, voltages may be applied via the electroporation catheter 22 to induce reversible electroporation at the same time as the catheter delivers the fragmented neurotoxin to the targeted region.

**[0074]** Referring to Figure 5, electroporation catheter system 20 further comprises a pulse generator 24 such as those generators available from Cytopulse Sciences, Inc. (Columbia, MD) or the Gene Pulser Xcell (Bio-Rad, Inc.), or IGEA (Carpi, Italy), electrically connected to a catheter having a proximal end and a distal end and adapted for minimally invasive insertion into the desired region of the body as described herein. The catheter further comprises an electroporation element 26 at a distal 28 end thereof. The electroporation element may include for example a first and second electrode 30 and 32 operatively connected to the pulse generator for delivering the desired number, duration, amplitude and frequency of pulses to affect the targeted cells. These parameters can be modified either by the system or the user, depending on the location of the catheter within the body (intervening tissues or structures), and the timing and duration of reversible cell poration desired. Figure 5A depicts an arrangement of electrodes 30 and 32 that produces an electric field concentrated in a lateral direction from the catheter body whereas, Figure 5B shows a device constructed to create a more uniform electric field about the shaft of the catheter body.

**[0075]** Further catheter device and electrode configurations are shown in Figures 6A-6D. Figure 6A depicts an elongate catheter 40 having first and second electrodes 42 and 44 near the distal tip thereof, and including a monitoring or stimulation electrode 46 in the vicinity of the active porating electrodes for localizing the treatment area. In some embodiments, the monitoring or stimulating function may be performed by one or more of the treatment electrodes. The catheter device may have an optional sharp tip 48 to facilitate percutaneous introduction. Cross-sectional view Figure 6AA shows various lumens provided for neurotoxin fragment delivery and other purposes.

**[0076]** Figure 6B is a similar catheter device 50 having electrodes 52, 54, and 56, but is further adapted to be steerable, or articulate at a region 53 near the distal end of the device, e.g., including a pull wire for deflecting the tip. Such steering ability enables the operator to

introduce the device into tight or tortuous spaces (such as the bronchial passages or cardiovascular vessels) so that optimal placement of the device at the target location may be achieved.

**[0077]** Figure 6C depicts a catheter device 60 having a needle 62 or other injection element to allow for the injection of a therapeutic agent such as a fragmented neurotoxin before, during or after the application of the pulsed energy or electroporation. The catheter 60 further includes electrodes 64 and 66 or other poration components as discussed herein. The injection element may be a needle 62 as shown in Figure 6C, an infusion port, or other infusion means. Needle 62 may also be used as an electrode in addition to an injection port. Electrode 68 comprises a monitoring or stimulating electrode. Figure 10 depicts the use of a catheter of Figure 6C to treat bronchial tissue in the lung for a variety of respiratory ailments such as asthma. Figure 6CC is a cross-sectional view taken along line 6CC-6CC in Figure 6, showing a co-axial sleeve design.

**[0078]** Figure 6D depicts a catheter device 70 having electrode elements 72 and 74 that are adapted to extend laterally from the main catheter body, and in some cases, penetrate the surrounding tissue prior to application of energy. In doing so the depth and direction of the energy field created by the electroporative process, may be further controlled. A monitoring/stimulating electrode 76 will usually also be provided. Elements 72 and 74 may also be used as injection ports for introduction of toxin or toxin fragments.

**[0079]** Figure 7 depicts the use of a catheter device 80 of the present invention for treatment of a respiratory tract, by positioning at least one electrode (82) at the target region, and a second electrode (84) remote from the target region, the target region being positioned between 82 and 84, such that activation of the electrodes produces an energy field (EF) therebetween, the size and intensity of which can be controlled by the placement of the electrodes relative to each other and the targeted region.

**[0080]** Figure 8 depicts catheter 90 constructed in accordance with the principles of the present invention utilizing an ultrasonic element 92 that may be particularly useful in delivery of the BoNT-LC to bronchial tissue (lung) that provides a broad but targeted transport of the LC across the target cell walls, for example, epithelial and goblet cell walls. In this device, ultrasound energy is delivered to the distal end of the catheter device via an ultrasonic waveguide 94 that is operatively connected to an ultrasound energy source (U/SES). The LC fragment would be delivered from a receptacle 96 via the same lumen as the waveguide via a

lumen provided the distal tip of the device. In operation, the ultrasonic energy would cause the LC solution to be nebulized, forming a mist or aerosol 98 within the lung, as shown in Figure 11. The aerosol 98 itself, in the appropriate concentrations, may act as an ultrasound coupler, conveying the ultrasonic energy to the wall of the lung or other targeted cellular structures, causing sonoporation of the targeted cells whereby the LC fragment is transmitted across the cell membranes to become an effective neurotransmitter blocker. In an alternative embodiment, an ultrasonic transducer may be located directly at the tip of the delivery device, eliminating the need for a wave guide. Various catheters useful for delivering vibrational energy to tissue are described in United States Patent 6,361,554 and 6,464,680 to Brisken, the contents of which are expressly incorporated herein by reference in their entirety, for various therapeutic effects, such as enhancing cellular absorption of a substance.

**[0081]** Since air is a very effective insulator against transmission of ultrasonic energy, the treatment area in the lung may be more precisely controlled by the concentration of the LC mist and the intensity of the ultrasonic energy. A fairly steep drop off in energy delivery would occur as mist concentration diffused, effectively protecting areas outside the predetermined radius surrounding the distal end of the delivery device. According to the present invention, since no functional neurotoxin exists without an effective membrane transport technology, terminating the energy application leaves a harmless mist that is then coughed up (if resident in the lungs) or otherwise metabolized and excreted by the body.

**[0082]** Any of the catheter devices described herein, or described in the contemporaneously filed United States Patent Application 60/701,747 (Attorney Docket No. 020979-003500US), previously incorporated by reference in its entirety, may be adapted to include an energy delivery element such as those described herein for purposes of providing a membrane transport system for delivery of a fragment of neurotoxin. In addition, certain catheter devices and methods such as those set forth in United States Patents 5,964,223 and 6,526,976 to Baran may be adapted to include energy transmission elements capable of producing a porative effect at the cellular level, including electrodes, ultrasonic elements and the like, for treatment in the respiratory tract.

**[0083]** Furthermore, any of the foregoing systems may include electrodes or other monitoring systems either located on the treatment catheter, or external to the patient, to determine the degree of treatment to the region, including, thermocouple, ultrasound transducers, fiberoptics, sensing or stimulating electrodes. Further, it may be desirable to

incorporate multiple pairs of electrodes that may be activated in pairs, in groups, or in a sequential manner in order to maximize the desired shape of the energy field (EF) while minimizing the field strength requirements.

**[0084]** Implantable Devices. Just as energy may be delivered to a targeted region to facilitate the delivery of fragmented neurotoxin via a catheter system, it is also within the scope of the present invention to deliver neurotoxins via an implantable system, including a pulse generator, lead and drug pump as depicted in Figures 12. A neuromodulation system 200 may be fully implantable, having a pulse generator and a power supply or battery and be operatively connected to a programmable drug delivery pump all housed within a module 202, including a reservoir in which the BoNT-LC is stored for delivery over time using the principles of the present invention and technology of the programmable drug pump. A catheter 204 can be adapted to deliver the drug and poration energy to a desired target location in the patient's body.

**[0085]** Examples of useful implantable devices of the present invention are, devices such as those set forth in United States Patent 5,820,589 to Torgerson et al, the entire contents of which are hereby incorporated by reference, the SynchroMed® programmable pump available from Medtronic, Inc. (Minneapolis, MN), and the neurostimulation units such as the RESTORE® or SynergyPlus® available from Medtronic, Inc., modified if necessary to delivery the desired voltage range for cell membrane permeabilization. Implantation of the neurostimulation device is further described in US Patent 6,847,849, incorporated herein by reference in its entirety.

**[0086]** The non-toxic nature of the BoNT in the absence of applied energy makes it possible to contemplate placing a bolus of neurotoxin in the body of a patient in what might otherwise be a toxic amount. This is particularly advantageous, since the traditional treatment regime using neurotoxins, is typically repeat injections of the toxins every 3 to 6 months and sometimes more frequently depending on the application. Certainly in more chronic conditions such as chronic pain, tremor, spasm, palsy and the like, such a fully implantable system may be highly desirable.

**[0087]** Non-Invasive Devices. It is within the scope of the invention to deliver either the energy or the therapeutic BoNT-LC non-invasively, or both. For example, Figure 13 depicts delivery of the BoNT-LC via a catheter 100 placed in the bronchial passageway with the energy field (EF) delivered from outside the patient in the form of an energy system 102 such

as focused ultrasound (HIFU), stereotactic x-ray beams, magnetic resonance transmission, and the like. As detailed in United States Patents 6,626,855 and 6,719,694 to Weng, the contents of which are expressly incorporated herein by reference in their entirety, an ultrasound beam can be controlled from outside the patient to focus the ultrasound beam in the desired location and intensity. For use in the present invention, it may be desirable to pulse or otherwise attenuate the ultrasound beam to achieve reversible cellular poration at the targeted site. Further, due to its non-toxic state, the BoNT-LC may be inhaled by the patient using a standard inhaler device such as those using pressurized aerosols known as metered does inhalers (MDI) available from Cardinal Health (Somerset, NJ), the OPTIHALER® available from National Allergy Supply Incorporated (Georgia, USA), or a nebulizer breathing machine such as a Pari DURANEB 3000 portable nebulizer available from Medinfinity, Co. (Fountain Valley, CA). In addition, certain technology currently under development employing thermal aerosols, such as a the STACCATO™ vaporization technology from Alexza Molecular Delivery (Palo Alto, CA) may also be useful within the scope of the present invention. Such devices 110 may be used as depicted in Figure 9 for treating a respiratory ailment such as asthma. Optionally, the drug can be delivered with the catheter 22 (as shown) or with the external sources of Fig. 13.

**[0088]** A combination of these non-invasive approaches may also be advantageous as shown in Figure 15, wherein an non-invasive inhaler 110 is used to deliver the BoNT-LC to the target region (such as the lung), and the energy is delivered to the target region by the non-invasive source 102 such as the focused ultrasound (HIFU), stereotactic x-ray, or magnetic resonance transmission as previously described. Due to its non-invasive technique, this approach may have broad appeal to a large patient population, including pediatric use, on an outpatient basis in a clinic designated for the treatment of specific respiratory ailments.

**[0089]** In a further aspect of the present invention, the fragmented molecule BoNT-LC may be delivered intravenously to a patient to achieve a systemic affect. A non-invasive energy application device, such as those described above, may then be targeted at the area of interest to porate the target area, thereby locally delivering the BoNT-LC to the region sufficiently porated by the applied energy.

**[0090]** Cosmetic and Myofacial Applications. For some conditions, it may be desirable to apply the energy field from the surface of the skin to produce a porative effect, while injecting the BoNT-LC fragment into the targeted facial muscles as shown in Figure 14. In

operation, an injection device 220 places the BoNT-LC in the muscle to be treated (target region), and an energy transmission device such as an ultrasonic pen 222 with a single, or a series of ultrasonic elements located on the distal end and coupled to an energy transmission system 224, follows along the target region to controllably discharge the BoNT-LC fragments to the targeted cells leaving a highly controlled treated region. In some instances for treatments around the eye, it may be desirable to limit the penetration of the BoNT-LC to dermal or subdermal layers. In these applications, BoNT-LC may be applied transdermally with ultrasound assistance using techniques similar to those set forth in US Patent 4,767,402 to Kost the contents of which is expressly incorporated herein in its entirety or through transdermal electroporation.

**[0091]** Intraluminal Devices. It may further be advantageous to position catheters of the present invention through vessels in the body to direct them to various regions to affect neurotransmitters in the cardiovascular system. Intraluminal catheters such as those shown in United States Patent Applications 2001/0044596 to Jaafar and 2002/0198512 to Seward, hereby incorporated by reference in their entirety, may be used in this application of the present invention.

**[0092]** Treatment Enhancements. In some applications of the present invention, it may be desirable to asses the appropriate location for the therapy prior to treatment, the therapeutic effect as it is delivered, and ultimately the resulting effect. To achieve this, once the treatment device is in place adjacent the tissue to be treated, the energy generator may be activated, causing an energized field to be generated in the target area. Prior to activation of therapeutic voltages and agent, stimulation using one or more electrodes may be used to elicit a nerve response or reflex. By observing the nerve response, a target treatment location can be confirmed. Similarly, once the therapy has been delivered, a similar stimulation response may be sought, to determine presence or lack of neurogenic response.

**[0093]** In operation, effects of electroporation and delivery of a therapeutic does of BoNT-LC may be selective due to the cellular structure and orientation of the targeted cells. For example, targeted cells may be preferentially affected due to size, avoiding smaller or cross-oriented tissue cells.

**[0094]** In a further aspect of the present invention, the method of delivering the LC fragment of the BoNT molecule may include the use of a media that contains microspheres or microbubbles, such as Optison™ sold by GE Healthcare (www.amershamhealth-

us.com/optison/). Delivery of an ultrasound energy (or other form of energy, for example, laser, RF, thermal, energy) to the media causes the microspheres to rupture, which causes a release of energy toward the targeted region. Such a technique may assist in the desired porative effect by reducing the amount of applied energy required to create poration in the targeted cell membrane. *Bioeffects Caused by Changes in Acoustic Cavitation Bubble Density and Cell Concentration: A Unified Explanation Based on Cell-to-Bubble Ratio and Blast Radius*, Guzman, et al. Ultrasound in Med. & Biol., Vol. 29, No. 8, pp. 1211-1222 (2003). In an alternative embodiment, the LC fragment may actually be contained or encapsulated within a microsphere to assist in delivery. Such enhancing elements may be delivered prior to energy application or during energy application.

**[0095]** In a further aspect of the present invention, it may be advantageous to heat the targeted cells or surrounding tissue by either applying thermal energy directly to the region, or directing a heated fluid, such as saline to the region through an injection element, to aid the cell poration process. Other substances may also be injected to aid in the transmission of the BoNT-LC into the intracellular membrane, such as amino acids, detergents or other agents that may facilitate the catalytic activity of the LC, in addition to the applied energy.

**[0096]** Referring now to Figs. 15A and 15B, a balloon catheter 300 may be delivered to a target site in the bronchus B of a lung (Fig. 15B). Typically, the catheter 300 will be delivered through an endoscope E, and the shaft 302 of the catheter will comprise at least one lumen for inflating the balloon 304. The inflation medium may carry the toxin fragment which is released through ports 306 formed in the balloon itself. Thus, inflation of the balloon both engages the ports against the wall of the bronchus B and provides the pressure necessary to infuse the neurotoxin fragments into the wall of the bronchus B. Usually, energy will be applied from electrodes 308 or other transducers located within the balloon 304.

**[0097]** Referring now Figs. 16A and 16B, the catheter 400 may also be delivered to a bronchus B of a lung through an endoscope E. Catheter shaft 402 terminates with a delivery port 404 near its distal end. A deflection balloon 406 (or other expandable element capable of pressing against the wall of the bronchus B to engage the port 404 against target tissue) is provided on a side of the catheter shaft 402 which is opposite to that of the port 404. Electrodes 408 are provided on either side of the port 404 in order to deliver the poration energy into the target tissue.

**[0098]** Although various illustrative embodiments of the present invention are described above, it will be evident to one skilled in the art that various changes and modifications may be made without departing from the scope of the invention. It will also be apparent that various changes and modifications may be made herein without departing from the invention. The appended claims are intended to cover all such changes and modifications that fall within the true spirit and scope of the invention.

WHAT IS CLAIMED IS:

1. A method for treating conditions affected by neurogenic function in a targeted region of mammalian cells, said method comprising:

delivering an active neurotoxin fragment to cells in the targeted region;

applying energy to the cells under conditions which cause a reversible poration in the cell membranes to permit delivery of the active fragment.

2. A method as in claim 1, wherein the active fragment is selected from the group consisting of botulinum toxin fragments, ricin fragments, exotoxin A fragments, diphtheria toxin fragments, cholera toxin fragments, and tetanus toxin fragments.

3. A method as in claim 2, wherein the active fragment comprises the botulinum light chain (BoNT-LC).

4. A method of claim 3, wherein the active fragment comprises an amount of BoNT-LC therapeutically effective to inhibit a neurogenic pathway associated with the neurogenic function.

5. A method of claim 4, wherein the active fragment is BoNT-LC derived from at least one of the botulinum toxins A, B, C, D, E, F or G.

6. A method of claim 1, wherein the neurogenic pathway is associated with and contributes to at least one symptom of asthma.

7. A method of claim 1, wherein delivering comprises advancing a catheter to said vicinity and releasing the active neurotoxin fragments from the catheter while applying energy from an applicator on the catheter.

8. A method of claim 7, wherein delivering comprises aerosolizing the fragment from the catheter.

9. A method as in claim 7, wherein delivering comprises injecting the fragment from a needle on the catheter.

10. A method as in claim 7, wherein delivery comprises engaging one or more ports on the catheter against tissue and releasing the fragments from the port(s).

11. A method as in claim 10, wherein engaging comprises inflating a balloon on the catheter to deflect the catheter.

12. A method of claim 1, wherein the delivering is achieved using an inhaler.

13. A method of claim 1, wherein the delivering is achieved transdermally

14. A method of claim 1, wherein the energy applied to the targeted region is an electric pulse.

15. A method of claim 14, wherein the electric pulse has a voltage between 1V and 500V.

16. A method of claim 14, wherein the electric pulse comprises radiofrequency energy.

17. A method of claim 16, wherein the radiofrequency energy is pulsed for durations between 5 microseconds to 100 milliseconds.

18. A method of claim 13, wherein the electric pulse comprises a direct current pulse.

19. A method of claim 13, wherein the electric pulse comprises an alternating current pulse.

20. A method of claim 1, wherein the energy applied to the targeted region comprises ultrasonic energy.

21. A method of claim 20, wherein the ultrasonic energy applied to the targeted region comprises focused ultrasound energy.

22. A method of claim 1, wherein the energy applied to the targeted region comprises an x-ray beam.

23. A method of claim 1, wherein the energy applied to the targeted region comprises microwave energy.

24. A method of claim 4, wherein the neurogenic pathway is associated with and contributes to at least one symptom of pain.

25. A method of treating a respiratory ailment, comprising the steps of:

providing a therapeutically effective amount of BoNT-LC, and

delivering the amount of BoNT-LC to a region of the respiratory system under conditions selected to permeabilize target cells within the region and allow entry of the BoNT-LC to enter the cells.

26. A system for delivering toxins to target cells in a mammalian target, said system comprising:

a catheter or other structure adapted to introduce a toxin to a region adjacent the target cells;

an energy applicator for applying energy to the target cells under conditions which cause poration of the cell membranes to enhance delivery of the toxin; and

a source of toxin suitable for introduction from the catheter.

27. A system as in claim 26, wherein the energy applicator is adapted to selectively apply energy to target cells within the region where toxin has been introduced.

28. A system as in claim 26, wherein the energy applicator is adapted to apply energy non-selectively within the region where toxin has been introduced.

29. A system as in claim 26, wherein the toxin comprises an intact toxin.

30. A system as in claim 29, wherein the toxin is an active toxin fragment.

31. A system as in claim 30, wherein the fragment is a light chain fragment.

32. A system as in claim 31, wherein the active fragment is selected from the group consisting of botulinum toxin fragments, ricin fragments, exotoxin A fragments, diphtheria toxin fragments, cholera toxin fragments, and tetanus toxin fragments.

33. A system as in claim 32, wherein the active fragment comprises the botulinum light chain (BoNT-LC).

34. A system as in claim 33, wherein the light chain fragment is derived from at least one of botulinum toxins A, B, C, D, E, F, and G.

35. A system as in claim 26, wherein the energy applicator is adapted to apply an electric pulse of between 1V and 500V to the target region.

36. A system as in claim 35, wherein the electric pulse is radiofrequency (RF) energy.

37. A system as in claim 35, wherein the RF energy is pulsed for durations between 5 microseconds to 100 milliseconds.

38. A system as in claim 35, wherein the electric pulse is produced by a DC power source.

39. A system as in claim 35, wherein the electric pulse is produced by an AC power source.

40. A system as in claim 26, wherein the energy applicator is adapted to apply ultrasonic energy to the targeted region.

41. A system as in claim 40, wherein the energy applicator is adapted to apply focused ultrasound to the targeted region.

42. A system as in claim 26, wherein the energy applicator is adapted to apply an x-ray beam to the targeted region.

43. A system as in claim 26, wherein the energy applicator is adapted to apply microwave to the targeted region.

44. A system as in claim 26, wherein the catheter comprises a needle for delivering the toxin.

45. A system as in claim 26, wherein the catheter comprises a port for aerosolizing the toxin.

46. A system as in claim 28, wherein the catheter comprises a balloon for deflecting one or more ports against target tissue.

47. A system as in claim 46, wherein the balloon comprises the one or more ports.

48. A system as in claim 26, wherein the energy applicator is on the catheter.

49. A system as in claim 48, wherein the energy applicator applies acoustic energy from a transducer on the catheter.

50. A system as in claim 48, wherein the energy applicator applies electrical energy from an electrode on the catheter.

51. A system as in claim 26, wherein the applicator applies energy from a source external to the patient.

52. A system as in claim 51, wherein the source is an acoustic energy transducer.

53. A system as in claim 52, wherein the acoustic energy transducer is focused ultrasound transducer.

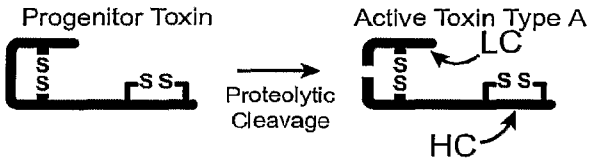

Progenitor Toxin
Active Toxin Type A
LC
Proteolytic
Cleavage
HC

FIG. 1

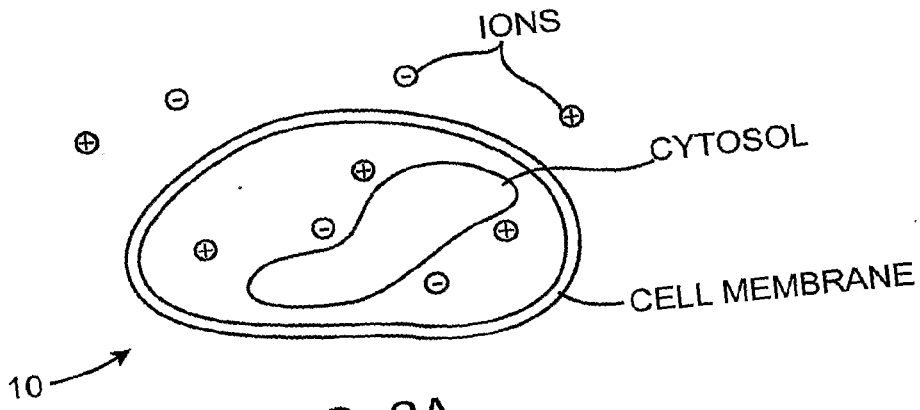



FIG. 2A

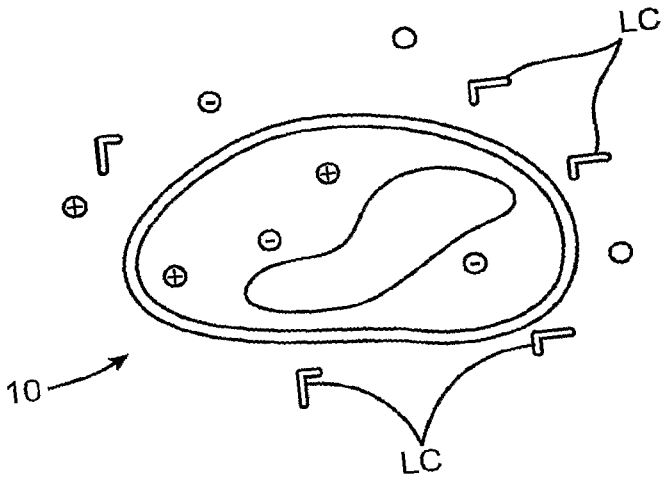



FIG. 2B

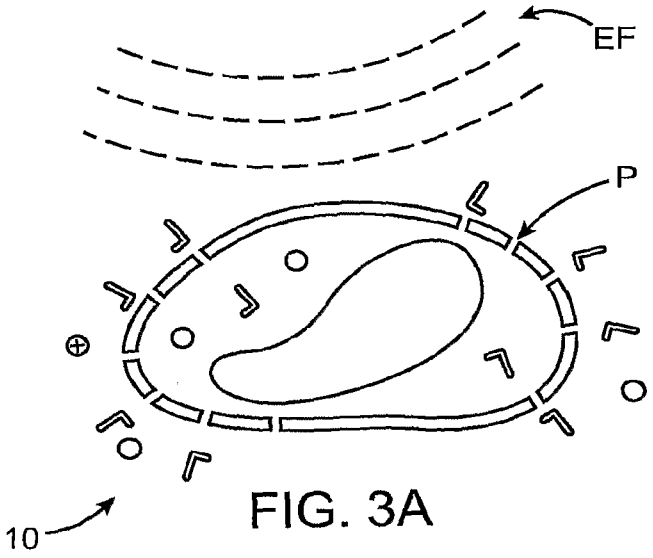



FIG. 3A

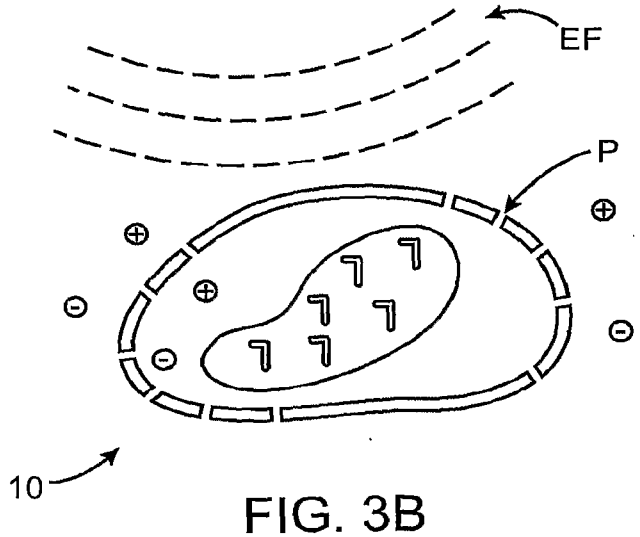



FIG. 3B

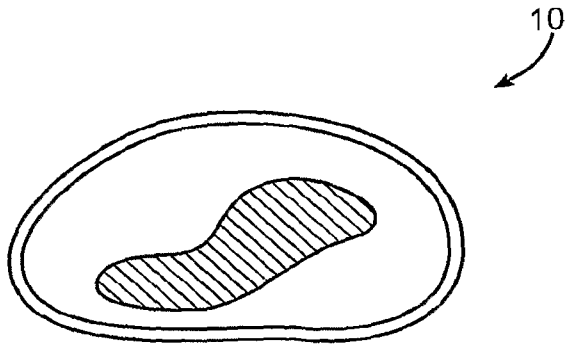



FIG. 4

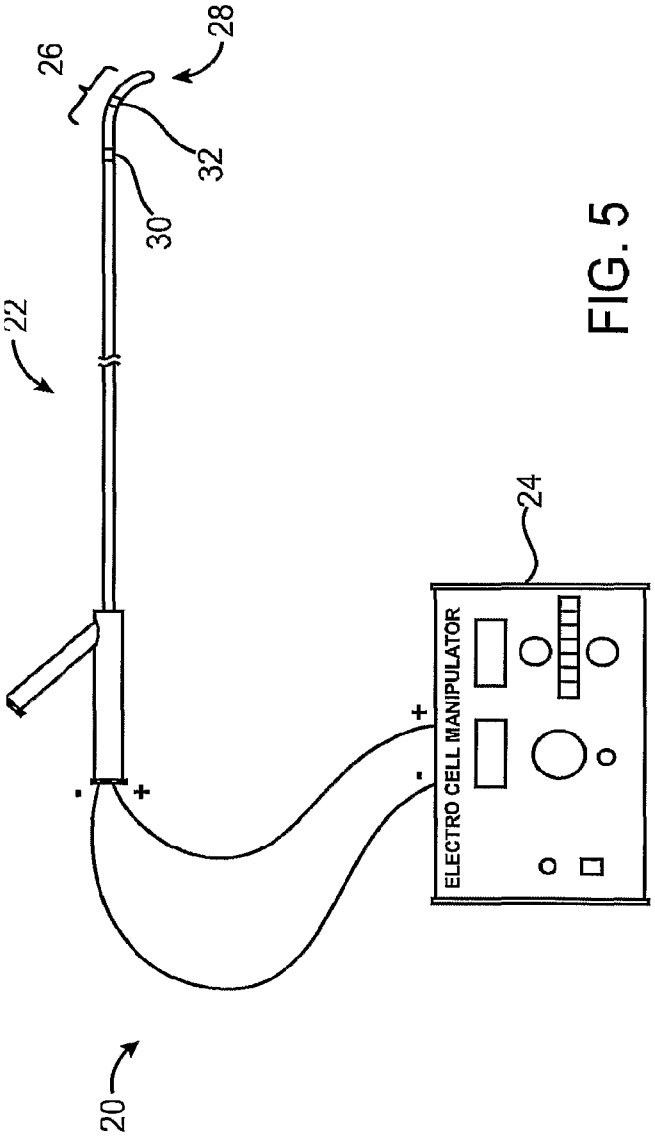



FIG. 5

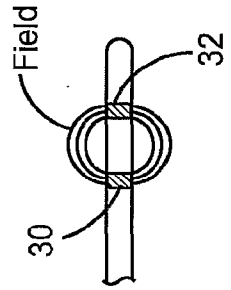



FIG. 5B

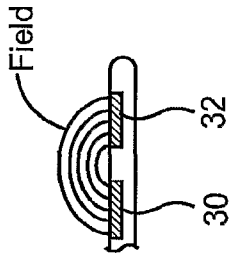



FIG. 5A

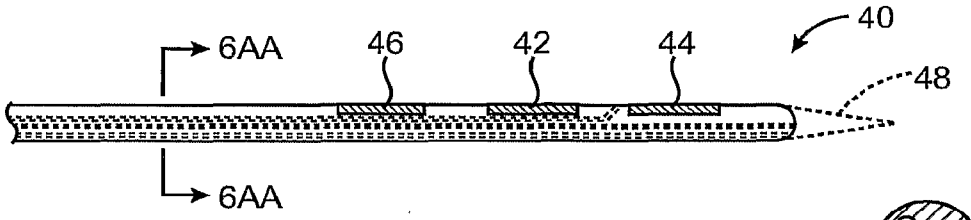



FIG. 6A

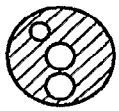


FIG. 6AA

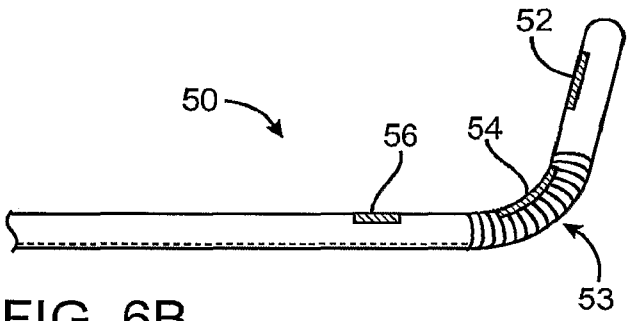



FIG. 6B

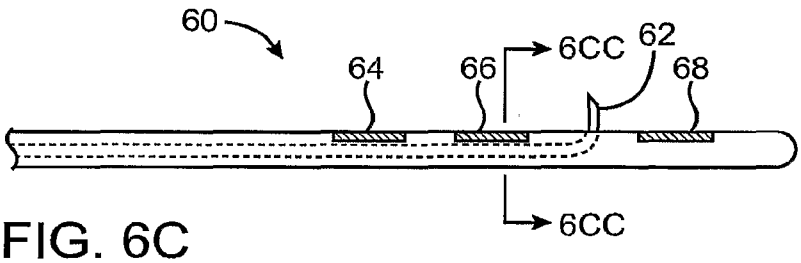



FIG. 6C



FIG. 6CC

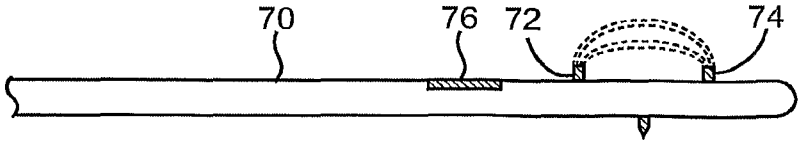



FIG. 6D

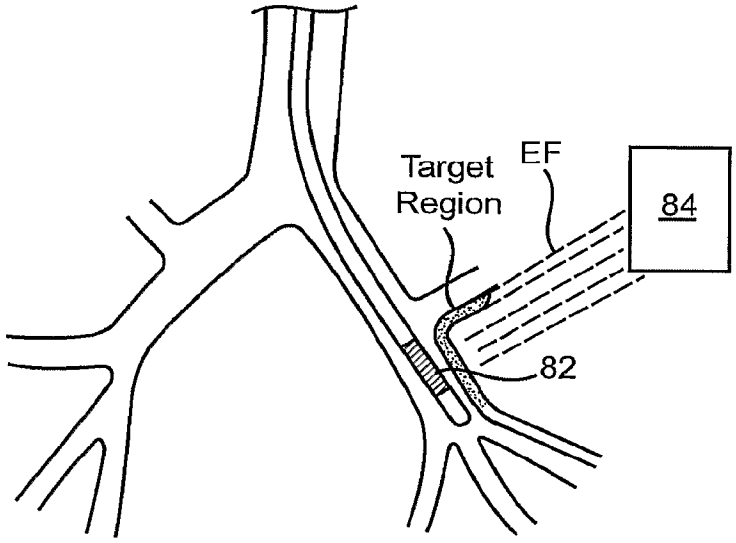



FIG. 7

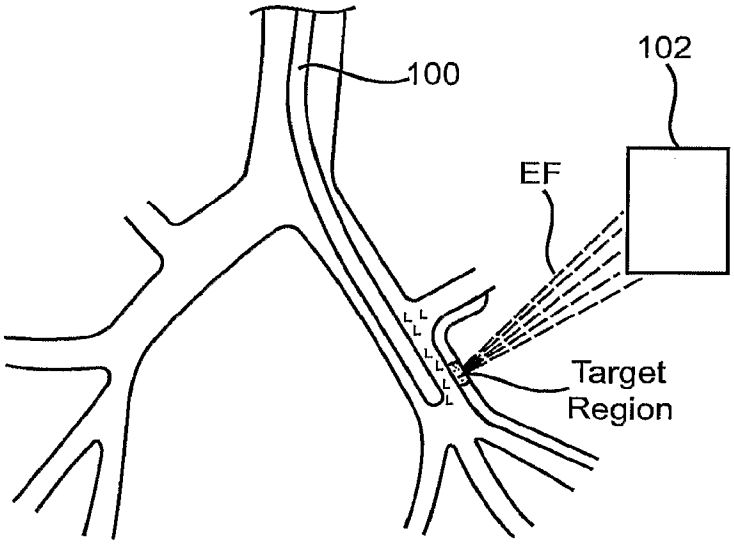



FIG. 13

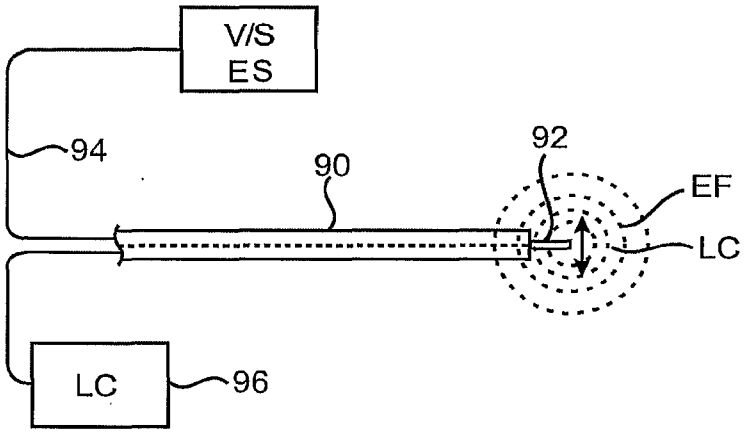



FIG. 8

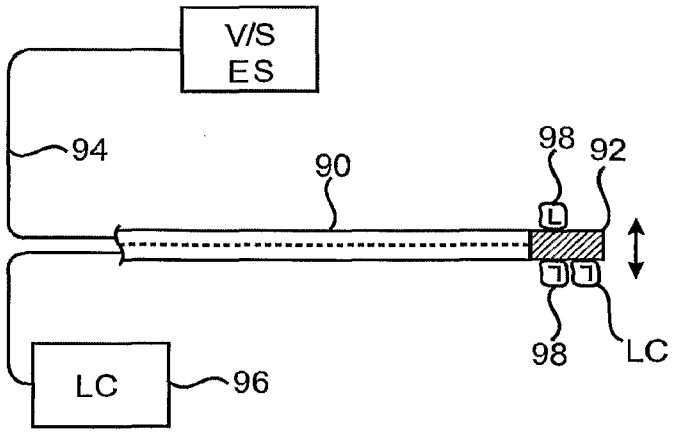



FIG. 11

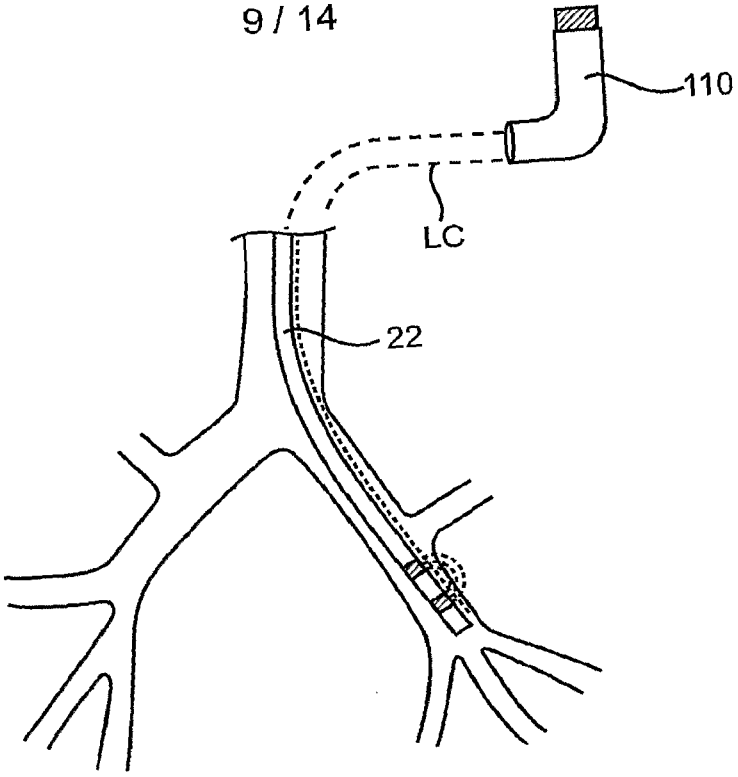



FIG. 9

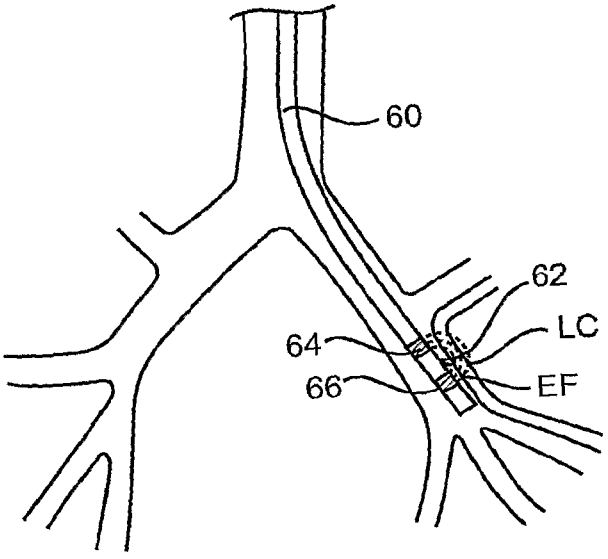



FIG. 10

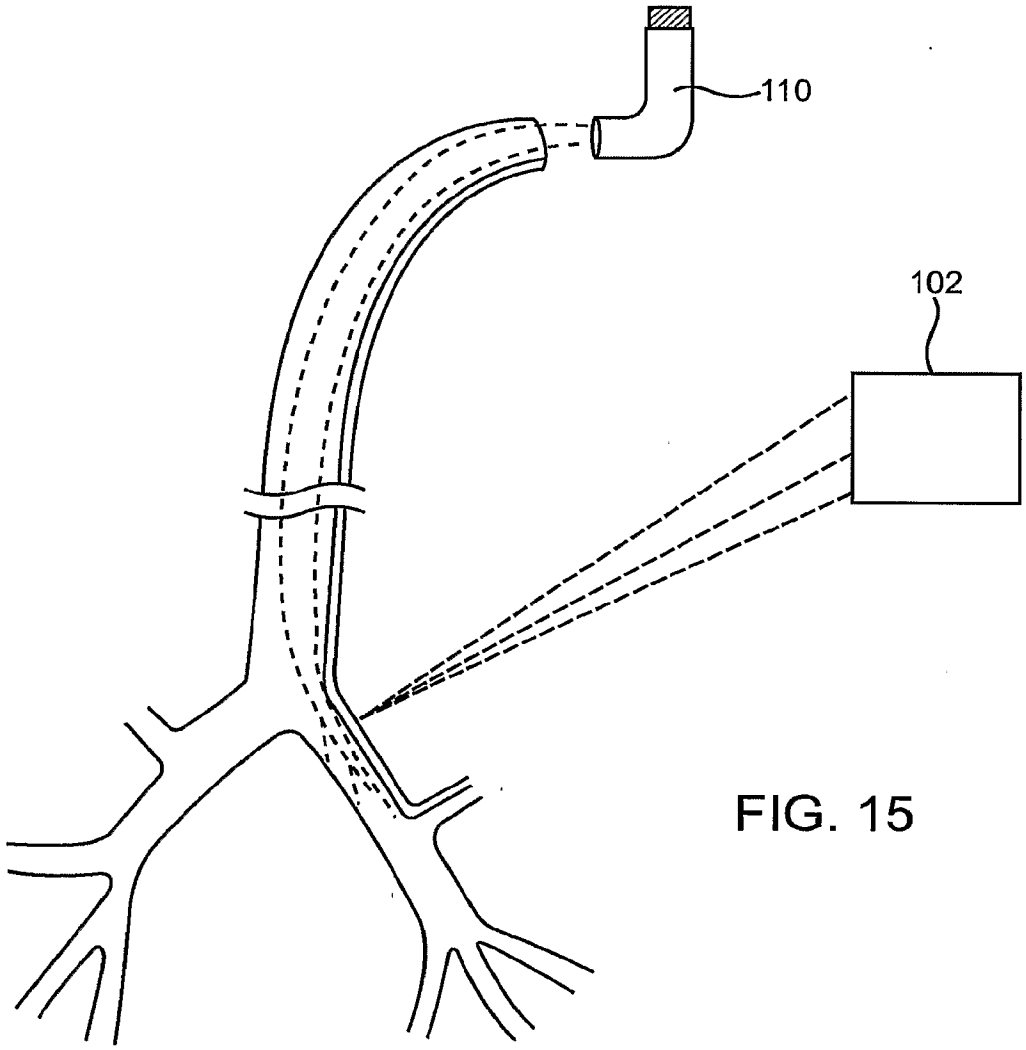



FIG. 15

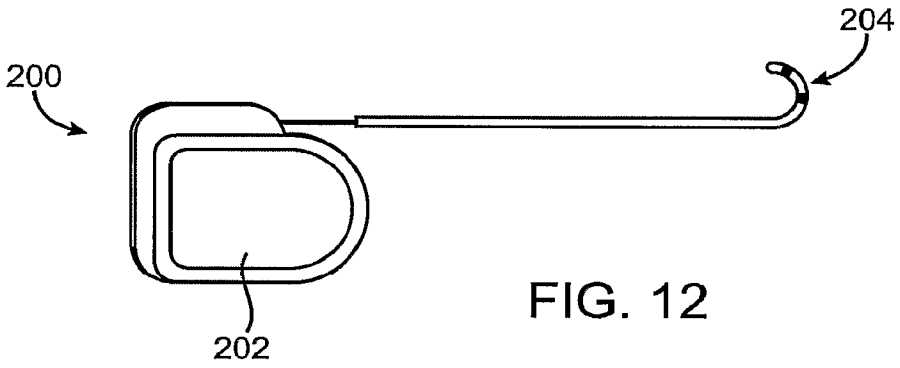



FIG. 12

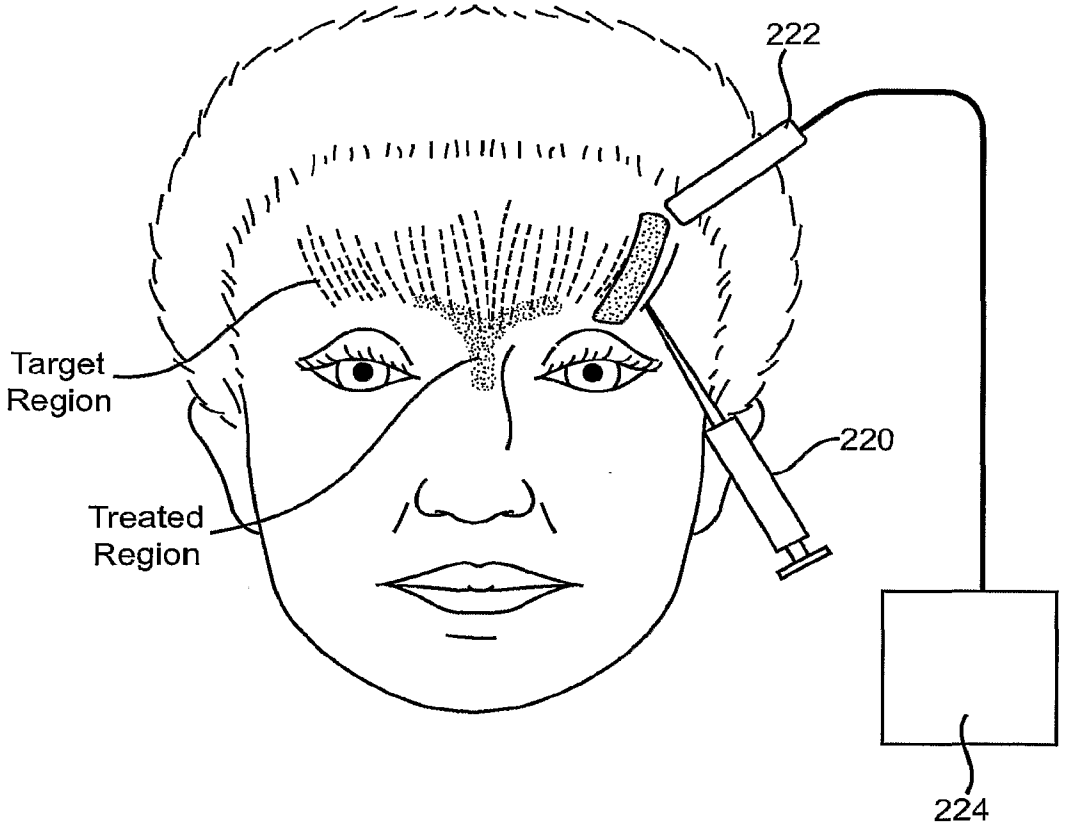



FIG. 14

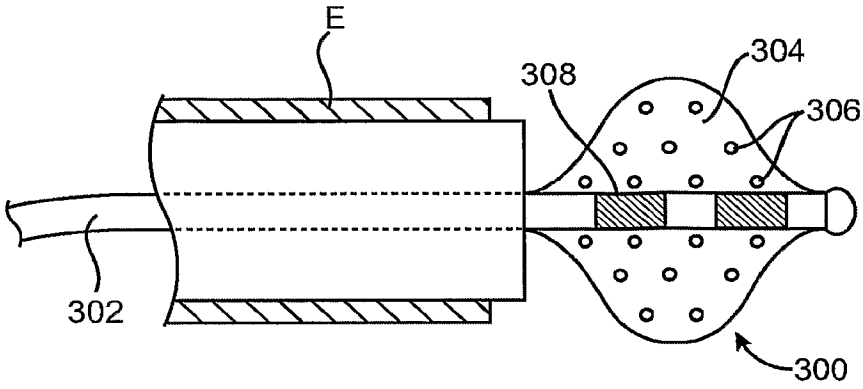



FIG. 15A

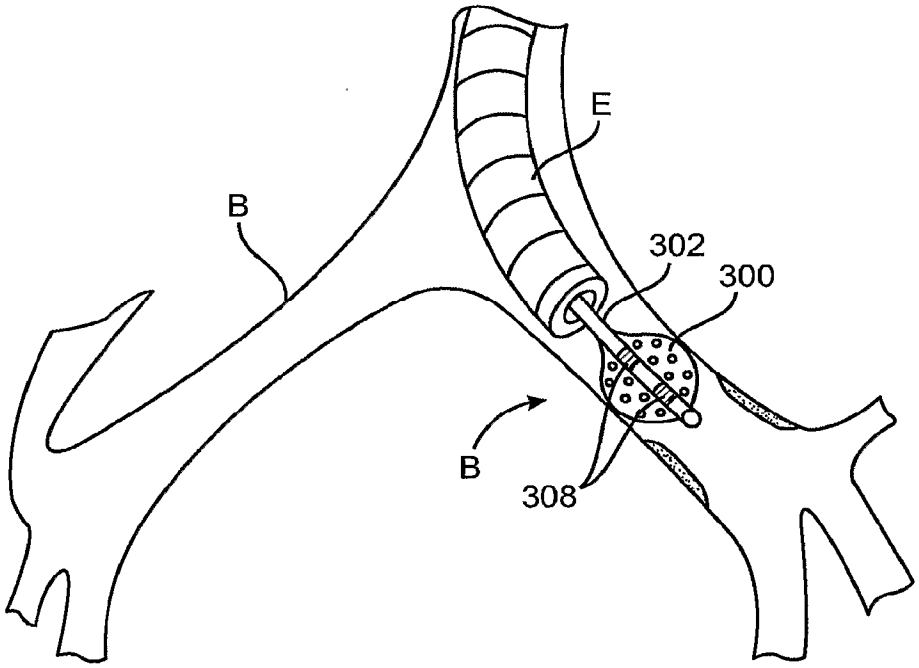



FIG. 15B

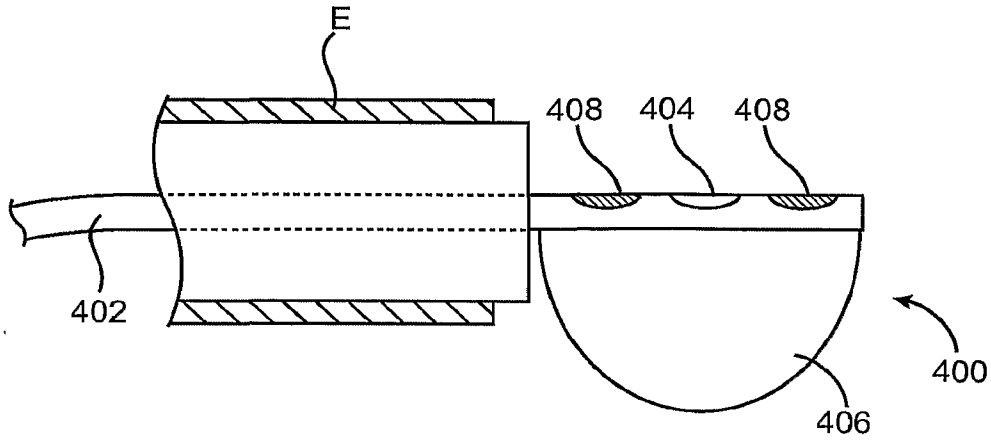



FIG. 16A

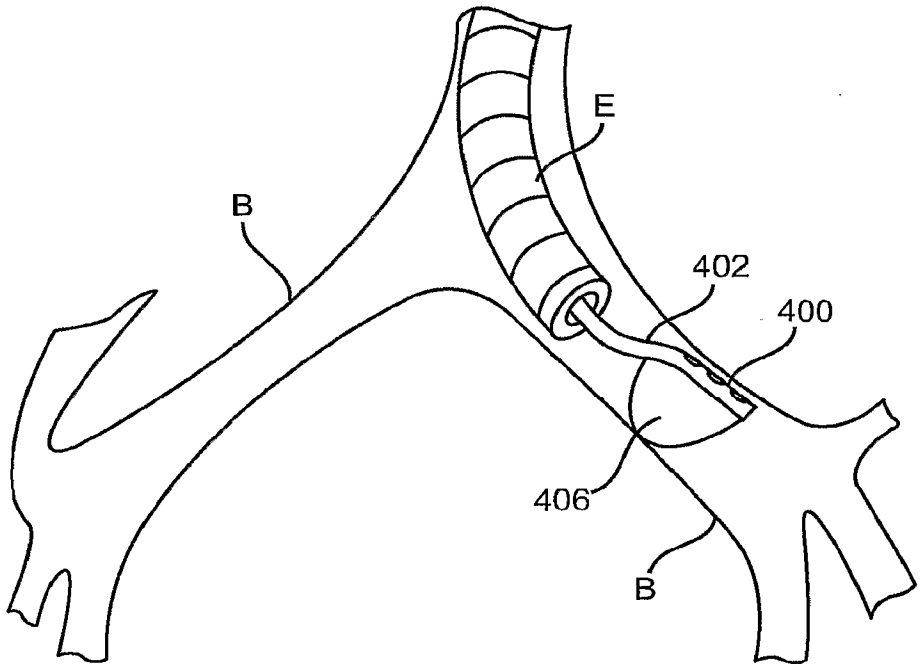



FIG. 16B

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(71) Applicant *(for all designated States except US)*: **THE FOUNDRY INC.** [US/US]; 199 Jefferson Drive, Menlo Park, California 94025 (US).

(72) Inventors; and
(75) Inventors/Applicants *(for US only)*: **DEEM, Mark, E.** [US/US]; 685 Sierra Avenue, Mountain View, California 94041 (US). **GIFFORD, Hanson, S.** [US/US]; 3180 Woodside Road, Woodside, California 94062 (US).

(74) Agents: **HESLIN, James, M.** et al.; Two Embarcadero Center, 8th Floor, San Francisco, California 94111-3834 (US).

(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LV, LY, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, LV, MC, NL, PL, PT, RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

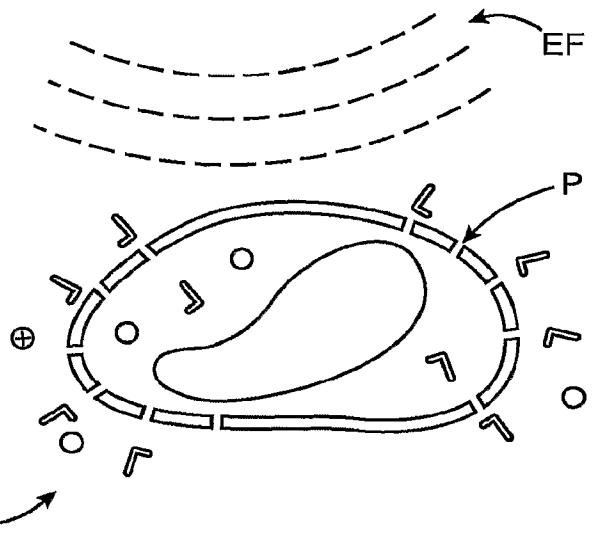
**Declaration under Rule 4.17:**
— *as to applicant's entitlement to apply for and be granted a patent (Rule 4.17(ii))*

**Published:**
— *with international search report*
— *before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments*

(88) Date of publication of the international search report:
4 October 2007

*For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.*

(54) Title: SYSTEMS AND METHODS FOR DELIVERY OF A THERAPEUTIC AGENT




(57) Abstract: Methods and apparatus are provided for applying an fragment of a neurotoxin such as the active light chain (LC) of the botulinum toxin (BoNT), such as one of the serotype A, B, C, D, E, F or G botulinum toxins, via permeabilization of targeted cell membranes to enable translocation of the botulinum neurotoxin light chain (BoNT-LC) molecule across the targeted cell membrane to the cell cytosol where a therapeutic response is produced in a mammalian system. The methods and apparatus include use of catheter based delivery systems, non-invasive delivery systems, and transdermal delivery systems.

WO 2007/014003 A3

# INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 06/28310

A. CLASSIFICATION OF SUBJECT MATTER
IPC(8) - A61K 9/12; A61K 39/02 (2007.01)
USPC 424/45; 424/236.1
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC(8) - A61K 9/12; A61K 39/02 (2007.01)
USPC 424/45; 424/236.1

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
PUBWEST(PGPB,USPT,USOC,EPAB,JPAB), GOOGLE SCHOLAR: BOTULINUM, TOXIN, NEUROTOXIN, LIGHT CHAIN, ELECTROPORATION, X-RAY, MICROWAVE, ULTRASONIC, ULTRASOUND, PERMEABLE, DELIVERY, CATHETER, NEUROTOXIN,

C. DOCUMENTS CONSIDERED TO BE RELEVANT

| Category* | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|---|---|---|
| X<br>---<br>Y | US 2004/0142005 A1 (Brooks et al.) 22 Jul 2004 (22.07.2004); para [0011], [0012], [0013] and [0036] | 1-5<br>---<br>6-53 |
| Y | WO 2004/101028 A2 (Deem et al.) 25 Nov 2004 (25.11.2004); para [0006], [0008], [0015], [0019], [0022], [0052] , [0061], [0063], [0063] and [0065], Fig 9B | 6, 8-11, 25, and 44-47 |
| Y | US 2004/0010290 A1 (Schroeppel et al.) 15 Jan 2004 (15.01.2004); para [0011], [0067], [0074], [0103], [0116], [0149], [0188], [0192], [0237], [0239] and [0297] | 7-11, 13-19, and 26-53 |
| Y | US 5,766,605 A (Sanders) 16 Jun 1998 (16.06.1998); col 10, ln 45-50 | 12 |
| Y | US 2003/0050591 A1 (McHale) 13 Mar 2003 (13.03.2003); para [0011], [0044], [0092] and [0093] | 20-23, 40-43, 49, 52, and 53 |
| Y | RAJ. Editorial Pain Practice. March 2004, 4(S1):S1-S3; pg S1, col 2; and pg S2, col 1 | 24 |

☐ Further documents are listed in the continuation of Box C. ☐

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier application or patent but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

| Date of the actual completion of the international search | Date of mailing of the international search report |
|---|---|
| 23 Jun 2007 (23.06.2007) | 08 AUG 2007 |
| Name and mailing address of the ISA/US<br>Mail Stop PCT, Attn: ISA/US, Commissioner for Patents<br>P.O. Box 1450, Alexandria, Virginia 22313-1450<br>Facsimile No. 571-273-3201 | Authorized officer:<br>Lee W. Young<br>PCT Helpdesk: 571-272-4300<br>PCT OSP: 571-272-7774 |

Form PCT/ISA/210 (second sheet) (April 2005)

# INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 07/69391

A. CLASSIFICATION OF SUBJECT MATTER
IPC(8) - A61K 39/08 (2007.01)
USPC - 424/239.1; 514/8
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC(8) - A61K 39/08 (2007.01)
USPC - 424/239.1; 514/8

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
PubWEST(USPT,PGPB,EPAB,JPAB); Google Patents; Google Scholar
Search terms: botulinum, toxin, nasal cavity, deliver or administer or administration, rhinorrhea, headache, handle, first, second, spring, actuator, applicator, nostril, electric, ultrasound, x-ray, microwave, electromagnetic, poration, transdermal

C. DOCUMENTS CONSIDERED TO BE RELEVANT

| Category* | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|---|---|---|
| Y | US 2006/0106361 A1 (MUNI et al.) 18 May 2006 (18.05.2006) para [0010], [0014]-[0016], [0075], [0077], [0095], [0102], [0104], [0105], [0107] and [0161] | 1-43, 68-78 |
| Y | US 1,695,107 A (KAHL) 11 December 1928 (11.12.1928) col 1, ln 1-4, 22-35 and 49-55; col 2, ln 56-60 and 65-75 | 1-30, 41-43 |
| Y | US 5,766,605 A (SANDERS et al.) 16 June 1998 (16.06.1998) col 2, ln 34-38 and 45; col 8, ln 29 and 33; col 10, ln 16-18 | 1-78 |
| Y | US 2005/0152924 A1 (VOET) 14 July 2005 (14.07.2005) para [0013]-[0014], [0043], [0055], [0065] and [0074] | 24-30, 52-53, 55-57 |
| Y | US 2004/0009180 A1 (DONOVAN) 15 January 2004 (15.01.2004) para [0081]-[0083] | 26-30, 44-78 |
| Y | US 2005/0107853 A1 (KRESPI et al.) 19 May 2005 (19.05.2005) para [0037], [0060], [0108]-[0109] and [0115] | 29, 59-67 |

☐ Further documents are listed in the continuation of Box C. ☐

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier application or patent but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

| Date of the actual completion of the international search | Date of mailing of the international search report |
|---|---|
| 30 December 2007 (30.12.2007) | 03 MAR 2008 |

| Name and mailing address of the ISA/US | Authorized officer: |
|---|---|
| Mail Stop PCT, Attn: ISA/US, Commissioner for Patents<br>P.O. Box 1450, Alexandria, Virginia 22313-1450<br>Facsimile No. 571-273-3201 | Lee W. Young<br>PCT Helpdesk: 571-272-4300<br>PCT OSP: 571-272-7774 |

# INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 07/69391

**Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)**

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

**Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)**

This International Searching Authority found multiple inventions in this international application, as follows:

-- see extra sheet

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying additional fees, this Authority did not invite payment of additional fees.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☒ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:
1-78

**Remark on Protest**

☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.

☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.

☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 07/69391

Continuation of Box No. III - Observations where unity of invention is lacking

This application contains the following inventions or groups of inventions which are not so linked as to from a single general inventive concept under PCT Rule 13.1.

Group I: claims 1-78 are directed to an apparatus for treating inflammation of a nasal membrane of a patient comprising: a handle comprising a proximal section, a first member and a second member, wherein the first member and second member are connected at the proximal section; a first applicator tip coupled to the first member; and a second applicator tip coupled to the second member; wherein the first applicator tip and second applicator tip are each configured for insertion into a nostril of the patient and placement within a nasal passageway of the patient and wherein each applicator tip is configured for delivering a toxin to a region of nasal tissue within the nasal cavity of the patient, thereby treating the inflammation.

Group II: claims 79-112 are directed to a system for delivering toxins to target cells in a nasal membrane, said system comprising: a catheter adapted to introduce a toxin to a region proximate the target cells; an energy applicator configured for applying energy to the target cells under conditions which cause portion of the cell membranes to enhance delivery of the toxin; and a source of toxin suitable for introduction from the catheter.

The inventions listed as Groups I-II do not relate to a single general inventive concept under PCT Rule 13.1 because under PCT Rule 13.2 they lack the same or corresponding technical features for the following reasons:

Group II does not include the inventive concept of an applicator of the type as disclosed in claim 1 of Group I.

Group I does not include the inventive concept of an energy applicator configured for applying energy to the target cells as disclosed in Group II.

Neither of these technical features is common to the other group, nor do they correspond to a special technical feature in the other group. Therefore, unity of invention is lacking.

# PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

To: James M. Heslin
Two Embarcadero Center, 8th Floor
San Francisco, CA 94111-3834

# PCT

WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY

(PCT Rule 43*bis*.1)

| | |
|---|---|
| Date of mailing *(day/month/year)* | 03 MAR 2008 |
| Applicant's or agent's file reference<br>20979-37-3PC | **FOR FURTHER ACTION**<br>See paragraph 2 below |

| International application No. | International filing date *(day/month/year)* | Priority date *(day/month/year)* |
|---|---|---|
| PCT/US 07/69391 | 21 May 2007 (21.05.2007) | 19 May 2006 (19.05.2006) |

International Patent Classification (IPC) or both national classification and IPC
IPC(8) - A61K 39/08 (2008.01)
USPC - 424/239.1; 514/8

Applicant The Foundry Inc.

1. This opinion contains indications relating to the following items:

- ☒ Box No. I Basis of the opinion
- ☐ Box No. II Priority
- ☐ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☒ Box No. IV Lack of unity of invention
- ☒ Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- ☐ Box No. VI Certain documents cited
- ☐ Box No. VII Certain defects in the international application
- ☐ Box No. VIII Certain observations on the international application

2. **FURTHER ACTION**

If a demand for international preliminary examination is made, this opinion will be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA") except that this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notified the International Bureau under Rule 66.1*bis*(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of 3 months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

3. For further details, see notes to Form PCT/ISA/220.

| Name and mailing address of the ISA/US | Date of completion of this opinion | Authorized officer: |
|---|---|---|
| Mail Stop PCT, Attn: ISA/US<br>Commissioner for Patents<br>P.O. Box 1450, Alexandria, Virginia 22313-1450<br>Facsimile No. 571-273-3201 | 30 December 2007 (30.12.2007) | for Lee W. Young<br>PCT Helpdesk: 571-272-4300<br>PCT OSP: 571-272-7774 |

Form PCT/ISA/237 (cover sheet) (April 2007)

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/US 07/69391

**Box No. I Basis of this opinion**

1. With regard to the **language**, this opinion has been established on the basis of:

   ☒ the international application in the language in which it was filed.

   ☐ a translation of the international application into _____ which is the language of a translation furnished for the purposes of international search (Rules 12.3(a) and 23.1(b)).

2. ☐ This opinion has been established taking into account the **rectification of an obvious mistake** authorized by or notified to this Authority under Rule 91 (Rule 43*bis*.1(a))

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, this opinion has been established on the basis of:

   a. type of material

      ☐ a sequence listing

      ☐ table(s) related to the sequence listing

   b. format of material

      ☐ on paper

      ☐ in electronic form

   c. time of filing/furnishing

      ☐ contained in the international application as filed

      ☐ filed together with the international application in electronic form

      ☐ furnished subsequently to this Authority for the purposes of search

4. ☐ In addition, in the case that more than one version or copy of a sequence listing and/or table(s) relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

5. Additional comments:

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/US 07/69391

**Box No. IV Lack of unity of invention**

1. ☒ In response to the invitation (Form PCT/ISA/206) to pay additional fees the applicant has, within the appicable time limit:

   ☐ paid additional fees

   ☐ paid additional fees under protest and, where applicable, the protest fee

   ☐ paid additional fees under protest but the applicable protest fee was not paid

   ☒ not paid additional fees

2. ☐ This Authority found that the requirement of unity of invention is not complied with and chose not to invite the applicant to pay additional fees.

3. This Authority considers that the requirement of unity of invention in accordance with Rule 13.1, 13.2 and 13.3 is

   ☐ complied with

   ☒ not complied with for the following reasons:

This application contains the following inventions or groups of inventions which are not so linked as to from a single general inventive concept under PCT Rule 13.1.

Group I: claims 1-78 are directed to an apparatus for treating inflammation of a nasal membrane of a patient comprising: a handle comprising a proximal section, a first member and a second member, wherein the first member and second member are connected at the proximal section; a first applicator tip coupled to the first member; and a second applicator tip coupled to the second member; wherein the first applicator tip and second applicator tip are each configured for insertion into a nostril of the patient and placement within a nasal passageway of the patient and wherein each applicator tip is configured for delivering a toxin to a region of nasal tissue within the nasal cavity of the patient, thereby treating the inflammation.

Group II: claims 79-112 are directed to a system for delivering toxins to target cells in a nasal membrane, said system comprising: a catheter adapted to introduce a toxin to a region proximate the target cells; an energy applicator configured for applying energy to the target cells under conditions which cause portion of the cell membranes to enhance delivery of the toxin; and a source of toxin suitable for introduction from the catheter.

The inventions listed as Groups I-II do not relate to a single general inventive concept under PCT Rule 13.1 because under PCT Rule 13.2 they lack the same or corresponding technical features for the following reasons:

Group II does not include the inventive concept of an applicator of the type as disclosed in claim 1 of Group I.

Group I does not include the inventive concept of an energy applicator configured for applying energy to the target cells as disclosed in Group II.

Neither of these technical features is common to the other group, nor do they correspond to a special technical feature in the other group. Therefore, unity of invention is lacking.

4. Consequently, this opinion has been established in respect of the following parts of the international application:

   ☐ all parts

   ☒ the parts relating to claims Nos. 1-78

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/US 07/69391

**Box No. V** **Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement**

1. Statement

| | | | |
|---|---|---|---|
| Novelty (N) | Claims | 1-78 | YES |
| | Claims | None | NO |
| Inventive step (IS) | Claims | None | YES |
| | Claims | 1-78 | NO |
| Industrial applicability (IA) | Claims | 1-78 | YES |
| | Claims | None | NO |

2. Citations and explanations:

Claims 31-40 lack an inventive step under PCT Article 33(3) as being obvious over US 2006/0106361 A1 to Muni et al. (hereinafter 'Muni') in view of US 5,766,605 A to Sanders et al. (hereinafter 'Sanders').

Regarding claim 31, Muni discloses an apparatus comprising: an applicator configured for (a) insertion into a nostril of the patient (para [0102]), (b) placement within a nasal passageway of the patient (para [0075]), and (c) delivering a therapeutically effective amount of a drug (para [0015]) to a region of nasal tissue within the nasal cavity of the patient (para [0075]); wherein the applicator comprises an inner member and an outer member (para [0016]). Muni does not expressly disclose wherein the drug is a toxin for treating a condition associated with inflammation of a nasal membrane of a patient selected from rhinorrhea. However, Sanders discloses wherein the drug is a toxin for treating a condition associated with inflammation of a nasal membrane of a patient selected from rhinorrhea (col 2, ln 34-36). It would have been obvious to one of ordinary skill in the art to combine the disclosures of Muni and Sanders because Muni states that the substance delivered by its apparatus may be any feasible drug (para [0077]) and Sanders discloses botulinum toxin used as a drug (col 2, ln 34-38).

Regarding claim 32, Muni discloses the apparatus of claim 31, wherein the applicator further comprises an impermeable lining configured for separating the inner member and outer member (para [0016]).

Regarding claim 33, Muni discloses the apparatus of claim 31, wherein the applicator is configured to be arranged in a low volume configuration for placement within the nasal passageway and an expanded volume configuration for delivering the toxin to the nasal tissue (para [0105]).

Regarding claim 34, Muni discloses the apparatus of claim 33, wherein wherein the inner member comprises a balloon (para [0161] - 'inflatable balloon').

Regarding claim 35, while Muni does not expressly disclose the apparatus of claim 33, wherein the inner member comprises a sponge, Muni discloses an inner core that contains a substance (para [0016]) and also discloses that a substance may be loaded within a sponge (para [0010]). Therefore it would have been obvious to one of ordinary skill in the art wherein the inner member comprises a sponge.

Regarding claim 36, while Muni does not expressly disclose the apparatus of claim 35, wherein the inner member further comprises a spring element, Muni discloses wherein the inner member is capable of causing an outer layer to expand (para [0161]). Since a spring may be employed to cause an outer layer to expand, it would have been obvious to one of ordinary skill in the art wherein the inner member further comprises a spring element.

Regarding claim 37, Muni discloses the apparatus of claim 31, wherein the outer member comprises a bioresorbable coating (para [0161] - 'biodegradable').

Regarding claim 38, Muni does not expressly disclose the apparatus of claim 31, wherein the outer member comprises a balloon and a sponge. However, Muni discloses wherein the outer member elutes a substance (para [0016]) and further discloses a balloon that releases a substance (para [0095]) and a sponge that releases a substance (para [0010]). Therefore, it would have been obvious to one of ordinary skill in the art wherein the outer member comprises a balloon and a sponge.

Regarding claim 39, Muni discloses the apparatus of claim 31, wherein the inner member is configured to expand (para [0161]).

Regarding claim 40, Muni discloses the apparatus of claim 39, wherein expansion of the inner member facilitates delivery of the toxin to the nasal tissue (para [0161] - 'inflatable balloon 418 is inflated by a user. This causes stent 410 to expand'; and para [0162] - 'material of stent 410 comprises . . . one or more substances to be delivered').

(see continuation of citations and explanations in first supplemental box)

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/US 07/69391

**Supplemental Box**

In case **the space in any of the preceding boxes is not sufficient.**
Continuation of:
Box No. V(2) -- citations and explanations

Claims 44-51, 54 and 58 lack an inventive step under PCT Article 33(3) as being obvious over Sanders in view of US 2004/0009180 A1 to Donovan (hereinafter 'Donovan').

Regarding claim 44, Donovan discloses a method for delivering toxins to target cells, said method comprising: introducing a toxin to a region proximate the target cells; and applying energy to the target cells to enhance delivery of the toxins to the cells (para [0083]). Donovan does not disclose wherein the target cells are in a nasal membrane. However, Sanders discloses wherein the target cells are in a nasal membrane (col 2, ln 34-36). It would have been obvious to one of ordinary skill in the art to combine the disclosures of Donovan and Sanders because Sanders suggests delivering botulinum toxin via a topical route (col 2, ln 34-36) and Donovan describes an improved topical method to deliver botulinum toxin (para [0083]).

Regarding claim 45, Sanders discloses the method of claim 44, wherein the region comprises at least a main nasal passage (col 10, ln 17).

Regarding claim 46, Sanders discloses the method of claim 44, wherein the region comprises substantially the entire nasal cavity (col 8, ln 29 and 33).

Regarding claim 47, while Sanders does not expressly disclose the method of claim 44, wherein the region comprises the nasopharynx, it would have been obvious to one of ordinary skill in the art that the nasopharynx comprises a nasal membrane and wherein the region comprises the nasopharynx.

Regarding claim 48, while Sanders does not expressly disclose the method of claim 44, wherein the target cells comprise epithelial or goblet cells, Sanders discloses wherein the toxin is targeted to the nasal mucosa (col 2, ln 34-36). Since epithelial or goblet cells function to secrete mucus, it would have been obvious to one of ordinary skill in the art that Sanders implies wherein the target cells comprise epithelial or goblet cells.

Regarding claim 49, Donovan discloses the method of claim 44, wherein the energy is selectively applied to target cells within the region where toxin has been introduced (para [0083]).

Regarding claim 50, while Donovan does not expressly disclose the method of claim 44, wherein the energy is applied non-selectively within the region where toxin has been introduced; it would have been obvious to one of ordinary skill in the art wherein the energy is applied non-selectively within the region where toxin has been introduced.

Regarding claim 51, Sanders discloses the method of claim 44, wherein the patient suffers from or is at risk of suffering from rhinorrhea (col 2, ln 34-36).

Regarding claim 54, Sanders discloses the method of claim 44, wherein the toxin comprises botulinum toxin (col 2, ln 35-36).

Regarding claim 58, Donovan discloses the method of claim 44, wherein the energy applied to the targeted region is an electric pulse (para [0083]).

Claims 1-23 and 41-43 lack an inventive step under PCT Article 33(3) as being obvious over Muni in view of Sanders and further in view of US 1,695,107 A to Kahl (hereinafter 'Kahl').

Regarding claim 1, Muni discloses an apparatus comprising: a handle (para [0095] - 'tube or elongate shaft') comprising a proximal section, a first member (para [0095]), wherein the first member is connected at the proximal section; and an applicator tip coupled to the first member (para [0095] - 'substance reservoir');
wherein the first applicator tip are each configured for insertion into a nostril of the patient and placement within a nasal passageway of the patient (para [0075]) and wherein the first applicator tip is configured for delivering a drug (para [0077]) to a region of nasal tissue within the nasal cavity of the patient (para [0075]). Muni does not expressly disclose wherein the apparatus has a second member and a second applicator tip coupled to the second member. However, Kahl discloses a second member (col 1, ln 22-35 - 'links') and a second applicator tip coupled to the second member (col 1, ln 22-35 - 'lamps'). It would have been obvious to one of ordinary skill in the art to combine the disclosures of Muni and Kahl because Muni suggests that its apparatus may be inserted into the nasal passage (para [0075]) and Kahl discloses an apparatus that is adapted for insertion into the nasal passage (col 1, ln 1-4). Moreover, it would have been obvious to one of ordinary skill in the art that a nose has two nostrils and that each nostril may require a member and an applicator tip. Muni also does not expressly disclose wherein the drug delivered is a toxin and that toxin delivery treats the inflammation. However, Sanders discloses wherein the drug delivered is a toxin and that toxin delivery treats the inflammation (col 2, ln 34-38). It would have been obvious to one of ordinary skill in the art to combine the disclosures of Muni and Sanders because Muni states that the substance delivered by its apparatus may be any feasible drug (para [0077]) and Sanders discloses botulinum toxin used as a drug (col 2, ln 34-38).

Regarding claim 2, Kahl discloses the apparatus of claim 1, wherein the handle further comprises a spring element (col 2, ln col 65-66).

Regarding claim 3, while Kahl does not expressly disclose the apparatus of claim 2, wherein the spring element is either a v-shaped spring or closed-loop spring, it would have been obvious to one of ordinary skill in the art that a v-shaped spring or closed-loops spring may act as the 'pressure spring' disclosed in Kahl.

(see continuation of citations and explanations in second supplemental box)

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/US 07/69391

**Supplemental Box**

**In case the space in any of the preceding boxes is not sufficient.**

Continuation of:
citations and explanations from first supplemental box

Regarding claim 4, Kahl discloses the apparatus of claim 2, wherein the handle is configured to be arranged in a compressed delivery configuration for placement of the applicator tips within the nasal passageway and an expanded treatment configuration for delivering a therapeutic to the region of nasal tissue (col 2, ln 65-75) and Sanders discloses wherein the therapeutic is a toxin (col 2, ln 34-38), as discussed above.

Regarding claim 5, Sanders discloses the apparatus of claim 1, wherein each applicator tip comprises gauze (col 10, ln 16-18) but does not expressly disclose a sponge. However, it would have been obvious to one of ordinary skill in the art to substitute one absorbent material, a sponge, for another absorbent material, gauze.

Regarding claim 6, Muni discloses the apparatus of claim 5, wherein each applicator tip is configured to be arranged in a low volume delivery configuration for placement within the nasal passageway and an expanded volume treatment configuration for delivering a drug to the region of nasal tissue (para [0105]) and Sanders discloses wherein the therapeutic is a toxin (col 2, ln 34-38), as discussed above.

Regarding claim 7, Muni discloses the apparatus of claim 6, wherein each applicator tip in the expanded volume treatment configuration is adapted to fit substantially within the nasal cavity of the patient (para [0104]).

Regarding claim 8, Kahl discloses the apparatus of claim 5, wherein each applicator tip further comprises a spring element (col 1, ln 49-55; col 2, ln 56-60).

Regarding claim 9, Kahl discloses the apparatus of claim 8, wherein each applicator tip is configured to be arranged in a compressed delivery configuration for placement within the nasal passageway and an expanded treatment configuration for delivering toxin to the region of nasal tissue (col 1, ln 49-55; col 2, ln 56-60).

Regarding claim 10, Muni discloses the apparatus of claim 9, wherein each applicator tip (para [0161] - 'self-expanding stent') further comprises an actuator (para [0161] - 'hollow guide or sheath'), wherein the actuator is configured for movement from an engaged position and a retracted position (para [0161]).

Regarding claim 11, Muni discloses the apparatus of claim 10, wherein the applicator tip is in a compressed delivery configuration when the actuator is in the engaged position (para [0161] - 'self-expanding stent . . . introduced through a hollow guide or sheath into an anatomical region').

Regarding claim 12, Muni discloses the apparatus of claim 10, wherein the applicator tip is in the expanded delivery configuration when the actuator isi n the retracted position (para [0161] - 'Stent may be pushed out of the hollow sheath or guide').

Regarding claim 13, Muni discloses the apparatus of claim 10, further comprising an engagement element, wherein the engagement element is configured to control the movement of an actuator (para [0161] - 'pusher'). Muni does not expressly disclose wherein the engagement element controls the movement of both actuators simultaneously. However, since toxin is being delivered into both nostrils, it would have been obvious to one of ordinary skill in the art wherein the engagement element controls the movement of both actuators simultaneously.

Regarding claim 14, Muni discloses the apparatus of claim 5, wherein each applicator tip further comprises an impermeable lining (para [0016]).

Regarding claim 15, Sanders discloses the apparatus of claim 1, wherein each applicator tip further comprises a muco-adhesive pad (col 10, ln 18 - 'gauze').

Regarding claim 16, Muni discloses the apparatus of claim 1, wherein the toxin is carried by a bioresorbable coating (para [0010]).

Regarding claim 17, Muni discloses the apparatus of claim 1, further comprising an infusion channel for delivering the dug to the applicator tips (para [0107] - 'substance introducing lumen') and Sanders discloses wherein the therapeutic is a toxin (col 2, ln 34-38), as discussed above.

Regarding claim 18, Muni discloses the apparatus of claim 17, further comprising an access port, wherein the apparatus is in fluid communication with a drug source via the access port (para [0107]) and Sanders discloses wherein the therapeutic is a toxin (col 2, ln 34-38), as discussed above.

Regarding claim 19, Sanders discloses the apparatus of claim 17, wherein the applicator tips are configured to receive the toxin prior to being positioned in the nasal passageway (col 10, ln 17-18 - 'gauzed soaked with a saline solution of botulinum toxin').

Regarding claim 20, Muni discloses the apparatus of claim 17, wherein the applicator tips are configured to receive the toxin after being positioned in the nasal passageway (para [0095]).

Regarding claim 21, Sanders discloses the apparatus of claim 1, wherein the toxin comprises a liquid (col 10, ln 18 -'solution').

Regarding claim 22, Sanders discloses the apparatus of claim 1, wherein the toxin comprises botulinum toxin (col 10, ln 18).

Regarding claim 23, Sanders discloses the apparatus of claim 22, wherein the botulinum toxin is botulinum toxin D (col 10, ln 18).

(see continuation of citations and explanations in third supplemental box)

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**Supplemental Box**

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Regarding claim 41, Muni discloses an apparatus comprising: a handle (para [0095] - 'tube or elongate shaft') comprising a proximal section, a first member (para [0095]), wherein the first member is connected at the proximal section; and an applicator tip coupled to the first member (para [0095] - 'substance reservoir');
wherein the first applicator tip are each configured for insertion into a nostril of the patient and placement within a nasal passageway of the patient (para [0075]) and wherein the first applicator tip is configured for delivering a drug (para [0077]) to a region of nasal tissue within the nasal cavity of the patient (para [0075]). Muni does not expressly disclose wherein the apparatus has a second member and a second applicator tip coupled to the second member. However, Kahl discloses a second member (col 1, ln 22-35 - 'links') and a second applicator tip coupled to the second member (col 1, ln 22-35 - 'lamps'). It would have been obvious to one of ordinary skill in the art to combine the disclosures of Muni and Kahl because Muni suggests that its apparatus may be inserted into the nasal passage (para [0075]) and Kahl discloses an apparatus that is adapted for insertion into the nasal passage (col 1, ln 1-4). Moreover, it would have been obvious to one of ordinary skill in the art that a nose has two nostrils and that each nostril may require a member and an applicator tip. Muni also does not expressly disclose wherein the drug delivered is a toxin and that the toxin treats a condition associated with inflammation of a nasal membrane of a patient selected from rhinorrhea. However, Sanders discloses wherein the drug delivered is a toxin and that the toxin treats a condition associated with inflammation of a nasal membrane of a patient selected from rhinorrhea (col 2, ln 34-38). It would have been obvious to one of ordinary skill in the art to combine the disclosures of Muni and Sanders because Muni states that the substance delivered by its apparatus may be any feasible drug (para [0077]) and Sanders discloses botulinum toxin used as a drug (col 2, ln 34-38).

Regarding claim 42, Kahl discloses the apparatus of claim 41, further comprising a spring element, wherein the spring element is configured to provide the applicator tips with an outward bias with the applicator tips are placed within the nasal passageway (col 1, ln 49-55; col 2, ln 56-60).

Regarding claim 43, while Kahl does not expressly disclose the apparatus of claim 42, wherein the outward bias presses each applicator tip against a turbinate in the nasal cavity, Kahl discloses wherein the springs exert pressure on the inner walls of the nose (col 2, ln 56-60). Since the nasal turbinates are the walls of the nasal cavity, it would have been obvious to one of ordinary skill in the art wherein the outward bias presses each applicator tip against a turbinate in the nasal cavity.

Claims 52-53 and 55-57 lack an inventive step under PCT Article 33(3) as being obvious over Sanders in view of Donovan and further in view of US 2005/0152924 A1 to Voet (hereinafter 'Voet').

Regarding claim 52, neither Sanders nor Donovan discloses the method of claim 44, wherein the patient suffers from or is at risk of suffering from sinus headaches. However, Voet discloses wherein the patient suffers from or is at risk of suffering from sinus headaches (para [0074]). It would have been obvious to one of ordinary skill in the art to combine the disclosure of Voet with the combination of Sanders and Donovan because Voet expressly makes reference to Sanders (para [0043]) and sinus headaches are a common ailment for which a therapeutic composition is used.

Regarding claim 53, Voet discloses the method of claim 44, wherein the patient suffers from or is at risk of suffering from migraine headaches (para [0043]).

Regarding claim 55, Voet discloses the method of claim 54, wherein the toxin is a fragment of botulinum toxin (para [0065]).

Regarding claim 56, Voet discloses the method of claim 55, wherein the fragment is a light chain fragment of botulinum toxin (para [0065] and [0013]-[0014]).

Regarding claim 57, Voet discloses the method of claim 56, wherein the light chain fragment is derived from at least one of botulinum toxins A, B, C, D, E, F and G (para [0055]).

Claims 59-67 lack an inventive step under PCT Article 33(3) as being obvious over Sanders in view of Donovan and further in view of US 2005/0107853 A1 to Krespi et al. (hereinafter 'Krespi').

Regarding claim 59, Donovan discloses the method of claim 58, wherein the energy applied to the target region is an electric pulse (Donovan para [0083]), but does not expressly disclose wherein the electric pulse is applied from between 1V to 500V. However, Krespi discloses wherein the electric pulse is applied from between 1V to 500V (para [0109] - '0.1 to about 5 J/cm2'). It would have been obvious to one of ordinary skill in the art to combine the disclosure of Krespi with the combination of Sanders and Donovan because Sanders suggests delivering botulinum toxin to the nasal passages (col 2, ln 34-36), Donovan describes an improved method for delivering botulinum toxin that uses application of energy (para [0083]), and Krespi discloses application of energy to the nasal passages (para [0037]).

Regarding claim 60, Krespi discloses the method of claim 58, wherein the electric pulse is an RF signal (para [0115]).

Regarding claim 61, Krespi discloses the method of claim 58, wherein the electric pulse is pulsed for durations between 5 microseconds to 100 milliseconds (para [0108]).

Regarding claim 62, Krespi discloses the method of claim 58, wherein the electric pulse is produced by a DC power source (para [0060]).

Regarding claim 63, Krespi discloses the method of claim 58, wherein the electric pulse is produced by an AC power source (para [0060]).

(see continuation of citations and explanations in fourth supplemental box)

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**Supplemental Box**

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Regarding claim 64, Donovan discloses the method of claim 44, wherein the energy applied to the target region is ultrasonic (para [0081]).

Regarding claim 65, Krespi does not expressly disclose the method of claim 44, wherein the energy applied to the targeted region is an x-ray beam, but discloses using electromagnetic energy (para [0037]. Since x-rays are a form of electromagnetic energy, it would have been obvious to one of ordinary skill in the art wherein the energy applied to the targeted region is an x-ray beam.

Regarding claim 66, Donovan discloses the method of claim 44, wherein the energy applied to the target region is ultrasonic (para [0081]) but does not expressly disclose focused ultrasound. However, it would have been obvious to one of ordinary skill in the art wherein the ultrasound used in the method is focused ultrasound.

Regarding claim 67, Krespi discloses the method of claim 44, wherein the energy applied to the targeted region is microwave (para [0115]).

Claims 68-78 lack an inventive step under PCT Article 33(3) as being obvious over Sanders in view of Donovan and further in view of Muni.

Regarding claim 68, neither Sanders nor Donovan discloses the method of claim 44, wherein the toxin is introduced to the target region through a catheter. However, Muni discloses wherein the toxin is introduced to the target region through a catheter (para [0095]). It would have been obvious to one of ordinary skill in the art to combine the disclosure of Muni with the combination of Sanders and Donovan because Muni states that the substance delivered by its apparatus may be any feasible drug (para [0077]) and Sanders discloses botulinum toxin used as a drug (col 2, ln 34-38).

Regarding claim 69, Muni discloses the method of claim 68, wherein the toxin is introduced through a balloon on the catheter (para [0095]).

Regarding claim 70, Muni discloses the method of claim 69, wherein the balloon is porous and the toxin is introduced through the balloon (para [0095]).

Regarding claim 71, Muni discloses the method of claim 68, wherein the toxin is introduced through a needle on the catheter (para [0014]).

Regarding claim 72, neither Sanders nor Donovan discloses the method of claim 68, wherein the toxin is introduced to the target region through a catheter. However, Muni discloses a catheter (para [0095]) and Sanders suggests aerosolizing the toxin (col 2, ln 45). Therefore it would have been obvious to one of ordinary skill in the art wherein the toxin is aerosolized from the catheter. It would have been obvious to one of ordinary skill in the art to combine the disclosure of Muni with the combination of Sanders and Donovan because Muni states that the substance delivered by its apparatus may be any feasible drug (para [0077]) and Sanders discloses botulinum toxin used as a drug (col 2, ln 34-38).

Regarding claim 73, neither Sanders nor Donovan discloses the method of claim 68, wherein energy is applied from a source on the catheter. However, Donovan suggests applying energy from a source close to the source for introducing the toxin (para [0081]). Muni discloses wherein the source for introducing the toxin is a catheter (para [0095]). Therefore it would have been obvious to one of ordinary skill in the art wherein energy is applied from a source on the catheter. It would have been obvious to one of ordinary skill in the art to combine the disclosure of Muni with the combination of Sanders and Donovan because Muni states that the substance delivered by its apparatus may be any feasible drug (para [0077]) and Sanders discloses botulinum toxin used as a drug (col 2, ln 34-38).

Regarding claim 74, neither Sanders nor Donovan discloses the method of claim 73, wherein acoustic energy is applied from a transducer on the catheter. However, Donovan suggests applying energy from a source close to the source for introducing the toxin (para [0081]) and also discloses wherein the energy is in the form of ultrasound (para [0081]). Muni discloses wherein the source for introducing the toxin is a catheter (para [0095]). Therefore it would have been obvious to one of ordinary skill in the art wherein acoustic energy is applied from a transducer on the catheter. It would have been obvious to one of ordinary skill in the art to combine the disclosure of Muni with the combination of Sanders and Donovan because Muni states that the substance delivered by its apparatus may be any feasible drug (para [0077]) and Sanders discloses botulinum toxin used as a drug (col 2, ln 34-38).

Regarding claim 75, neither Sanders nor Donovan discloses the method of claim 74, wherein electrical energy is applied from an electrode on the catheter. However, Donovan suggests applying energy from a source close to the source for introducing the toxin (para [0081]) and also discloses wherein the energy is in the form of electricity (para [0083]). Muni discloses wherein the source for introducing the toxin is a catheter (para [0095]). Therefore it would have been obvious to one of ordinary skill in the art wherein electrical energy is applied from an electrode on the catheter. It would have been obvious to one of ordinary skill in the art to combine the disclosure of Muni with the combination of Sanders and Donovan because Muni states that the substance delivered by its apparatus may be any feasible drug (para [0077]) and Sanders discloses botulinum toxin used as a drug (col 2, ln 34-38).

Regarding claim 76, Donovan discloses the method of claim 44, wherein the energy is delivered from a source external to the patient (para [0082] - 'to the skin').

Regarding claims 77 and 78, Donovan discloses the method of claim 76, wherein the energy is ultrasound (para [0081]-[0082]), therefore it would have been obvious to one of ordinary skill in the art wherein the source is an acoustic energy transducer and wherein the acoustic energy transducer is a focused ultrasound transducer.

(see continuation of citations and explanations in fourth supplemental box)

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**Supplemental Box**

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Claims 24-25 lack an inventive step under PCT Article 33(3) as being obvious over Muni in view of Sanders and in view of Kahl and further in view of Voet.

Regarding claim 24, Sanders discloses the apparatus of claim 22, wherein the toxin comprises botulinum toxin (col 10, ln 18). Muni, Kahl and Sanders fail to expressly disclose wherein the toxin is a fragment of botulinum toxin. However, Voet discloses wherein the toxin is a fragment of botulinum toxin (para [0065]). It would have been obvious to one of ordinary skill in the art to combine the disclosure of Voet with the combination of Muni, Kahl and Sanders because Voet expressly references Sanders (para [0043]).

Regarding claim 25, Voet discloses the apparatus of claim 24, wherein the fragment is a light chain fragment of botulinum toxin (para [0065] and [0013]-[0014]).

Claims 26-28 and 30 lack an inventive step under PCT Article 33(3) as being obvious over Muni in view of Sanders and in view of Kahl and in view of Voet and further in view of Donovan.

Regarding claim 26, Kahl discloses the apparatus of claim 25, further comprising an energy delivery applicator configured for delivering energy to the region of nasal tissue (col 1, ln 22-35). Kahl does not expressly disclose wherein the delivery of energy enhances delivery of the toxin. However, Donovan discloses wherein the delivery of energy enhances delivery of the toxin (para [0081]-[0083]). It would have been obvious to one of ordinary skill in the art to combine the disclosure of Donovan with the combination of Muni, Kahl, Sanders and Voet because Kahl discloses delivery of energy to nasal tissues (col 1, ln 22-35) and Donovan discloses an advantage of that energy delivery (para [0081]-[0083]).

Regarding claim 27, Donovan discloses the apparatus of claim 27, wherein the energy delivery applicator is adapted to deliver energy under conditions which cause poration of at least one cell in the region of nasal tissue (para [0081] - 'permeablilizes the skin').

Regarding claim 28, Donovan discloses the apparatus of claim 26, wherein the energy delivery applicator is adapted to deliver an electric pulse (para [0083]).

Regarding claim 30, Donovan discloses the apparatus of claim 26, wherein the energy delivery is adapted to deliver ultrasound energy (para [0081]-[0082]).

Claim 29 lacks an inventive step under PCT Article 33(3) as being obvious over Muni in view of Sanders and in view of Kahl and in view of Voet and in view of Donovan and further in view of Krespi.

Regarding claim 29, Donovan discloses the apparatus of claim 28, wherein the energy delivery applicator is adapted to deliver an electric pulse (para [0083]). Donovan does not expressly disclose wherein the pulse is an RF signal. However, Krespi discloses wherein the pulse is an RF signal (para [0115]). It would have been obvious to one of ordinary skill in the art to combine the disclosure of Krespi with the combination of Kahl, Sanders, Voet and Donovan because Sanders suggests delivering botulinum toxin to the nasal passages (col 2, ln 34 -36), Donovan describes an improved method for delivering botulinum toxin that uses application of energy (para [0083]), and Krespi discloses application of energy to the nasal passages (para [0037]).

Claims 1-78 have industrial applicability as defined by PCT Article 33(4) because the subject matter can be made or used in industry.

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| 9 | Non Patent Literature | Z-ESR-SO-06-18-10-EP-07784000-7.pdf | 284121<br>c861c0a63ae74dc0d2dcae0e530374ab5c3b0b4b | no | 8 |

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(54) **Title:** TREATMENT OF MAMMALIAN PHYSIOLOGICAL REACTION OF IgE ANTIBODIES PRESENT IN SAID MAMMAL UPON CONTACT WITH THE CORRESPONDING ANTIGEN

(57) **Abstract:** A method is disclosed for blocking or reducing physiological reaction in a mammal to the interaction of IgE antibodies present in said mammal upon contact with the corresponding antigen, by the administration to said mammal of a therapeutically effective amount of a neurotoxin (CnT) derived from Clostridia sp.

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# TREATMENT OF MAMMALIAN PHYSIOLOGICAL REACTION OF IgE ANTIBODIES PRESENT IN SAID MAMMAL UPON CONTACT WITH THE CORRESPONDING ANTIGEN.

## FIELD OF THE INVENTION

A method is disclosed for blocking or reducing physiological reaction in a mammal to the interaction of IgE antibodies present in said mammal upon contact with the corresponding antigen, by the administration to said mammal of a therapeutically effective amount of a neurotoxin (CnT) derived from Clostridia sp.

## BACKGROUND OF THE INVENTION

Throughout this application various publications are referred to within parentheses or by footnote. The contents of these publications are hereby incorporated by reference in their entirety.

### Introduction

The physiological reaction in a mammal to the interaction of IgE antibodies present in said mammal upon contact with the corresponding antigen is generally referred to as allergy. It is believed that the allergic response evolved to combat infections with parasites. As parasitic infections are rare in industrialized countries this mechanism becomes pathologic in certain susceptible (atopic) individuals. Characteristic of allergies is that the antigen, also called the allergen, is normally innocuous, and the body's reaction is inappropriate.

Allergic reactions can involve all body tissues but are most prominent in the boundaries with the external environment: the airway, eye, gastrointestinal tract and skin. The conditions are known as allergic rhinitis in the nose (hay fever), allergic asthma in the lungs, food allergies in the GI tract and allergic hypersensitivity (hives) or dermatitis in the skin. Anaphylaxis refers to the systemic reaction that occurs when an allergen is introduced directly into the circulation, such as occurs with injection of drugs and insect stings. A massive early phase reaction occurs throughout the body. Symptoms include diffuse airway swelling and hypotension which can be life threatening.

Each year more than 50 million Americans suffer from allergic diseases, costing the health care system $18 billion annually (American Academy of Allergy,

Asthma and Immunology (AAAAI). The Allergy Report: Science Based Findings on the Diagnosis & Treatment of Allergic Disorders, 1996-2001)

Alarmingly, the prevalence and severity of allergic disorders has rapidly increased in the United States over the past twenty years, so there is a need for new therapies for these conditions.

In 1998, an estimated 15 million Americans, or 6.4 percent of the population, had asthma, with 5 million being children. Children account for 4.8 million of Americans with asthma. Each year, 1.8 million emergency room visits are for asthma, nearly 500,000 Americans are hospitalized and more than 5,000 die from the disease. Although asthma deaths are infrequent, they have increased significantly during the last two decades. From 1975-1979, the death rate was 8.2 per 100,000 people. That rate jumped in 1993-1995 to 17.9 per 100,000. Asthma cost the U.S. economy an estimated $10.7 billion in 1994, including a direct health care cost of $6.1 billion and indirect costs, such as lost workdays, of $4.6 billion.

Approximately 16.7 million office visits to health care providers each year are attributed to allergic rhinitis alone (CDC. Fast Stats A-Z, Vital and Health Statistics, Series 10, no. 13. 1999

A related condition, chronic sinusitis, is the most commonly reported chronic disease, affecting 12.6 percent of people (approximately 38 million) in the United States in 1996. Another related condition, serous otitis media, is the most common condition in children requiring an office visit to a health care provider.

Atopic dermatitis is one of the most common skin diseases, particularly in infants and children. The estimated prevalence in the United States is 9 percent[1] Rudikoff D and Lebwohl M. "Atopic dermatitis." Lancet 351(9117): 1715-21. 1998[i]

Experts estimate that food allergy occurs in 8 percent of children 6 years of age or under, and in 1 to 2 percent of adults Sampson HA. In Allergy, Principles and Practice, 5th Ed., E. Middleton et al, ed. Mosby, St. Louis, p. 1162. 1998[ii].

**Pathophysiology of allergy**

Allergy is an ailment that affects millions of individuals worldwide. Attempts to desensitize an individual against a material that causes an allergic response (hereafter designated as an "allergen") by injection of measured dosages of the allergen heretofore has failed to achieve complete relief of allergy symptoms reproducibly in all allergic individuals. An allergic response is a term of art and has a well-defined meaning. Within the context of the present invention, an allergic or reagenic response includes, in particular, at least one of the features of 1.) production of an abnormally high level of IgE in an individual's serum, 2.) immunologic interaction between an allergen, an individual's IgE and leukocytes resulting in release of histamines, 3.) production of hives, rashes, wheal and flare and similar dermatological manifestation of hypersensitivity, and 4.) anaphylaxis.

An allergic response is a state of hypersensitivity in which an exaggerated immune response is induced by the exposure to a particular antigen or allergen. Hypersensitivity reactions can be classified as immediate or delayed. Immediate or type I hypersensitivity (or anaphylactic response) is an allergic reaction which develops very quickly, i.e., within seconds or minutes of exposure of the patient to the causative allergen, and it is mediated by IgE antibodies produced by B lymphocytes. In non-allergic patients, there is no IgE antibody of clinical relevance. However, in a person suffering with allergic diseases, IgE antibody mediates immediate hypersensitivity by sensitizing mast cells which are abundant in the skin, membranes of the eye, nose and mouth, and in the respiratory tract and intestines.

IgE secreted from activated B cells can attach to Fc receptors located on the surface of mast cells and basophil granulocytes, which contain numerous cytoplasmic granules packed with chemical mediators e.g. histamine (J. Klein, "Immunology", Blackwell Sci. Pub., London, 1990; E. Benjamini & S. Leskowitz, "Immunology", Wiley-Liss, N.Y. 1991). This receptor binds circulating IgE with very high affinity and retains it at the mast cell surface for extended periods of time. Activation is accomplished through the binding of an allergen simultaneously to more than one polyvalent molecule of Fc receptor-bound IgE. This "cross linking" of at least two surface-bound IgE molecules brings Fc receptor proteins into close association with one another in the plane of the mast cell plasma membrane. When the bound IgE is contacted by the appropriate allergen, the mast cell becomes

activated. Kinases associated with these receptors become activated as a result of this proximity. They initiate the second messenger cascade, which results in the fusion of the granules with the cell surface membrane, leading to the exocytosis of the granule contents, such as histamine, cytokines, and leukotrienes into the surrounding tissue, and the concomitant induction of allergic symptoms. It is the activity of these substances which is responsible for the clinical symptoms typical of immediate hypersensitivity. These include contraction of smooth muscle in the airways or the intestine, the dilation of small blood vessels and the increase in their permeability to water and plasma proteins, the secretion of thick sticky mucus, and in the skin, , swelling and the stimulation of nerve endings that results in itching.

Delayed type hypersensitivity (DTH) reactions are mediated by T-cells and macrophages and become evident only after 1 to 2 days and persist from several days to a few weeks. DTH is also referred to as cell-mediated hypersensitivity (i.e., T-cell mediated) and is part of a larger group of reactions called cell-mediated immunity.

Anaphylaxis, or anaphylactic shock, is an acute systemic (whole body) type of allergic reaction, It occurs when a person has become sensitized to a certain substance or allergen (that is, the immune system has been abnormally triggered to recognize that allergen as a threat to the body). On the second or subsequent exposure to the substance, an allergic reaction occurs. This reaction is sudden, severe, and involves the whole body. Anaphylaxis is life-threatening and can occur at any time.

Therapeutically, many agents are used to try to prevent the release of mediators from mast cells and basophils and/or to treat the downstream events by blocking or ameliorating the effects of the mediators on target tissues. Therapeutic agents commonly employed fall under the following main groups.

Antihistamines block and mop up the released histamine, i.e. the major mediator of the allergic response.

01 02 agonists, e.g., Epinephrine, Salbutamol overcome indirectly the downstream effects on vasculature and smooth muscle.

Chromoglycate is useful for primary prevention of mast cells/basophil degranulation.

This prophylactic must be taken continuously. It does not prevent the cross-linking of IgE but it somehow interferes with subsequent events. Theophylline and other phosphodiesterase inhibitors again influence downstream biochemical events particularly associated with cyclic nucleotides. Steroids have multiple sites of activities against the allergic response. They are either administered locally and/or systematically/ systernically.

None of the above treatments are ideal for the modulation of allergic responses because each has specific problems such as side effects including drowsiness, they also lack specificity in the immune system leading to global immuno-suppression. Also many of these therapeutic agents need to be administered continuously. Therefore, new improved treatments are constantly being sought to control the allergic response prophylactically and/or therapeutically without the above-mentioned limitations.

Individuals who wish to become desensitized against an allergen often must submit himself/herself to injections of measured doses of the allergen, first administered at weekly or biweekly intervals, then gradually decreases to bimonthly or monthly intervals throughout the year. Such injections generally commence with a small dose of the allergen and then gradually increasing the dosage until a maximally-tolerated maintenance dose is achieved. The individual is then kept on a maintenance dose of the allergen for long periods of time or until the individual no longer exhibits an allergic reaction to the allergen.

Other treatment regimes have been devised to reduce or eliminate an allergic response.

Allergen injection therapy (allergen immunotherapy also known as subcutaneous immunotherapy (SCIT) is known to reduce the severity of allergic rhinitis. This treatment is theorized to involve the production of a different form of antibody, a protective antibody which is termed a "blocking antibody" (Cooke, RA et al., Serologic Evidence of Immunity with Coexisting Sensitization in a Type of Human Allergy, Exp. Med. 1935; 62:733). Chemical agents have been developed which inhibit the interactions between the IgE and its receptor (Cheng et al., U.S. Patent No. 5,965,605 and Ra et al., U.S. Patent No. 6,090,034). IgE antagonists have also been used to treat allergic disease (Presta et al., U.S. Patent No 5,965709) and compounds that exhibit immunosuppressive activity and inhibits the release of

histamine (Bycroft et al., U.S. Patent No. 5,969,158). St. Remy et al., U.S. Patent No. 4,740,371, discloses an immune complex of an allergen for treating allergies involving a combination of the specific allergen and the corresponding antibody to that allergen. The injection of the complex into a patient is said to reduce a patient's allergic reaction to that specific allergen. Others have suggested that certain human proteins can neutralize IgE by blocking it from interacting with the mast cells, but this has not been established clearly as a clinically effective therapy (Stanworth, et al., Allergy Treatment with a Peptide Vaccine, Lancet 1990; 336:1279-81). Patterson et al., U.S. Patent No. 5,314,690 disclosed a method and preparations for reducing IgE antibodies to allergens in allergic subjects wherein substance P (a neuropeptide) and an allergen or fragments of allergens or haptens acting as allergens are administered together to the allergic subjects through a non-oral route.

Cholera Toxin and B Subunit as Adjuvants Cholera toxin (CT) and the closely related heat-labile toxin (LT) from Escherichia coli are known as exceptionally potent immunoadjuvants when co-administered with antigens by various mucosal routes (Elson et al., J. humunol. 1984; 133:2892-2897; Hohngren et al., Vaccine 1973; 1 1: 1 179-1184; Lycke et al, Eur. J. Immunol. 1992; 22:2277-228 1. Both CT and LT are recognized as "AB" toxins in that they are composed of two distinct structural and functional components: a single toxic-active A subunit component and a non-toxic cell-binding B subunit. The latter is a honiopentamer component with strong binding affinity for GMI ganglioside receptors (Holingren et al., Nature 19 8 1; 292:413 -417). Such receptors are known to be present on most mammalian cells, e.g., on skin and other epithelial cells, on all known antigen-presenting cells including dendritic cells (DC) and Langerhan's cells (LC), as well as on B and T lymphocytes. Recently, Gleim et al., U.S. Patent No. 5,980,898 disclosed a system for transcutaneous immunization that induces an immune response (e.g., humoral and/or cellular effectors) in an animal or human. The system provides a simple application to intact skin of both rodents and humans of a formulation comprised of antigen and an adjuvant that was whole cholera toxin.

Common to allergies is the involvement of the IgE class of antibody. Individuals are not born with allergies; rather they acquire them by exposure to allergens. The steps of the IgE allergic reaction are sensitization upon first exposure to the allergen, and then the allergic response to subsequent exposures. The allergic response consists of an immediate and delayed response referred to as the early

and late phase responses respectively. In atopic individuals, those prone to allergies, the initial exposure to an antigen results in the production of IgE antibodies that specifically recognize that allergen. This process is called sensitization.

The early phase response (ERP) is the immediate reaction that occurs within minutes of exposure to an allergen. IgE are bound to the surface of a neuroimmune cell called the mast cell (in the circulation these cells are called basophils). Sufficient numbers of bound IgE antibodies that react with an allergen causes the mast cell to release its content of secretory vesicles, a process known as degranulation. The secretory vesicles contain histamine and other stored substances such as nerve growth factor (NGF). In addition the mast cell and T cells immediately begin manufacturing leukotrienes, cytokines, enzymes and substances that activate blood platelets and attract secondary cells such as eosinophils. Symptoms vary depending on the site, but common reactions are smooth muscle contraction, mucus secretion, vascular permeability, and sensory nerve stimulation.

The late phase response (LPR) develops over hours to days of exposure as eosinophils and other cells are attracted to the area. Eosinophils produce major basic protein, eosinophil cationic protein, leukotrienes and nerve growth factor. TH2 lymphocytes release cytokines that promote further IgE production and eosinophil chemo attraction, and increased numbers of mast cells.

**Nerve involvement in allergy**

The sensory nerve stimulation causes reflexes that are designed to aid in defending the tissue. These reflexes are often a larger problem then the local allergic response. Reflexes can range from large gross motor actions to regional afferent and efferent arcs or even local axon-axonal reflexes involving a single neuron.

Some reflexes recruit major motor actions that are well recognized. In the nose sneezing is a reflex attempt to expel unwanted material and coughing is the equivalent response in the lungs.

Regional reflex arcs involve the sensing of the stimulus by the sensory neuron, the transfer of the message to the ganglia and the central nervous system and an efferent response via autonomic neurons. Reflex excitation by the autonomic nervous system directly causes mast cell to degranulate, thereby spreading the reaction. In addition these reflexes control a variety of other functions. In the nose

these reflexes cause increased mucus production, increased cilia movement, nasal congestion and sneezing. In the lungs reflexes cause bronchospasm, increased mucosal congestion, production of airway secretions and coughing. In the GI tract reflexes cause dysmotility, mucosal congestion and secretions. In the skin the reflexes cause swelling and itching.

Finally there are local axon-axonal reflexes in sensory nociceptive nerve fibers. Allergic stimulation of a single neuron causes release of mediators from other axons of the same neuron. (Barnes P et al. 1991 Neuropeptides in the respiratory tract. Am Rev Resp Dis 144:1187-1198, 1391-1399)

In chronic allergic stimulation the mast cells and eosinophils releases nerve growth factor which causes growth of the nerves in the region. Thereby allowing for increased neural responses and hyper reactivity. This hyper reactivity is not limited to allergic reactions but extends to non-allergic conditions such as respiratory tract infections including viral and bacterial infections. Specifically viral rhinitis, viral and bacterial sinusitis, suppurative otitis media, bronchitis and pneumonia. Therefore individuals become more susceptible to these conditions and have more frequent and severe infections.

Furthermore the repeated allergic reactions cause changes in the qualitative response of the neural reflexes such that they are inappropriately activated. This negatively effects non-allergic conditions, such as bronchospasm mucus production and coughing in non-allergic lung conditions such as bronchitis and emphysema.

**Allergic reactions differ from inflammatory reactions**

Allergic reactions differ from inflammation. Allergies represent the body's inappropriate response to what is in essence a harmless antigen. It is believed that the IgE allergic reactions evolved to combat parasitic infections which are now rare in industrialized societies. In contrast, inflammation is the body's response to actual tissue damage or infection. Inflammation is clinically distinguished by the classical symptoms of calor, rubor and dolor: heat, redness and pain. Inflammation is a process that triggers a cascade of mediators with wide effects, both locally and systemically. Local reactions include pain, vasodilation and migration of macrophages and neutrophils. Systemic reactions include fever. Certain conditions, such as rhinitis or asthma, can be triggered by allergies, infections, irritating

chemicals or may be entirely neurogenic, the result of nerve activity without prior inflammatory or allergic stimulation.

**Specific Allergic Conditions**

**Rhinitis**

**Allergic rhinitis**

The inner lining of the nose is a mucosa that contains serous and mucus glands and large numbers of mast cells. This mucosa extends to the openings leading to the sinuses as well as the Eustachian tube where it is continuous with the mucosa of the sinuses and middle ear, respectively. The EPR of the nasal mucosa causes mast cell degranulation. The release of histamine, heparin and neuropeptides provokes vasodilation and acute swelling of the mucosa and has some minor direct stimulatory effect on the mucus secreting glands. Reflex excitation causes reflex sneezing, congestion and neural stimulation of the seromucinous glands and further congestion. LPR attracts eosinophils and prolongs the reaction.

Allergic reactions can also be chronic, a condition known as perennial rhinitis. In these cases airborne allergens are constantly in the environment. Chronic low-level allergic reactions cause a thickening of the nasal mucosa due to edema and hypertrophy of glandular elements. As a result the primary symptoms of perennial rhinitis are nasal congestion, and postnasal drip. After each allergic reaction the mucosa swells; repeated allergic reactions enlarges the mucosa permanently and may form polyps. Thickening of the mucosa can cause obstruction of the small openings that allow drainage from the sinus. Obstruction of these openings allows nasal secretions to collect and become infected, thereby causing sinusitis.

Topical treatment of allergic rhinitis includes steroid sprays and chromalyn sodium (Nasocrom®) a chemical that blocks mast cell degranulation, and/or nasal decongestants (Neosynephrine). Systemic treatment includes oral anti-histamines and non-sedating antihistamines (Allegra®, Zyrtec®, Claritin®). Long-term therapy requires immune desensitization to the allergen by progressive intradermal injections of the allergen over months to years. rhinitis can lead

Allergic rhinitis can lead to pulmonary disease, including but not limited to asthma and emphysema, suitably asthma caused by hyperreactivity and/or the

symptoms of bronchoconstriction, mucosal edema, increased secretions and cough. These can be treated by the application of CnT to the nasal cavity of patients with allergic rhinitis. It is well known in the art that allergic conditions of the nose can cause reflex changes in the lung that mimic or exacerbate asthma. (McCusker C et al 2002, Site-specific sensitization in a murine model of allergic rhinitis: Role of the upper airway in lower airway disease, J Allergy Clin Immunol, 110:891-898)

**Perennial allergic rhinitis**

Perenial rhinitis is a chronic condition and certain symptoms, such as nasal congestion, are more prominent then others such as sneezing. Therefore therapy for this condition needs to be over more prolonged period, if not indefinitely. Although the same treatments as disclosed for seasonal allergic rhinitis can be used repeatedly, certain method of treatment asre disclosed here that are more efficient and convenient for longer term therapy.

Parasympathetic neurons do not extend from the central nervous system to their target organs in the nose. Instead parasympathetic preganglionic neurons have their cell bodies in the brain stem and have an axon that extends partway and synapses on the cell body of a second neuron called the postganglionic neuron. The axons of the postganglionic neurons extend into nose and sinuses and modulate many of the biological responses seen during allergic reactions. The cell body of the post ganglionic parasympathetic neuron also receives collateral afferent synapses from sensory neurons that are stimulated during allergic reactions. Therefore much of the neuronal circuit involved in the allergic reaction converges onto the cell body of the postganglionic neuron.

All of the postganglionic neuron cell bodies are concentrated in small structure called the sphenopalatine ganglion. Moreover all afferent synaptic connections on these neurons is cholinergic, the neurotransmitter most sensitive to BoNT. Therefore application of CnT to the sphenopalatine ganglion is the most efficient way of blocking the allergic neural reaction.

The sphenopalatine ganglion is accessible to needle injection via the sphenopalatine canal. This canal passes though the hard palate and is accesible about one centimeter medial to the the second molar. Injections of anesthetic and

vasoconstrictor agents are commonly performed by clinicians skilled ion the art of nasal surgery.

**Infectious rhinitis**

Although they share some of the same symptoms, allergic rhinitis differs from infectious rhinitis. The most common cause of infectious rhinitis is a viral infection, known as the common cold. Bacterial and fungal infections of the nose occur also but these are comparatively rare as primary events. During viral infections the epithelial cells release secretions that trigger an inflammatory response. The classic signs of caldor, rubor and dolor; heat, redness, and pain characterize inflammation. White blood cells such as macrophages and neutrophils migrate from small blood vessels in the area to the infected mucosa. These cells in turn release a variety of chemical mediators that increase the inflammation. Infectious rhinitis is characterized by a purulent or pus like postnasal drip, and nasal congestion. In many viral infections there are systemic symptoms such as fever. Treatment of viral infectious is symptomatic with topical and systemic decongestants, and antipyretic and anti-inflammatory drugs.

**Vasomotor and other causes of rhinitis**

Vasomotor rhinitis is strictly a neural hyper stimulation of the serous secretory glands of the nose. This condition is characterized by a watery nasal discharge with a very small content of mucus. Vasomotor rhinitis results directly from neural stimulation of temperature changes or while eating, and associated other symptoms such as congestion, and sneezing are not prominent. US 5,766, 605 discloses a method of blocking the symptom of rhinorrhea in vasomotor rhinitis using clostridia neurotoxins.

**Serous otitis media**

Direct reaction of the middle ear mucosa to allergens, or indirect effects by blockage of the Eustachian tube, leads to serous otitis media. In this condition the middle ear fills with fluid and hearing is impaired. As this condition most often affects young children they are risk of learning disabilities due to the decreased hearing acuity.

**Sinusitis, a complication of rhinitis**

Sinusitis is an infection of the sinuses. The sinuses are air filled cavities surrounding and opening into the nasal cavity via small openings called ostia. The maxillary sinuses compose the mass of the cheeks and the ostia are between the inferior and middle turbinate. The frontal sinuses are above the brow underneath the skin of the forehead, they open into the nasal cavity via a duct that enters beneath the middle turbinate. The sphenoid sinuses are in the nasopharynx and have ostia on their anterior surface. The ethmoid sinuses are located between the eyes and are composed of numerous small air cells. The anterior and posterior cells drain independently. The anterior ethmoid region is especially important due to the confluence of drainage ostia. The area is called the infundibulum, and a small amount of obstruction can cause widespread sinus infections.

Sinus infections are either acute or chronic. In acute sinusitis a bacterial infection follows a viral infection of the upper respiratory tract. However, sinusitis can also occur from obstruction of the draining ostia of the sinuses by inflammation or mass lesion. Topical nasal decongestants and systemic antibiotics are used to treat acute sinusitis. Severe or complicated infections may require surgical drainage of the involved sinus. Chronic sinusitis is a low-grade ongoing or recurrent infection of the sinuses. In these cases the mucosa of the sinuses has become thickened and enlarged due to edema and increased secretory glandular elements. In these cases small abscess may persist and relatively mild inflammatory stimuli may cause obstruction of the narrowed sinus ostia. Treatment of chronic sinusitis includes topical steroid sprays, systemic anti histamines and decongestants, and/or surgical removal of diseased mucosa with enlargement of the ostia.

**Asthma**

Asthma is a general term given to a similar constellation of symptoms: bronchospasm, mucosal swelling and increased secretions. Allergic stimulation, infections, irritating chemicals, cold air or exercise can trigger asthma.

Allergic asthma is a specific subset of asthma that is initiated by allergens and involves the IgE mediated reaction. Local and organ reactions include bronchial smooth muscle constriction, mucosal swelling and increased secretions.

**Other Allergic conditions**

Other allergic conditions include food allergies, and allergic dermatitis.

**Clostridia neurotoxins (CnT)**

Clostridium (C.) botulinum and the closely related species C. butyricum and beratti produce an extremely powerful neurotoxin that causes the paralytic condition known as botulism. The botulinum neurotoxin (BoNT) protein consists of a light and heavy chain that together weigh approximately 150 kD. In botulism the primary target is the synapse of the motor neuron with the muscle fiber. Here BoNT is taken up by the membrane of the motor neuron and is internalized. The effect of BoNT is to inhibit the release of neurotransmitters and neuropeptides by neurons. In clinical use each serotype appears to differ in its potency in blocking different classes of neurons.

BoNT works by a two-stage mechanism, uptake and molecular action. Peripheral nerve terminals take up BoNT. After translocation across the cell membrane BoNT interferes with the molecular mechanism of neurosecretion. Specifically, BoNT cleaves the proteins involved in synaptic vesicle docking and release called the SNARE complex. The result is to block neural signals.

C. tetani produce tetanus neurotoxin (TeNT). TeNT is similar to the BoNTs in that it interferes with vesicle release by cleaving VAMP, one of the SNARE family of proteins. However the in vivo biological activity of TeNT is usually quite different from BoNT. The systemic disorder tetanus results from TnT produced at a wound site and disseminated throughout the body via the blood stream. The TeNT is taken up by peripheral motor neurons and transported to the central nervous system. The TeNT then preferentially blocks inhibitory neurons connecting to the motor neuron, thereby allowing unopposed excitatory input. However, at higher doses TeNT and when introduced directly into the neuron also blocks all neurons in the same manner as BoNT. In this application it is assumed that the when BoNT is discussed is includes the TeNT when used at higher blocking doses.

At present seven immunologically distinct serotypes of the BoNT are known, named A, B, C, D, E, F and G. The type C serotype is now known to be divided into three different toxins with distinct biological effects. Only C1 is a neurotoxin, whereas C2 and C3 are not. C2 is distinctive for blocking actin formation, which can prevent mast cell degranulation. Although all BoNT serotypes interfere with proteins that

cause the release of synaptic vesicles from cells they each interfere with different proteins, or different parts of the same protein:

BoNT A & E cleave SNAP-25 (synapse associated protein)

BoNT C cleaves SNAP-25 and syntaxin

BoNT B, D, F & G (and TeNT) cleave VAMP (vesicle associated membrane protein)

Most if not all cell types use the vesicle system for secretion, although the molecules within these vesicles differ for each type of cell. If experimentally introduced into any cell BoNT appears capable of blocking its vesicle release. However, in nature BoNT appears to be internalized into neurons, particularly the efferent neurons. The vesicles within neurons contain classical neurotransmitters (acetylcholine, epinephrine, nor epinephrine, dopamine, serotonin, glutamate, GABA and others) and/or neuropeptides (substance P, neurokinin A, calcitonin gene related peptide (CGRP), neuropeptide Y, interleukins, growth factors and others). Although the highest affinity of BoNT is for cholinergic neurons, in various preparations BoNT has been shown to block secretion of all these molecules.

**The clinical effects of botulinum toxin on different classes of neurons**

**Voluntary motor nerves**

The first and still primary use of BoNT is to block motor nerve communication with muscle fibers. BT is injected within the target muscle. The BoNT is then internalized into motor neurons where it decreases or stops the release of the neurotransmitter acetylcholine (AChE), thereby causing paresis or paralysis of the muscle. Scott introduced the concept of localized muscular injections of BoNT in the specific condition of strabismus (squint, crossed eyes). Later BoNT was found to be particularly useful for movement disorders such as tics, spasms, contractures, cramps and tremors. More recently, the injection of BoNT into facial muscles has been found to ameliorate skin wrinkling and lines related to aging. Another recent application of BoNT injections is to decrease the pain accompanying muscle tension in conditions such as headache and temporo-mandibular joint syndrome.

**Autonomic motor neurons**

Effector neurons of the autonomic system innervate and control the contraction of smooth muscles using AChE as the neurotransmitter. Injections of BoNT have been used to decrease tone in the smooth muscles of the lower esophageal sphincter, esophagus, stomach wall, and pyloric sphincter, sphincter of Odi, anal sphincter, and urinary bladder.

**Autonomic secretory neurons**

Effector neurons of the autonomic system control or modulate the secretion of various water and mucoid fluids throughout the body. BoNT injections have been used to decrease sweating, salivary gland flow, gastric secretions including acid production, nasal and other respiratory secretions, and tearing.

**Sensory neurons**

Sensory neurons release a wide variety of neuropeptides, cytokines, growth factors and other substances that effect parenchymal cells, blood vessels and immune cells. Notable is that these substances can activate mast cells directly thereby extending the allergic reaction. Except for nitrous oxide these substances are released via the SNARE mechanism and can be blocked by CnT.

## SUMMARY OF THE INVENTION

As used herein 'local administration' includes but is not limited to injection by needle and in-dwelling catheter (including pressure jet injectors), topical administration in lyophilized powder, liquid solutions, creams, ointments, aerosolized or introduced by liposomal (niosomes) vectors, or as nucleic acid introduced by viral or other vectors. The CnT may also be embedded in biopolymers or delivered by implanted pumps to release the CnT into solution over prolonged periods.

By "therapeutically effective amount" it is meant of purposes of this invention that the CnT is administered in a non-toxic amount sufficient to cause reduction in the occurrence or magnitude of the symptoms being targeted.

By "unit" it is meant the biological equivalent of the current unit measure used for botulinum toxin A marketed as Botox. At present BoNT is measured by biological assay; a unit of BoNT is the amount that causes death to 50% of mice when injected intraperitoneally. BoNT-A is marketed as Botox by Allergan Corp, Irvine Ca, and as Dysport by Ipsen Ltd, Berks United Kingdom. Although the biological assay is done the same way the in vivo effect of Botox and Dysport vary. BoNT-B is marketed as Myobloc by Elan Pharmaceuticals, Dublin, Ireland. TeNT is not commercially available but other assays have compared the potency of the blocking effect of TeNT to BoNT. All serotypes of BoNT as well as TeNT are commercially available from List Biological laboratories). A therapeutically effective amount of BoNT will vary depending on the organ to be treated, how much of the organ will be treated, the method of application and the exact preparation of BoNT used. A therapeutically effective amount will vary from a fraction of a unit to hundreds of units as is it currently does with intramuscular injections. The exact dosage will not require undo experimentation by those skilled in the art.

Where solutions or suspensions of BoNT or CnT are referred to, unless indicated to the contrary, this means the designated number of units in 1 ml of Normal saline.

By "CnT" it is meant that any biological substance having essentially the same biological effect within cells as the wild types of clostridia neurotoxins. Specifically, to block or decrease the activity of the SNARE family of proteins involvled in secretion of allergy related neurohumors. Numerous substitutions for the major parts of the CnT have been disclosed and these are all included in this specification. This would include fragments, altered forms, and recombinant forms of CnT. Also included are chimeras, hybrids and conjugates. Also included are the use of DNA and RNA sequences that are directly applied and translated in the allergic sites. Also included are "vectors", various compositions that deliver a botulinum or tetanus toxin light chain or its equivalent such as Protease A across cell membranes. These vectors include but are not limited to viruses, liposomes, noisomes, and protein transduction domains (US Provisional Application 60/449,107).

Allergic "neurohumors" are neurotransmitters, neuropeptides and cytokines that participate in allergic reactions and whose secretion or action can be blocked by CnT. They include acetylcholine, noradrenaline, neuropeptide Y, substance P,

calcitonin gene reactive protein (CGRP), histamine, nerve growth factor, and interleukins.

The invention is directed to a method of blocking or reducing physiological reaction in a mammal, suitably but not limited to H. sapiens, .to the interaction of IgE antibodies present in said mammal upon contact with the corresponding antigen. This blocking is achieved by the administration to said mammal of a therapeutically effective amount of a neurotoxin (CnT) derived from Clostridia sp. Suitably, the CnT is derived from a species of Clostridia selected from the group consisting of C. botulinum, C. butyricum, C. beratti, C. tetani . The neurotoxins (BoNT), derived from C. botulinum, are derived from serotypes A, B, C1, D, E, F and G, while neurotoxin (TeNT), is derived from C.tetani

BoNT/A is marketed as Botox® by Allergan Inc and as Dysport® by Ipsen Ltd as a lyophilized powder that is reconstituted with preservative free normal saline prior to use. BoNT/B is marketed as Myobloc® by Elan Pharmaceuticals in normal saline solution. The light chains and holotoxins for each BoNT serotypes and TeNT can be obtained from List Biological Labs and/or Metabologics Inc.

CnT compositions of the present inventions are prepared in a variety of forms depending on whether the composition is injected or implanted, topically applied to respiratory mucosa of the nasal cavity or lungs, gastrointestinal mucosa, or to skin.

For all injectable CnT compositions fluid dosage forms are prepared utilizing the compound and a pyrogen-free sterile vehicle. The compound, depending on the vehicle and concentration used, can be either dissolved or suspended in the vehicle. In preparing solutions the compound can be dissolved in the vehicle, the solution being made isotonic if necessary by addition of sodium chloride and sterilized by filtration through a sterile filter using aseptic techniques before filling into suitable sterile vials or ampoules and sealing. Alternatively, if solution stability is adequate, the solution in its sealed containers may be sterilized by autoclaving. Advantageously additives such as buffering, solubilizing, stabilizing, preservative or bactericidal, suspending or emulsifying agents and/or local anaesthetic agents may be dissolved in the vehicle.

Dry powders, which are dissolved or suspended in a suitable vehicle prior to

use, may be prepared by filling pre-sterilized drug substance and other ingredients into a sterile container using aseptic technique in a sterile area. Alternatively the drug and other ingredients may be dissolved into suitable containers using aseptic technique in a sterile area. The product is then freeze-dried and the containers are sealed aseptically.

In the respiratory and gastrointestinal systems, CnT binds to mucosal epithelial cells and is actively transcytosed across the mucosa. Compositions suitable for administration to the respiratory tract include aerosols, nebulisable solutions or micro-fine powders for insufflation. In the latter case, particle size of less than 50 microns, especially less than I 0 microns, is preferred.

Compositions suitable for topical mucosal application include normal saline solutions as described above for injections. Other suitable compositions include gels and creams.

The skin presents a formidable barrier to the application of CnT. CnT may be mechanically propelled across the dermal barier with air or water pressure injectors or in association with micro-pellets . Other suitable forms of transdermal delivery include iontophoresis .CnT may be encapsulated into liposomes or niosomes to form suitable trans-dermal compositions.

The method of administration may take many forms, including topical, intra-dermal, sub-cutaneous, trans-cutaneous, intra cavital and by inhalation of the CnT in a suitable carrier. Examples of such administration include, but are not limited to contact with absorbant pledgets having CnT absorbed thereon, contact with biodegradable micropellets having CnT embedded therein. Also included is injection, for example, injection to the nasal mucosa or injection into the pterygoplatine space through the palate, or injection into affected areas of the surface skin. More invasively, by myringotomy and injection into the middle ear space. tympanic membranes. Alternatively less invasive methods include by drops into the inner eyelid and inhalation of an aqueous mist containing same.

The physiological reaction reactions dealt with herein include but are not limited to conditions such as allergic rhinitis, Infectious rhinitis, vasomotor rhinitis, serous otitis media, sinusitis, asthma, food allergies and allergic dermatitis.

The amount of CnT administered per administration may be, but is not limited to between about 0.1 and about 1000 units, suitably between about 1 and about 100 units per administration, preferably between about 1 and about 20 units.

The invention is also directed to use of a neurotoxin (CnT) derived from Clostridia sp for the production of a medicament for blocking or reducing physiological reaction in a mammal to the interaction of IgE antibodies present in said mammal upon contact with the corresponding antigen. The formulations of CnT, including BoNT and TeNT, which are suitable for the purposes designated herein are well known, but have not previously been designated for this purpose.

There is a great need for an effective treatment for allergic disorders. It has long been thought that the allergic reaction involved only histamine release by mast cells. Therefore first line therapy for allergy was antihistamines, or more recently the non-sedating antihistamines. Other therapies are directed to block the effects of the mast cell secretions with adrenergic agonists. It is not obvious to those skilled in the art that a central role in allergic disorders involves the autonomic nervous system and that this nerve activity can be blocked by CnT for a beneficial effect.

It is an object of the invention to provide a treatment for allergic conditions. Included particularly are allergy related rhinitis, asthma, gastroenteritis, serous otitis, sinusitis and dermatitis) and their related conditions (such as sinusitis and serous otitis media that occur secondary to allergy induced mucosal swelling). Treatment is by local application of therapeutically effective amounts of CnTs to the body structure and/or the nerves and nerve ganglia supplying these structures. CnT interfere with the allergic process by:

1) Directly blocking neuroimmune secretions by the mast cell or other immune cell types including but not limited to eosinophils ()

2) Block the release of neurohumors by mast cells induced by autonomic nerve activity.

3) Decrease neurohumoral release during axonal reflexes.

4) Decrease the parasympathetic effector arm of reflex allergic responses

5) Decrease the increased tonic activity of the autonomic systemic that is related to prior allergic reactions.

6) Decrease the enlargement and hypersensitivity of sensory nerves induced by nerve growth factor and other neurohumors released during allergic reactions.

7) Reverse certain complications of allergic reactions such as mucosal thickening by decreasing autonomic nerve activity.

The beneficial effect of this treatment in the:

1) Nasal area, is to decrease the symptoms of sneezing, itching, nasal congestion and post nasal drip, as well as related conditions including nasal polyps and mucosal thickening, and complications such as sinusitis and serous otitis.

2) Lungs, is to decrease coughing and wheezing (bronchoconstriction, edema) and the non-specific sensory hypersensitivity related to chronic allegic reactions.

3) Eye, is to decrease itching, tearing and redness.

4) Skin, is to decrease itching and swelling.

5) Gastrointestinal tract, is to decrease gastrointestinal dysmotility.

## Examples

### Example 1. Seasonal allergic rhinitis

1a) A 30-year-old male has seasonal allergic rhinitis. In May, prior to pollen formation, 30 units of BoNT topically applied in each nostril. Specifically, the nasal cavity is sprayed with a solution of 1% lidocaine and ½% neosynephrine to anesthetize and decongest the nasal mucosa, respectively. Then 1 cc of normal saline containing 30 units of BoNT is sprayed into each nasal cavity. This method of delivery, although commonly used for application of nasal medication, is inherently inefficient as a significant percentage of a sprayed medication will exit the posterior nasal cavity and be exhaled or swallowed.

1b) In another embodiment, the patient is treated by placing 1 x 3 $cm^2$ cotton pledgets impregnated with 20 units of BoNT onto the medial surface of the turbinates and left for one hour, then removed by the physician. This delivery method is more efficient then a spray, however a significant percentage of the BoNT will not diffuse from the pledgets to the mucosa.

1c) Alternatively, the patient has topical anesthesia applied only to a localized area, preferably the anterior end of the inferior turbinate. Then, patient has a 1$cm^2$ cotton pledget impregnated with 10 units of BoNT placed onto the mucosa of the anterior turbinate for one hour and then removed. Within the nasal cavity a mucociliary blanket transports fluids and particles posteriorly, thereby distributing the BoNT. This is an example of applying a BoNT to a localized region of the nasal cavity and using the normal physiology of the nasal cavity for distribution. The routes of mucociliary clearance of the nose and sinus cavities are known so that other variations of this method are apparent to those skilled in the art.

1d) In another embodiment, using a topical biodegradable depot to deliver BoNT over an extended time period to nasal mucosa is used for treating the patient. Various biodegradable compounds are known in the art that vary in consistency and rate of dissolution.

An example is oxidized cellulose (marketed as Surgicel® by Johnson & Johnson, New Brunswick, NJ). The oxidized cellulose can be manufactured with BoNT as an integral component, or the BoNT can be added to the oxidized cellulose before its clinical use. Surgicel is available in the form of a thin flexible sheet that is

often cut to fit the area of the body to which it will be applied. For intranasal use the size may vary from a few square millimeters to a 4 by 8 $cm^2$ sheet that could contact the entire exposed mucosa of the nasal cavity. BoNT can be added to the Surgicel as a lyophilized powder or after reconstitution into solution. If added as a powder it can homogeneously applied onto one side of the Surgicel and the material can be folded. The material is then moistened with normal saline to bind the material together and immobilize the BoNT prior to clinical use. In contrast the BoNT can first be constituted into solution and then absorbed into the material.

As an example a 2 x 6 $cm^2$ piece of oxidized cellulose is saturated with 1 cc of normal saline containing a total of 10 units of BoNT. Using a nasal speculum the nostril is dilated and the nasal cavity is visualized and the saturated cellulose place therein. The cellulose will gradually dissolve over hours while releasing a small continual dose of BoNT directly onto the nasal mucosa.

Alternatively the patient is of 0.5 cc. of normal saline containing 5 units of BoNTis applied to the oxidized cellulose which is grasped with bayonet forceps and placed flat onto the medial surface of the anterior end of the inferior turbinate of each nasal cavity. As disclosed above the mucociliary action of the nasal mucosa transports liquids and particles from the anterior to posterior nasal cavity.

1e) In another embodiment the patient is injected with BoNT solution directly into the nasal mucosa. After anesthetizing and decongesting the mucosa, 5 units of BoNT in 1 cc of saline are injected beneath the mucosa throughout the length of the inferior turbinate with a 25 gauge spinal needle coupled to a 1 cc syringe.

1f) Alternatively the patient can be treated with TeNT.

Compositions of TeNT for intranasal administration, can range in dose from .1 to 1000 units in 0.1cc to 10 cc of solution. One preferable composition is 10 units of TeNT in 1 cc of normal saline.

As an example the same patient is treated by spraying each nostril with 1 cc of normal saline solution containing 10 units of TeNT.

Alternatively, if only decongestion is desired 10 units of TeNT can be topically applied.

In another embodiment, 1 unit of recombinant DNA coding for TeNT is pressure injected across the nasal mucosa to transfect mucosal cells. These cells then express the TeNT for months.

**Example 2. Perennial allergic rhinitis**

2a) Direct injection of the sphenopalatine ganglia.

A 40-year-old female has chronic nasal congestion due to perennial rhinitis. Skin testing demonstrates that she is allergic to numerous environmental antigens and intranasal examination shows enlarged turbinate mucosa and nasal polyps. Testing of nasal secretions shows eosinophilia. An injection of 20 units of BoNT in a 1cc solution of normal saline is made through the sphenopalatine canal into the area of the sphenopalatine ganglia.

In another embodiment, 100 units of BoNT embedded in 0.1 micron biodegradable pellets suspended in solution is injected into the mucosa of each turbinate to slowly release its contents over 6 months.

Alternatively a biodegradable carrier containing 5 units of BoNT is placed intranasally in the most superior and posterior aspect of the lateral nasal wall. This permits the BoNT to diffuse across the nasal wall to the underlying sphenopalatine ganglia.

**Example 3. Serous otitis media**

A 3-year male has a history of serous otitis media. Under general anesthesia a myringotomy is made into the tympanic membranes and 2 units of BoNT in .5 cc of normal saline is injected.

**Example 4. Sinusitis**

A fifty-year-old male has a history of allergic rhinitis and recurrent sinusitis. Ten units of BoNT are injected through the palate into the pterygopalatine space to block the sphenopalatine ganglion.

**Example 5. Allergic dermatitis.**

A seventy-year-old male has severe allergic dermatitis of the forearm skin. Each forearm is injected with 10 injections of 0.3 units BoNT in 0.1 cc of normal saline. Each injection is made intradermally at 3 cm intervals.

**Example 6. Allergic asthma**

A 13-year-old boy has severe allergic asthma. He is treated by bimonthly inhalation therapy of an aerosilized solution of 5 units of botulinum toxin in 5 cc of normal saline.

Alternatively the same botulinum solution can be injected directly into the trachea and bronchi. After injecting local anesthesia into the skin overlying the cricothyroid membrane a needle is passed directly through the skin and cricothyroid membrane and the BoNT solution is sprayed into the trachea. The solution drips down to reach the bronchial mucosa where it is topically absorbed. and is absorbed

**Example 7 Allergic rhinitis**

A 40 year old male has allergic rhinitis and an associated reflex chronic cough. Application of CnT to the nasal cavity as described above or alternatively injected or aerosilized topical application of BoNT to the lungs is used to treat the cough.

**Example 8. Food allergies**

A 10-year-old boy with food allergies manifested by bloating and diarrhea is treated with a rectal suppository containing 50 units of BoNT. The suppository is composed of biocompatible material designed to be solid at room temperature but to dissolve at body temperature. Sufficient materials for the composition are coacoa butter, glycerinated gelatin, hydrogenated vegetable oils, polyethylene glycols of various molecular weights and fatty esters of polyethylene glycol.

**Example 9. Infectious rhinitis**

Chronic allergic exposure causes the nervous system to become hyper responsive to non-allergic stimulation such as that caused by viral infections.

A patient with rhinitis is given 10 units of BoNT and 5 units of TeNT prior to spring.

I Claim

1. A method of blocking or reducing physiological reaction in a mammal to the interaction of IgE antibodies present in said mammal upon contact with the corresponding antigen, by the administration to said mammal of a therapeutically effective amount of a neurotoxin (CnT) derived from Clostridia sp.

2. The method of claim 1 wherein the mammal is a member of H. sapiens.

3. The method of claim 2 wherein the neurotoxin is derived from a species of Clostridia selected from the group consisting of C. botulinum, C. butyricum, C. beratti, C. tetani .

4. The method of claim 3 wherein the neurotoxins (BoNT), derived from C. botulinum, are derived from serotypes A, B, C1, D, E, F and G

5. The method of claim 3 wherein the neurotoxin (TeNT) is derived from C.tetani.

6. The method of claim 1 wherein CnT is administered by contact with absorbant pledgets having CnT absorbed thereon.

7. The method of claim 1 wherein CnT is administered by contact with biodegradable carrier containing CnT .

8. The method of claim 1 wherein CnT is administered by injection.

9. The method of claim 1 wherein CnT is administered by myringotomy into tympanic membranes.

10. The method of claim 1 wherein CnT is administered by injection into the pterygoplatine space through the palate.

11. The method of claim 7 wherein CnT is administered to pass through the nasal wall to the sphenopalatine ganglia .

12. The method of claim 1 wherein CnT is administered by inhalation of an aqueous mist containing same.

13. The method of claim 1 wherein CnT is administered by injection to the nasal mucosa.

14. The method of claim 1 wherein CnT is administered by application of a suppository containing same.

15. The method of claim 1 wherein the physiological reaction is manifested by a condition or symptoms selected from the group consisting of allergic rhinitis, infectious rhinitis, serous otitis media, sinusitis, pulmonary disease, food allergies, allergic dermatitis, and sneezing, coughing, itching and excess mucous secretion related to allergic reactions.

16. The method of claim 15 wherein the pulmonary disease is selected from the group consisting of bronchitis, emphysema and hypereactive asthma.

17. The method of claim 1 wherein CnT is adminstered by contact with absorbant pledgets having CnT absorbed thereon.

18. The method of claim 1 wherein the amount of CnT administered per administration is between about 0.1 and about 1000 units per administration.

19. The method of claim 1 wherein the amount of CnT administered per administration is between about 1 and about 100 units per administration.

20. The method of claim 1 wherein the amount of CnT administered per administration is between about 1 and about 20 units per administration.

21. The use of a neurotoxin (CnT) derived from Clostridia sp for the production of a medicament for blocking or reducing physiological reaction in a mammal to the interaction of IgE antibodies present in said mammal upon contact with the corresponding antigen.

22. The use of claim 21 wherein the physiological reaction is manifested by a condition selected from the group consisting of allergic rhinitis, infectious rhinitis, serous otitis media, sinusitis, pulmonary disease, food allergies , allergic

dermatitis and sneezing, coughing, itching and excess mucous secretion related to allergic reactions.

23. The use of claim 22 wherein the pulmonary disease is selected from the group consisting of asthma and/or the symptoms of broncho-constriction, bronchitis, mucosal edema, emphysema increased secretions and cough,

24. A medicament for blocking or reducing physiological reaction in a mammal to the interaction of IgE antibodies present in said mammal upon contact with the corresponding antigen comprising a neurotoxin (CnT) derived from Clostridia sp and a pharmacologically acceptable carrier.

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**Declaration under Rule 4.17:**
— *of inventorship (Rule 4.17(iv)) for US only*

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— *before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments*

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*For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.*

(54) Title: TREATMENT OF MAMMALIAN REACTION TO IGE INTERACTIONS

(57) Abstract: A method is disclosed for blocking or reducing physiological reaction in a mammal to the interaction of IgE antibodies present in said mammal upon contact with the corresponding antigen, by the administration to said mammal of a therapeutically effective amount of a neurotoxin (CnT) derived from Clostridia sp.

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# INTERNATIONAL SEARCH REPORT

International application No.
PCT/US03/37286

**A. CLASSIFICATION OF SUBJECT MATTER**

IPC(7) : A61K 39/00, 39/395, 39/02, 39/08, 38/00; C07K 1/00
US CL : 424/236.1, 234.1, 239.1, 247.1, 810, 805; 530/825, 350; 514/2, 826, 886, 849

According to International Patent Classification (IPC) or to both national classification and IPC

**B. FIELDS SEARCHED**

Minimum documentation searched (classification system followed by classification symbols)
U.S. : 424/236.1, 234.1, 239.1, 247.1, 810, 805; 530/825, 350; 514/2, 826, 886, 849

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
Please See Continuation Sheet

**C. DOCUMENTS CONSIDERED TO BE RELEVANT**

| Category * | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|---|---|---|
| X<br>---<br>Y | WO 95/28171 A1 (MOUNT SINAI SCHOOL OF MEDICINE OF THE CITY UNIVERSITY OF NEW YORK) 26 Octobrer 1995 (26.10.1995), claims; Examples; and Summary of the invention | 1-4, 6-15, 17-22 and 24<br>---<br>5, 16 and 23 |
| X<br>---<br>Y | SHAARI, C.M. et al. Rhinorrhea is decreased in dogs after nasal application of botulinum toxin. Otolaryngology-Head and Neck Surgery. April 1995, Vol. 112, No. 4, 566-571, entire document. | 1-4, 11-13, 15 and 24<br>---<br>5-10, 14, 16-23 |

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" carlier application or patent published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

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Form PCT/ISA/210 (second sheet) (July 1998)

# INTERNATIONAL SEARCH REPORT

International application No.
PCT/US03/37286

**Box I Observations where certain claims were found unsearchable (Continuation of Item 1 of first sheet)**

This international report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claim Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claim Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claim Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

**Box II Observations where unity of invention is lacking (Continuation of Item 2 of first sheet)**

This International Searching Authority found multiple inventions in this international application, as follows:
Please See Continuation Sheet

1. ☒ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

**Remark on Protest**

☐ The additional search fees were accompanied by the applicant's protest.
☐ No protest accompanied the payment of additional search fees.

Form PCT/ISA/210 (continuation of first sheet(1)) (July 1998)

# INTERNATIONAL SEARCH REPORT

**Continuation of Item 4 of the first sheet:**
The title shall be short and precise, PCT Rule 4.3, suggested new title follows: "TREATMENT OF MAMMALIAN REACTION TO IGE INTERACTIONS"

## BOX II. OBSERVATIONS WHERE UNITY OF INVENTION IS LACKING

This application contains the following inventions or groups of inventions which are not so linked as to form a single general inventive concept under PCT Rule 13.1. In order for all inventions to be examined, the appropriate additional examination fees must be paid.

Group I, claims 1-20, drawn to a method of blocking physiological reaction to the interaction of IgE with the corresponding antigen in a mammal by administering a clsotridial neurotoxin.
Group II, claims 21-23, drawn to the use of a clostridial neurotoxin for the production of a medicament.
Group III, claim 24, drawn to a medicament comprising a clostridial neurotoxin and a pharmaceutically acceptable carrier.

The inventions listed as Groups I-III do not relate to a single general inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, they lack the same or corresponding special technical features for the following reasons:

The special technical feature of invention I is a method of blocking physiological reaction to the interaction of IgE with the corresponding antigen in a mammal by administering a clsotridial neurotoxin.
However, such a method is already disclosed in the prior art, for example, by Shaari *et al.* (*Otolaryngology-Head and Neck Surgery* 112 (4): April 1995. See abstract; Methods; Results; and Discussion. The special technical features of inventions II and III respectively are the use of a clostridial neurotoxin for the production of a medicament, and a medicament comprising a clostridial neurotoxin. These are also disclosed in the prior art, for example, by MOUNT SINAI SCHOOL OF MEDICINE OF THE CITY UNIVERSITY OF NEW YORK (WO 9528171). The special technical features do not define over the prior art.

**Continuation of B. FIELDS SEARCHED Item 3:**
DIALOG, WEST, MEDLINE, TOXLINE, BIOSIS, EMBASE, DERWENT
clostrid?, neurotoxin?, BOTOX, IgE, allerg?, rhinitis, otitis, sinusitis, dermatitis, sneez?, cough?, itch?

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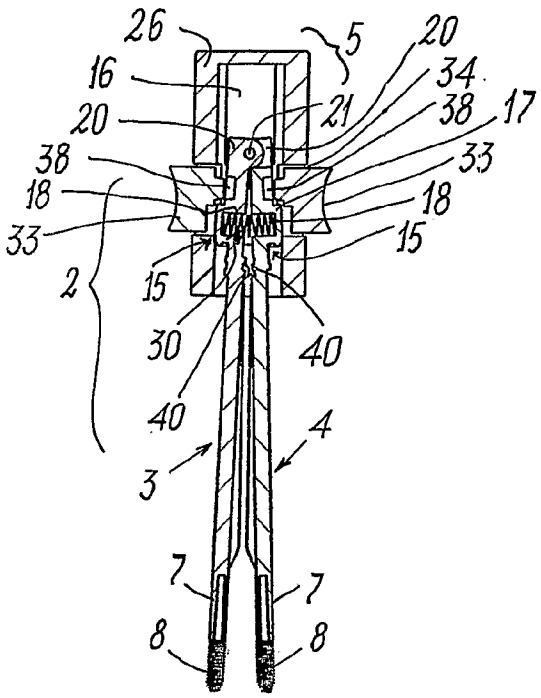
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(54) Title: MASCARA APPLICATOR WITH MOVABLE ARMS




(57) Abstract: A mascara applicator comprises a wand (2) presenting two side-by-side arms (3, 4) movable relative to each other, at least one of said arms (3, 4) carrying an element (8) for interacting with the eyelashes and a part for applying the mascara to the eyelashes. The arms (3, 4) are connected together and can be made to elastically approach each other, said arms being partially contained within a retaining member (5), this latter presenting members (6) for controlling the movement of said arms (3, 4), enabling them to be closed together so that they can interact with the eyelashes.

WO 2004/077987 A1

"MASCARA APPLICATOR WITH MOVABLE ARMS"

The present invention relates to a mascara applicator in accordance with the introduction to the main claim.

Mascara applicators substantially of tweezer form have been known for some time, they presenting two adjacent arms movable relative to each other, one of these arms carrying an element or brush for depositing the cosmetic product on the user's eyelashes. The second of these brushes can support a curved element for curling the eyelashes, or another element for their surface treatment.

These known arrangements present the most disparate configurations: for example they can comprise a one-piece V-shaped wand defined by the aforesaid arms joined together (integrally) at their free end; or they can present a scissor configuration with the said arms forming ends of substantially straight parts hinged together as scissor arms. In another embodiment, these known arrangements comprise pairs of V-shaped arms carrying eyelash support elements and mascara applicators at their ends.

These known arrangements present various drawbacks: for example, they are of large dimensions and hence

difficult to use and to deposit in a compartment of a small case or, as in the case of one-piece V-shaped applicators, the user can make contact with the cosmetic product during its application, with obvious inconvenience.

An object of the present invention is to provide a mascara applicator which is of improved construction and use compared with known arrangements.

Another object is to provide a mascara applicator of the stated type which enables the user to easily move the adjacent arms while making it difficult for the user to make contact with the mascara while depositing it on the eyelashes.

These and other objects which will be apparent to the expert of the art are attained by a mascara applicator in accordance with the accompanying claims.

The present invention will be better understood from the accompanying drawing, which is provided by way of non-limiting example and in which:

Figure 1 is a perspective view of a first applicator according to the invention, taken from below;

Figure 2 is a side perspective view of the applicator

of Figure 1;

Figure 3 is a side perspective view of the applicator of Figure 1, but in a different utilization position;

Figure 4 is a section on the line 4-4 of Figure 2;

Figure 5 is a section on the line 5-5 of Figure 2;

Figure 6 is an exploded perspective view of the applicator of Figure 1;

Figures 7-9 are longitudinal sections showing the various steps in using a mascara provided with a container and an applicator according to the invention; and

Figures 10-13 show different elements which can be associated with the applicator of Figure 1;

Figure 14 is a perspective view of a second applicator of the invention, seen from below;

Figure 15 is an exploded side perspective view of the applicator of Figure 14;

Figure 16 is a longitudinal side section through the applicator of Figure 14;

Figure 17 is a longitudinal section through a mascara provided with a container and the applicator of Figure 14;

Figures 18-20 are longitudinal sections showing the

various steps in using the mascara of Figure 17;

Figure 21 is a perspective view of a third applicator according to the invention; and

Figures 22 and 23 are longitudinal sections through the applicator of Figure 21 in two different utilization positions.

With reference to Figures from 1 to 13, a mascara applicator is indicated overall by 1. It comprises a wand 2 presenting elongate arms 3 and 4 positioned side by side and movable relative to each other. These arms are associated with a retaining member 5 provided with manipulator means 6 for their manipulation, said arms carrying at a first end 7 an interacting element 8 able to interact with the eyelashes to deposit mascara thereon or to provide a mechanical curling or combing action. These interacting elements 8 comprise (see Figures 10-13) brushes 10, a small comb 11, an arcuate element 12 or an element 13 with a helical surface projection; the elements 11-13 are generally associated with one of said arms 3, 4, the other arm carrying the brush 10. The elements 10-13 are associated with a seat 14 provided in the first end 7.

Each arm 3, 4 presents a second end 15 inserted into a cavity 16 of the retaining member 5. Said second end comprises a widened part 17 external to the arm, presenting an inner cavity 18 and a terminal part 20 provided with a through hole 21. The terminal part 20 of the arm 3 is flat and is inserted into the terminal part 20 of the arm 4 which instead is fork-shaped. Both said terminal parts 20 can evidently be fork-shaped or flat, similar to the part 20 of the arm 3 visible in Figure 6.

The retaining member 5 presents a jacket 26 defining its cavity 16. In this jacket, in opposing positions on the same axis K, there are provided two through holes 27 to receive a pin 28. This latter is inserted into the through holes 21 in the terminal parts 20 of the arms 3 and 4 when these have been fitted together such that their holes lie coaxial with said axis K. The pin 28 acts as a mutual fixing element for the arms 3 and 4 and enables them to be moved away from and towards each other about the pin, against the action of a spring 30 inserted into the inner cavities 18 of the externally widened parts 17 of said arms when fitted together.

To enable the arms to be moved towards each other against the spring 30, manipulator means 6 are provided. These comprise pushbuttons 33 movably inserted into lateral cavities 34 in the jacket 26 of the retaining member 5 communicating with the inner cavity 16 in this latter. These pushbuttons 33 present a part 35 which is external to the jacket 36 of the retaining member, and a part 36 arranged to cooperate with the terminal part 20 of the arms 3 and 4; the part 36 has a projecting shape able to engage a seat 38 provided in said part 20 of said arms 3 and 4, so becoming rigid with said part 20.

Each arm 3 and 4 also presents in proximity to the widened part 17 a series of transverse recesses 40 to receive corresponding transverse projections 41 of the other arm 4 and 3 when the two arms are closed for their insertion into a mascara container 42. This latter is shown in Figures 7-9 and comprises a hollow body 43 provided with an aperture 44 where a usual scraper 45 is positioned through which the mascara applicator 1 is inserted with its arms closed. They are closed (arrows F of Figure 8) by pressing the pushbuttons 33 towards the retaining member

(arrows G of Figure 8). On releasing the pushbuttons 33, the spring 30 forces the arms apart so that they open (arrows K1 of Figure 9).

The arms 3 and 4 may be opened and closed several times in applying mascara to a user's eyelashes and possibly in subjecting them to mechanical curling or other action depending on the interacting element 8 carried by one of the arms.

Reference will now be made to Figures 14-20. In these the mascara applicator is indicated overall by 100. It comprises a wand 102 presenting elongate arms 103 and 104 positioned side by side and movable relative to each other. These arms are associated with a cup-shaped retaining member 105 provided with manipulator means 106 for their manipulation, said arms carrying, in any known manner, at a first end 107 an interacting element 108 able to interact with the eyelashes to deposit mascara thereon or to provide a mechanical curling or combing action. These interacting elements 108 comprise, for example, brushes, a small comb, an arcuate element or other similar element. The elements 108 are connected to said arms 103, 104 for example by a

part

Each arm 103, 104 presents a second end 115 inserted into a cavity 116 provided in the retaining member 105 and closed by an upper plug 111. Said second end of each arm forms one piece with an interconnection element 113 which hence connects said two arms together. These latter, together with the element 113, hence define a single member partially inserted into said cavity 116.

Said second end 115 of each arm 103, 104 presents a widened part 117 external to the arm. This part 117 penetrates into a lateral cavity 118 provided in the jacket of the part 105 where movable elements 120 are present acting as pushbuttons for manipulating the arms 103 and 104 and defining the aforesaid means 106.

By pressing on the elements 120 towards the interior of the cavity 116 (arrows E of Figure 18) these act on the parts 117 to elastically urge the ends 107 of the arms 103 and 104 together (arrows M of Figure 18), to enable the mascara to be applied to the eyelashes while maintaining then elements 120 pressed.

The element 113 is externally threaded at 124 (Figure

15) and cooperates with an internal thread 125 provided in the cavity 116. A lower end 129 of the part 105 is internally threaded to cooperate with a thread 126 provided on the open terminal part 127 of a container 128 for the mascara where a scraper 129 with two apertures 130 for the arms 103 and 104 is positioned. The thread on the lower end 124 is opposite to that provided in the cavity 116 so that on screwing the part 105 onto the container 128, the arms 103 and 104 remain at rest, while moving relative to, i.e. translate upwards within, the cavity 16 of this part (so that the element 13 moves close to the upper plug 111, arrow L of Figure 20).

The arms 103 and 104 may be opened and closed several times in applying mascara to a user's eyelashes and possibly in subjecting them to mechanical curling or other action depending on the interacting element 108 carried by one of these arms.

With reference to Figures 21, 22 and 23, these show a mascara applicator 200 comprising a wand 202 presenting arms 203 and 204 positioned side by side and movable relative to each other. These arms are associated with a

cup-shaped retaining member 205 provided with manipulator means 206 for their manipulation, said arms carrying at a first end 207 an interacting element 208 able to interact with the eyelashes to deposit mascara thereon or to provide a mechanical curling or combing action. These interacting elements 208 are similar to the elements 8 and 108 already described in relation to the preceding figures and will therefore not be further described.

Each arm 203, 204 presents a second end 215 inserted into a cavity 216 provided in the retaining member 205 (for example of cup shape). The second ends 215 of the arms 203, 204 are connected together by a spring 230 having a first end 231 mounted about a projection 232 on the first arm 203 and a second end 234 inserted into a recess 235 in the second arm 204. This latter is associated with (or, as in the figures, integral with) a pushbutton movable within an aperture 236 of the retaining member 205. The pushbutton and the second arm 204 move against the action of the springs 230 towards the first arm 203, which is itself fixed to the retaining member 205.

In this manner, by acting on said pushbutton, the arms

203 and 204 can be elastically closed together to apply the mascara.

Specific embodiments of the invention have been described. Others are however possible in the light of the preceding description: for example the expert of the art can provide a different configuration of the manipulator means 6, 106, 206 such that they do not project from the member 5, 105, 205 or that they take the form of a pushbutton movable towards the arms (3, 103, 203; 4, 104, 204).

These embodiments are also to be considered as falling within the scope of the present document as defined by the accompanying claims.

CLAIMS

1. A mascara applicator comprising a wand (2, 102, 202) presenting two side-by-side arms (3, 4: 103, 104: 203, 204) movable relative to each other, at least one of said arms (3, 4: 103, 104: 203, 204) carrying an element (8, 108, 208) for interacting with the eyelashes and a part for applying the mascara to the eyelashes, characterised in that said arms (3, 4: 103, 104: 203, 204) are connected together and can be made to elastically approach each other, said arms (3, 4: 103, 104: 203, 204) being partially contained within a retaining member (5, 105, 205) acting as a lid for a mascara container (28, 128), said retaining member (5, 105, 205) presenting means (6, 106, 206) for controlling the movement of said arms (3, 4: 103, 104: 203, 204), enabling them to be closed together so that they can interact with the eyelashes and to apply mascara thereto.

2. A mascara applicator as claimed in claim 1, characterised in that each arm (3, 4: 103, 104: 203, 204) presents a first end (7, 107, 207) carrying the element (8, 108, 208) for interacting with the eyelashes and a second end (15, 115, 215) inserted into a cavity (16, 116, 216) of

the retaining member, said second ends (15) of said movable arms (3, 4) being hinged together and moving against the action of elastic means (30) contained in the retaining member (5).

3. A mascara applicator as claimed in claim 2, characterised in that the second ends (15) of the movable arms (3, 4) present through holes (21) arranged to lie coaxially with each other and with at least one hole (27) provided in the retaining member, in these holes (21, 27) there being inserted a pin (28) acting as a hinge for the movement of the movable arms (3, 4).

4. A mascara applicator as claimed in claim 3, characterised in that the pin (28) joins the movable arms (3, 4) to the retaining member (5).

5. A mascara applicator as claimed in claim 2, characterised in that the second end (15) of one of said movable arms (3, 4) comprises a fork-shaped terminal part (20) arranged to receive a flat terminal part (20) of the other movable arm (4, 3).

6. A mascara applicator as claimed in claim 2, characterised in that the elastic means (30) are positioned

between the movable arms (3, 4).

7. A mascara applicator as claimed in claim 6, characterised in that said elastic means (30) are a spring positioned between seats (18) provided in parts (17) of said arms (3, 4), said seats (18) being opposing.

8. A mascara applicator as claimed in claim 1, characterised in that each arm (103, 104) presents a first end (107) carrying the element (108) for interacting with the eyelashes and a second end (115) inserted into a cavity (116) of the retaining member, said second end (115) of said movable arms (1031, 104) being integral with an interconnection element (113) located in said cavity.

9. A mascara applicator as claimed in claim 8, characterised in that the interconnection element (113) is movable within the cavity (116) of the retaining member (105).

10. A mascara applicator as claimed in claim 9, characterised in that the interconnection element (113) is threaded (at 124) and cooperates with a thread (1125) provided in the cavity (116) of the retaining member (105).

11. A mascara applicator as claimed in claim 1,

characterised in that the each arm (203, 204) presents a first end (207) carrying the element (208) for interacting with the eyelashes and a second end (215) inserted into a cavity (216) of the retaining member (105), a first (203) of said arms being rigid with said part (205) and the second (204) of said arms being movable relative to the first against the action of elastic means (230) interposed between the second ends (215) of said arms (203, 204).

12. A mascara applicator as claimed in claim 11, characterised in that the elastic means (230) are a spring having a first end (231) rigid with the first arm (203) and a second end (232) rigid with the second arm and movable therewith.

13. A mascara applicator as claimed in claim 11, characterised in that the second arm (204) is rigid with the control means (6).

14. A mascara applicator as claimed in claim 1, characterised in that the control means (6, 106, 206) are at least one pushbutton (33, 120).

15. A mascara applicator as claimed in claim 14, characterised in that the control means (6) are pushbuttons

(33, 120) movably inserted into lateral cavities (34, 118, 236) of the retaining member (5, 105, 205).

16. A mascara applicator as claimed in claim 15, characterised in that each pushbutton (33) engages a seat (38) provided in a corresponding movable arm (3, 4).

17. A mascara applicator as claimed in claim 15, characterised in that each pushbutton projects from the retaining member (5, 105, 205).

18. A mascara applicator as claimed in claim 15, characterised in that each pushbutton is coplanar between a free end surface with the outer surface of the retaining member (5, 105, 205)

19. A mascara applicator as claimed in claim 14, characterised in that the is only one pushbutton, this moving axially on the retaining member.

20. A mascara applicator as claimed in claim 1, characterised in that the retaining member (105) presents a threaded end (129) cooperating, by screwing, with a threaded free end (127) of a container (128), said threaded free end (127) supporting a scraper (129).

21. A mascara applicator as claimed in claim 5,

characterised in that the scraper (129) presents separate apertures (130) for the movable arms (103, 104), said arms being torsionally immovable when screwing the retaining member (105) onto the container.

22. A mascara applicator as claimed in claim 1, characterised in that the element (8, 108, 208) for interacting with the eyelashes comprises a brush (10).

23. A mascara applicator as claimed in claim 1, characterised in that the element (8, 108, 208) for interacting with the eyelashes comprises an eyelash curler (12).

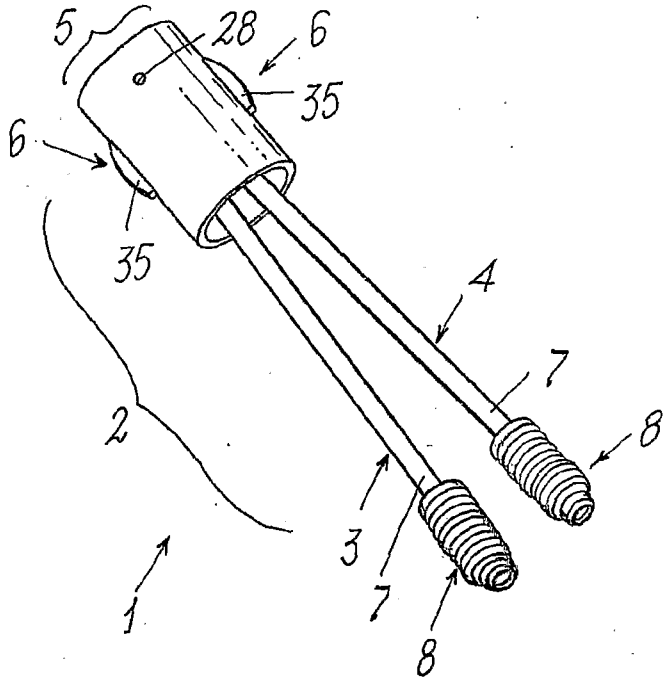



FIG. 1

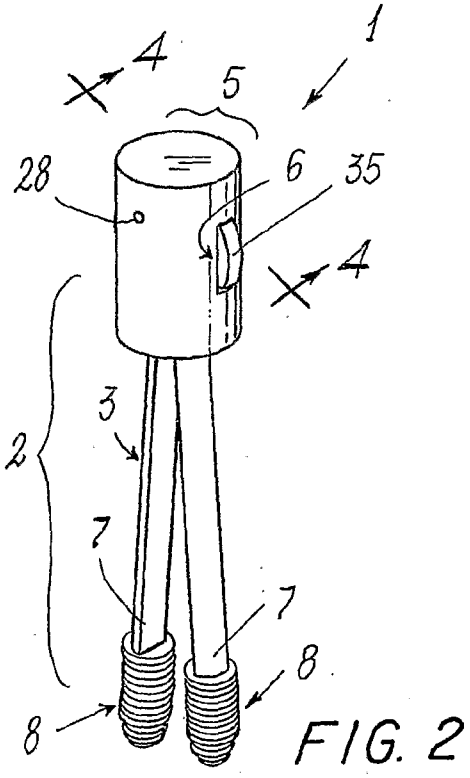



FIG. 2

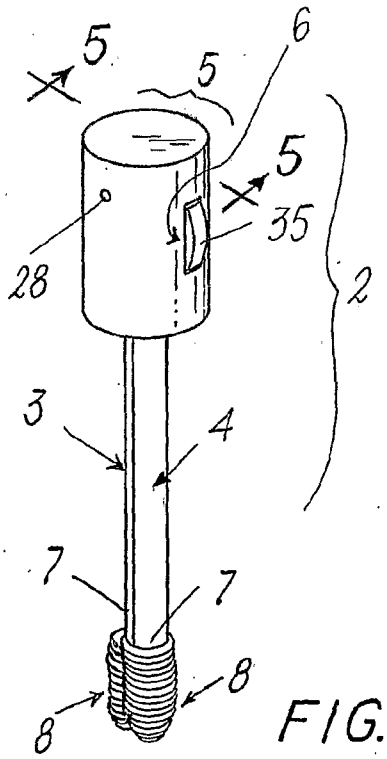



FIG. 3

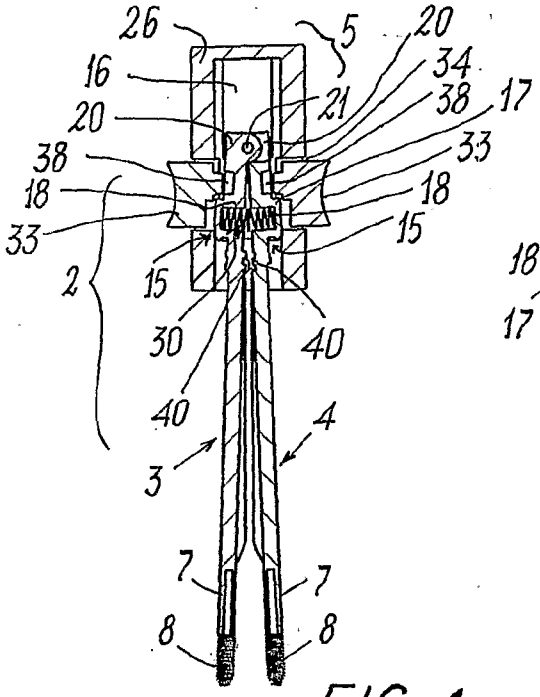



FIG. 4

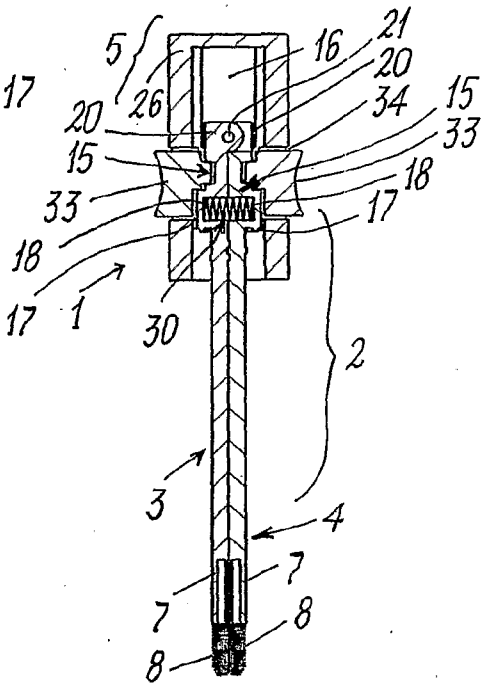



FIG. 5

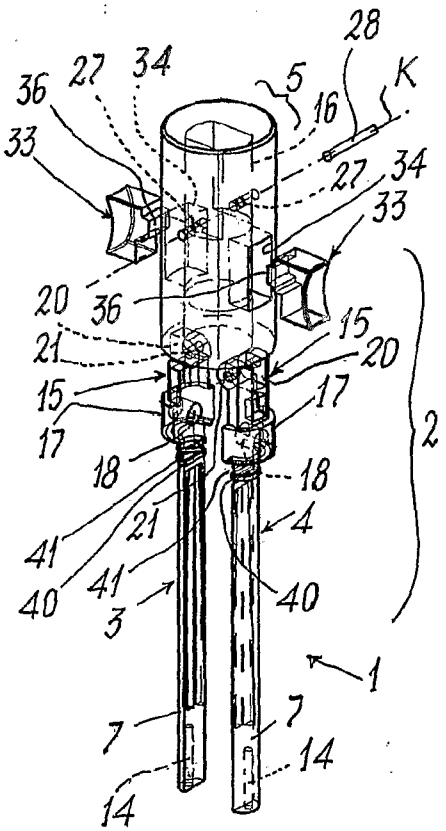



FIG. 6

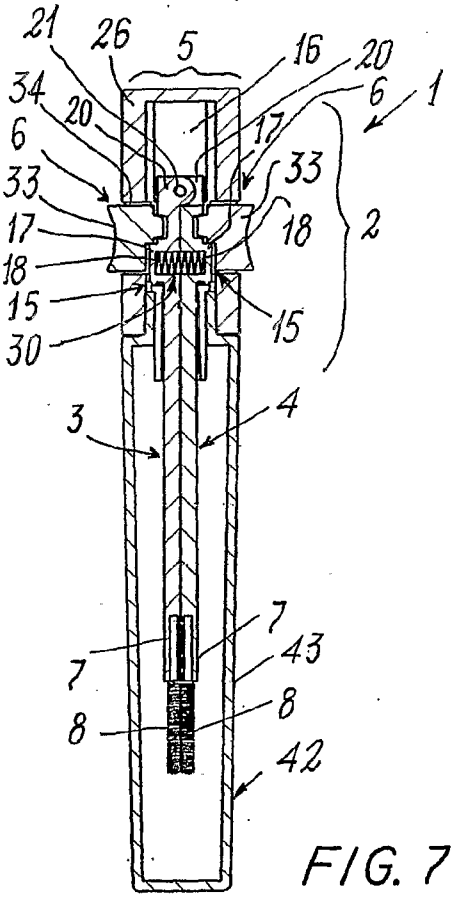
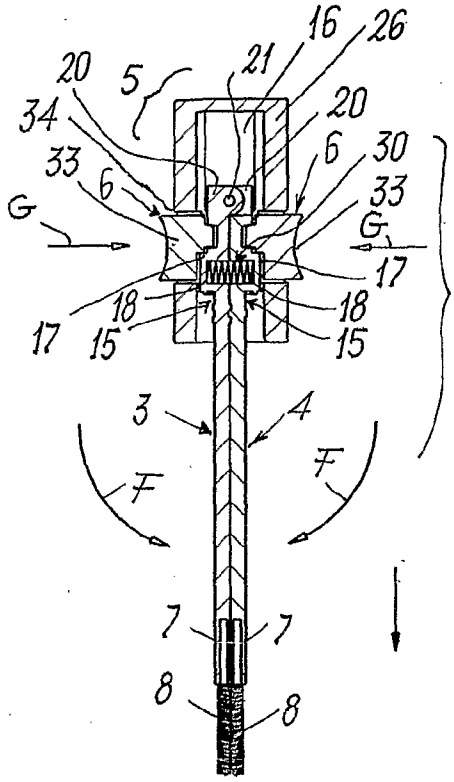
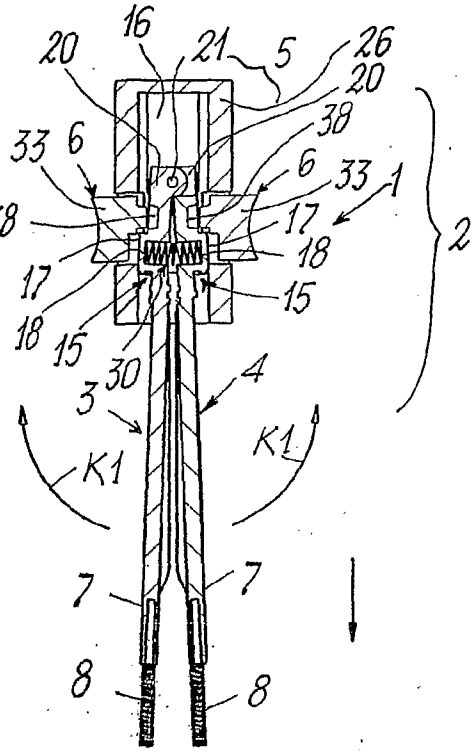



FIG. 7



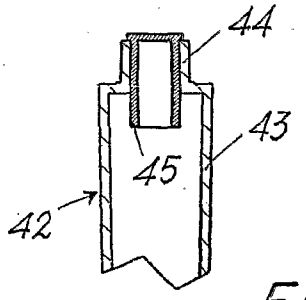




FIG. 8

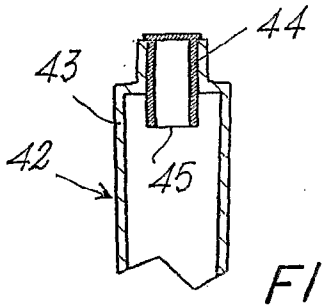



FIG. 9

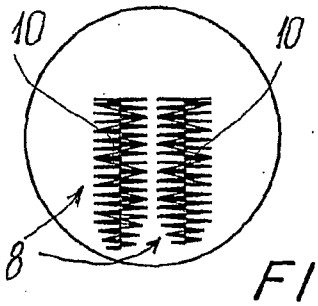



FIG. 10

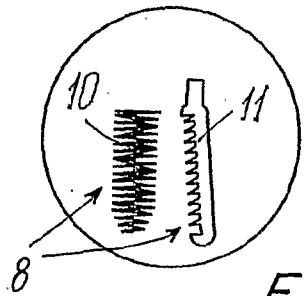



FIG. 11

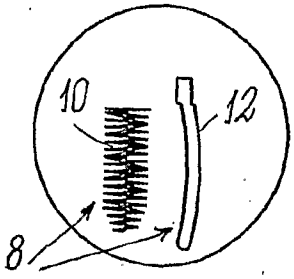



FIG. 12

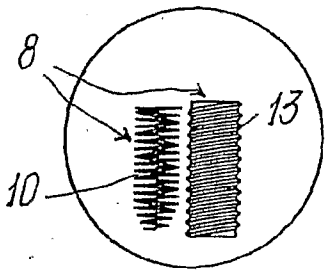



FIG. 13

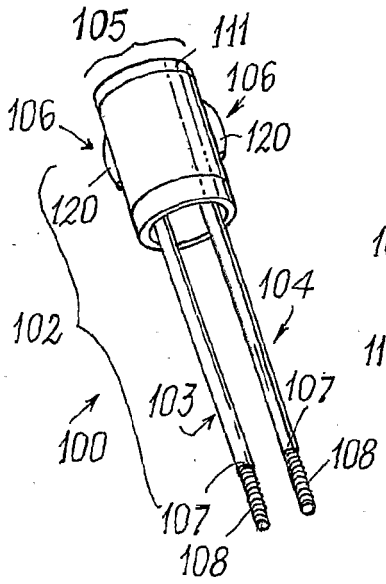



FIG. 14

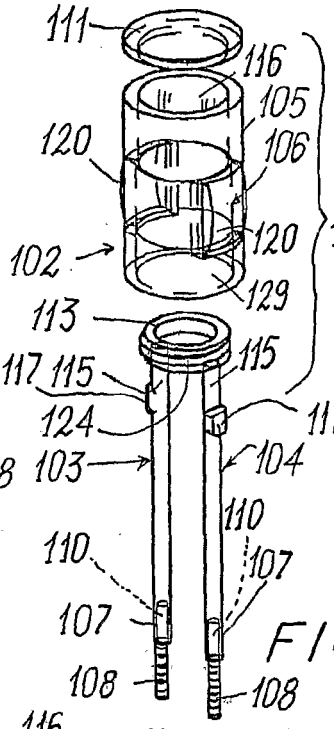



FIG. 15

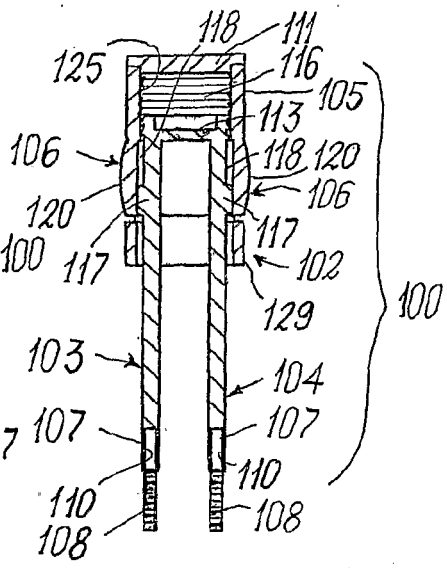



FIG. 16

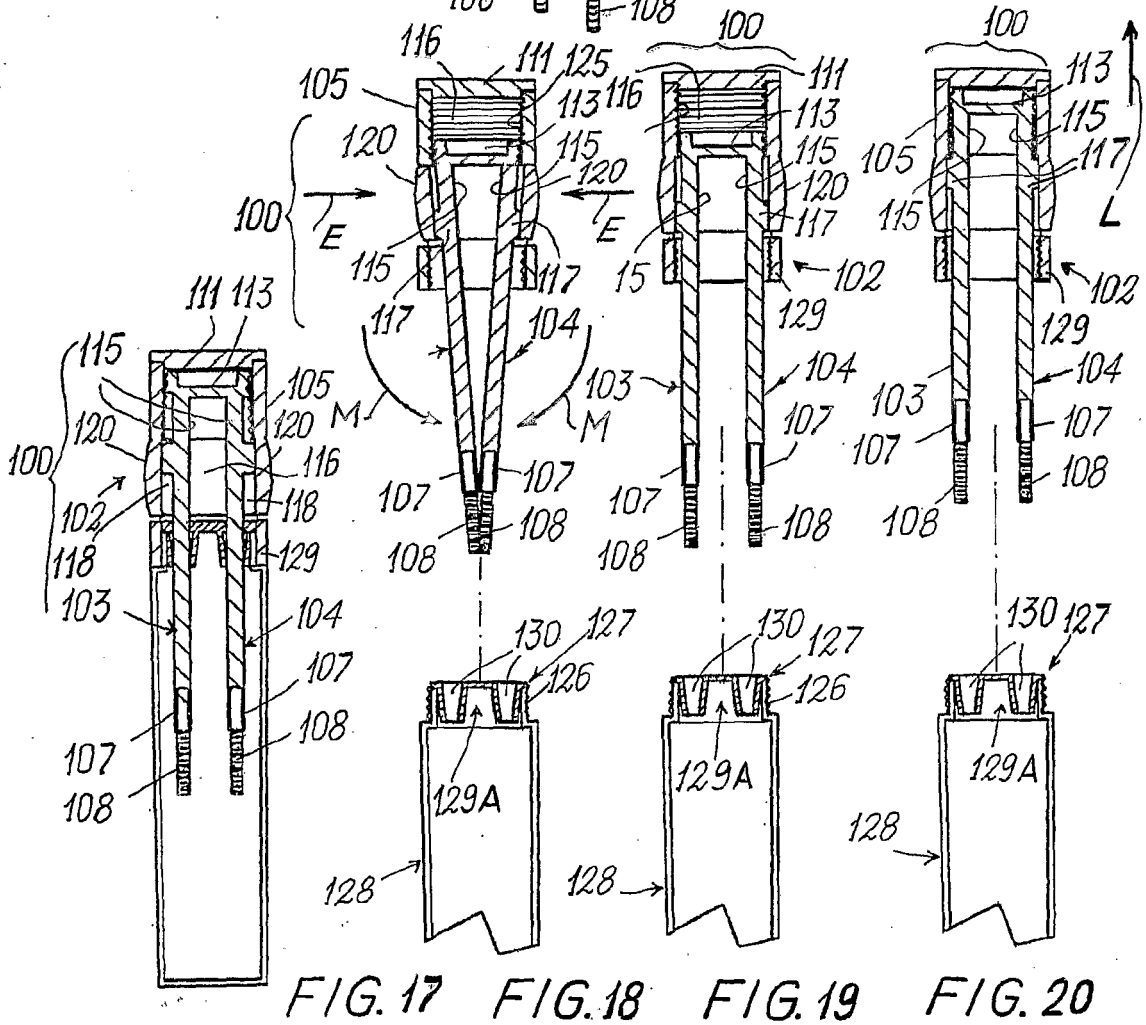



FIG. 17 FIG. 18 FIG. 19 FIG. 20

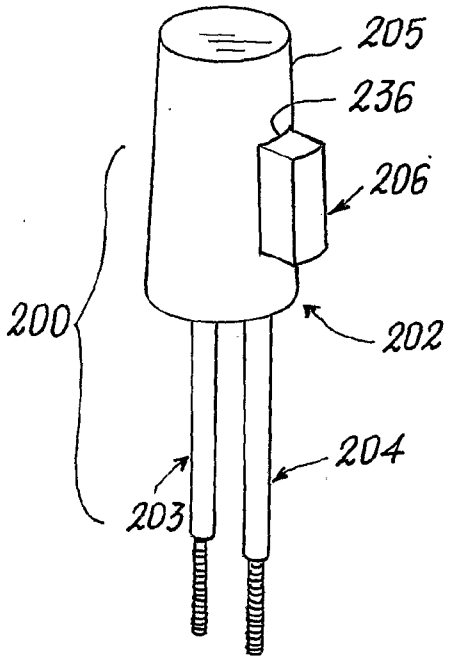



FIG.21

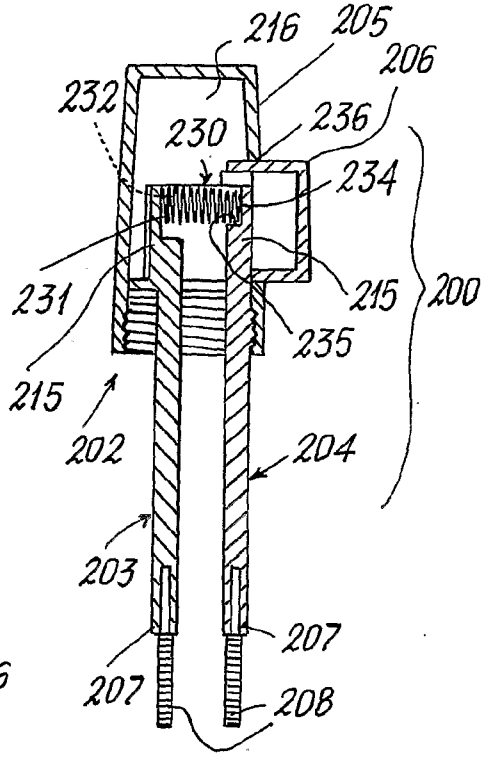



FIG. 22

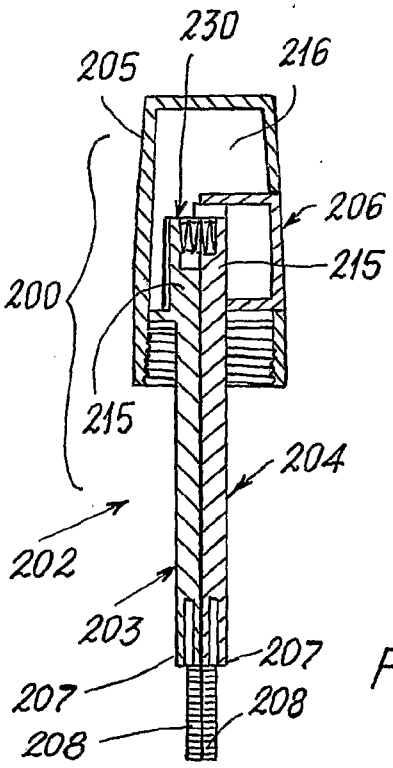



FIG. 23

# INTERNATIONAL SEARCH REPORT

International Application No
PCT/IB2004/000794

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A45D40/26 A45D2/48

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A45D A46B

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, WPI Data, PAJ

C. DOCUMENTS CONSIDERED TO BE RELEVANT

| Category ° | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|---|---|---|
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| X | DE 820 792 C (HEROLD WILFRIED) 12 November 1951 (1951-11-12) page 2, line 28,29; claims; figures --- | 1,22 |
| | -/-- | |

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

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| Date of the actual completion of the international search | Date of mailing of the international search report |
|---|---|
| 17 June 2004 | 30/06/2004 |

| Name and mailing address of the ISA | Authorized officer |
|---|---|
| European Patent Office, P.B. 5818 Patentlaan 2<br>NL – 2280 HV Rijswijk<br>Tel. (+31–70) 340–2040, Tx. 31 651 epo nl,<br>Fax: (+31–70) 340–3016 | Herry, M |

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# INTERNATIONAL SEARCH REPORT

International Application No
PCT/IB2004/000794

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

| Category ° | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
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| A | DE 817 945 C (KEHDER OTTO)<br>22 October 1951 (1951-10-22)<br>figures | 1 |

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International Application No
PCT/IB2004/000794

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| DE 817945 C | 22-10-1951 | NONE | |

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(71) Applicant *(for all designated States except US)*: **THE FOUNDRY, INC.** [US/US]; 199 Jefferson Drive, Menlo Park, CA 94025 (US).

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(72) Inventors: **DEEM, Mark, E.** [US/US]; 685 Sierra Avenue, Mountain View, California 94041 (US). **GIFFORD, Hanson, S.** [US/US]; 3180 Woodside Road, Woodside, CA 94062 (US).

(74) Agent: **HEISEY, David, E.**; Luce, Forward, Hamilton & Scripps LLP, 11988 El Camino Real, Suite 200, San Diego, CA 92130 (DE).

(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.

(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

**Published:**
— *without international search report and to be republished upon receipt of that report*

*For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.*

(54) Title: APPARATUS AND METHODS FOR TREATING ASTHMA USING NEUROTOXIN

(57) Abstract: Apparatus providing intrabronchial delivery of neurotoxin to control the effects of asthma comprises a shaft having proximal and distal ends and a neurotoxin applicator assembly disposed on the distal end, wherein the neurotoxin applicator assembly comprises a deployable needle assembly, a rotating needle assembly, a needle-less injection assembly, a nebulizer assembly or a microporous tip. Further embodiments involve apparatus comprising drug-eluting bioabsorbable stents having one or more layers of asthma-fighting drugs.

WO 2004/101028 A2

# APPARATUS AND METHODS FOR TREATING ASTHMA USING NEUROTOXIN

## Field of the Invention

**[0001]** The present invention relates to apparatus for treating asthma by controlled delivery of neurotoxin using a neurotoxin applicator assembly.

## Background of the Invention

**[0002]** The lung is made up of progressively smaller bronchial bifurcations stemming downward from the trachea. The trachea and proximal bronchi are lumens consisting of an outer layer of fascia surrounding a U-shaped inner cartilaginous layer, wherein the open portion of the U is spanned by smooth muscle. Inside the cartilaginous layer are a collagenous elastic layer and an innermost epithelial layer. Mucus secreting goblet cells and transport cilial cells are interspersed within these inner layers.

**[0003]** As the bronchi branch and get smaller, the cartilaginous layer changes from a U-shape to irregular and helical shapes. In addition, the smooth muscle layer becomes helical bands surrounding the entire circumference of the bronchi, the goblet cells gradually decrease in numbers and the ciliated cells get smaller

and fewer in number. In the most distal bronchi, the outer cartilaginous layer disappears completely, the smooth muscle layer becomes the outermost layer and goblet cells and ciliated cells disappear completely.

[0004] Asthma is a complex disease of the bronchial tree, characterized by airway hyperresponsiveness to allergens, stress and environmental triggers. Environmental triggers include irritants such as pollutants and non-allergenic triggers such as exposure to cold air. Airway hyperresponsiveness results in acute narrowing of the entire bronchial tree reducing airflow through the lungs, compromising respiration and limiting gas exchange in the alveoli. The narrowing of the bronchial tree is a result of three basic characteristic physiologic responses: (1) smooth muscle contraction; (2) increased mucus production; and (3) edema caused by arterial dilatation and increased arterial permeability. The triggering mechanisms for these physiologic responses are part of the body's inflammatory response system.

[0005] Chronic uncontrolled asthma can result in structural changes to the bronchial wall itself. Smooth muscle hyperplasia results in thickening of the smooth muscle components of the bronchial wall. Thickening of the subepithelial collagen layer that lies between the airway epithelium and the smooth muscle layer results in progressive stiffening of the wall of the bronchi. Studies have shown that stiffening of the airway wall results in more profound narrowing of the airway for a given asthma attack. This is due to changes in the ability of the mucosal layer to fold in response to the smooth muscle layer contraction.

[0006] Recently, the controlled injection of neurotoxin has become a common procedure for controlling

skeletal muscle spasms. A frequently used neurotoxin for this procedure is the botulinum toxin, serotype A, sold commercially by Allergan, Inc. as Botox™. Botulinum toxin blocks the release of neurotransmitter from the nerves that control the contraction of the target muscles. Many applications for botulinum toxin have been proposed and/or clinically tested, including cervical dystonia, cosmetic relief of frown lines and tremor associated with cerebral palsy. Recently, botulinum toxin has become the subject of clinical study for the relief of hyperhidrosis (profuse sweating) and hypersalivation. These studies indicate that botulinum toxin can be used to control the action of cholinergic parasympathetic nerves as well as large skeletal muscle groups. The recent findings open the possibility of using neurotoxins such as botulinum toxin to control some of the main mechanisms of airway narrowing in asthmatic attacks, specifically smooth muscle contraction and hypersecretion of mucus from the goblet cells. Additionally, there is evidence that some part of the inflammatory response of asthma is stimulated by the release of the neurotransmitters that botulinum toxin inhibits. This opens the possibility that botulinum toxin also may work to mitigate the inflammatory cycle itself.

**[0007]** The use of neurotoxin for the control of asthma is described in U.S. Patent No. 6,063,768 to First, wherein asthma is included in a list of neurogenic inflammatory disorders that may be controlled through the action of neurotoxins such as botulinum toxin but does not describe the methods or devices used to do so. An earlier patent, U.S. Patent No. 5,766,605 to Sanders, et.al., describes the use of botulinum toxin to treat

asthma and COPD. That patent also describes that botulinum toxin could be aerosolized and introduced into the lungs. Further mention of botulinum toxin in connection with asthma is provided in a press release dated February 7, 2003 by the University of Alberta in describing the work of Dr. Redwan Moqbel. The release mentions that Dr. Moqbel and others are researching the possible use of neurotoxins such as tetanus and botulinum toxin to prevent eosinophils from activating and starting the inflammatory cascade that results in an asthma attack.

**[0008]** While it may be possible to simply aerosolize neurotoxins for introduction into the lungs, introducing it into the patient through traditional inhalation means would expose the mouth, tongue, epiglottis, vocal cords, etc. to the actions of the neurotoxin, with obvious deleterious results. Much more controlled and direct application of the neurotoxin to the desired tissue is required for safe and effective therapy.

**[0009]** Accordingly, it would be desirable to provide apparatus that enables controlled delivery of a neurotoxin to target treatment areas within a patient's bronchial airways.

**[0010]** It also would be desirable to provide an apparatus permitting the controlled injection of neurotoxin into the bronchial wall of a patient.

**[0011]** It would further be desirable to provide a needle-less injection apparatus to eliminate potential complications related to the presence of needles within a patient's bronchial airways.

**[0012]** Additionally, it would be desirable to provide an apparatus permitting the application of neurotoxin

onto a target treatment area within a patient's bronchial airways.

**[0013]** In addition, implantable drug eluting devices for treating various diseases also have been developed. Examples include drug eluting coronary stents such as those under clinical investigation and commercial sale from such companies as Boston Scientific and Cordis Corporation. Bioabsorbable devices for drug delivery have likewise been contemplated, such as those under development by Synecor, Inc. (recently acquired by Guidant), and by numerous university and hospital-based development efforts. Examples of such efforts are provided in Blindt, et al., *Development of a New Biodegradable Intravascular Polymer Stent with Simultaneous Incorporation of Bioactive Substances*, Int'l J. Artif. Organs, 22(12):843-853 (1998) and Tsuji, et al., *Biodegradable Stents as a Platform to Drug Loading*, Int'l J. Cardio. Interv., 13-16 (2003).

**[0014]** Other uses for biodegradable stents include restoring patency of the urethra following treatment of prostatic hyperplasia and maintaining the patency of bronchial airways after impingement by lung tumors. Biodegradable and non-biodegradable implants for the controlled release of neurotoxin for the treatment of various diseases is described in U.S. Patent Nos. 6,306,423, 6,506,399 and 6,383,509. Further, U.S. Patent No. 5,766,605 describes the use of neurotoxin to treat autonomic nerve dysfunction, including specific claims involving treating asthma and chronic obstructive pulmonary disease (COPD). Additionally, U.S. Patent Publication No. 2002/0082197 describes the use of neurotoxin for treating mucus secreting disease, such as asthma and COPD, as does WO 00/10598.

[0015] It further would be desirable to provide implantable apparatus that provides a sustained or periodic dosage of asthma-fighting drugs to a target treatment area within a patient's bronchial airways.

Summary of the Invention

[0016] In view of the foregoing, it is an object of the present invention to provide apparatus that enables the controlled delivery of a neurotoxin to target treatment areas within a patient's bronchial airways.

[0017] It is a further object of the present invention to provide an apparatus permitting the controlled injection of neurotoxin into the bronchial wall of a patient.

[0018] It is an additional object of the present invention to provide a needle-less injection apparatus to eliminate potential complications related to the presence of needles within a patient's bronchial airways.

[0019] It is another object of the present invention to provide an apparatus permitting the application of neurotoxin onto a target treatment area within a patient's bronchial airways.

[0020] It still further is an object of this invention to provide implantable apparatus that provides a sustained or periodic dosage of asthma-fighting drugs to a target treatment area within a patient's bronchial airways.

[0021] These and other objects of the present invention are accomplished by providing an intrabronchial neurotoxin delivery system for controlled delivery of neurotoxin to a target treatment area within a patient's bronchial airways to lessen the effects of asthma. The introduction of neurotoxin into the bronchial airways

disables the hyperresponsive smooth muscle layer and controls the hypersecretion of mucus.

**[0022]** In accordance with a first aspect of the present invention, the intrabronchial neurotoxin delivery system comprises neurotoxin applicator assembly. The distal end of the neurotoxin applicator assembly may comprise a needle tip, a rotating needle assembly, a needle-less injection assembly, a nebulizer, or a micro-porous tip. This and all following applicator embodiments may be designed to work through or in concert with a standard bronchoscope, or may be incorporated into a stand-alone system for accessing and treating the airways.

**[0023]** In accordance with this aspect of the invention, the neurotoxin applicator assembly comprises an elongated shaft having a lumen in fluid communication with a source of liquid neurotoxin. The distal end of the shaft includes one or more needles that are preformed to contract radially when disposed within a lumen of the bronchoscope, but may be extended to penetrate and inject small doses of neurotoxin into the bronchial wall of a patient.

**[0024]** Alternatively, the distal end of the neurotoxin applicator assembly may carry a rotating needle assembly including plural needles disposed along the circumference of a wheel, so that the wheel may be rolled across a target treatment area. Optionally, the rotating needle assembly may include a fender to protect a portion of the bronchial wall substantially opposite the target treatment area.

**[0025]** In another alternative embodiment, the distal end of the neurotoxin applicator assembly may comprise a needle-less injection assembly that may be used to inject

neurotoxin into the bronchial wall without needle penetration. An inflatable balloon optionally may be provided to help position a port of the needle-less injection assembly adjacent to the target treatment area.

**[0026]** In a further alternative embodiment, the distal end of the neurotoxin applicator assembly comprises a nebulizer assembly having an atomizer that converts the liquid neurotoxin into a fine spray or mist that is directed onto the target treatment area. The particle size of the mist can be controlled using injection pressure or atomizer head design to access specific portions of the lung adjacent to or downstream of the treatment device. An inflatable balloon optionally may be provided to facilitate positioning the atomizer adjacent the target treatment area, and further serves to isolate the lung segment downstream of the device to prevent reflux of the mist into undesired portions of the airway. In addition, lumens optionally may be disposed between the balloon and atomizer to provide a ventilation system that allows pressure control of the treatment area to prevent over-inflation of the lung, mixing of the atomized fluid, and evacuation of remaining mist at termination of therapy, prior to balloon deflation.

**[0027]** In a still further embodiment, the distal end of the neurotoxin applicator assembly may comprises an articulable region of the shaft including a micro-porous tip that mediates flow of asthma-fighting solution through the lumen and out of the distal tip.

**[0028]** In accordance with another aspect of the present invention, the intrabronchial neurotoxin delivery system comprises a drug-eluting bioabsorbable stent comprising one or more layers of asthma-fighting drugs.

Brief Description of the Drawings

**[0029]** The above and other objects and advantages of the present invention will be apparent upon consideration of the following detailed description, taken in conjunction with the accompanying drawings, in which like reference characters refer to like parts throughout, and in which:

**[0030]** FIG. 1 is a side view of an intrabronchial neurotoxin delivery system of the present invention;

**[0031]** FIG. 2 is a perspective view of an illustrative embodiment of a neurotoxin applicator assembly of the present invention;

**[0032]** FIGS. 3A and 3B are cross-sectional views of the neurotoxin applicator assembly of FIG. 2 in retracted and extended positions, respectively;

**[0033]** FIG. 4 is a perspective view of an alternative embodiment of a neurotoxin applicator assembly of the present invention;

**[0034]** FIGS. 5A and 5B are partial cross-sectional views of the neurotoxin applicator assembly of FIG. 4 in retracted and extended positions, respectively;

**[0035]** FIG. 6 is a perspective view of another alternative embodiment of a neurotoxin applicator assembly of the present invention;

**[0036]** FIG. 7A and 7B are partial cross-sectional views of the neurotoxin applicator assembly of FIG. 6 in retracted and extended positions, respectively;

**[0037]** FIG. 8 is a perspective view of a yet further alternative embodiment of a neurotoxin applicator assembly of the present invention;

**[0038]** FIGS. 9A and 9B are partial cross-sectional views of the neurotoxin applicator assembly of FIG. 8 in retracted and extended positions, respectively;

[0039] FIG. 10 is a side view of a distal end of a neurotoxin applicator assembly for topically applying an asthma-fighting solution to a patient's bronchi;

[0040] FIGS. 11A-11C are side views of the applicator of FIG. 10 depicting the curved distal segment in different configurations;

[0041] FIG. 12 is a perspective view of a syringe that is employed to provide pressurization at the proximal end of the applicator of FIG. 10;

[0042] FIG. 13 is a perspective view of an alternative syringe that is employed to provide pressurization at the proximal end of the applicator of FIG. 10;

[0043] FIG. 14 is a side view of a drug-eluting bioabsorbable stent of the present invention;

[0044] FIG. 15 is a side view of another drug-eluting bioabsorbable stent of the present invention;

[0045] FIG. 16 is a cross-sectional view of the drug-eluting bioabsorbable stent of FIG. 14;

[0046] FIG. 17 is a perspective view depicting the delivery of drug-eluting bioabsorbable stents within a patient's bronchi;

[0047] FIG. 18 is a perspective view depicting the delivery of alternative drug-eluting bioabsorbable stents within a patient's bronchi; and

[0048] FIG. 19 is a perspective view depicting the delivery of further alternative drug-eluting bioabsorbable stents within a patient's bronchi.

Detailed Description of the Invention

[0049] Referring to FIG. 1, apparatus for controlled delivery of neurotoxin to a target treatment area within a patient's bronchial airways to lessen the effects of asthma is described. Preferably, the apparatus comprises bronchoscope 10 and neurotoxin applicator assembly 20.

Bronchoscope 10 has proximal end 12, distal end 13, and lumen 14. As is conventional, bronchoscope 10 also includes a light source for illuminating the interior of a patient's lung and optics, such as a miniature camera, that enables the physician to view the interior of the patient's lung. Alternatively, bronchoscope 10 may omit the light source and optics, and instead comprise an outer sheath. In this latter case, device 10 and neurotoxin applicator 20 would be observed using a separate conventional bronchoscope or through a light source and optics that are built into the neurotoxin applicator 20.

**[0050]** In accordance with the principles of the present invention, neurotoxin applicator assembly 20, of which various illustrative embodiments are described hereinbelow, enables the physician to selectively administer controlled doses of neurotoxin to or within selected treatment sites in the patient's lung. More specifically, neurotoxin applicator assembly 20 may be selectively advanced through lumen 14 of bronchoscope 10 to deliver a neurotoxin, such as botulinum toxin, serotype A, to a target treatment area.

**[0051]** Neurotoxin applicator assembly 20 includes shaft 21 coupled to at its proximal end to handle 22, distal end 23 having neurotoxin applicator 24, and lumen 25. Lumen 25 provides fluid communication between proximal end and handle 22 and applicator 24. Syringe 26 having plunger 27 is coupled to a port on proximal end 22. Syringe 26 is filled with neurotoxin in liquid form, and applies the neurotoxin to applicator 24 via lumen 25 when plunger 27 is actuated.

**[0052]** Handle 22 enables the physician to extend and retract applicator 24 from within lumen 14 of

bronchoscope 10, and to manipulate distal end 23 of neurotoxin applicator assembly 20 under direct visual observation using the optics of bronchoscope 10. The neurotoxin applicator assembly preferably remains retracted within lumen 14 of the bronchoscope during insertion of the catheter into the patient's bronchial airways, and is deployed once the applicator is in a desired position. Alternatively, applicator 20 may be housed inside of a retaining sheath, and both units can be advanced through lumen 14 together.

**[0053]** Referring now to FIGS. 2-3, a first illustrative embodiment of applicator 24 of neurotoxin applicator assembly 20 constructed in accordance with the principles of the present invention is described. Applicator 24 comprises needle assembly 28 having at least one needle 30 with lumen 31 in fluid communication with lumen 25. The needles are configured to penetrate the airway epithelium and directly inject small amounts of neurotoxin from the syringe into the collagenous and smooth muscle layers of bronchial wall **B**.

**[0054]** In FIG. 3A, needle assembly 28 is depicted retracted with lumen 14 of bronchoscope 10. Alternatively, device 10 may comprise an outer sheath that is dimensioned to be slidably accept neurotoxin applicator assembly 20, and which is selectively retractable to expose needle assembly 28. Again, in the case where device 10 is an outer sheath, visualization could be achieved through a separate bronchoscope or through built-in optics. In a further embodiment, a retaining sheath housed within lumen 14 and covering applicator 20 is selectably retractable to expose needle assembly 28. As depicted in FIG. 3B, needles 30 comprise a material capable of retaining a preformed shape, such

as nickel-titanium, and are preformed to deflect radially outward when extended beyond distal end 13 of bronchoscope 10 (or the distal end of the outer sheath, if present). Each needle 30 optionally includes hilt 36 disposed a pre-selected distance from the distal end of the needle to control the depth of penetration of the needle tip into the bronchial wall.

**[0055]** When needle assembly 30 is deployed, as illustrated in FIGS. 2 and 3B, needles 30 penetrate target treatment area **T** of bronchial wall **B** so that neurotoxin may be injected in the bronchial wall. Syringe 26 may include graduations that enable the physician to inject a pre-determined amount of neurotoxin at each target treatment area.

**[0056]** Referring now to FIGS. 4 and 5, an alternative embodiment of applicator 24 of neurotoxin applicator assembly 20 is described. Applicator 24 in this embodiment comprises rotating needle assembly 38, including wheel 39 mounted to rotate about hub 40. While wheel 39 illustratively is round, it alternatively may comprise a ellipse or hexagon or other polygonal shape. Plurality of needles 41 is disposed around the circumference of the wheel, each needle 41 having lumen 42 in fluid communication with lumen 25 via a passageway in hub 40. Optional fender 45 protects a portion of the bronchial wall substantially opposite the target treatment area.

**[0057]** In FIG. 5A, rotating needle assembly 38 is shown retracted within outer sheath 37. Outer sheath 37 is dimensioned to fit within lumen 14 of bronchoscope 10, and may be selectively retracted to expose rotating needle assembly 38. Alternatively, rotating needle assembly 38 extends through lumen 14 and past the tip of

bronchoscope 10. In this embodiment, the wheel is covered by a retractable protection sheath which covers the wheel during insertion of the system. In FIGS. 4 and 5B, rotating needle assembly 38 is shown in the extended position. When so deployed, wheel 39 may be rolled across target treatment area **T**, so that as the wheel rotates needles 41 alternately penetrate and inject neurotoxin into bronchial wall **B**.

**[0058]** Suitable needles materials for needle assembly 28 of FIGS. 2-3 and rotating needle assembly 38 of FIGS. 4-5 include shape memory alloys such as nickel titanium alloys and spring tempered stainless steel alloys. Advantageously, either needle assembly permits direct injection of neurotoxin into the bronchial wall. This prevents the cilial transport system from trapping the neurotoxin and transporting it to other regions of the respiratory system, e.g., the oropharynx, where potentially unintended targets may be exposed to the neurotoxin, and prevents accidental exhalation of aerosolized neurotoxin.

**[0059]** Referring now to FIGS. 6 and 7, another alternative embodiment of applicator 24 of the neurotoxin applicator assembly of the present invention is described. Applicator 24 of FIGS. 6-7 comprises a needle-less injection assembly 46, which uses pressurized injection to deliver neurotoxin from the proximal controller to target treatment area **T**. Advantageously, the needle-less injection assembly allows controlled introduction of neurotoxin across the airway epithelium without the potential complications of introducing needles proximate to the delicate bronchial tissues, and may allow a lower profile system.

[0060] Needle-less injection assembly 46 comprises shaft 47 including at least one port 48 in fluid communication with lumen 25. Inflatable balloon 49 optionally may be coupled to shaft 47, and used to position the shaft adjacent target treatment area **T**. Balloon 49 is inflated with a fluid introduced through a lumen of shaft 47. When the shaft is aligned with the target treatment area, pulses of pressurized gas may be employed to inject predetermined amounts of neurotoxin across the airway wall and into the collagenous and smooth muscle layers.

[0061] In FIG. 7A, needle-less injection assembly 46, with balloon 49 deflated, is depicted housed within the lumen 14 of bronchoscope 10 (or a separate outer sheath). FIGS. 6 and 7B depict needle-less injection assembly 46 with balloon 49 inflated to place ports 48 in apposition to target treatment area **T**. Once the physician has confirmed placement of needle-less injection assembly 46, e.g., by visualization using the optics of bronchoscope 10, x-ray, fluoroscopy or other suitable means, a controller attached to the proximal end of neurotoxin applicator assembly 20 (instead of syringe 26), may be activated to deliver the desired doses of neurotoxin to the bronchial wall. As an alternative to the balloon 49, the assembly may have 2 or more needle-less injectors arranged to position against opposite walls of the bronchial passage. For instance, they might be spring loaded to expand the sections away from the midline and contact the bronchial wall. As a further alternative, the shaft of the assembly may be pre-curved or actively curved with an activation mechanism to urge the injector against the wall of the bronchial passage. Yet another alternative includes lower-pressure injection of

neurotoxin through port(s) 48, creating a weeping-balloon applicator. In this case, transport of neurotoxin across the epithelial surface is achieved by cellular endocytosis of the neurotoxin.

**[0062]** With respect to FIGS. 8 and 9, a yet further alternative embodiment of applicator 24 of the neurotoxin applicator assembly constructed in accordance with the present invention is described. Applicator 24 comprises nebulizer assembly 50 having shaft 55 with atomizer 51 disposed at its distal end and in fluid communication with central lumen 25. Atomizer 51 converts the liquid neurotoxin from the syringe into a fine spray or mist. Particle size of the mist can be controlled through nebulizer head design or by varying injection pressure in order to control the depth of penetration of the mist into the target segment.

**[0063]** Nebulizer assembly 50 may also include optional inflatable balloon 52 disposed on shaft 55 proximal of atomizer 51. Selective inflation of balloon 52 allows positioning of atomizer 51 so that aerosolized neurotoxin may be directly sprayed onto target treatment area **T**. Balloon 52 also acts to isolate the treatment area from the rest of the lung, preventing reflux of mist into unintended areas. As for the embodiment of FIGS. 6-7, balloon 52 may be inflated using a fluid introduced through an auxiliary lumen in shaft 55.

**[0064]** In FIG. 9A, the nebulizer assembly, including deflated balloon 52, is disposed within lumen 14 of bronchoscope 10, or alternatively, in an outer sheath that is slidably received in lumen 14. Alternatively, the nebulizer assembly may be inserted within a separate delivery sheath, with the bronchoscope inserted separately or with the optics and/or steering mechanisms

built into the nebulizer assembly. In FIGS. 8 and 9B, nebulizer assembly 50 is depicted deployed from lumen 14 (or the outer sheath, if present), with balloon 52 inflated. Advantageously, nebulizer assembly 50 can be dimensioned to access very small bronchial passageways, and also may be used to deliver neurotoxin to upstream regions of the lung.

**[0065]** Still referring to FIGS. 9A and 9B, shaft 55 optionally also may include an additional auxiliary lumen or lumens coupled to inlet port 53 and outlet port 54 disposed between the balloon and the atomizer. Inlet port 53 allows the introduction of gas (such as fresh air) near the target treatment area, while outlet port 54 allows air or gas mixed with atomized neurotoxin to be removed. Inlet and outlet ports 53 and 54 therefore provide a ventilation system that shields tissue adjacent and proximal to target treatment area **T** from being inadvertently exposed to the atomized neurotoxin. Inlet and outlet ports 53 and 54 further serve to either actively inflate and deflate the isolated segment, or simply to normalize pressure within the lung near the target treatment area. A control unit may be connected to the proximal outlets of ports 53 & 54 to control the introduction and removal of gases from the lung without allowing escape of atomized neurotoxin to the environment or patient.

**[0066]** According to some embodiments, the nebulizer assembly may be built into a single, disposable fiberoptic unit having a unidirectional tip-deflection element having an integral isolation balloon and aerosolizing tip. A neurotoxin containing canister can also be provided integral with the nebulizer assembly. Advantageously, such an assembly permits a much lower

profile, user-friendly system suitable for trans-nasal introduction past the vocal cords and into the lung.

**[0067]** With respect to FIGS. 10-13, another alternative embodiment of a neurotoxin applicator of the present invention is described. In this embodiment, neurotoxins or other therapeutic drugs are delivered to the patient's bronchial tree via sub-selective topical application of toxin to the bronchial lining. The applicator assembly may be inserted through the working channel of a bronchoscope (as in FIG. 1) and used to paint a solution containing neurotoxins onto the epithelial surface of the airways of the lung.

**[0068]** Referring now to FIG. 10, neurotoxin applicator assembly 60 comprises proximal shaft 62, spring-reinforced distal segment 64, and beveled distal tip 66 comprising a micro-porous filter material that functions as a topical applicator for the asthma-fighting solution. Distal segment 64 preferably is bendable into an infinite number of configurations having various radii of curvature. Additionally, torsional rotation of distal tip 66 is provided in response to torque applied to proximal shaft 62. In the illustrated embodiment, neurotoxin applicator assembly 60 comprises a wire-braid reinforced tube that provides desirable characteristics of high burst strength and good torque response, and may be formed of a nickel-titanium alloy.

**[0069]** Referring to FIGS. 11A-11C, curved distal segment 64 of neurotoxin applicator assembly 60 extends out of the tip of bronchoscope 70. Neurotoxin applicator assembly 60 preferably may be rotated with respect to and in conjunction with bronchoscope 70. The variable curve of distal segment 64 and the beveled termination of distal tip 66 provide intimate contact of distal tip 66

against bronchial walls having different diameters. The beveled distal tip 66 allows for easy introduction through the working channel of the bronchoscope 70. Distal segment 64 preferably is spring-biased into a curved configuration to permit self-adjustment of the device to a wide range of inner bronchial diameters. FIGS. 11 demonstrate that the curved distal segment will remain in contact with the walls of very small bronchi having a diameter of 5 mm or less (FIG. 11A), average bronchi having a diameter of 5 mm to 15 mm (FIG. 11B), as well as very large bronchi having a diameter of 15 mm or more (FIG. 11C).

**[0070]** In operation, the asthma-fighting solution is induced to flow through a central lumen running through neurotoxin applicator assembly 60. According to some embodiments, the rotation of distal tip 66 using torque applied at the proximal end of proximal shaft 62, in addition to proximal end pressure, is used to control the flow of solution through distal tip 66. This flow control aspect, in combination with the variable curve of distal segment 64, allows a rotational "painting" onto the walls of the bronchi.

**[0071]** Referring to FIG. 12, syringe 72 is employed to provide pressurization at the proximal end of neurotoxin applicator assembly 60 for controlling the flow of asthma-fighting solution through the central lumen and distal tip of the device. Syringe 72 comprises syringe barrel 73 and threaded plunger 74, which terminates in finger slot 75. A proximal end of syringe barrel 73 terminates in an outwardly-projecting rim 76, whereas a distal end of syringe barrel 73 is fixedly attached to the proximal end of torque-responsive neurotoxin applicator assembly 60. Syringe 73 preferably further

comprises a threaded half-collar 77 adapted to slide into place over syringe barrel 73 and threaded plunger 74. Half-collar 77 preferably comprises internal threads corresponding to the threads on threaded plunger 74. Moreover, half-collar 77 preferably further comprises a recess that engages rim 76. When slid into place over syringe 72, threaded half-collar 77 locks the threaded plunger in place with respect to the barrel.

**[0072]** When collar 77 is in place, rotation of syringe barrel 73 (e.g., in a clockwise direction) results in a controlled deflection of plunger 74 relative to barrel 73. The deflection of plunger 74 increases the pressure within the central lumen of neurotoxin applicator assembly 60, thereby causing a controlled amount of solution to be dispensed from distal tip 66. By altering the pitch of the thread on the plunger and half-collar, the volume of fluid dispensed per revolution may be varied. Since syringe barrel 73 is fixedly attached to torque-responsive neurotoxin applicator assembly 60, rotation of syringe barrel 73 results in corresponding rotation of distal tip 66. The half-collar may be removed from the assembly to allow conventional syringe operation for rapid filling or emptying of syringe 72.

**[0073]** Referring to FIG. 13, standard syringe 80 is attached to the proximal end of torque-responsive neurotoxin applicator assembly 60, which is disposed within bronchoscope 85. Syringe comprises syringe barrel 82 and non-threaded plunger 83. In this embodiment, a collar is not provided, and flow control is provided by manually modulating the force applied to plunger 83. The force applied to plunger 83, in addition to the rotation of syringe 80 (which causes corresponding rotation of

neurotoxin applicator assembly 60) dispenses the asthma-fighting solution onto the patient's bronchial walls.

**[0074]** In accordance with another aspect of the present invention, implantable devices and methods for treating asthma are described with respect to FIGS. 14-19. The bioabsorbable implants are employed to controllably introduce one or more neurotoxins into the walls of a patient's bronchial tree, which control asthma by disabling the hyperresponsive smooth muscle layer and controlling hypersecretion of mucus.

**[0075]** More specifically, delivery of neurotoxins or other therapeutic drugs to the bronchial tree is achieved through drug elution from bioabsorbable implants placed within the bronchial passages. The implants preferably are bioabsorbable, but alternatively may comprise permanent devices with refillable reservoirs as well as elution devices that may be removed and replaced at periodic intervals, e.g., when drug supplies are determined be depleted.

**[0076]** In accordance with the principles of the present invention, a system for treating asthma comprises one or more drug-eluting bioabsorbable stents. Referring to FIG. 14, stent 102 comprises a single wire 104 including a plurality of turns 106. According to some embodiments, the stent system comprises one or more discrete-length coiled stents. Alternatively, the stent system comprises one or more custom-length coiled stents, which are deployed and cut to length at the end point of delivery by a cutting mechanism that is part of the stent delivery system. Bioabsorbable stent 102 preferably is loaded with neurotoxin and/or other asthma-fighting drugs. Gradual elution of the neurotoxin and/or other asthma-fighting drugs treats the underlying inflammatory

disease that causes the asthmatic response. Advantageously, stent 102 also lends mechanical reinforcement to the patient's bronchi.

**[0077]** Referring to FIG. 15, alternative drug-eluting bioabsorbable stent 108 is shown, and comprises a plurality of wires 110 that are intertwined to form a slotted or knitted tube. As will be appreciated by those of skill in the art, many other known stent designs may be used to deliver the asthma-fighting drugs without departing from the scope of the present invention. Suitable materials for stents 102, 108 include PEG, PLLA, collagen and copolymers of these materials. Appropriate drugs include the array of steroids and bronchodilators that are currently used systemically to treat asthmatic conditions. Examples of other suitable asthma-fighting drugs include corticosteroid and albuterol.

**[0078]** Additionally, a neurotoxin composition such as botulinum toxin or tetanus may be delivered using the stent. According to some embodiments, stents 102 encapsulate the neurotoxin, releasing it gradually onto the bronchial wall, thereby greatly extending the effective working life of the neurotoxin past its usual 3+ month active lifespan.

**[0079]** Since the effect of neurotoxin on the smooth muscle and inflammatory responses related to asthma are not permanent, it is desirable to provide doses of neurotoxin that are automatically delivered at predetermined intervals. FIG. 16 is a cross-sectional view of stent wire 104 of drug-eluting bioabsorbable stent 102. Wire 110 forming drug-eluting bioabsorbable stent 108 may comprises a substantially similar cross-section.

**[0080]** In the illustrated embodiment, stent wire comprises alternating layers of drug-loaded and non-drug-loaded resorbable materials. More particularly stent wire 104 comprises inner drug-eluting layer 114 that is substantially circular in cross-section and barrier layer 116 disposed around the perimeter of inner layer 114. Stent wire 104 further comprises outer drug-eluting layer 118 surrounding barrier layer 116, and protective outer coating 120 surrounding outer layer 118. In this manner, the drug is loaded into the implant in discrete dosing layers 114, 118 and delivered at predetermined intervals.

**[0081]** After the drug-eluting stent is implanted within a patient's bronchial airways, protective outer coating 20 dissolves, thereby exposing outer drug-eluting layer 118. The outer layer is slowly absorbed, thus providing a first dose of asthma-fighting drugs to a target treatment area within the patient's bronchi. After outer layer 118 is absorbed, barrier layer 116 dissolves within the bronchi over a predetermined amount of time. Then, inner layer 114 is slowly absorbed, thereby providing a second dose of asthma-fighting drugs to the target treatment area. Of course, as would be understood by those of ordinary skill in the art, additional drug-eluting layers (and barrier layers) may be employed to deliver additional doses of asthma-fighting drugs at predetermined intervals without departing from the scope of the present invention. In this manner, the first dose is administered shortly after implantation, and then subsequent doses are released at predetermined intervals, for example every 3 months.

**[0082]** Delivery of the drug-eluting stents of the present invention preferably is achieved through the working channel of a conventional bronchoscope, either

oral or nasal, or through a custom device specifically designed for placing the loaded stents. Referring to FIG. 17, one or more drug-eluting bioabsorbable stents 102 are delivered to target treatment area within a patient's bronchi **B** through the working channel of bronchoscope 122. Stent 102 is a continuous length of coiled drug-loaded wire 104 that is initially delivered at the distal end of a target bronchial passage. Then, stent 102 is unwound along the target bronchial passage to the desired proximal termination point. Manipulation of the bronchoscope during deployment allows the physician to avoid placing coils across side branches of the bronchial tree. When the proximal termination point is reached, a cutting mechanism is used to cut the implant coil.

**[0083]** Alternatively, as depicted with respect to FIGS. 18 and 19, one or more discrete length drug-eluting bioabsorbable coiled stents 108, 130, may be deployed within the patient's bronchi **B**. Stents 108 and 130 are formed of wire segments that preferably include alternating layers of drug-loaded and non-drug-loaded materials, such as described with respect to FIG. 16. Stents 108 and 130 preferably are delivered through the working channel of a bronchoscope or through another delivery device. As would be understood by those of skill in the art, stents 108 and 130 may comprise any number of different sizes and configurations without departing from the scope of the present invention.

**[0084]** Deployment of the inventive stents described hereinabove may be accomplished using conventional stent delivery catheters and procedures, via either self-expansion or balloon expansion of the stents, by heating and setting a final size with a purpose-built delivery

system, or any other suitable procedure. Delivery may be achieved one stent at a time, or multiple implants may be placed from a single multi-stent delivery system.

**[0085]** Although preferred illustrative embodiments of the present invention are described above, it will be evident to one skilled in the art that various changes and modifications may be made without departing from the invention. It is intended in the appended claims to cover all such changes and modifications that fall within the true spirit and scope of the invention.

What is claimed is:

1. Apparatus for intrabronchial delivery of medication to treat lung disease, the apparatus comprising:

a shaft having a proximal end including at least one inlet port, a distal end and a lumen extending between the inlet ports and the distal end; and

a medication applicator disposed on the distal end of the shaft in fluid communication with the lumen.

2. The apparatus of claim 1, wherein the medication is a neurotoxin.

3. The apparatus of claim 1, further comprising a bronchoscope having proximal and distal ends, and a lumen extending therebetween, and wherein the shaft is dimensioned to slidably pass through the lumen of the bronchoscope.

4. The apparatus of claim 1, wherein the neurotoxin applicator includes a needle assembly.

5. The apparatus of claim 4, wherein the needle assembly has a retracted delivery position and a deployed position wherein at least one needle extends radially outward from the shaft to penetrate bronchial tissue.

6. The apparatus of claim 4, wherein the needle assembly comprises a wheel having a circumference and a plurality of needles disposed around the

circumference, wherein the plurality of needles are in fluid communication with the lumen of the shaft.

7. The apparatus of claim 6, wherein the wheel further comprises a hub that forms an axis of rotation for the wheel.

8. The apparatus of claim 6, wherein the wheel is adapted to be rolled across a target treatment area within a patient's bronchial airways.

9. The apparatus of claim 8, wherein the needle assembly further comprises a fender that protects an area of the patient's bronchial airways opposite the target treatment area.

10. The apparatus of claim 2, wherein the neurotoxin is a serotype of botulinum toxin.

11. The apparatus of claim 10, wherein the serotype of botulinum toxin is selected from the group consisting of serotype A and serotype B.

12. The apparatus of claim 2, wherein the neurotoxin is tetanus or a tetanus derivative.

13. The apparatus of claim 1, wherein the applicator uses pressurized fluid to inject neurotoxin into a target treatment area.

14. The apparatus of claim 13, wherein the shaft includes a portion defining a port in fluid communication with the lumen.

15. The apparatus of claim 13, further comprising a deflection means disposed on the shaft to position the port adjacent to the target treatment area.

16. The apparatus of claim 15, wherein the deflection means is an inflatable balloon.

17. The apparatus of claim 13, wherein the applicator further comprises an atomizer in fluid communication with the lumen.

18. The apparatus of claim 17, further comprising an inflatable balloon disposed proximal to the atomizer.

19. The apparatus of claim 18, further comprising at least one lumen disposed between the balloon and the atomizer to ventilate tissue adjacent the target treatment area.

20. The apparatus of claim 1 wherein the medication applicator comprises a micro-porous filter material.

21. The apparatus of claim 1 wherein the shaft is selectively bendable.

22. The apparatus of claim 1 wherein the shaft is steerable.

23. The apparatus of claim 1 further comprising an optical component disposed in operative relation to the medication applicator.

24. The apparatus of claim 20 further comprising a syringe coupled to the proximal end of the shaft for controlling the flow of medication.

25. Apparatus for treating lung disease by intrabronchial delivery of medication, the apparatus comprising:

an elongate shaft having a proximal end including at least one inlet port, a distal end and a lumen extending between the inlet port and the distal end; and

a medication applicator disposed on the distal end of the shaft in fluid communication with the lumen, the medication applicator having a contracted delivery position, and a deployed position adapted to deliver medication to a target tissue area of a patient's bronchial wall.

26. The apparatus of claim 25, wherein the neurotoxin applicator includes a needle assembly.

27. The apparatus of claim 25, wherein the needle assembly comprises at least one needle that extend radially outward from the shaft to penetrate bronchial tissue.

28. The apparatus of claim 25, wherein the needle assembly comprises a wheel having a circumference and a plurality of needles disposed around the circumference, wherein the plurality of needles are in fluid communication with the lumen of the shaft.

29. The apparatus of claim 28, wherein the needle assembly further comprises a fender that protects an area of the patient's bronchial airways opposite the target treatment area.

30. The apparatus of claim 25, wherein the neurotoxin is botulinum toxin.

31. The apparatus of claim 25, wherein the applicator uses pressurized fluid to inject neurotoxin into a target treatment area.

32. The apparatus of claim 31, wherein the shaft includes a portion defining at least one port in fluid communication with the lumen.

33. The apparatus of claim 25, wherein the applicator further comprises an atomizer in fluid communication with the lumen.

34. The apparatus of claim 25 wherein the medication applicator comprises a micro-porous filter material.

35. The apparatus of claim 25 wherein a distal portion of the elongated shaft is selectively bendable.

36. The apparatus of claim 25 further comprising a syringe coupled to the proximal end of the shaft for controlling the flow of medication.

37. Apparatus for intrabronchial delivery of medication to treat asthma, the apparatus comprising:

a drug-eluting bioabsorbable stent comprising one or more layers of asthma-fighting drugs.

38. The apparatus of claim 37, wherein the stent comprises a single wire including a plurality of turns.

39. The apparatus of claim 37, wherein the stent comprises a plurality of wires that are intertwined to form a slotted or knitted tube.

40. The apparatus of claim 37, wherein the asthma-fighting drug is a neurotoxin.

41. The apparatus of claim 40, wherein the neurotoxin is botulinum toxin

42. The apparatus of claim 40, wherein the neurotoxin is tetanus.

43. The apparatus of claim 37, wherein the asthma-fighting drug is a steroid or bronchodilator.

44. The apparatus of claim 37, wherein the stent comprises alternating layers of drug-loaded and non-drug-loaded resorbable materials.

45. The apparatus of claim 44, wherein the material for the non-drug-loaded resorbable materials is chosen from the group consisting of PLLA, collagen and copolymers of these materials.

46. The apparatus of claim 44, wherein the non-drug-loaded resorbable materials encapsulate the drug-loaded resorbable materials such that the asthma-fighting drug is released gradually into the bronchial airways.

47. The apparatus of claim 37, wherein the stent comprises:

an inner drug-eluting layer; and

a barrier layer disposed around the perimeter of the inner layer.

48. The apparatus of claim 47, further comprising:

an outer drug-eluting layer surrounding the barrier layer; and

a protective outer coating surrounding the outer layer.

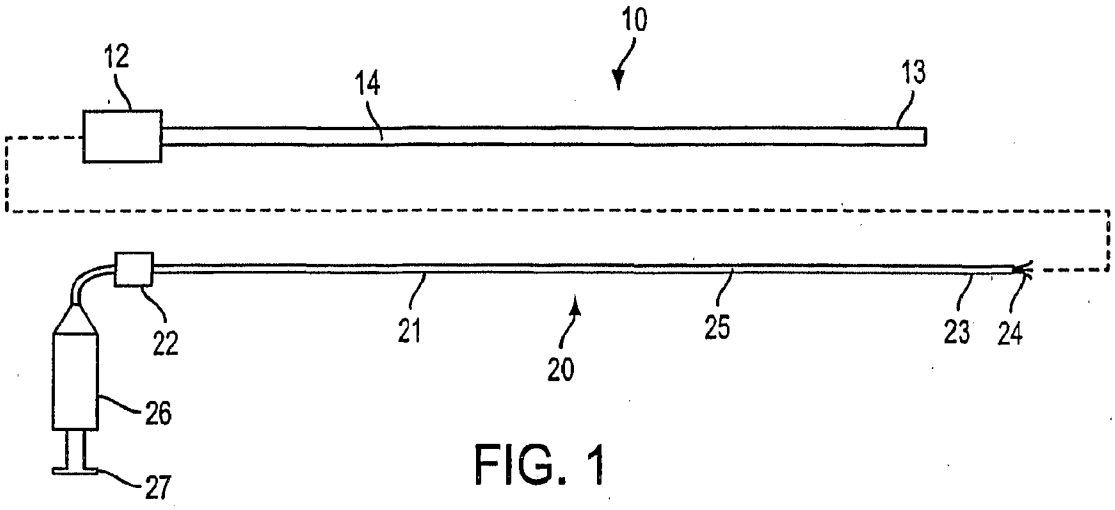



FIG. 1

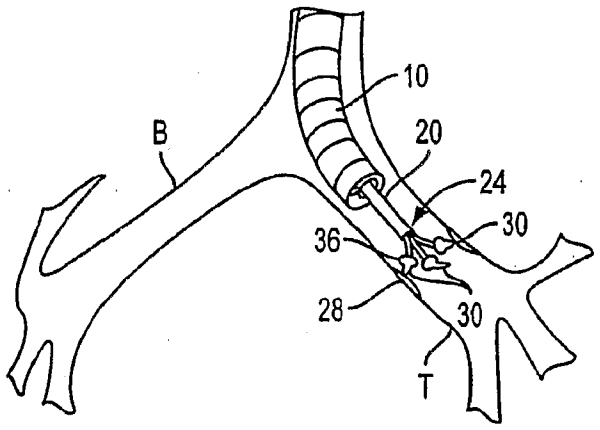



FIG. 2

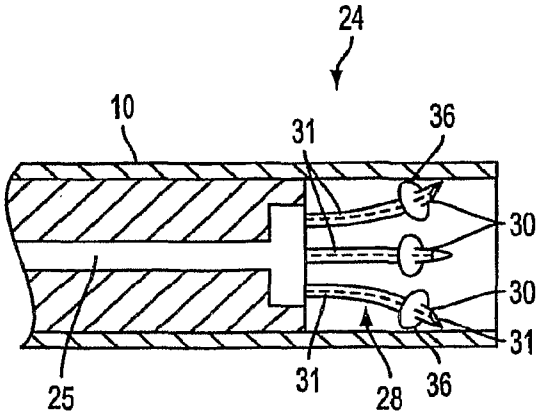



FIG. 3A

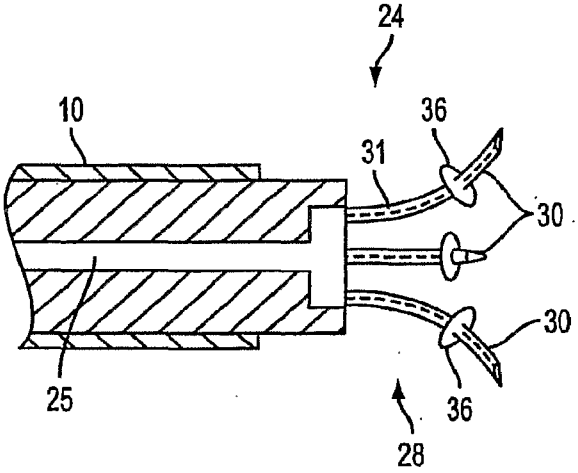



FIG. 3B

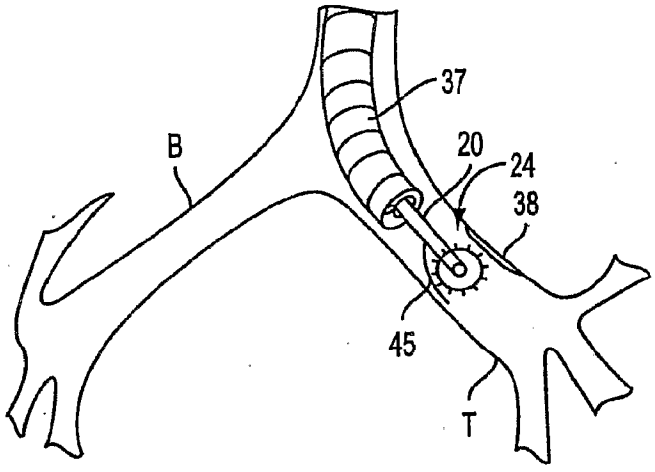



FIG. 4

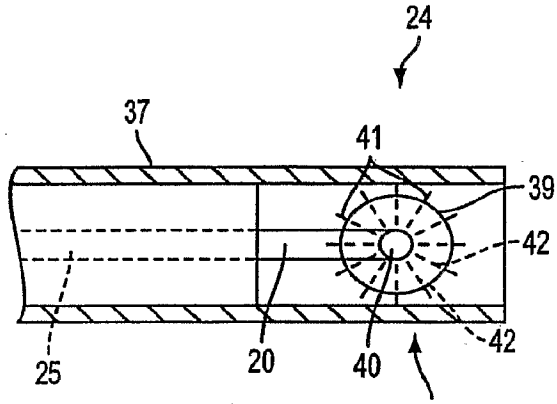



FIG. 5A

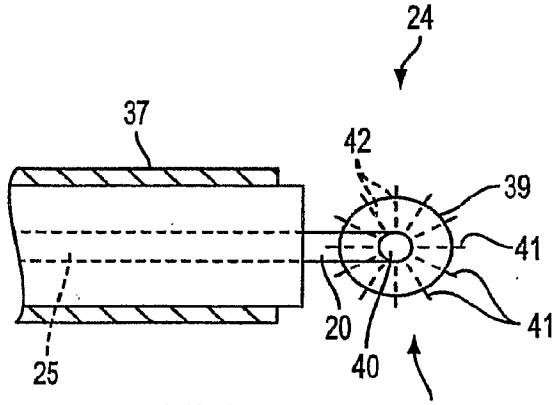



FIG. 5B

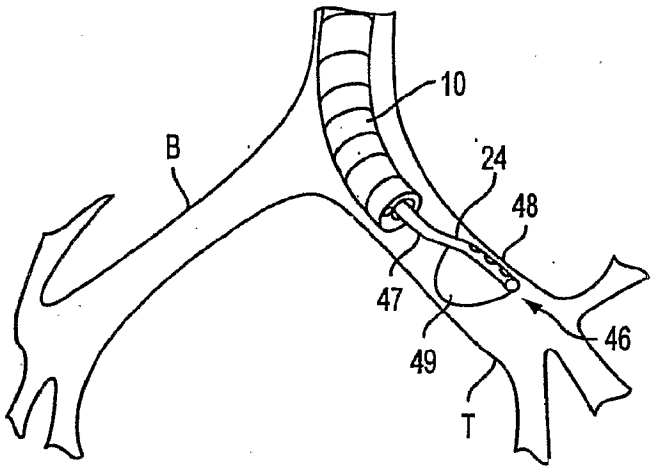



FIG. 6

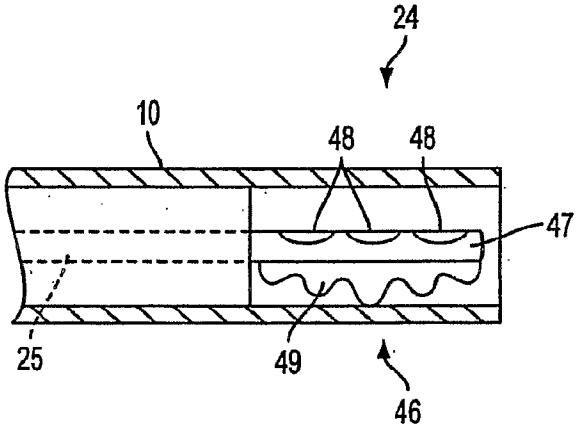



FIG. 7A

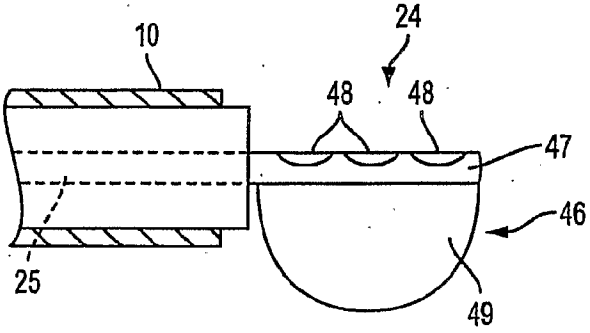



FIG. 7B

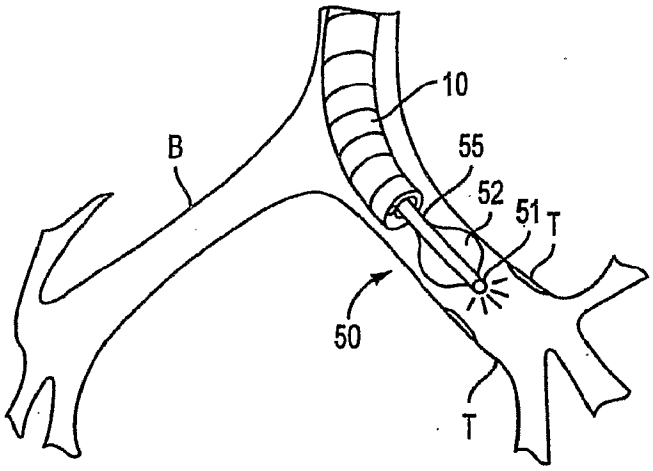



FIG. 8

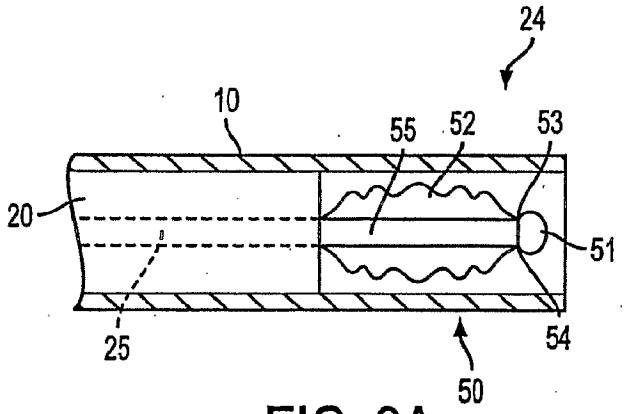



FIG. 9A

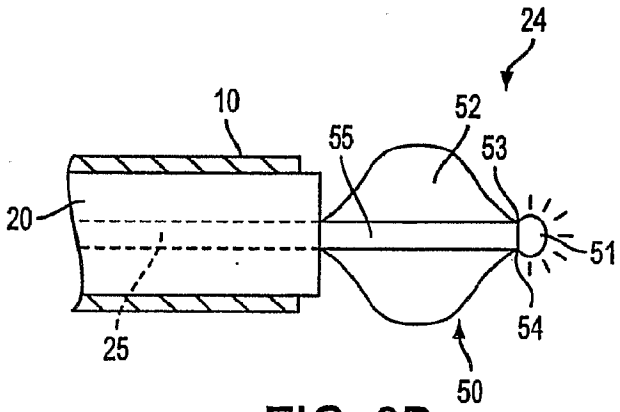



FIG. 9B

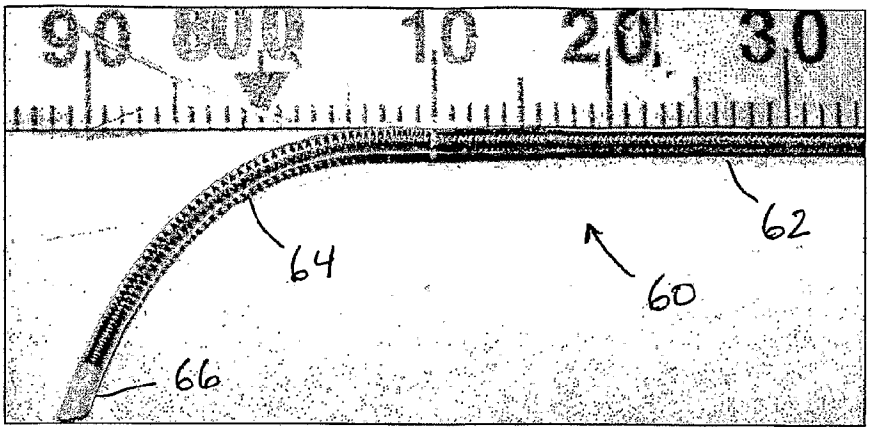



FIG. 10

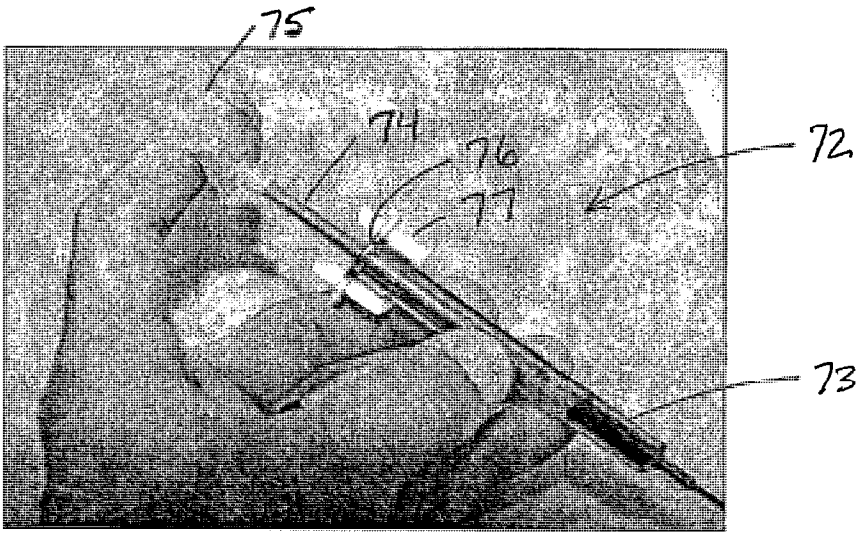



FIG. 12

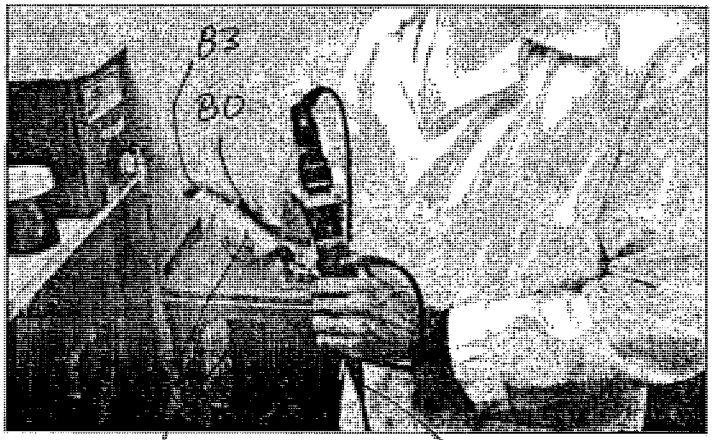



FIG. 13

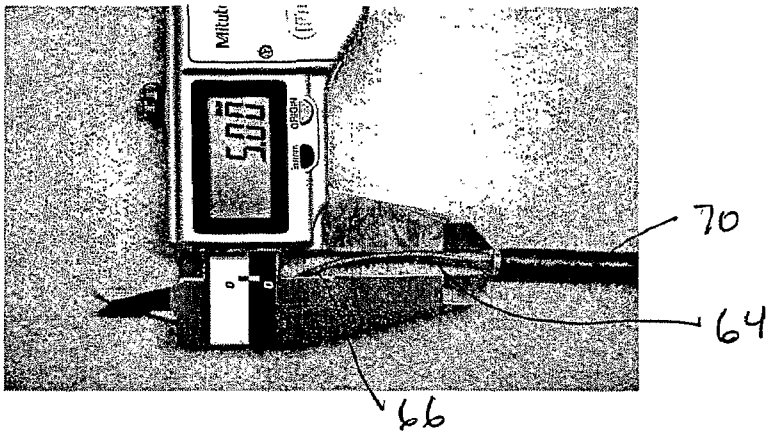



FIG. 11A

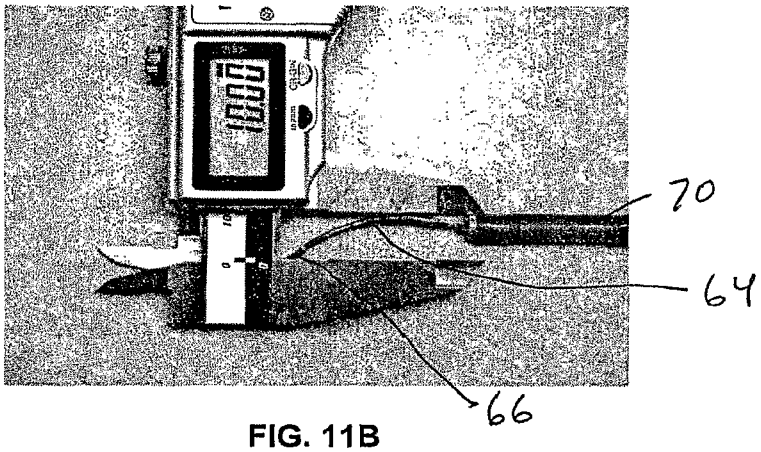



FIG. 11B

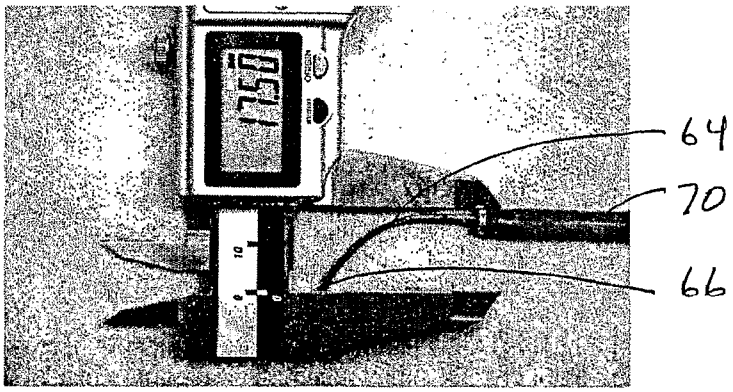



FIG. 11C

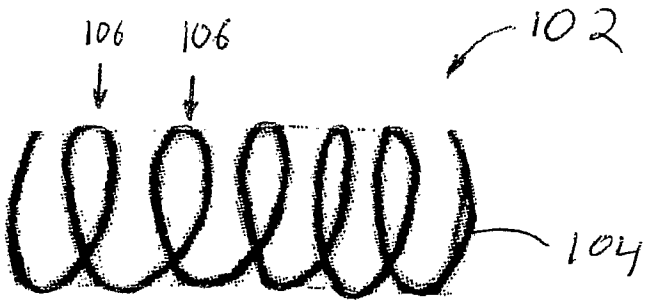



FIG. 14

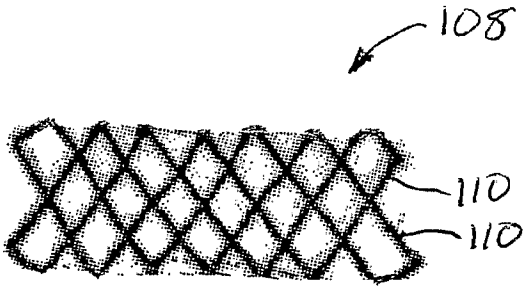



FIG. 15

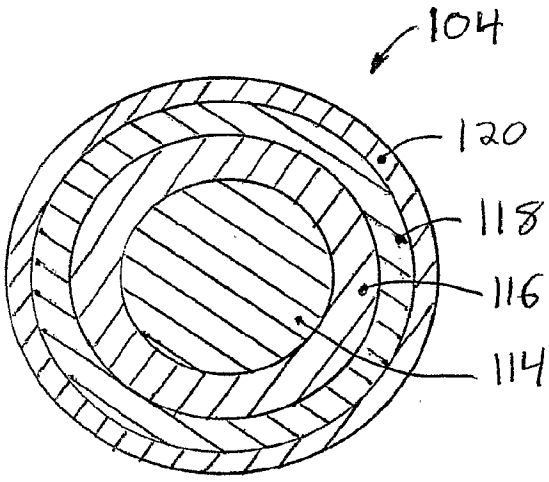



FIG. 16

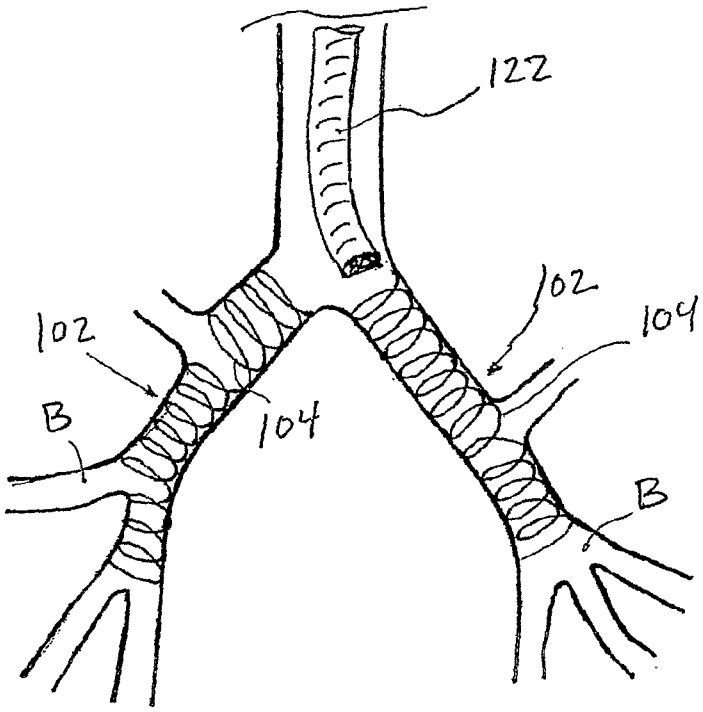



FIG. 17

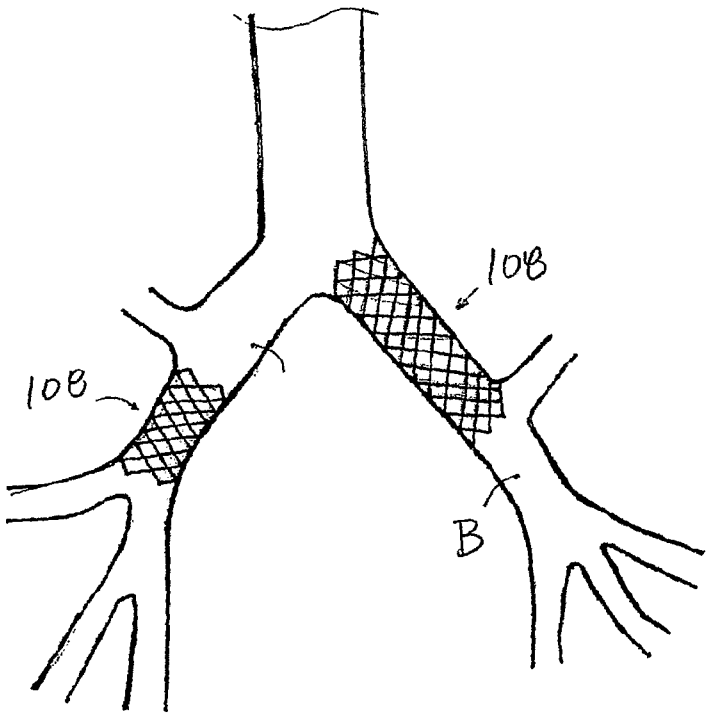



FIG. 18

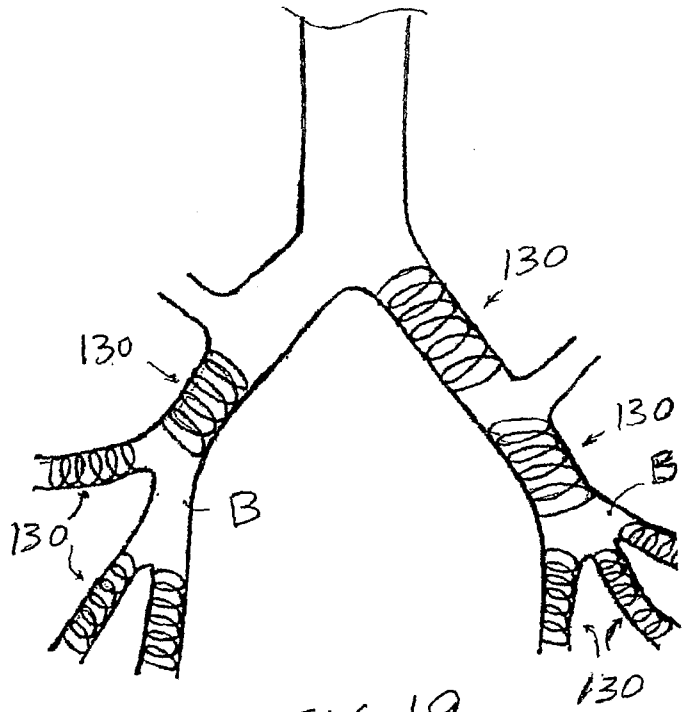



FIG. 19

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(74) Agents: **HESLIN, James** et al.; Townsend and Townsend and Crew LLP, Two Embarcadero Center, 8th Floor, San Francisco, CA 94111-3834 (US).

(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.

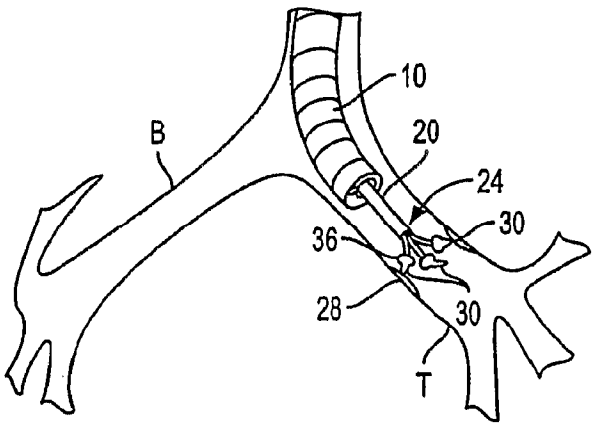
(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

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— *with international search report*
— *before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments*

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14 December 2006

*For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.*

(54) Title: APPARATUS AND METHODS FOR TREATING ASTHMA USING NEUROTOXIN




(57) Abstract: Apparatus providing intrabronchial delivery of neurotoxin to control the effects of asthma comprises a shaft having proximal and distal ends and a neurotoxin applicator assembly disposed on the distal end, wherein the neurotoxin applicator assembly comprises a deployable needle assembly, a rotating needle assembly, a needle-less injection assembly, a nebulizer assembly or a microporous tip. Further embodiments involve apparatus comprising drug-eluting bioabsorbable stents having one or more layers of asthma-fighting drugs.

WO 2004/101028 A3

# INTERNATIONAL SEARCH REPORT

International application No.
PCT/US04/15222

**A. CLASSIFICATION OF SUBJECT MATTER**
IPC: **A61M 16/00**( 2006.01)

USPC: 128/207.14
According to International Patent Classification (IPC) or to both national classification and IPC

**B. FIELDS SEARCHED**

Minimum documentation searched (classification system followed by classification symbols)
U.S. : 128/207.14, 207.15, 207.16, 200.14, 200.21, 200.18, 200.24

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

**C. DOCUMENTS CONSIDERED TO BE RELEVANT**

| Category * | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|---|---|---|
| X<br>---<br>Y | US 5,964,223 (BARAN) 12 October 1999 (12.10.1999), See Figures. | 1, 3, 25 |
| Y | US 5,766,605 A (SANDERS et al) 16 June 1998 (16.06.1998), column 7, lines 10-13 & column 10, lines 46-50. | 2, 4, 10-24, 26, 30-36 |
| A | US 6,546,932 B1 (NAHON et al) 15 April 2003 (15.04.2003), Figure 10. | 1-36 |
| A | US 2002/0111620 A1 (COOPER et al) 15 August 2002 (15.08.2002), Figure 5J. | 1-36 |

☐ Further documents are listed in the continuation of Box C.

☐ See patent family annex.

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| Date of the actual completion of the international search | Date of mailing of the international search report |
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| 06 April 2006 (06.04.2006) | 05 OCT 2006 |
| Name and mailing address of the ISA/US<br>Mail Stop PCT, Attn: ISA/US<br>Commissioner of Patents<br>P.O. Box 1450<br>Alexandria, Virginia 22313-1450<br>Facsimile No. (571) 273-3201 | Authorized officer<br>For Henry Bennett<br>Telephone No. (571) 272-0000 |

Form PCT/ISA/210 (second sheet) (July 1998)

# INTERNATIONAL SEARCH REPORT

International application No.
PCT/US04/15222

## Box I Observations where certain claims were found unsearchable (Continuation of Item 1 of first sheet)

This international report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claim Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claim Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claim Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

## Box II Observations where unity of invention is lacking (Continuation of Item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:
Please See Continuation Sheet

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☒ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.: 1-36

**Remark on Protest**

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.

Form PCT/ISA/210 (continuation of first sheet(1)) (July 1998)

**BOX II. OBSERVATIONS WHERE UNITY OF INVENTION IS LACKING**

This application contains claims directed to more than one species of the generic invention. These species are deemed to lack unity of invention because they are not so linked as to form a single general inventive concept under PCT Rule 13.1.

In order for more than one species to be examined, the appropriate additional examination fees must be paid. The species are as follows:

Group I, claim(s) 1-36, drawn to an apparatus for intrabronchial delivery of a medication using a medication applicator disposed on the distal end of a shaft.

Group II, claim(s) 37-48, drawn to an apparatus for intrabronchial delivery of medication using a drug-eluting bioabsorbable stent comprising one or more layers of drugs.

The species listed above do not relate to a single general inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, the species lack the same or corresponding special technical features for the following reasons: each group corresponds to a distinctly different means for intrabronchial delivery of medication.

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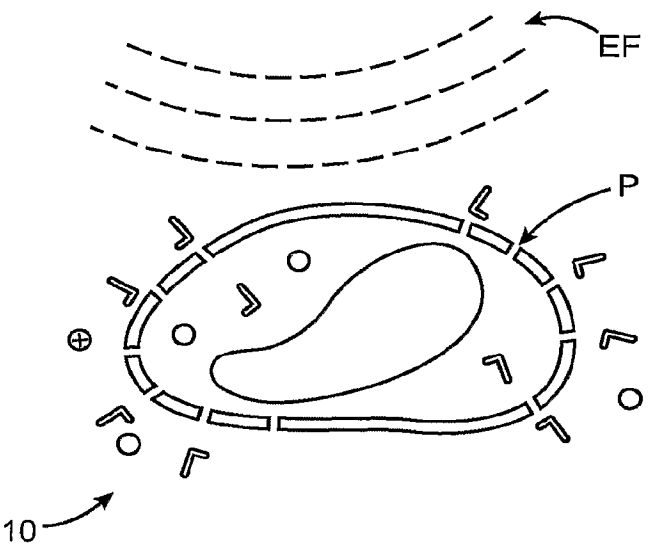
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(54) Title: SYSTEMS AND METHODS FOR DELIVERY OF A THERAPEUTIC AGENT




(57) Abstract: Methods and apparatus are provided for applying an fragment of a neurotoxin such as the active light chain (LC) of the botulinum toxin (BoNT), such as one of the serotype A, B, C, D, E, F or G botulinum toxins, via permeabilization of targeted cell membranes to enable translocation of the botulinum neurotoxin light chain (BoNT-LC) molecule across the targeted cell membrane to the cell cytosol where a therapeutic response is produced in a mammalian system. The methods and apparatus include use of catheter based delivery systems, non-invasive delivery systems, and transdermal delivery systems.

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# SYSTEMS AND METHODS FOR DELIVERY OF A THERAPEUTIC AGENT

## BACKGROUND OF THE INVENTION

**[0001]** 1. Field of the Invention. The present invention relates to methods and apparatus for the control of autonomic nerve function comprising delivery via permeabilization of targeted cell membranes a therapeutically effective amount of a portion or fragment of a neurotoxin such as botulinum toxin (BoNT), the active portion known as the light chain (LC), to cause a clinical benefit in various regions within the body.

**[0002]** First used for medical purposes over 20 years ago for treatment of blepharospasm and strabismus and other skeletal muscle abnormalities, certain neurotoxins have found widespread use in millions of patients worldwide for a variety of conditions.

**[0003]** Controlled injection of neurotoxins has become a common procedure to control skeletal muscle spasms. While the primary application of neurotoxins such as BOTOX®, commercially sold by Allergan, Inc. (Irvine, CA), has been focused on cosmetic applications, such as treatment of facial wrinkles, other uses for the compound are now common. Certain applications include treatment of cervical dystonia, tremor, headache (migraine), spasticity, torticollis, hemifacial spasm, blepharospasm, meige syndrome, spastic dysphonia, writers cramp, hyperhydrosis, hypersalivation, bladder dysfunction multiple sclerosis, spinal cord injury, cystic fibrosis, stroke paralysis, stuttering, and all types of pain.

**[0004]** *Clostridium botulinum* neurotoxins (BoNTs) block the release of acetylcholine from peripheral cholinergic nerve endings thereby disabling the release of neurotransmitters from the cells (Bigalke, H. and Shoer, L.F. (1999) *Clostridial Neurotoxins in Handbook of Experimental Pharmacology* 45, 407-443). This mechanism of action is well defined. Seven immunologically distinct serotypes of neurotoxin, designated types A through G, have been identified as discussed by Simpson, L.L., Schmidt, J.J. and Middlebrook, J.L. (1988) in *Methods Enzymol.* 165, 76-85. There are general structural and functional similarities among the various types of neurotoxins, but they all have preferred recipients, for example some favor use in humans and other in non-human species.

**[0005]** A frequently used neurotoxin for many applications in the human body is Botulinum Toxin Type A (BoNT\A), a protein produced by the bacterium Clostridium botulinum and sold commercially by Allergan, inc., as BOTOX®. Botulinum toxin blocks the release of neurotransmitter from the nerves that control the contraction of the target muscles. When used in medical settings, small doses of the toxin are injected into the affected muscles and block the release of a chemical acetylcholine that signals the muscle to contract. The toxin thus paralyzes or weakens the injected muscle.

**[0006]** In addition, use of neurotoxin for control of the following conditions has been proposed in United States Patents 6,063,768 to First, and 5,766,605 to Sanders, including: rhinorrhea, asthma, COPD, excessive stomach acid secretion, spastic colitis, otitus media, arthritis, tensoynovitis, lupus, connective tissue disease, inflammatory bowel disease, gout, tumors, musculo-skeletal abnormalities, reflex sympathetic dystrophies, tendonitis, bursitis, and peripheral neuropathy. Various other patents contemplate the use of a neurotoxin for additional applications such as, neuromuscular disorders (6,872,397), essential tremor (6,861,058), pancreatitis (6,843,998), muscle spasm (6,841,156), sinus headache (6,838,434), endocrine disorders (6,827,931), priapism (6,776,991), thyroiditis (6,773,711), cardiovascular disease (6,767,544), thyroid disorders (6,740,321), hypocalcemia (6,649,161), hypercalcemia (6,447,785), tardive dyskenesia (6,645,496), fibromyalgia (6,623,742), Parkinson's Disease (6,620,415) cerebral palsy (6,448,231), inner ear disorders (6,358,926), cancers (6,139,845), otic disorders (6,265,379), appetite reduction ((US2004/0253274), compulsive disorders (US2004/0213814, US2004/0213813), uterine disorders ((US2004/0175399), neuropsychiatric disorders (US2003/0211121), dermatological or transdermal applications (US2004/00091880), focal epilepsy (US2003/0202990) the contents of which are expressly incorporated herein by reference in their entirety.

**[0007]** The patent authors have further detailed devices and methods for treating asthma with local delivery of the intact botulinum toxin in United States Patent Application 10/437,882, filed on May 13, 2003, the contents of which are expressly incorporated by reference herein in its entirety.

**[0008]** Due to their extreme toxicity, neurotoxins are highly controlled and can have disastrous consequences if not used and controlled properly, especially when used *in vivo*. In addition, due to their toxicity, the body tends to build up a resistance to their use, resulting in

lower efficacy, the need for increased treatments, or the need to discontinue their use all together in certain patients.

**[0009]** In light of the foregoing, it would be desirable to provide methods and apparatus for delivering neurotoxins such as botulinum toxins non-toxically.

**[0010]** It would also be desirable to provide methods and apparatus for treating various conditions with a neurotoxin such as botulinum toxin fragments via *in vivo* cell permeabilization.

**[0011]** In would also be desirable to provide a system of devices, including catheters, trocars, needles, endoscopes, inhalers, nebulizers and aerosolizers and other mechanisms to deliver fragmented neurotoxins non-toxically.

**[0012]** Further, it would be desirable to couple energy delivery devices with the delivery of fragmented neurotoxins to deliver active neurotoxins, non-toxically, including catheter based energy systems, and non-invasive energy systems.

**[0013]** All publications and patents or patent applications mentioned in this specification are herein incorporated by reference to the same extent as if each individual publication, patent or patent application was specifically and individually so incorporated by reference.

## BRIEF SUMMARY OF THE INVENTION

**[0014]** According to the present invention, an active fragment (sometimes referred to as a catalytic portion) of a neurotoxin such as the botulinum neurotoxin (BoNT), preferably the light chain (LC) portion of BoNT, is delivered to target cells via cell membrane permeabilization. Such delivery provides a non-toxic delivery scheme for deriving a variety of clinical benefits. Although botulinum toxins are used broadly for a variety of clinical applications, the present invention provides enhanced methods of delivery and use of the isolated active fragments or portions of the toxin. Other neurotoxins which may be used in the methods and systems of the present invention include ricin and its active fragments, exotoxin A and its active fragments, diphtheria toxin and its active fragments, cholera toxin and its active fragments, tetanus toxin and its active fragments, and the like.

**[0015]** The present invention contemplates application to all of the conditions listed herein, collectively defined as "therapeutic target conditions", and any other conditions for which BoNT and other neurotoxins are known to or can be shown to provide a therapeutic benefit.

Certain examples have been detailed below for specific applications, but it is within the scope of the present invention that the methods and devices detailed herein have specific applications to many or all of the conditions wherein the intact neurotoxins have shown or proposed to show a therapeutic benefit or effect.

**[0016]** In one aspect of the present invention, BoNT-LC or other active neurotoxin fragment is delivered with the application of energy to achieve cell membrane permeabilization.

**[0017]** In another aspect of the present invention methods and apparatus are provided for altering autonomic nerve function by utilizing an electric field or ultrasonic energy generated by a pulse or pulses of a designated duration and amplitude to alter tissue at the cellular level via permeabilization of the cell membrane to facilitate the translocation of the BoNT-LC or other active neurotoxin fragment to the cell cytosol.

**[0018]** A further aspect of the invention is to provide methods and apparatus for treating or inhibiting a variety of diseases or syndromes that have an underlying neurogenic component, by disrupting the neurogenic activities of the promoters or mediators of the disease or syndrome. Such disruption is facilitated by delivering an active fragment of botulinum toxin, such as the light chain portion of botulinum toxin serotype A (BoNT-LC/A), in the presence of an electric field or ultrasonic energy applied to permeabilize the wall of targeted cell under conditions which induce reversible poration of the cellular membrane and efficient passage of the BoNT-LC fragment to the cell cytosol, its catalytic environment.

**[0019]** In addition to the methods described thus far, the present invention further provides systems for delivering toxins to target cells in a mammalian host. The target cells may be in any of the target regions described above or in any other target region which may benefit from the specific and enhanced delivery of a neurotoxin to cells within the region. Systems comprise catheter or other structure adapted to introduce the toxin or toxin fragment to a region adjacent the target cells. The systems further comprise an energy applicator for applying energy to the target cells under condition which cause poration of the cell membranes to enhance delivery of the toxins and/or their active fragments. The systems still further comprise a source of the toxin or active fragments suitable for introduction from the catheter or other delivery structure.

**[0020]** The energy applicator will typically be adapted to selectively apply energy to target cells within the region where the toxin is to be introduced, e.g., by focusing energy

distribution to the particular target cells or regions which are rich with the target cells. Alternatively, the energy applicator may be adapted to apply energy non-selectively within the target region where both target cells and other cell types may receive the energy.

**[0021]** In some instances, the toxin may comprise an intact toxin, but more usually will comprise an active toxin fragment as defined elsewhere in this application. In the exemplary embodiments, the active toxin fragment is the light chain fragment of the botulinum toxin (BoNT-LC). The light chain fragment may be derived from any one of at least botulinum toxins A, B, C, D, E, F, and G.

**[0022]** The energy applicators of the systems of the present invention may be adapted to apply electric energy, typically pulses between 1 V and 500 V to the targeted region. The electric energy may be radiofrequency (RF) energy, where the energy may be pulsed for durations between 5 microseconds to 100 milliseconds. Alternatively, the electrical energy can be direct current (DC), alternating current (AC), or combinations thereof.

**[0023]** In addition to electrical energy, the energy applicator may be adapted to deliver ultrasonic energy, X-ray beam energy, microwave energy, or any other energy type which can achieve a reversible poration of the target cell walls.

**[0024]** There are at least two general power categories of medical ultrasound waves which may be utilized in the present invention. One category of medical ultrasound wave is high acoustic pressure ultrasound. Another category of medical ultrasound wave is low acoustic pressure ultrasound. Acoustic power is expressed in a variety of ways by those skilled in the art. One method of estimating the acoustic power of an acoustic wave on tissue is the Mechanical Index. The Mechanical Index (MI) is a standard measure of the acoustic output in an ultrasound system. High acoustic pressure ultrasound systems generally have a MI greater than 10. Low acoustic pressure systems generally have a MI lower than 5. For example, diagnostic ultrasound systems are limited by law to a Mechanical Index not to exceed 1.9. Another measurement used by those skilled in the art is the spatial peak, peak average intensity (Isppa). The intensity of an ultrasound beam is greater at the center of its cross section than at the periphery. Similarly, the intensity varies over a given pulse of ultrasound energy. Isppa is measured at the location where intensity is maximum averaged over the pulse duration. Isppa for high acoustic pressure or high intensity focused ultrasound (HIFU) applications ranges from approximately 1500W/cm2. to 9000 $W/cm_2$. Diagnostic ultrasound equipment, for instance, will generally have, and an Isppa less than 700 $W/cm_2$.

Yet another way in which ultrasound waves can be characterized is by the amplitude of their peak negative pressure. High acoustic pressure or HIFU applications employ waves with peak amplitudes in excess of 10MPa. Low acoustic pressure ultrasound will generally have peak negative pressures in the range of 0.01 to 5.0 MPa . Diagnostic ultrasound equipment, for example, will generally have a peak amplitude less than 3.0MPa. Both high and low acoustic pressure ultrasound systems generally operate within the frequency range of 20KHz – 10.0 MHz Interventional applications (such as in blood vessels) operate clinically up to about 50 MHz. Also opthalmologic applications up to about 15 MHz. Diagnostic imaging typically uses frequencies of about 3 to about 10 MHz. Physical therapy ultrasound systems generally operate at frequencies of either 1.0MHz or 3.3MHz. High acoustic pressure ultrasound or high intensity focused ultrasound has been used for tissue disruption, for example for direct tumor destruction. High intensity focused ultrasound using high acoustic pressure ultrasound is most commonly focused at a point in order to concentrate the energy from the generated acoustic waves in a relatively small focus of tissue.

**[0025]** Systems and methods for permeabilization of target tissue cell membranes according to the present invention may employ either high acoustic pressure or low acoustic pressure ultrasound. Some embodiments may preferably employ relatively low acoustic pressure, for example the systems described herein where the transducers are mounted on the delivery devices and operate inside the body. Other systems may operate at interim acoustic pressure ranges. For example, systems described herein which employ an external ultrasound generator and transducer and which conduct the ultrasound to the target tissues through the use of a wave guide. In these systems, losses due to transduction through the wave guide can be compensated for by increasing the input power to the wave guide until adequate power is delivered to the target tissue. Finally, some systems described herein may employ focused or partially focused higher pressure ultrasound, for example the systems which employ an external mask to conduct the ultrasonic power through the tissues to the target tissues. It should be appreciated that combinations of high and low acoustic pressure systems may also be employed.

**[0026]** The catheter or other structure may be adapted to introduce the toxin to the target cells in a variety of ways. For example, catheters may comprise a needle for injecting the toxin, optionally a needle which is deployable axially or radially from the catheter body.

Alternatively or additionally, catheters may be provided with nozzles or other ports for aerosolizing the toxin, particularly within regions of the lung as described herein. Still further alternatively or additionally, the catheters may comprise balloons or other expandable elements for deflecting an end of the catheter to engage one or more ports on the catheter against the tissue where the toxin fragments are released through the port(s). In a specific embodiment, the ports may be in the balloon itself where the toxin fragments are released through the ports in the balloon as the balloon is inflated with the medium containing the fragments. With such balloon embodiments, the electrodes or other energy transducers will typically be located within the balloon for applying the poration energy to the target tissue. Further optionally, the energy applicators may be mounted directly on the catheters, for example in the form of acoustic transducers, RF or other electrical electrodes, or the like. Alternatively, the energy applicator may be provided separately from the toxin delivery catheter or other source, typically being an external source, such as an external high intensity focused ultrasound (HIFU) source or an external electrode array for delivering radiofrequency or other electroporation energy.

**[0027]** In a further aspect of the invention, it may be desirable to provide methods and devices that utilize a non-toxic delivery mechanism to target cells to reduce the potential for an immunogenic response to the delivered toxin over time.

**[0028]** In a further aspect of the invention, it may be desirable to deliver the therapeutic neurotoxin fragment and energy via a catheter.

**[0029]** In a further aspect of the invention, it may be desirable to deliver the therapeutic neurotoxin fragment via an aerosolizer or nebulizer.

**[0030]** In a further aspect of the invention, it may be desirable to deliver the therapeutic neurotoxin fragment via an inhaler.

**[0031]** In a further aspect of the invention, it may be desirable to deliver the therapeutic neurotoxin fragment and membrane transport energy transdermally.

**[0032]** In a further aspect of the invention, it may be desirable to deliver the therapeutic neurotoxin fragment via a catheter, or aerosolizer or inhaler, and the energy via a catheter placed in the vicinity of the targeted cell.

**[0033]** In a further aspect of the invention, it may be desirable to delivery the therapeutic neurotoxin fragment and the membrane transport energy via an implantable generator and drug delivery pump.

**[0034]** In a further aspect of the invention, it may be desirable to deliver the therapeutic neurotoxin fragment via a catheter, or aerosolizer (nebulizer) or inhaler, and the energy via an external energy source adapted to target the applied energy in the vicinity of the targeted cell.

## BRIEF DESCRIPTION OF THE DRAWINGS

**[0035]** Further features of the invention, its nature and various advantages will be more apparent from the accompanying drawings and the following detailed description, in which:

**[0036]** Figure 1 – depicts a schematic of the creation of neurotoxin Botulinum Toxin Type A (BoNT/A), including the light chain (LC) fragment or portion.

**[0037]** Figure 2A – depicts a schematic of a target cell, including the cell membrane, and inner cellular matrices.

**[0038]** Figure 2B – depicts a schematic of the target cell wherein LC molecule has been introduced.

**[0039]** Figure 3A-3B – depicts a the target cell of Figure 2 showing application of an energy field (EF) to produce permeabilization or pores (P) in the cell membrane, and introduction of the LC fragment therethrough.

**[0040]** Figure 4 – depicts a schematic of a cell wherein the energy field has been discontinued, and neurotransmission of the cell has been effectively blocked.

**[0041]** Figures 5, 5A-5B – depicts various embodiments of a delivery device of the present invention utilizing multiple energy transmission elements and an energy transmission system.

**[0042]** Figures 6A-D, 6AA, and 6CC – depict various electrode catheter configurations adapted to deliver energy or energy and therapeutic agents to target tissue.

**[0043]** Figure 7 – depicts an alternative embodiment of the present invention wherein one of the multiple energy transmission elements is placed at the targeted cell site, and the other in a location remote therefrom.

**[0044]** Figure 8 - depicts an embodiment of the present invention utilizing an ultrasound element on a catheter device.

**[0045]** Figure 9 - depicts an embodiment of the present invention utilizing an inhaler with an *in vivo* energy delivery source.

**[0046]** Figure 10 - depicts an interstitial method of use of the present invention.

**[0047]** Figure 11 – depicts an embodiment of the present invention utilizing an aerosolizing element.

**[0048]** Figure 12 – depicts a fully implantable pulse generator, lead and agent delivery pump of the present invention.

**[0049]** Figure 13 – depicts an embodiment of the present invention utilizing an external energy delivery source applied to the therapeutic agent applied in the vicinity of a targeted cell.

**[0050]** Figure 14 – depicts an embodiment of the present invention wherein the energy and therapeutic agent are delivered transdermally.

**[0051]** Figure 15 – depicts a method of use of a noninvasive agent delivery device coupled with a non-invasive energy source for treating a lumen or tract of the respiratory system.

**[0052]** Figures 15A and 15B – depict use of a balloon for delivering toxin fragments in a lung.

**[0053]** Figures 16A and 16B – depict use of a deflected catheter tip for delivering toxin fragments in a lung.

## DETAILED DESCRIPTION OF THE INVENTION

**[0054]** The present invention is directed to methods and apparatus for targeting the non-toxic delivery of a fragment of a neurotoxin, while still maintaining the catalytic or toxic effect of the neurotoxin fragment once it is non-toxically delivered to its targeted cell. For purposes of this specification, the term "non-toxic", "non-toxically" and the like refer to the state of the fragment molecule prior to delivery to a target location. In this description, the fragment neurotoxin is intended to retain its toxic effect once delivered to its catalytic environment; the intracellular matrix or cytosol of the targeted cell.

**[0055]** Devices and methods of the present invention may be directed to suitable "targeted regions" such as muscle cells in various regions of the body related to the various "therapeutic target conditions" or syndromes to be treated, as detailed in this specification

above. Some particular examples include targeting mucosal and muscular lining of the lung, cholinergic cells in the region of tumors, myofacial regions, vascular smooth muscle cells, musculoskeletal regions and the like.

**[0056]** According to the present invention, energy fields (EF) may be applied to target regions in conjunction with the delivery of a fragmented neurotoxin such as BoNT-LC to facilitate the transfer of the neurotoxin fragment into the targeted cell, non-toxically via *in vivo* target cell permeabilization.

**[0057]** Use of Isolated Light Chain of Botulinum Neurotoxins. Generally, the BoNT molecule is synthesized as a single polypeptide chain of 150kD molecular weight. The neurotoxin is then exposed to enzymes, either during cultivation of the *Clostridium botulinum* organism or subsequent to purification of the toxin, wherein specific peptide bonds are cleaved or "nicked" resulting in the formation of a dichain molecule referred to as BoNT. As shown in Figure 1, dichain neurotoxin is composed of a light chain (LC) region 50kD molecular weight linked by disulfide bonds to a heavy chain (HC) 100kD molecular weight (Kistner, A., Habermann, E. (1992) *Naunyn Schmiedebergs Arch. Pharmacol.* 345, 227-334). When the light chain is separated from the heavy chains of botulinum toxin, neither chain is capable of blocking neurotransmitter release, however, the light chain alone is capable of blocking acetylcholine release if transported directly into the cell cytosol. (Ahnert-Hilger, G., Bader, M.F., Bhakdi, S., Gratzl, M. (1989) *J. Neurochem.* 52, 1751-1758 and Simpson, L.L. (1981) *Pharmacol. Rev.* 33, 155-188.) Focusing on the light chain, the isolation or separation process essentially renders the light chain "non-toxic" in a general environment, while still maintaining its effect or toxicity, once it is transported through the target cell membrane.

**[0058]** Over the past several years, the separation and purification of the light chain and heavy chain of BoNT has seen significant development activity. In the case of the heavy chain (HC), researchers are interested in its ability to bond with a target cell and deliver certain molecules into that cell. For example, various drug delivery applications have been suggested, for example, using the HC to bind to tPA so that a patient could inhale the HC-bound tPA allowing it to cross the membrane of the lungs and be transported into the bloodstream for anticoagulation. Of particular interest to the present invention are the efforts to isolate and purify the light chain (LC) of the botulinum molecule. In its isolated and purified form, all HC elements are removed, rendering the LC incapable of crossing the cell

membrane without assistance. Thus, the LC is non-toxic until delivered to the target cell cytosol by the delivery protocols of the present invention.

**[0059]** Various groups have been active in the area of isolation and purification. For example, companies such as Metabiologics, a group affiliated with the University of Wisconsin, the Center for Applied Microbiology and Research (CAMR), a division of the UK Health Protection Agency, List Biological Laboratories, Inc. of California, and other research groups throughout the world. Many of these companies provide purified preparations of botulinum neurotoxins from *Clostridium botulinum* types A and B. List Laboratories in particular provides recombinantly produced light chains from both types A, B, C, D and E.

**[0060]** According to the present invention, the therapeutic use and delivery of the light chain only may significantly improve the safety profile of certain applications of therapies utilizing BoNT. BoNT are some of the most lethal toxins known to man. All concerns about migration of the neurotoxin into unintended regions, and harm or toxicity to the patient or physician are eliminated by storing, handling, injecting and metabolizing the light chain only. In the absence of a specific membrane binding technology, the LC is completely non-toxic. In certain applications, such as the treatment of asthma, this is of critical import. In using BoNT to treat asthma, a large quantity of the purified LC substance may be introduced directly into the lung, and then specifically transported to target cells in the exact location and only during the period of use of application of the membrane transport technology, such as cell membrane permeabilization by energy. Once the membrane transport technology has been removed, turned off or otherwise inactivated, the remaining LC which has not been transported into target cells can simply be removed from the body by standard biologic processes for expelling foreign materials, e.g. coughing, immune system or lymphatic system transport and the like.

**[0061]** In addition, therapeutic use of only the LC of the neurotoxin BoNT may reduce the likelihood of the body developing an immunogenic response to the therapy that is seen with delivery of the intact toxin. This could be a major advantage in light of the repetitive application or injection of the toxin that is required to maintain a therapeutic effect.

**[0062]** Non-Toxic Membrane Transport Mechanisms. To date, the main application of purified or isolated light chain has been the study of its mechanism of action. To further this research, literature has reported the use of certain detergent based permeabilization

techniques to deliver fragment BoNT (Bittner MA, DasGupta BR, Holz RW. Isolated light chains of botulinum neurotoxins inhibit exocytosis. Studies in digitonin-permeabilized chromaffin cells. J Biol Chem 1989 Jun 25; 264(18):10354–10360.) Further reference to the mechanism of permeability of cell membranes to deliver botulinum toxin are mentioned in United States Patent 6,063,768 to First, and United States Patent No. 6,632,440 to Quinn, Chaddock, et al "Expression and Purification of Catalytically Active Non-Toxic Endopeptidase Derivatives of Clostridium botulinum toxin type A", *Protein Expression and Purification*, 25 (2002) 219-228, contemplating the insertion of the light chain of BoNT into a target cell without the heavy chain for purposes of deriving vaccines or in bench top studies of cell mechanisms of action. The contents of these references are expressly incorporated by reference in their entirety. None of the teachings contemplate a delivery of a fragment of neurotoxin using a clinically acceptable permeabilization technique *in vivo* for therapeutic uses as is contemplated by the present invention.

**[0063]** For purposes of this specification, the term "poration" includes various forms of electroporation, such as the use of pulsed electric fields (PEFs) , nanosecond pulsed electric fields (nsPEFs), ionophoreseis, electrophoresis, electropermeabilization, as well as other energy mediated permeabilization, including sonoporation (mediated by ultrasonic or other acoustic energy), and/or combinations thereof, to create temporary pores in a targeted cell membrane. Similarly, the term "electrode" or "energy source" used herein, encompasses the use of various types of energy producing devices, including x-ray, radiofrequency (RF), DC current, AC current, microwave, ultrasound, adapted and applied in ranges to produce membrane permeabilization in the targeted cell.

**[0064]** Reversible electroporation, first observed in the early 1970's, has been used extensively in medicine and biology to transfer chemicals, drugs, genes and other molecules into targeted cells for a variety of purposes such as electrochemotherapy, gene transfer, transdermal drug delivery, vaccines, and the like.

**[0065]** In general, electroporation may be achieved utilizing a device adapted to activate an electrode set or series of electrodes to produce an electric field. Such a field can be generated in a bipolar or monopolar electrode configuration. When applied to cells, depending on the duration and strength of the applied pulses, this field operates to increase the permeabilization of the cell membrane and reversibly open the cell membrane for a short period of time by causing pores to form in the cell lipid bilayer allowing entry of various therapeutic elements

or molecules, after which, when energy application ceases, the pores spontaneously close without killing the cell after a certain time delay. As characterized by Weaver, *Electroporation: A General Phenomenon for Manipulating Cells and* Tissues Journal of Cellular Biochemistry, 51:426-435 (1993), short(1-100μs) and longer (1-10ms) pulses have induced electroporation in a variety of cell types. In a single cell model, most cells will exhibit electroporation in the range of 1-1.5V applied across the cell (membrane potential).

**[0066]** In addition, it is known in the art that macromolecules can be made to cross reversibly created pores at voltages of 120V or less applied to cells for durations of 20 microseconds to many milliseconds. For applications of electroporation to cell volumes, ranges of 10 V/cm to 10,000 V/cm and pulse durations ranging from 1 nanosecond to 0.1 seconds can be applied. In one example, a relatively narrow (μsec) high voltage (200V)pulse can be followed by a longer (>msec) lower voltage pulse (<100V). The first pulse or series of pulses open the pores and the second pulse or series of pulses assist in the movement of the BoNT-LC across the cell membrane and into the cell.

**[0067]** Certain factors affect how a delivered electric field will affect a targeted cell, including cell size, cell shape, cell orientation with respect to the applied electric field, cell temperature, distance between cells (cell-cell separation), cell type, tissue heterogeneity, properties of the cellular membrane and the like.

**[0068]** Various waveforms or shapes of pulses may be applied to achieve electroporation, including sinusoidal AC pulses, DC pulses, square wave pulses, exponentially decaying waveforms or other pulse shapes such as combined AC/DC pulses, or DC shifted RF signals such as those described by Chang in *Cell Poration and Cell Fusion using and Oscillating Electric Field*, Biophysical Journal October 1989, Volume 56 pgs 641-652, depending on the pulse generator used or the effect desired. The parameters of applied energy may be varied, including all or some of the following: waveform shape, amplitude, pulse duration, interval between pulses, number of pulses, combination of waveforms and the like.

**[0069]** A schematic example of the methods of the present invention are shown in Figures 2-4 in a simplified single cell model. A targeted cell 10 is shown in Figure 2A. Fragmented neurotoxin such as BoNT-LC (LC) is introduced into the vicinity of the targeted cell as depicted in Figure 2B. An energy field (EF) is applied in accordance with the present invention resulting in the transfer of the BoNT-LC through pores P to the intracellular matrix (cytosol) as shown in Figures 3A and 3B. Once this transfer has occurred, the release of

neurotransmitters of the target cell are then blocked or disrupted, and once energy application is discontinued, the pores P in the cell membrane recover or close as depicted in Figure 4.

**[0070]** Of particular interest for application in certain therapeutic target conditions is the developing field of sonoporation. Just as pulses of high voltage electricity can open transient pores in the cell membrane, ultrasonic energy can do the same. See for example Guzman et al. "Equilibrium Loading of Cells with Macromolecules by Ultrasound: Effects of Molecular Sizing and Acoustic Energy," *Journal of Pharmaceutical Sciences*, 91:7, 1693-1701, which examines the viability of ultrasound to deliver molecules of a variety of sizes into target cells. In addition, techniques for nebulizing fluids and aqueous drugs are well known in the art, and as such, devices of the present invention may be adapted to introduce a BoNT-LC solution to a target region, such as the lung and then effect selective membrane transport of the BoNT-LC into the cell using sonoporation.

**[0071]** For example, United States Patent 6,601,581 to Babaev, hereby incorporated by reference in its entirety, describes certain techniques for delivering therapeutic agents using ultrasound for pulmonary delivery via an aerosolizing technique. Further, Guzman, et al, depicts delivery of molecules from a low of 62Da up to 464 kDa (a range of 0.6-18.5nm radius). Since the LC of the botulinum toxin is in the 50kDa range, the LC would be very susceptible to sonoporetic delivery. Furthermore, Guzman, et al also showed that for all size ranges tested, levels of macromolecule within the cell reached thermodynamic equilibrium with the extracellular environment, and the cell uptake also depended on the energy delivered, as expressed in $J/cm^2$. As such, the sonoporetic delivery of LC to the targeted regions may be controlled by adjusting the concentration of the LC exposed to the target region (e.g. wall or membrane of the lung), the energy delivered to the target region, or both.

**[0072]** Catheter Devices. To achieve the goals of the present invention, it may be desirable to employ methods and apparatus for achieving cell membrane permeabilization via the application of an energy source, either from a catheter located directly in the vicinity of the targeted cells, or an externally focused energy system. For purposes of this specification, the term "catheter" may be used to refer to an elongate element, hollow or solid, flexible or rigid and capable of percutaneous introduction to a body (either by itself, or through a separately created incision or puncture), such as a sheath, a trocar, a needle, a lead. Further descriptions of certain electroporation catheters are described in United States Patent Application

60/701,747 (Attorney Docket No. 020979-003500US), filed on July 22, 2005, the full disclosure of which is expressly incorporated herein by reference.

**[0073]** Figures 5 and 5A-5B depict a system 20 utilizing an electroporation catheter 22 for selective electroporation of targeted cells. In certain configurations of the present invention, voltages may be applied via the electroporation catheter 22 to induce reversible electroporation at the same time as the catheter delivers the fragmented neurotoxin to the targeted region.

**[0074]** Referring to Figure 5, electroporation catheter system 20 further comprises a pulse generator 24 such as those generators available from Cytopulse Sciences, Inc. (Columbia, MD) or the Gene Pulser Xcell (Bio-Rad, Inc.), or IGEA (Carpi, Italy), electrically connected to a catheter having a proximal end and a distal end and adapted for minimally invasive insertion into the desired region of the body as described herein. The catheter further comprises an electroporation element 26 at a distal 28 end thereof. The electroporation element may include for example a first and second electrode 30 and 32 operatively connected to the pulse generator for delivering the desired number, duration, amplitude and frequency of pulses to affect the targeted cells. These parameters can be modified either by the system or the user, depending on the location of the catheter within the body (intervening tissues or structures), and the timing and duration of reversible cell poration desired. Figure 5A depicts an arrangement of electrodes 30 and 32 that produces an electric field concentrated in a lateral direction from the catheter body whereas, Figure 5B shows a device constructed to create a more uniform electric field about the shaft of the catheter body.

**[0075]** Further catheter device and electrode configurations are shown in Figures 6A-6D. Figure 6A depicts an elongate catheter 40 having first and second electrodes 42 and 44 near the distal tip thereof, and including a monitoring or stimulation electrode 46 in the vicinity of the active porating electrodes for localizing the treatment area. In some embodiments, the monitoring or stimulating function may be performed by one or more of the treatment electrodes. The catheter device may have an optional sharp tip 48 to facilitate percutaneous introduction. Cross-sectional view Figure 6AA shows various lumens provided for neurotoxin fragment delivery and other purposes.

**[0076]** Figure 6B is a similar catheter device 50 having electrodes 52, 54, and 56, but is further adapted to be steerable, or articulate at a region 53 near the distal end of the device, e.g., including a pull wire for deflecting the tip. Such steering ability enables the operator to

introduce the device into tight or tortuous spaces (such as the bronchial passages or cardiovascular vessels) so that optimal placement of the device at the target location may be achieved.

**[0077]** Figure 6C depicts a catheter device 60 having a needle 62 or other injection element to allow for the injection of a therapeutic agent such as a fragmented neurotoxin before, during or after the application of the pulsed energy or electroporation. The catheter 60 further includes electrodes 64 and 66 or other poration components as discussed herein. The injection element may be a needle 62 as shown in Figure 6C, an infusion port, or other infusion means. Needle 62 may also be used as an electrode in addition to an injection port. Electrode 68 comprises a monitoring or stimulating electrode. Figure 10 depicts the use of a catheter of Figure 6C to treat bronchial tissue in the lung for a variety of respiratory ailments such as asthma. Figure 6CC is a cross-sectional view taken along line 6CC-6CC in Figure 6, showing a co-axial sleeve design.

**[0078]** Figure 6D depicts a catheter device 70 having electrode elements 72 and 74 that are adapted to extend laterally from the main catheter body, and in some cases, penetrate the surrounding tissue prior to application of energy. In doing so the depth and direction of the energy field created by the electroporative process, may be further controlled. A monitoring/stimulating electrode 76 will usually also be provided. Elements 72 and 74 may also be used as injection ports for introduction of toxin or toxin fragments.

**[0079]** Figure 7 depicts the use of a catheter device 80 of the present invention for treatment of a respiratory tract, by positioning at least one electrode (82) at the target region, and a second electrode (84) remote from the target region, the target region being positioned between 82 and 84, such that activation of the electrodes produces an energy field (EF) therebetween, the size and intensity of which can be controlled by the placement of the electrodes relative to each other and the targeted region.

**[0080]** Figure 8 depicts catheter 90 constructed in accordance with the principles of the present invention utilizing an ultrasonic element 92 that may be particularly useful in delivery of the BoNT-LC to bronchial tissue (lung) that provides a broad but targeted transport of the LC across the target cell walls, for example, epithelial and goblet cell walls. In this device, ultrasound energy is delivered to the distal end of the catheter device via an ultrasonic waveguide 94 that is operatively connected to an ultrasound energy source (U/SES). The LC fragment would be delivered from a receptacle 96 via the same lumen as the waveguide via a

lumen provided the distal tip of the device. In operation, the ultrasonic energy would cause the LC solution to be nebulized, forming a mist or aerosol 98 within the lung, as shown in Figure 11. The aerosol 98 itself, in the appropriate concentrations, may act as an ultrasound coupler, conveying the ultrasonic energy to the wall of the lung or other targeted cellular structures, causing sonoporation of the targeted cells whereby the LC fragment is transmitted across the cell membranes to become an effective neurotransmitter blocker. In an alternative embodiment, an ultrasonic transducer may be located directly at the tip of the delivery device, eliminating the need for a wave guide. Various catheters useful for delivering vibrational energy to tissue are described in United States Patent 6,361,554 and 6,464,680 to Brisken, the contents of which are expressly incorporated herein by reference in their entirety, for various therapeutic effects, such as enhancing cellular absorption of a substance.

**[0081]** Since air is a very effective insulator against transmission of ultrasonic energy, the treatment area in the lung may be more precisely controlled by the concentration of the LC mist and the intensity of the ultrasonic energy. A fairly steep drop off in energy delivery would occur as mist concentration diffused, effectively protecting areas outside the predetermined radius surrounding the distal end of the delivery device. According to the present invention, since no functional neurotoxin exists without an effective membrane transport technology, terminating the energy application leaves a harmless mist that is then coughed up (if resident in the lungs) or otherwise metabolized and excreted by the body.

**[0082]** Any of the catheter devices described herein, or described in the contemporaneously filed United States Patent Application 60/701,747 (Attorney Docket No. 020979-003500US), previously incorporated by reference in its entirety, may be adapted to include an energy delivery element such as those described herein for purposes of providing a membrane transport system for delivery of a fragment of neurotoxin. In addition, certain catheter devices and methods such as those set forth in United States Patents 5,964,223 and 6,526,976 to Baran may be adapted to include energy transmission elements capable of producing a porative effect at the cellular level, including electrodes, ultrasonic elements and the like, for treatment in the respiratory tract.

**[0083]** Furthermore, any of the foregoing systems may include electrodes or other monitoring systems either located on the treatment catheter, or external to the patient, to determine the degree of treatment to the region, including, thermocouple, ultrasound transducers, fiberoptics, sensing or stimulating electrodes. Further, it may be desirable to

incorporate multiple pairs of electrodes that may be activated in pairs, in groups, or in a sequential manner in order to maximize the desired shape of the energy field (EF) while minimizing the field strength requirements.

**[0084]** Implantable Devices. Just as energy may be delivered to a targeted region to facilitate the delivery of fragmented neurotoxin via a catheter system, it is also within the scope of the present invention to deliver neurotoxins via an implantable system, including a pulse generator, lead and drug pump as depicted in Figures 12. A neuromodulation system 200 may be fully implantable, having a pulse generator and a power supply or battery and be operatively connected to a programmable drug delivery pump all housed within a module 202, including a reservoir in which the BoNT-LC is stored for delivery over time using the principles of the present invention and technology of the programmable drug pump. A catheter 204 can be adapted to deliver the drug and poration energy to a desired target location in the patient's body.

**[0085]** Examples of useful implantable devices of the present invention are, devices such as those set forth in United States Patent 5,820,589 to Torgerson et al, the entire contents of which are hereby incorporated by reference, the SynchroMed® programmable pump available from Medtronic, Inc. (Minneapolis, MN), and the neurostimulation units such as the RESTORE® or SynergyPlus® available from Medtronic, Inc., modified if necessary to delivery the desired voltage range for cell membrane permeabilization. Implantation of the neurostimulation device is further described in US Patent 6,847,849, incorporated herein by reference in its entirety.

**[0086]** The non-toxic nature of the BoNT in the absence of applied energy makes it possible to contemplate placing a bolus of neurotoxin in the body of a patient in what might otherwise be a toxic amount. This is particularly advantageous, since the traditional treatment regime using neurotoxins, is typically repeat injections of the toxins every 3 to 6 months and sometimes more frequently depending on the application. Certainly in more chronic conditions such as chronic pain, tremor, spasm, palsy and the like, such a fully implantable system may be highly desirable.

**[0087]** Non-Invasive Devices. It is within the scope of the invention to deliver either the energy or the therapeutic BoNT-LC non-invasively, or both. For example, Figure 13 depicts delivery of the BoNT-LC via a catheter 100 placed in the bronchial passageway with the energy field (EF) delivered from outside the patient in the form of an energy system 102 such

as focused ultrasound (HIFU), stereotactic x-ray beams, magnetic resonance transmission, and the like. As detailed in United States Patents 6,626,855 and 6,719,694 to Weng, the contents of which are expressly incorporated herein by reference in their entirety, an ultrasound beam can be controlled from outside the patient to focus the ultrasound beam in the desired location and intensity. For use in the present invention, it may be desirable to pulse or otherwise attenuate the ultrasound beam to achieve reversible cellular poration at the targeted site. Further, due to its non-toxic state, the BoNT-LC may be inhaled by the patient using a standard inhaler device such as those using pressurized aerosols known as metered does inhalers (MDI) available from Cardinal Health (Somerset, NJ), the OPTIHALER® available from National Allergy Supply Incorporated (Georgia, USA), or a nebulizer breathing machine such as a Pari DURANEB 3000 portable nebulizer available from Medinfinity, Co. (Fountain Valley, CA). In addition, certain technology currently under development employing thermal aerosols, such as a the STACCATO™ vaporization technology from Alexza Molecular Delivery (Palo Alto, CA) may also be useful within the scope of the present invention. Such devices 110 may be used as depicted in Figure 9 for treating a respiratory ailment such as asthma. Optionally, the drug can be delivered with the catheter 22 (as shown) or with the external sources of Fig. 13.

**[0088]** A combination of these non-invasive approaches may also be advantageous as shown in Figure 15, wherein an non-invasive inhaler 110 is used to deliver the BoNT-LC to the target region (such as the lung), and the energy is delivered to the target region by the non-invasive source 102 such as the focused ultrasound (HIFU), stereotactic x-ray, or magnetic resonance transmission as previously described. Due to its non-invasive technique, this approach may have broad appeal to a large patient population, including pediatric use, on an outpatient basis in a clinic designated for the treatment of specific respiratory ailments.

**[0089]** In a further aspect of the present invention, the fragmented molecule BoNT-LC may be delivered intravenously to a patient to achieve a systemic affect. A non-invasive energy application device, such as those described above, may then be targeted at the area of interest to porate the target area, thereby locally delivering the BoNT-LC to the region sufficiently porated by the applied energy.

**[0090]** Cosmetic and Myofacial Applications. For some conditions, it may be desirable to apply the energy field from the surface of the skin to produce a porative effect, while injecting the BoNT-LC fragment into the targeted facial muscles as shown in Figure 14. In

operation, an injection device 220 places the BoNT-LC in the muscle to be treated (target region), and an energy transmission device such as an ultrasonic pen 222 with a single, or a series of ultrasonic elements located on the distal end and coupled to an energy transmission system 224, follows along the target region to controllably discharge the BoNT-LC fragments to the targeted cells leaving a highly controlled treated region. In some instances for treatments around the eye, it may be desirable to limit the penetration of the BoNT-LC to dermal or subdermal layers. In these applications, BoNT-LC may be applied transdermally with ultrasound assistance using techniques similar to those set forth in US Patent 4,767,402 to Kost the contents of which is expressly incorporated herein in its entirety or through transdermal electroporation.

**[0091]** Intraluminal Devices. It may further be advantageous to position catheters of the present invention through vessels in the body to direct them to various regions to affect neurotransmitters in the cardiovascular system. Intraluminal catheters such as those shown in United States Patent Applications 2001/0044596 to Jaafar and 2002/0198512 to Seward, hereby incorporated by reference in their entirety, may be used in this application of the present invention.

**[0092]** Treatment Enhancements. In some applications of the present invention, it may be desirable to asses the appropriate location for the therapy prior to treatment, the therapeutic effect as it is delivered, and ultimately the resulting effect. To achieve this, once the treatment device is in place adjacent the tissue to be treated, the energy generator may be activated, causing an energized field to be generated in the target area. Prior to activation of therapeutic voltages and agent, stimulation using one or more electrodes may be used to elicit a nerve response or reflex. By observing the nerve response, a target treatment location can be confirmed. Similarly, once the therapy has been delivered, a similar stimulation response may be sought, to determine presence or lack of neurogenic response.

**[0093]** In operation, effects of electroporation and delivery of a therapeutic does of BoNT-LC may be selective due to the cellular structure and orientation of the targeted cells. For example, targeted cells may be preferentially affected due to size, avoiding smaller or cross-oriented tissue cells.

**[0094]** In a further aspect of the present invention, the method of delivering the LC fragment of the BoNT molecule may include the use of a media that contains microspheres or microbubbles, such as Optison™ sold by GE Healthcare (www.amershamhealth-

us.com/optison/). Delivery of an ultrasound energy (or other form of energy, for example, laser, RF, thermal, energy) to the media causes the microspheres to rupture, which causes a release of energy toward the targeted region. Such a technique may assist in the desired porative effect by reducing the amount of applied energy required to create poration in the targeted cell membrane. *Bioeffects Caused by Changes in Acoustic Cavitation Bubble Density and Cell Concentration: A Unified Explanation Based on Cell-to-Bubble Ratio and Blast Radius*, Guzman, et al. Ultrasound in Med. & Biol., Vol. 29, No. 8, pp. 1211-1222 (2003). In an alternative embodiment, the LC fragment may actually be contained or encapsulated within a microsphere to assist in delivery. Such enhancing elements may be delivered prior to energy application or during energy application.

**[0095]** In a further aspect of the present invention, it may be advantageous to heat the targeted cells or surrounding tissue by either applying thermal energy directly to the region, or directing a heated fluid, such as saline to the region through an injection element, to aid the cell poration process. Other substances may also be injected to aid in the transmission of the BoNT-LC into the intracellular membrane, such as amino acids, detergents or other agents that may facilitate the catalytic activity of the LC, in addition to the applied energy.

**[0096]** Referring now to Figs. 15A and 15B, a balloon catheter 300 may be delivered to a target site in the bronchus B of a lung (Fig. 15B). Typically, the catheter 300 will be delivered through an endoscope E, and the shaft 302 of the catheter will comprise at least one lumen for inflating the balloon 304. The inflation medium may carry the toxin fragment which is released through ports 306 formed in the balloon itself. Thus, inflation of the balloon both engages the ports against the wall of the bronchus B and provides the pressure necessary to infuse the neurotoxin fragments into the wall of the bronchus B. Usually, energy will be applied from electrodes 308 or other transducers located within the balloon 304.

**[0097]** Referring now Figs. 16A and 16B, the catheter 400 may also be delivered to a bronchus B of a lung through an endoscope E. Catheter shaft 402 terminates with a delivery port 404 near its distal end. A deflection balloon 406 (or other expandable element capable of pressing against the wall of the bronchus B to engage the port 404 against target tissue) is provided on a side of the catheter shaft 402 which is opposite to that of the port 404. Electrodes 408 are provided on either side of the port 404 in order to deliver the poration energy into the target tissue.

**[0098]** Although various illustrative embodiments of the present invention are described above, it will be evident to one skilled in the art that various changes and modifications may be made without departing from the scope of the invention. It will also be apparent that various changes and modifications may be made herein without departing from the invention. The appended claims are intended to cover all such changes and modifications that fall within the true spirit and scope of the invention.

WHAT IS CLAIMED IS:

1. A method for treating conditions affected by neurogenic function in a targeted region of mammalian cells, said method comprising:

delivering an active neurotoxin fragment to cells in the targeted region;

applying energy to the cells under conditions which cause a reversible poration in the cell membranes to permit delivery of the active fragment.

2. A method as in claim 1, wherein the active fragment is selected from the group consisting of botulinum toxin fragments, ricin fragments, exotoxin A fragments, diphtheria toxin fragments, cholera toxin fragments, and tetanus toxin fragments.

3. A method as in claim 2, wherein the active fragment comprises the botulinum light chain (BoNT-LC).

4. A method of claim 3, wherein the active fragment comprises an amount of BoNT-LC therapeutically effective to inhibit a neurogenic pathway associated with the neurogenic function.

5. A method of claim 4, wherein the active fragment is BoNT-LC derived from at least one of the botulinum toxins A, B, C, D, E, F or G.

6. A method of claim 1, wherein the neurogenic pathway is associated with and contributes to at least one symptom of asthma.

7. A method of claim 1, wherein delivering comprises advancing a catheter to said vicinity and releasing the active neurotoxin fragments from the catheter while applying energy from an applicator on the catheter.

8. A method of claim 7, wherein delivering comprises aerosolizing the fragment from the catheter.

9. A method as in claim 7, wherein delivering comprises injecting the fragment from a needle on the catheter.

10. A method as in claim 7, wherein delivery comprises engaging one or more ports on the catheter against tissue and releasing the fragments from the port(s).

11. A method as in claim 10, wherein engaging comprises inflating a balloon on the catheter to deflect the catheter.

12. A method of claim 1, wherein the delivering is achieved using an inhaler.

13. A method of claim 1, wherein the delivering is achieved transdermally

14. A method of claim 1, wherein the energy applied to the targeted region is an electric pulse.

15. A method of claim 14, wherein the electric pulse has a voltage between 1V and 500V.

16. A method of claim 14, wherein the electric pulse comprises radiofrequency energy.

17. A method of claim 16, wherein the radiofrequency energy is pulsed for durations between 5 microseconds to 100 milliseconds.

18. A method of claim 13, wherein the electric pulse comprises a direct current pulse.

19. A method of claim 13, wherein the electric pulse comprises an alternating current pulse.

20. A method of claim 1, wherein the energy applied to the targeted region comprises ultrasonic energy.

21. A method of claim 20, wherein the ultrasonic energy applied to the targeted region comprises focused ultrasound energy.

22. A method of claim 1, wherein the energy applied to the targeted region comprises an x-ray beam.

23. A method of claim 1, wherein the energy applied to the targeted region comprises microwave energy.

24. A method of claim 4, wherein the neurogenic pathway is associated with and contributes to at least one symptom of pain.

25. A method of treating a respiratory ailment, comprising the steps of:

providing a therapeutically effective amount of BoNT-LC, and

delivering the amount of BoNT-LC to a region of the respiratory system under conditions selected to permeabilize target cells within the region and allow entry of the BoNT-LC to enter the cells.

26. A system for delivering toxins to target cells in a mammalian target, said system comprising:

a catheter or other structure adapted to introduce a toxin to a region adjacent the target cells;

an energy applicator for applying energy to the target cells under conditions which cause poration of the cell membranes to enhance delivery of the toxin; and

a source of toxin suitable for introduction from the catheter.

27. A system as in claim 26, wherein the energy applicator is adapted to selectively apply energy to target cells within the region where toxin has been introduced.

28. A system as in claim 26, wherein the energy applicator is adapted to apply energy non-selectively within the region where toxin has been introduced.

29. A system as in claim 26, wherein the toxin comprises an intact toxin.

30. A system as in claim 29, wherein the toxin is an active toxin fragment.

31. A system as in claim 30, wherein the fragment is a light chain fragment.

32. A system as in claim 31, wherein the active fragment is selected from the group consisting of botulinum toxin fragments, ricin fragments, exotoxin A fragments, diphtheria toxin fragments, cholera toxin fragments, and tetanus toxin fragments.

33. A system as in claim 32, wherein the active fragment comprises the botulinum light chain (BoNT-LC).

34. A system as in claim 33, wherein the light chain fragment is derived from at least one of botulinum toxins A, B, C, D, E, F, and G.

35. A system as in claim 26, wherein the energy applicator is adapted to apply an electric pulse of between 1V and 500V to the target region.

36. A system as in claim 35, wherein the electric pulse is radiofrequency (RF) energy.

37. A system as in claim 35, wherein the RF energy is pulsed for durations between 5 microseconds to 100 milliseconds.

38. A system as in claim 35, wherein the electric pulse is produced by a DC power source.

39. A system as in claim 35, wherein the electric pulse is produced by an AC power source.

40. A system as in claim 26, wherein the energy applicator is adapted to apply ultrasonic energy to the targeted region.

41. A system as in claim 40, wherein the energy applicator is adapted to apply focused ultrasound to the targeted region.

42. A system as in claim 26, wherein the energy applicator is adapted to apply an x-ray beam to the targeted region.

43. A system as in claim 26, wherein the energy applicator is adapted to apply microwave to the targeted region.

44. A system as in claim 26, wherein the catheter comprises a needle for delivering the toxin.

45. A system as in claim 26, wherein the catheter comprises a port for aerosolizing the toxin.

46. A system as in claim 28, wherein the catheter comprises a balloon for deflecting one or more ports against target tissue.

47. A system as in claim 46, wherein the balloon comprises the one or more ports.

48. A system as in claim 26, wherein the energy applicator is on the catheter.

49. A system as in claim 48, wherein the energy applicator applies acoustic energy from a transducer on the catheter.

50. A system as in claim 48, wherein the energy applicator applies electrical energy from an electrode on the catheter.

51. A system as in claim 26, wherein the applicator applies energy from a source external to the patient.

52. A system as in claim 51, wherein the source is an acoustic energy transducer.

53. A system as in claim 52, wherein the acoustic energy transducer is focused ultrasound transducer.

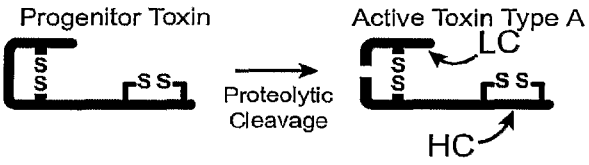

Progenitor Toxin
S
S
S S
Proteolytic
Cleavage
Active Toxin Type A
LC
S
S
S S
HC

FIG. 1

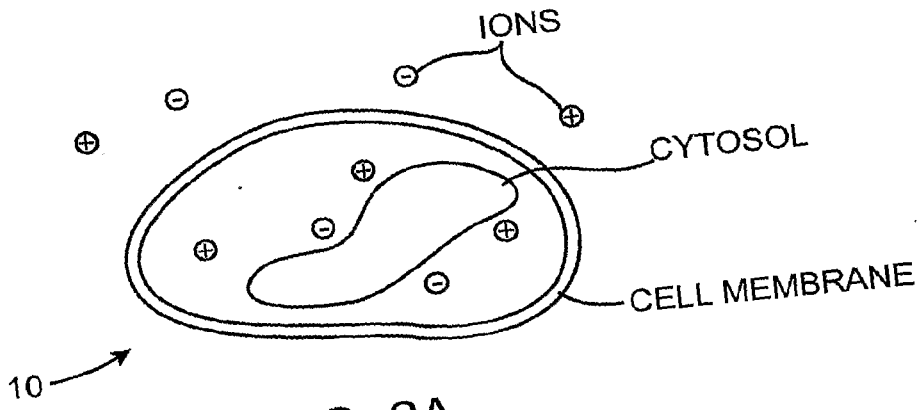



FIG. 2A

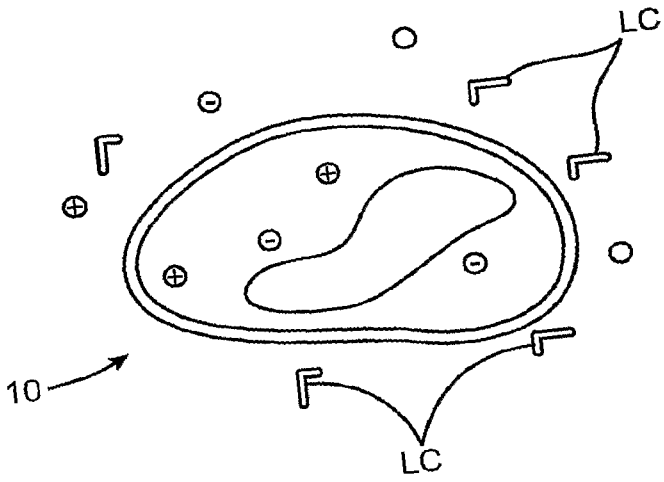



FIG. 2B

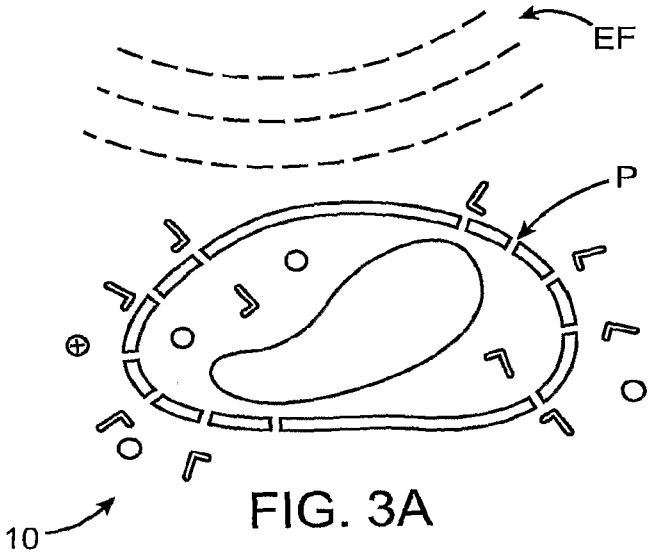



FIG. 3A

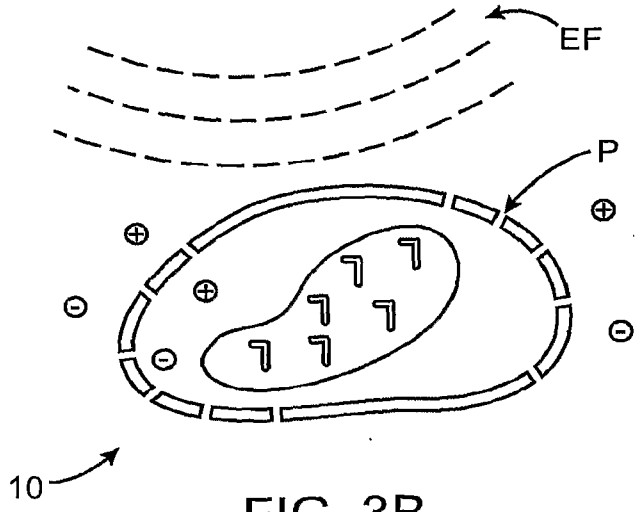



FIG. 3B

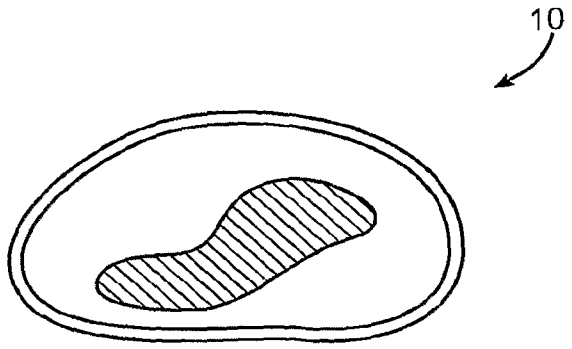



FIG. 4

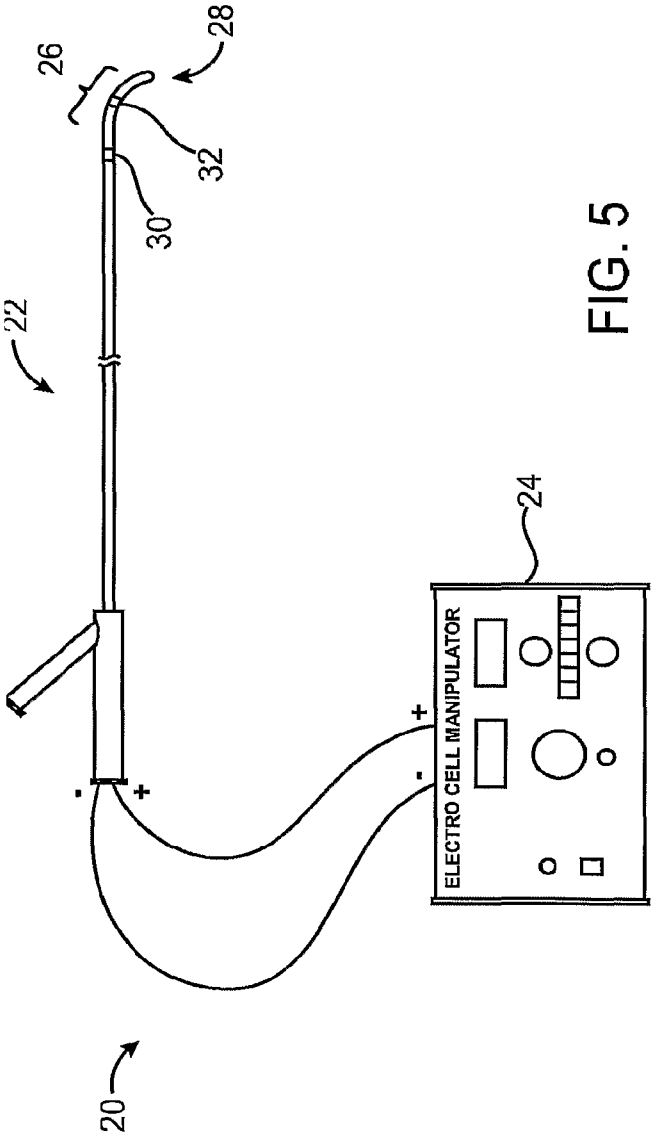



FIG. 5

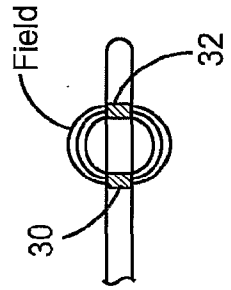



FIG. 5B

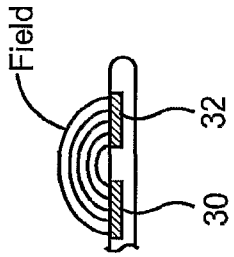



FIG. 5A

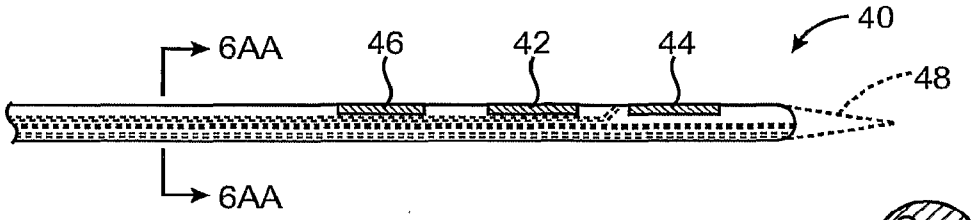



FIG. 6A

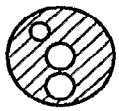


FIG. 6AA

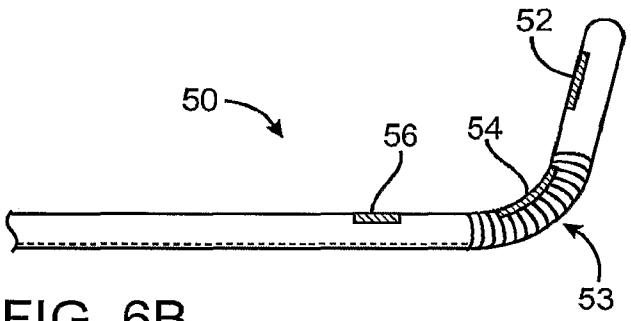



FIG. 6B

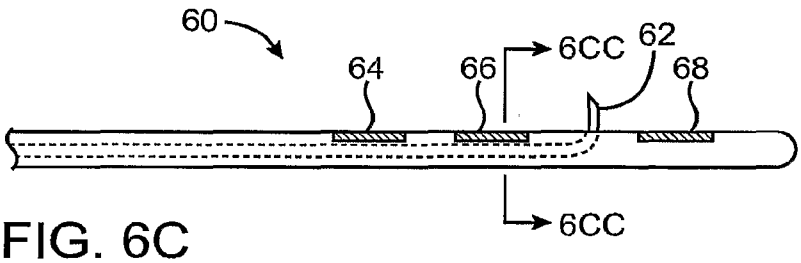



FIG. 6C



FIG. 6CC

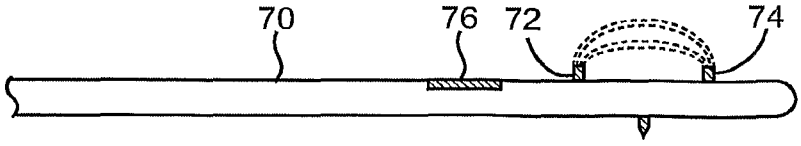



FIG. 6D

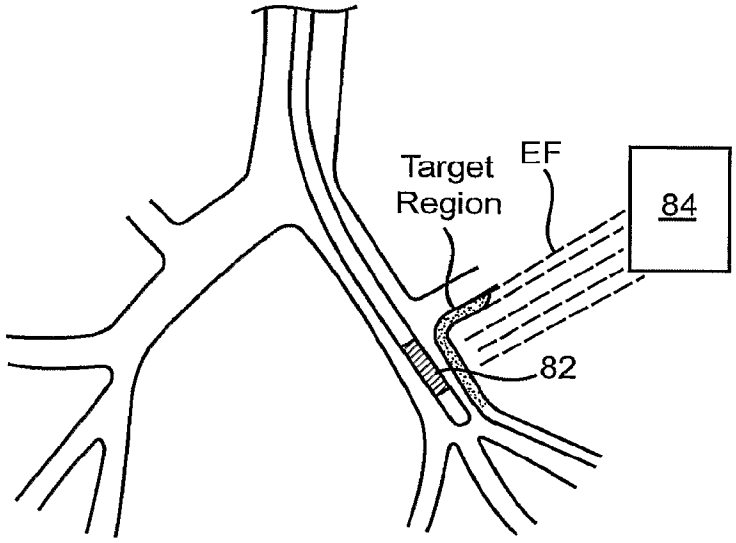



FIG. 7

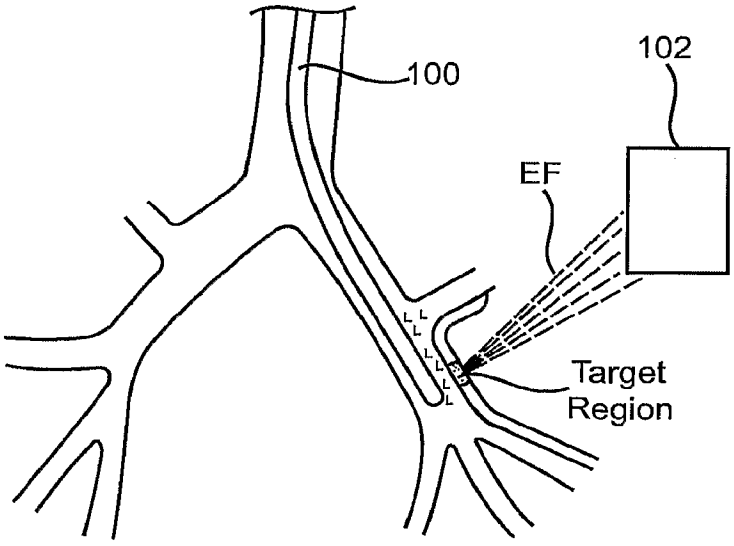



FIG. 13

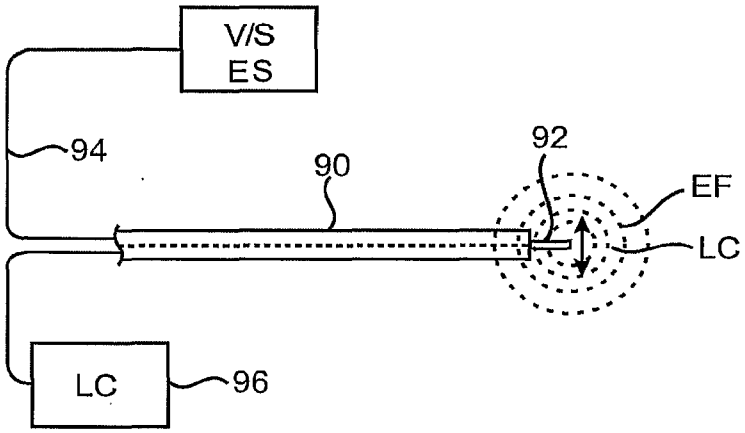



FIG. 8

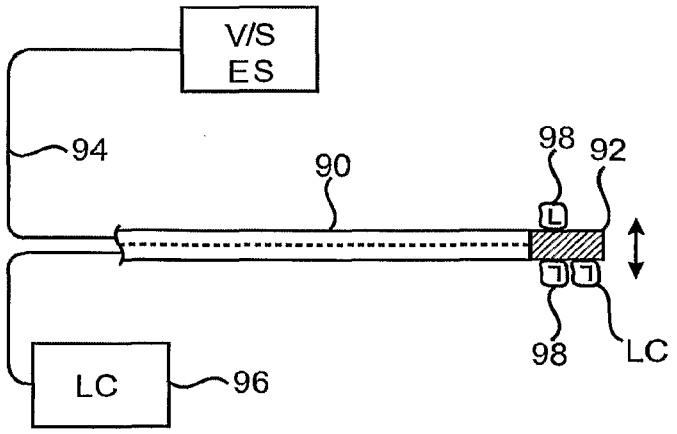



FIG. 11

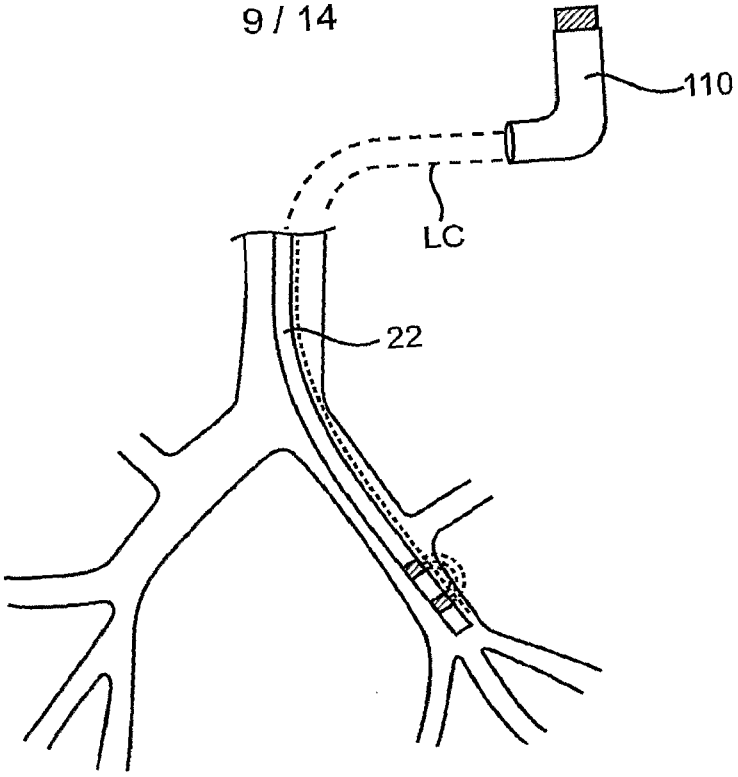



FIG. 9

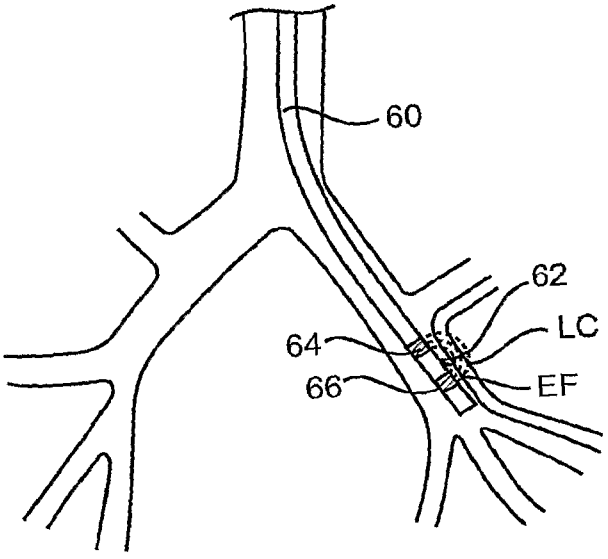



FIG. 10

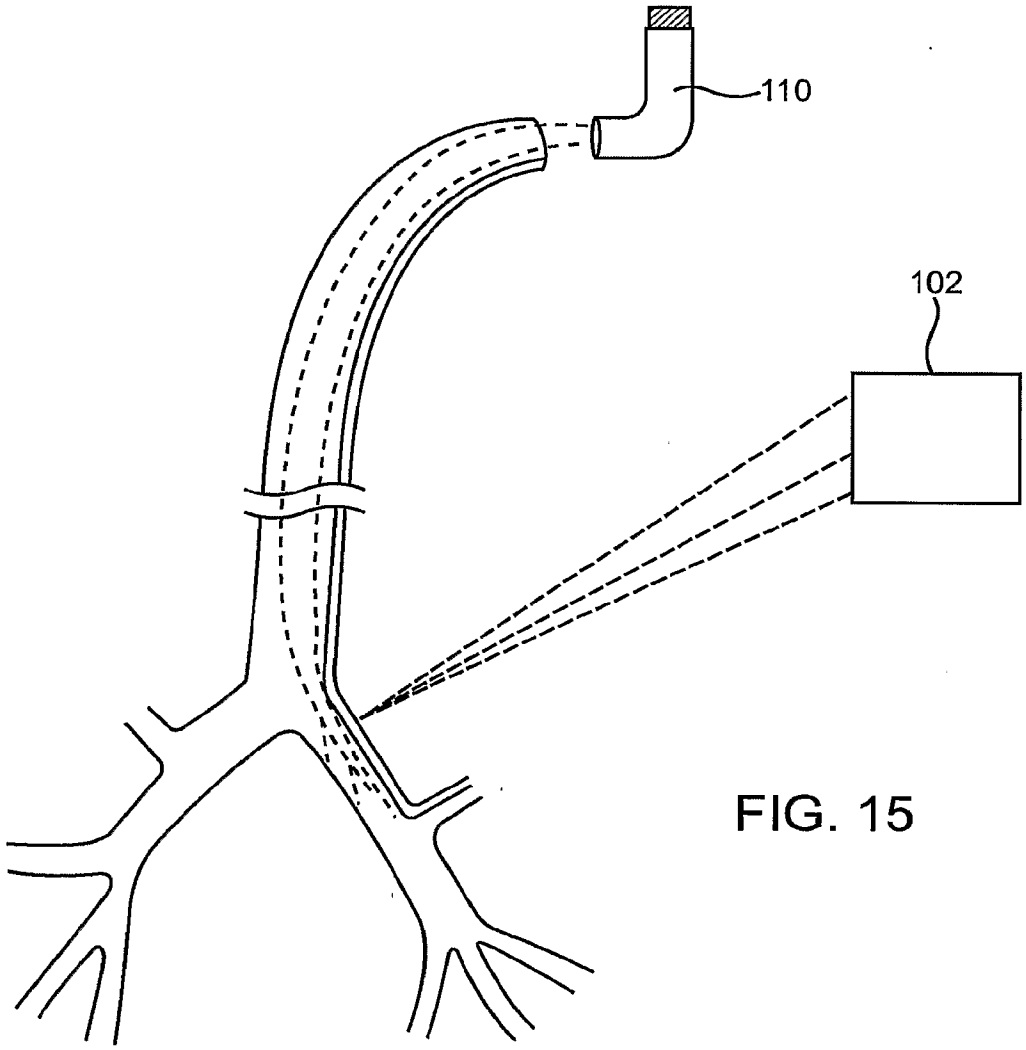



FIG. 15

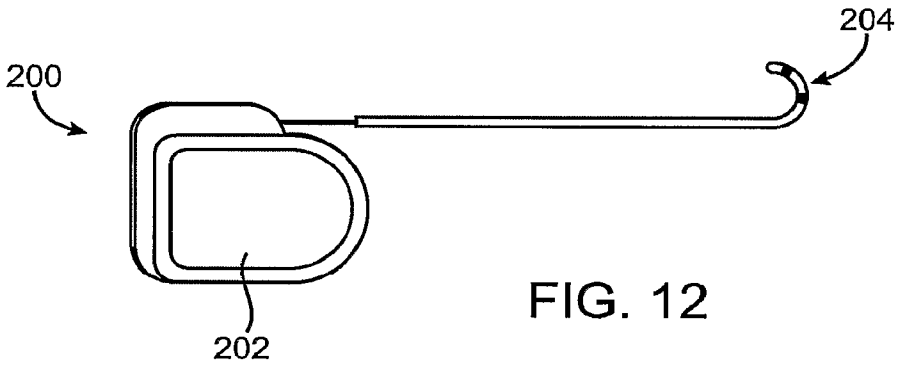



FIG. 12

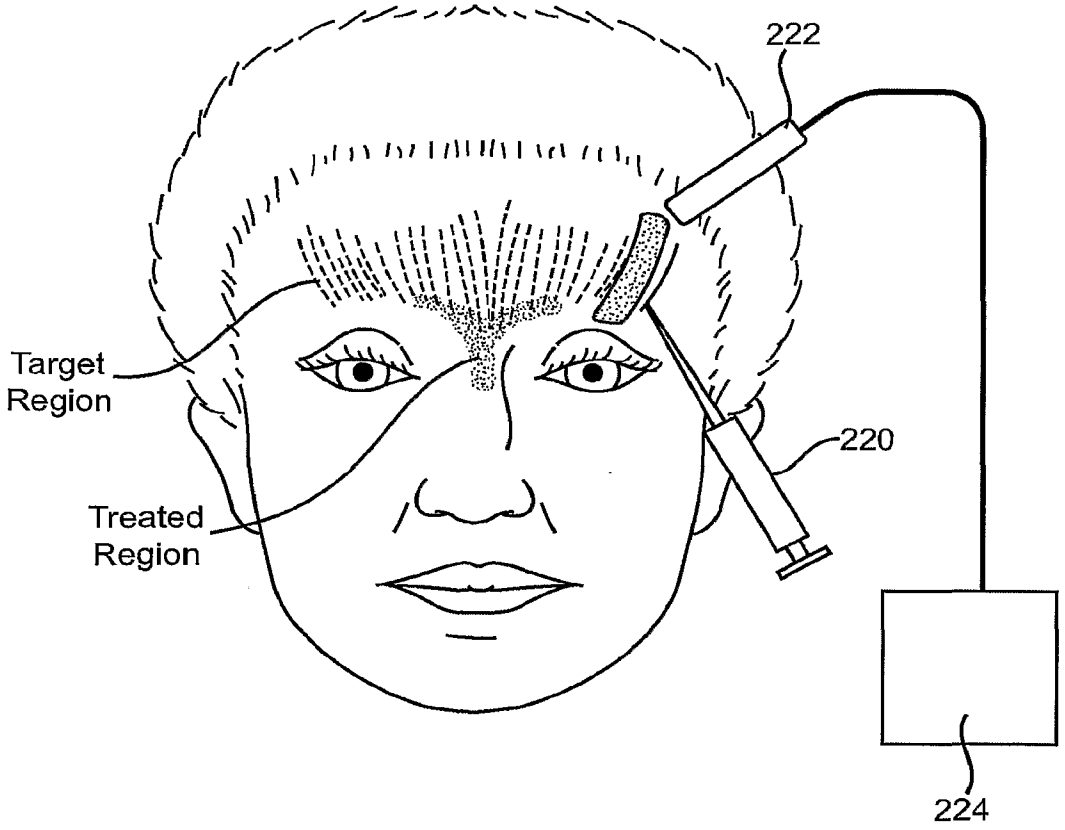



FIG. 14

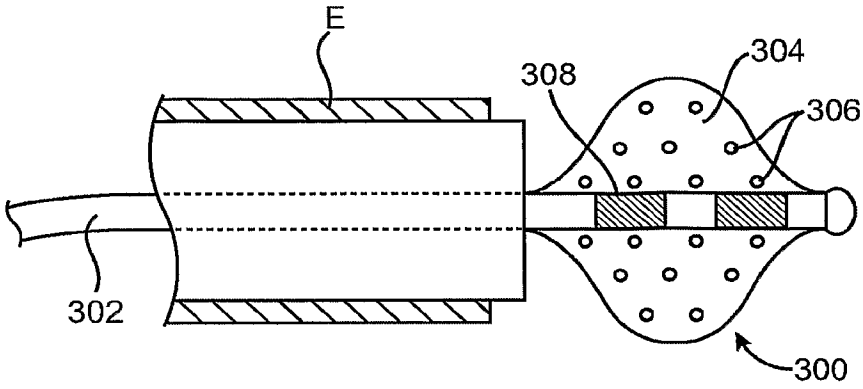



FIG. 15A

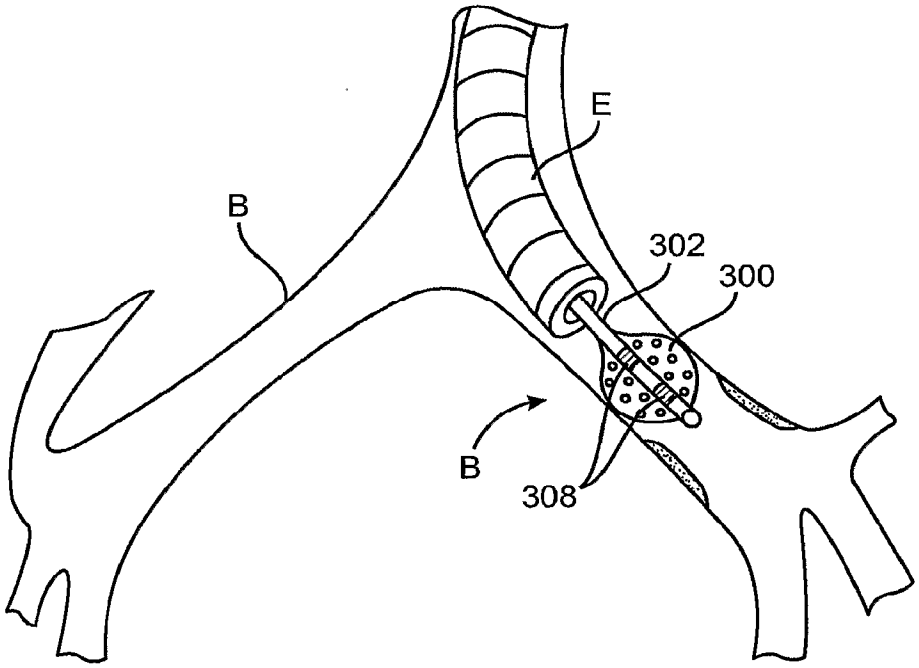



FIG. 15B

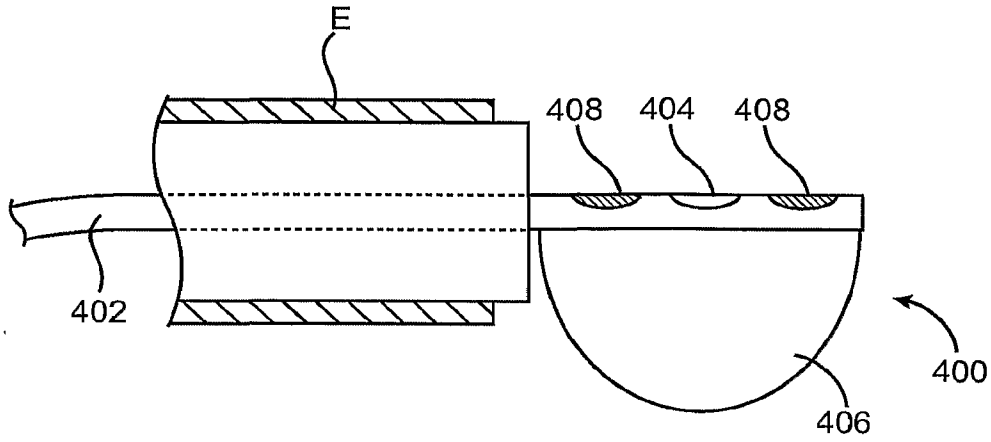



FIG. 16A

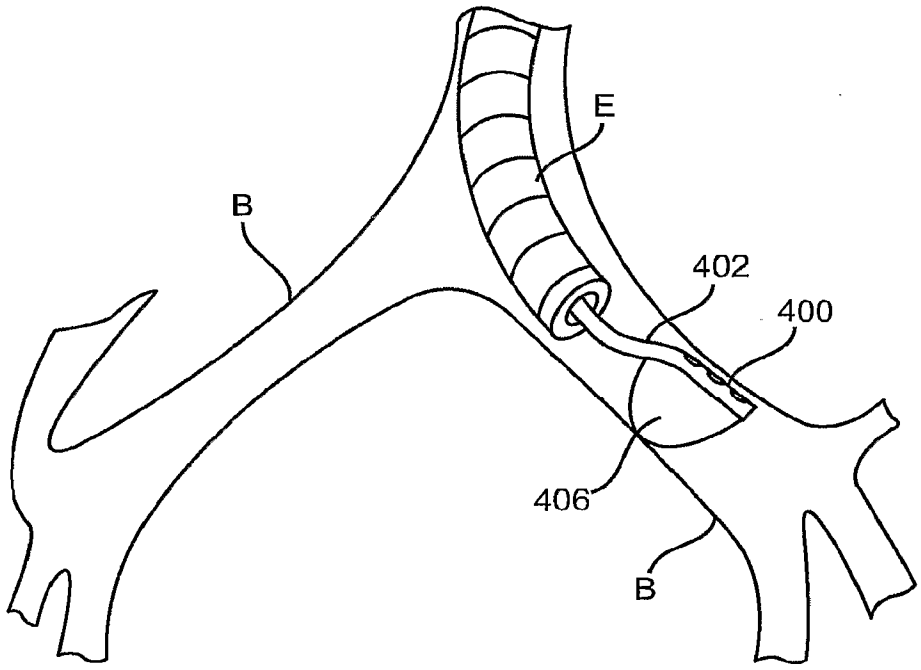



FIG. 16B

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

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1 February 2007 (01.02.2007)

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(21) International Application Number:
PCT/US2006/028310

(22) International Filing Date: 21 July 2006 (21.07.2006)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
60/702,077 22 July 2005 (22.07.2005) US
60/747,771 19 May 2006 (19.05.2006) US

(71) Applicant *(for all designated States except US)*: **THE FOUNDRY INC.** [US/US]; 199 Jefferson Drive, Menlo Park, California 94025 (US).

(72) Inventors; and
(75) Inventors/Applicants *(for US only)*: **DEEM, Mark, E.** [US/US]; 685 Sierra Avenue, Mountain View, California 94041 (US). **GIFFORD, Hanson, S.** [US/US]; 3180 Woodside Road, Woodside, California 94062 (US).

(74) Agents: **HESLIN, James, M.** et al.; Two Embarcadero Center, 8th Floor, San Francisco, California 94111-3834 (US).

(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LV, LY, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, LV, MC, NL, PL, PT, RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

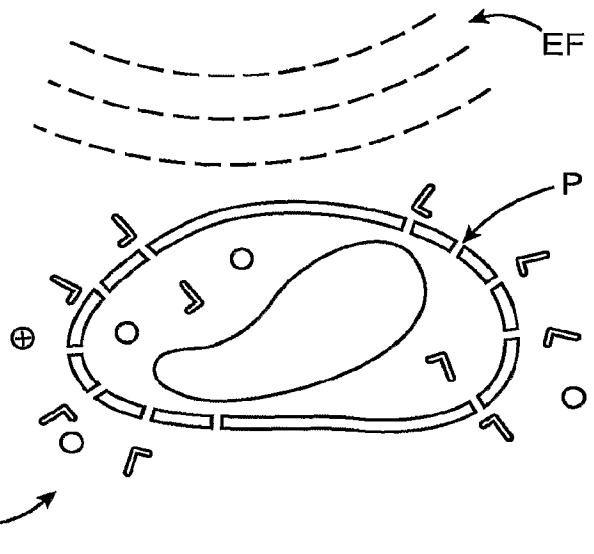
**Declaration under Rule 4.17:**
— *as to applicant's entitlement to apply for and be granted a patent (Rule 4.17(ii))*

**Published:**
— *with international search report*
— *before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments*

(88) Date of publication of the international search report:
4 October 2007

*For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.*

(54) Title: SYSTEMS AND METHODS FOR DELIVERY OF A THERAPEUTIC AGENT




(57) Abstract: Methods and apparatus are provided for applying an fragment of a neurotoxin such as the active light chain (LC) of the botulinum toxin (BoNT), such as one of the serotype A, B, C, D, E, F or G botulinum toxins, via permeabilization of targeted cell membranes to enable translocation of the botulinum neurotoxin light chain (BoNT-LC) molecule across the targeted cell membrane to the cell cytosol where a therapeutic response is produced in a mammalian system. The methods and apparatus include use of catheter based delivery systems, non-invasive delivery systems, and transdermal delivery systems.

WO 2007/014003 A3

# INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 06/28310

A. CLASSIFICATION OF SUBJECT MATTER
IPC(8) - A61K 9/12; A61K 39/02 (2007.01)
USPC 424/45; 424/236.1
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC(8) - A61K 9/12; A61K 39/02 (2007.01)
USPC 424/45; 424/236.1

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
PUBWEST(PGPB,USPT,USOC,EPAB,JPAB), GOOGLE SCHOLAR: BOTULINUM, TOXIN, NEUROTOXIN, LIGHT CHAIN, ELECTROPORATION, X-RAY, MICROWAVE, ULTRASONIC, ULTRASOUND, PERMEABLE, DELIVERY, CATHETER, NEUROTOXIN,

C. DOCUMENTS CONSIDERED TO BE RELEVANT

| Category* | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|---|---|---|
| X<br>---<br>Y | US 2004/0142005 A1 (Brooks et al.) 22 Jul 2004 (22.07.2004); para [0011], [0012], [0013] and [0036] | 1-5<br>---<br>6-53 |
| Y | WO 2004/101028 A2 (Deem et al.) 25 Nov 2004 (25.11.2004); para [0006], [0008], [0015], [0019], [0022], [0052] , [0061], [0063], [0063] and [0065], Fig 9B | 6, 8-11, 25, and 44-47 |
| Y | US 2004/0010290 A1 (Schroeppel et al.) 15 Jan 2004 (15.01.2004); para [0011], [0067], [0074], [0103], [0116], [0149], [0188], [0192], [0237], [0239] and [0297] | 7-11, 13-19, and 26-53 |
| Y | US 5,766,605 A (Sanders) 16 Jun 1998 (16.06.1998); col 10, ln 45-50 | 12 |
| Y | US 2003/0050591 A1 (McHale) 13 Mar 2003 (13.03.2003); para [0011], [0044], [0092] and [0093] | 20-23, 40-43, 49, 52, and 53 |
| Y | RAJ. Editorial Pain Practice. March 2004, 4(S1):S1-S3; pg S1, col 2; and pg S2, col 1 | 24 |

☐ Further documents are listed in the continuation of Box C. ☐

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier application or patent but published on or after the international filing date
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"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

| Date of the actual completion of the international search | Date of mailing of the international search report |
|---|---|
| 23 Jun 2007 (23.06.2007) | 08 AUG 2007 |
| Name and mailing address of the ISA/US<br>Mail Stop PCT, Attn: ISA/US, Commissioner for Patents<br>P.O. Box 1450, Alexandria, Virginia 22313-1450<br>Facsimile No. 571-273-3201 | Authorized officer:<br>Lee W. Young<br>PCT Helpdesk: 571-272-4300<br>PCT OSP: 571-272-7774 |

Form PCT/ISA/210 (second sheet) (April 2005)

# INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 07/69391

A. CLASSIFICATION OF SUBJECT MATTER
IPC(8) - A61K 39/08 (2007.01)
USPC - 424/239.1; 514/8
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC(8) - A61K 39/08 (2007.01)
USPC - 424/239.1; 514/8

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
PubWEST(USPT,PGPB,EPAB,JPAB); Google Patents; Google Scholar
Search terms: botulinum, toxin, nasal cavity, deliver or administer or administration, rhinorrhea, headache, handle, first, second, spring, actuator, applicator, nostril, electric, ultrasound, x-ray, microwave, electromagnetic, poration, transdermal

C. DOCUMENTS CONSIDERED TO BE RELEVANT

| Category* | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|---|---|---|
| Y | US 2006/0106361 A1 (MUNI et al.) 18 May 2006 (18.05.2006) para [0010], [0014]-[0016], [0075], [0077], [0095], [0102], [0104], [0105], [0107] and [0161] | 1-43, 68-78 |
| Y | US 1,695,107 A (KAHL) 11 December 1928 (11.12.1928) col 1, ln 1-4, 22-35 and 49-55; col 2, ln 56-60 and 65-75 | 1-30, 41-43 |
| Y | US 5,766,605 A (SANDERS et al.) 16 June 1998 (16.06.1998) col 2, ln 34-38 and 45; col 8, ln 29 and 33; col 10, ln 16-18 | 1-78 |
| Y | US 2005/0152924 A1 (VOET) 14 July 2005 (14.07.2005) para [0013]-[0014], [0043], [0055], [0065] and [0074] | 24-30, 52-53, 55-57 |
| Y | US 2004/0009180 A1 (DONOVAN) 15 January 2004 (15.01.2004) para [0081]-[0083] | 26-30, 44-78 |
| Y | US 2005/0107853 A1 (KRESPI et al.) 19 May 2005 (19.05.2005) para [0037], [0060], [0108]-[0109] and [0115] | 29, 59-67 |

☐ Further documents are listed in the continuation of Box C. ☐

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier application or patent but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

| Date of the actual completion of the international search | Date of mailing of the international search report |
|---|---|
| 30 December 2007 (30.12.2007) | 03 MAR 2008 |

| Name and mailing address of the ISA/US | Authorized officer: |
|---|---|
| Mail Stop PCT, Attn: ISA/US, Commissioner for Patents<br>P.O. Box 1450, Alexandria, Virginia 22313-1450<br>Facsimile No. 571-273-3201 | Lee W. Young<br>PCT Helpdesk: 571-272-4300<br>PCT OSP: 571-272-7774 |

## INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 07/69391

**Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)**

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

**Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)**

This International Searching Authority found multiple inventions in this international application, as follows:

-- see extra sheet

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying additional fees, this Authority did not invite payment of additional fees.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☒ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:
1-78

**Remark on Protest**

☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.

☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.

☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 07/69391

Continuation of Box No. III - Observations where unity of invention is lacking

This application contains the following inventions or groups of inventions which are not so linked as to from a single general inventive concept under PCT Rule 13.1.

Group I: claims 1-78 are directed to an apparatus for treating inflammation of a nasal membrane of a patient comprising: a handle comprising a proximal section, a first member and a second member, wherein the first member and second member are connected at the proximal section; a first applicator tip coupled to the first member; and a second applicator tip coupled to the second member; wherein the first applicator tip and second applicator tip are each configured for insertion into a nostril of the patient and placement within a nasal passageway of the patient and wherein each applicator tip is configured for delivering a toxin to a region of nasal tissue within the nasal cavity of the patient, thereby treating the inflammation.

Group II: claims 79-112 are directed to a system for delivering toxins to target cells in a nasal membrane, said system comprising: a catheter adapted to introduce a toxin to a region proximate the target cells; an energy applicator configured for applying energy to the target cells under conditions which cause portion of the cell membranes to enhance delivery of the toxin; and a source of toxin suitable for introduction from the catheter.

The inventions listed as Groups I-II do not relate to a single general inventive concept under PCT Rule 13.1 because under PCT Rule 13.2 they lack the same or corresponding technical features for the following reasons:

Group II does not include the inventive concept of an applicator of the type as disclosed in claim 1 of Group I.

Group I does not include the inventive concept of an energy applicator configured for applying energy to the target cells as disclosed in Group II.

Neither of these technical features is common to the other group, nor do they correspond to a special technical feature in the other group. Therefore, unity of invention is lacking.

# PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

To: James M. Heslin
Two Embarcadero Center, 8th Floor
San Francisco, CA 94111-3834

# PCT

WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY

(PCT Rule 43*bis*.1)

| | |
|---|---|
| Date of mailing *(day/month/year)* | 03 MAR 2008 |
| Applicant's or agent's file reference<br>20979-37-3PC | **FOR FURTHER ACTION**<br>See paragraph 2 below |

| International application No. | International filing date *(day/month/year)* | Priority date *(day/month/year)* |
|---|---|---|
| PCT/US 07/69391 | 21 May 2007 (21.05.2007) | 19 May 2006 (19.05.2006) |

International Patent Classification (IPC) or both national classification and IPC
IPC(8) - A61K 39/08 (2008.01)
USPC - 424/239.1; 514/8

Applicant The Foundry Inc.

1. This opinion contains indications relating to the following items:

- ☒ Box No. I Basis of the opinion
- ☐ Box No. II Priority
- ☐ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☒ Box No. IV Lack of unity of invention
- ☒ Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- ☐ Box No. VI Certain documents cited
- ☐ Box No. VII Certain defects in the international application
- ☐ Box No. VIII Certain observations on the international application

2. **FURTHER ACTION**

If a demand for international preliminary examination is made, this opinion will be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA") except that this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notified the International Bureau under Rule 66.1*bis*(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of 3 months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

3. For further details, see notes to Form PCT/ISA/220.

| Name and mailing address of the ISA/US | Date of completion of this opinion | Authorized officer: |
|---|---|---|
| Mail Stop PCT, Attn: ISA/US<br>Commissioner for Patents<br>P.O. Box 1450, Alexandria, Virginia 22313-1450<br>Facsimile No. 571-273-3201 | 30 December 2007 (30.12.2007) | for Lee W. Young<br>PCT Helpdesk: 571-272-4300<br>PCT OSP: 571-272-7774 |

Form PCT/ISA/237 (cover sheet) (April 2007)

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/US 07/69391

**Box No. I Basis of this opinion**

1. With regard to the **language**, this opinion has been established on the basis of:

   ☒ the international application in the language in which it was filed.

   ☐ a translation of the international application into _____ which is the language of a translation furnished for the purposes of international search (Rules 12.3(a) and 23.1(b)).

2. ☐ This opinion has been established taking into account the **rectification of an obvious mistake** authorized by or notified to this Authority under Rule 91 (Rule 43*bis*.1(a))

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, this opinion has been established on the basis of:

   a. type of material

      ☐ a sequence listing

      ☐ table(s) related to the sequence listing

   b. format of material

      ☐ on paper

      ☐ in electronic form

   c. time of filing/furnishing

      ☐ contained in the international application as filed

      ☐ filed together with the international application in electronic form

      ☐ furnished subsequently to this Authority for the purposes of search

4. ☐ In addition, in the case that more than one version or copy of a sequence listing and/or table(s) relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

5. Additional comments:

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**Box No. IV Lack of unity of invention**

1. ☒ In response to the invitation (Form PCT/ISA/206) to pay additional fees the applicant has, within the appicable time limit:

   ☐ paid additional fees

   ☐ paid additional fees under protest and, where applicable, the protest fee

   ☐ paid additional fees under protest but the applicable protest fee was not paid

   ☒ not paid additional fees

2. ☐ This Authority found that the requirement of unity of invention is not complied with and chose not to invite the applicant to pay additional fees.

3. This Authority considers that the requirement of unity of invention in accordance with Rule 13.1, 13.2 and 13.3 is

   ☐ complied with

   ☒ not complied with for the following reasons:

This application contains the following inventions or groups of inventions which are not so linked as to from a single general inventive concept under PCT Rule 13.1.

Group I: claims 1-78 are directed to an apparatus for treating inflammation of a nasal membrane of a patient comprising: a handle comprising a proximal section, a first member and a second member, wherein the first member and second member are connected at the proximal section; a first applicator tip coupled to the first member; and a second applicator tip coupled to the second member; wherein the first applicator tip and second applicator tip are each configured for insertion into a nostril of the patient and placement within a nasal passageway of the patient and wherein each applicator tip is configured for delivering a toxin to a region of nasal tissue within the nasal cavity of the patient, thereby treating the inflammation.

Group II: claims 79-112 are directed to a system for delivering toxins to target cells in a nasal membrane, said system comprising: a catheter adapted to introduce a toxin to a region proximate the target cells; an energy applicator configured for applying energy to the target cells under conditions which cause portion of the cell membranes to enhance delivery of the toxin; and a source of toxin suitable for introduction from the catheter.

The inventions listed as Groups I-II do not relate to a single general inventive concept under PCT Rule 13.1 because under PCT Rule 13.2 they lack the same or corresponding technical features for the following reasons:

Group II does not include the inventive concept of an applicator of the type as disclosed in claim 1 of Group I.

Group I does not include the inventive concept of an energy applicator configured for applying energy to the target cells as disclosed in Group II.

Neither of these technical features is common to the other group, nor do they correspond to a special technical feature in the other group. Therefore, unity of invention is lacking.

4. Consequently, this opinion has been established in respect of the following parts of the international application:

   ☐ all parts

   ☒ the parts relating to claims Nos. 1-78

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

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**Box No. V** **Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement**

1. Statement

| | | | |
|---|---|---|---|
| Novelty (N) | Claims | 1-78 | YES |
| | Claims | None | NO |
| Inventive step (IS) | Claims | None | YES |
| | Claims | 1-78 | NO |
| Industrial applicability (IA) | Claims | 1-78 | YES |
| | Claims | None | NO |

2. Citations and explanations:

Claims 31-40 lack an inventive step under PCT Article 33(3) as being obvious over US 2006/0106361 A1 to Muni et al. (hereinafter 'Muni') in view of US 5,766,605 A to Sanders et al. (hereinafter 'Sanders').

Regarding claim 31, Muni discloses an apparatus comprising: an applicator configured for (a) insertion into a nostril of the patient (para [0102]), (b) placement within a nasal passageway of the patient (para [0075]), and (c) delivering a therapeutically effective amount of a drug (para [0015]) to a region of nasal tissue within the nasal cavity of the patient (para [0075]); wherein the applicator comprises an inner member and an outer member (para [0016]). Muni does not expressly disclose wherein the drug is a toxin for treating a condition associated with inflammation of a nasal membrane of a patient selected from rhinorrhea. However, Sanders discloses wherein the drug is a toxin for treating a condition associated with inflammation of a nasal membrane of a patient selected from rhinorrhea (col 2, ln 34-36). It would have been obvious to one of ordinary skill in the art to combine the disclosures of Muni and Sanders because Muni states that the substance delivered by its apparatus may be any feasible drug (para [0077]) and Sanders discloses botulinum toxin used as a drug (col 2, ln 34-38).

Regarding claim 32, Muni discloses the apparatus of claim 31, wherein the applicator further comprises an impermeable lining configured for separating the inner member and outer member (para [0016]).

Regarding claim 33, Muni discloses the apparatus of claim 31, wherein the applicator is configured to be arranged in a low volume configuration for placement within the nasal passageway and an expanded volume configuration for delivering the toxin to the nasal tissue (para [0105]).

Regarding claim 34, Muni discloses the apparatus of claim 33, wherein wherein the inner member comprises a balloon (para [0161] - 'inflatable balloon').

Regarding claim 35, while Muni does not expressly disclose the apparatus of claim 33, wherein the inner member comprises a sponge, Muni discloses an inner core that contains a substance (para [0016]) and also discloses that a substance may be loaded within a sponge (para [0010]). Therefore it would have been obvious to one of ordinary skill in the art wherein the inner member comprises a sponge.

Regarding claim 36, while Muni does not expressly disclose the apparatus of claim 35, wherein the inner member further comprises a spring element, Muni discloses wherein the inner member is capable of causing an outer layer to expand (para [0161]). Since a spring may be employed to cause an outer layer to expand, it would have been obvious to one of ordinary skill in the art wherein the inner member further comprises a spring element.

Regarding claim 37, Muni discloses the apparatus of claim 31, wherein the outer member comprises a bioresorbable coating (para [0161] - 'biodegradable').

Regarding claim 38, Muni does not expressly disclose the apparatus of claim 31, wherein the outer member comprises a balloon and a sponge. However, Muni discloses wherein the outer member elutes a substance (para [0016]) and further discloses a balloon that releases a substance (para [0095]) and a sponge that releases a substance (para [0010]). Therefore, it would have been obvious to one of ordinary skill in the art wherein the outer member comprises a balloon and a sponge.

Regarding claim 39, Muni discloses the apparatus of claim 31, wherein the inner member is configured to expand (para [0161]).

Regarding claim 40, Muni discloses the apparatus of claim 39, wherein expansion of the inner member facilitates delivery of the toxin to the nasal tissue (para [0161] - 'inflatable balloon 418 is inflated by a user. This causes stent 410 to expand'; and para [0162] - 'material of stent 410 comprises . . . one or more substances to be delivered').

(see continuation of citations and explanations in first supplemental box)

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

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**Supplemental Box**

In case **the space in any of the preceding boxes is not sufficient.**
Continuation of:
Box No. V(2) -- citations and explanations

Claims 44-51, 54 and 58 lack an inventive step under PCT Article 33(3) as being obvious over Sanders in view of US 2004/0009180 A1 to Donovan (hereinafter 'Donovan').

Regarding claim 44, Donovan discloses a method for delivering toxins to target cells, said method comprising: introducing a toxin to a region proximate the target cells; and applying energy to the target cells to enhance delivery of the toxins to the cells (para [0083]). Donovan does not disclose wherein the target cells are in a nasal membrane. However, Sanders discloses wherein the target cells are in a nasal membrane (col 2, ln 34-36). It would have been obvious to one of ordinary skill in the art to combine the disclosures of Donovan and Sanders because Sanders suggests delivering botulinum toxin via a topical route (col 2, ln 34-36) and Donovan describes an improved topical method to deliver botulinum toxin (para [0083]).

Regarding claim 45, Sanders discloses the method of claim 44, wherein the region comprises at least a main nasal passage (col 10, ln 17).

Regarding claim 46, Sanders discloses the method of claim 44, wherein the region comprises substantially the entire nasal cavity (col 8, ln 29 and 33).

Regarding claim 47, while Sanders does not expressly disclose the method of claim 44, wherein the region comprises the nasopharynx, it would have been obvious to one of ordinary skill in the art that the nasopharynx comprises a nasal membrane and wherein the region comprises the nasopharynx.

Regarding claim 48, while Sanders does not expressly disclose the method of claim 44, wherein the target cells comprise epithelial or goblet cells, Sanders discloses wherein the toxin is targeted to the nasal mucosa (col 2, ln 34-36). Since epithelial or goblet cells function to secrete mucus, it would have been obvious to one of ordinary skill in the art that Sanders implies wherein the target cells comprise epithelial or goblet cells.

Regarding claim 49, Donovan discloses the method of claim 44, wherein the energy is selectively applied to target cells within the region where toxin has been introduced (para [0083]).

Regarding claim 50, while Donovan does not expressly disclose the method of claim 44, wherein the energy is applied non-selectively within the region where toxin has been introduced; it would have been obvious to one of ordinary skill in the art wherein the energy is applied non-selectively within the region where toxin has been introduced.

Regarding claim 51, Sanders discloses the method of claim 44, wherein the patient suffers from or is at risk of suffering from rhinorrhea (col 2, ln 34-36).

Regarding claim 54, Sanders discloses the method of claim 44, wherein the toxin comprises botulinum toxin (col 2, ln 35-36).

Regarding claim 58, Donovan discloses the method of claim 44, wherein the energy applied to the targeted region is an electric pulse (para [0083]).

Claims 1-23 and 41-43 lack an inventive step under PCT Article 33(3) as being obvious over Muni in view of Sanders and further in view of US 1,695,107 A to Kahl (hereinafter 'Kahl').

Regarding claim 1, Muni discloses an apparatus comprising: a handle (para [0095] - 'tube or elongate shaft') comprising a proximal section, a first member (para [0095]), wherein the first member is connected at the proximal section; and an applicator tip coupled to the first member (para [0095] - 'substance reservoir');
wherein the first applicator tip are each configured for insertion into a nostril of the patient and placement within a nasal passageway of the patient (para [0075]) and wherein the first applicator tip is configured for delivering a drug (para [0077]) to a region of nasal tissue within the nasal cavity of the patient (para [0075]). Muni does not expressly disclose wherein the apparatus has a second member and a second applicator tip coupled to the second member. However, Kahl discloses a second member (col 1, ln 22-35 - 'links') and a second applicator tip coupled to the second member (col 1, ln 22-35 - 'lamps'). It would have been obvious to one of ordinary skill in the art to combine the disclosures of Muni and Kahl because Muni suggests that its apparatus may be inserted into the nasal passage (para [0075]) and Kahl discloses an apparatus that is adapted for insertion into the nasal passage (col 1, ln 1-4). Moreover, it would have been obvious to one of ordinary skill in the art that a nose has two nostrils and that each nostril may require a member and an applicator tip. Muni also does not expressly disclose wherein the drug delivered is a toxin and that toxin delivery treats the inflammation. However, Sanders discloses wherein the drug delivered is a toxin and that toxin delivery treats the inflammation (col 2, ln 34-38). It would have been obvious to one of ordinary skill in the art to combine the disclosures of Muni and Sanders because Muni states that the substance delivered by its apparatus may be any feasible drug (para [0077]) and Sanders discloses botulinum toxin used as a drug (col 2, ln 34-38).

Regarding claim 2, Kahl discloses the apparatus of claim 1, wherein the handle further comprises a spring element (col 2, ln col 65-66).

Regarding claim 3, while Kahl does not expressly disclose the apparatus of claim 2, wherein the spring element is either a v-shaped spring or closed-loop spring, it would have been obvious to one of ordinary skill in the art that a v-shaped spring or closed-loops spring may act as the 'pressure spring' disclosed in Kahl.

(see continuation of citations and explanations in second supplemental box)

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**Supplemental Box**

**In case the space in any of the preceding boxes is not sufficient.**

Continuation of:

citations and explanations from first supplemental box

Regarding claim 4, Kahl discloses the apparatus of claim 2, wherein the handle is configured to be arranged in a compressed delivery configuration for placement of the applicator tips within the nasal passageway and an expanded treatment configuration for delivering a therapeutic to the region of nasal tissue (col 2, ln 65-75) and Sanders discloses wherein the therapeutic is a toxin (col 2, ln 34-38), as discussed above.

Regarding claim 5, Sanders discloses the apparatus of claim 1, wherein each applicator tip comprises gauze (col 10, ln 16-18) but does not expressly disclose a sponge. However, it would have been obvious to one of ordinary skill in the art to substitute one absorbent material, a sponge, for another absorbent material, gauze.

Regarding claim 6, Muni discloses the apparatus of claim 5, wherein each applicator tip is configured to be arranged in a low volume delivery configuration for placement within the nasal passageway and an expanded volume treatment configuration for delivering a drug to the region of nasal tissue (para [0105]) and Sanders discloses wherein the therapeutic is a toxin (col 2, ln 34-38), as discussed above.

Regarding claim 7, Muni discloses the apparatus of claim 6, wherein each applicator tip in the expanded volume treatment configuration is adapted to fit substantially within the nasal cavity of the patient (para [0104]).

Regarding claim 8, Kahl discloses the apparatus of claim 5, wherein each applicator tip further comprises a spring element (col 1, ln 49-55; col 2, ln 56-60).

Regarding claim 9, Kahl discloses the apparatus of claim 8, wherein each applicator tip is configured to be arranged in a compressed delivery configuration for placement within the nasal passageway and an expanded treatment configuration for delivering toxin to the region of nasal tissue (col 1, ln 49-55; col 2, ln 56-60).

Regarding claim 10, Muni discloses the apparatus of claim 9, wherein each applicator tip (para [0161] - 'self-expanding stent') further comprises an actuator (para [0161] - 'hollow guide or sheath'), wherein the actuator is configured for movement from an engaged position and a retracted position (para [0161]).

Regarding claim 11, Muni discloses the apparatus of claim 10, wherein the applicator tip is in a compressed delivery configuration when the actuator is in the engaged position (para [0161] - 'self-expanding stent . . . introduced through a hollow guide or sheath into an anatomical region').

Regarding claim 12, Muni discloses the apparatus of claim 10, wherein the applicator tip is in the expanded delivery configuration when the actuator isi n the retracted position (para [0161] - 'Stent may be pushed out of the hollow sheath or guide').

Regarding claim 13, Muni discloses the apparatus of claim 10, further comprising an engagement element, wherein the engagement element is configured to control the movement of an actuator (para [0161] - 'pusher'). Muni does not expressly disclose wherein the engagement element controls the movement of both actuators simultaneously. However, since toxin is being delivered into both nostrils, it would have been obvious to one of ordinary skill in the art wherein the engagement element controls the movement of both actuators simultaneously.

Regarding claim 14, Muni discloses the apparatus of claim 5, wherein each applicator tip further comprises an impermeable lining (para [0016]).

Regarding claim 15, Sanders discloses the apparatus of claim 1, wherein each applicator tip further comprises a muco-adhesive pad (col 10, ln 18 - 'gauze').

Regarding claim 16, Muni discloses the apparatus of claim 1, wherein the toxin is carried by a bioresorbable coating (para [0010]).

Regarding claim 17, Muni discloses the apparatus of claim 1, further comprising an infusion channel for delivering the dug to the applicator tips (para [0107] - 'substance introducing lumen') and Sanders discloses wherein the therapeutic is a toxin (col 2, ln 34-38), as discussed above.

Regarding claim 18, Muni discloses the apparatus of claim 17, further comprising an access port, wherein the apparatus is in fluid communication with a drug source via the access port (para [0107]) and Sanders discloses wherein the therapeutic is a toxin (col 2, ln 34-38), as discussed above.

Regarding claim 19, Sanders discloses the apparatus of claim 17, wherein the applicator tips are configured to receive the toxin prior to being positioned in the nasal passageway (col 10, ln 17-18 - 'gauzed soaked with a saline solution of botulinum toxin').

Regarding claim 20, Muni discloses the apparatus of claim 17, wherein the applicator tips are configured to receive the toxin after being positioned in the nasal passageway (para [0095]).

Regarding claim 21, Sanders discloses the apparatus of claim 1, wherein the toxin comprises a liquid (col 10, ln 18 -'solution').

Regarding claim 22, Sanders discloses the apparatus of claim 1, wherein the toxin comprises botulinum toxin (col 10, ln 18).

Regarding claim 23, Sanders discloses the apparatus of claim 22, wherein the botulinum toxin is botulinum toxin D (col 10, ln 18).

(see continuation of citations and explanations in third supplemental box)

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No. PCT/US 07/69391

**Supplemental Box**

In case **the space in any of the preceding boxes is not sufficient.**
Continuation of:
citations and explanations from second supplemental box

Regarding claim 41, Muni discloses an apparatus comprising: a handle (para [0095] - 'tube or elongate shaft') comprising a proximal section, a first member (para [0095]), wherein the first member is connected at the proximal section; and an applicator tip coupled to the first member (para [0095] - 'substance reservoir');
wherein the first applicator tip are each configured for insertion into a nostril of the patient and placement within a nasal passageway of the patient (para [0075]) and wherein the first applicator tip is configured for delivering a drug (para [0077]) to a region of nasal tissue within the nasal cavity of the patient (para [0075]). Muni does not expressly disclose wherein the apparatus has a second member and a second applicator tip coupled to the second member. However, Kahl discloses a second member (col 1, ln 22-35 - 'links') and a second applicator tip coupled to the second member (col 1, ln 22-35 - 'lamps'). It would have been obvious to one of ordinary skill in the art to combine the disclosures of Muni and Kahl because Muni suggests that its apparatus may be inserted into the nasal passage (para [0075]) and Kahl discloses an apparatus that is adapted for insertion into the nasal passage (col 1, ln 1-4). Moreover, it would have been obvious to one of ordinary skill in the art that a nose has two nostrils and that each nostril may require a member and an applicator tip. Muni also does not expressly disclose wherein the drug delivered is a toxin and that the toxin treats a condition associated with inflammation of a nasal membrane of a patient selected from rhinorrhea. However, Sanders discloses wherein the drug delivered is a toxin and that the toxin treats a condition associated with inflammation of a nasal membrane of a patient selected from rhinorrhea (col 2, ln 34-38). It would have been obvious to one of ordinary skill in the art to combine the disclosures of Muni and Sanders because Muni states that the substance delivered by its apparatus may be any feasible drug (para [0077]) and Sanders discloses botulinum toxin used as a drug (col 2, ln 34-38).

Regarding claim 42, Kahl discloses the apparatus of claim 41, further comprising a spring element, wherein the spring element is configured to provide the applicator tips with an outward bias with the applicator tips are placed within the nasal passageway (col 1, ln 49-55; col 2, ln 56-60).

Regarding claim 43, while Kahl does not expressly disclose the apparatus of claim 42, wherein the outward bias presses each applicator tip against a turbinate in the nasal cavity, Kahl discloses wherein the springs exert pressure on the inner walls of the nose (col 2, ln 56-60). Since the nasal turbinates are the walls of the nasal cavity, it would have been obvious to one of ordinary skill in the art wherein the outward bias presses each applicator tip against a turbinate in the nasal cavity.

Claims 52-53 and 55-57 lack an inventive step under PCT Article 33(3) as being obvious over Sanders in view of Donovan and further in view of US 2005/0152924 A1 to Voet (hereinafter 'Voet').

Regarding claim 52, neither Sanders nor Donovan discloses the method of claim 44, wherein the patient suffers from or is at risk of suffering from sinus headaches. However, Voet discloses wherein the patient suffers from or is at risk of suffering from sinus headaches (para [0074]). It would have been obvious to one of ordinary skill in the art to combine the disclosure of Voet with the combination of Sanders and Donovan because Voet expressly makes reference to Sanders (para [0043]) and sinus headaches are a common ailment for which a therapeutic composition is used.

Regarding claim 53, Voet discloses the method of claim 44, wherein the patient suffers from or is at risk of suffering from migraine headaches (para [0043]).

Regarding claim 55, Voet discloses the method of claim 54, wherein the toxin is a fragment of botulinum toxin (para [0065]).

Regarding claim 56, Voet discloses the method of claim 55, wherein the fragment is a light chain fragment of botulinum toxin (para [0065] and [0013]-[0014]).

Regarding claim 57, Voet discloses the method of claim 56, wherein the light chain fragment is derived from at least one of botulinum toxins A, B, C, D, E, F and G (para [0055]).

Claims 59-67 lack an inventive step under PCT Article 33(3) as being obvious over Sanders in view of Donovan and further in view of US 2005/0107853 A1 to Krespi et al. (hereinafter 'Krespi').

Regarding claim 59, Donovan discloses the method of claim 58, wherein the energy applied to the target region is an electric pulse (Donovan para [0083]), but does not expressly disclose wherein the electric pulse is applied from between 1V to 500V. However, Krespi discloses wherein the electric pulse is applied from between 1V to 500V (para [0109] - '0.1 to about 5 J/cm2'). It would have been obvious to one of ordinary skill in the art to combine the disclosure of Krespi with the combination of Sanders and Donovan because Sanders suggests delivering botulinum toxin to the nasal passages (col 2, ln 34-36), Donovan describes an improved method for delivering botulinum toxin that uses application of energy (para [0083]), and Krespi discloses application of energy to the nasal passages (para [0037]).

Regarding claim 60, Krespi discloses the method of claim 58, wherein the electric pulse is an RF signal (para [0115]).

Regarding claim 61, Krespi discloses the method of claim 58, wherein the electric pulse is pulsed for durations between 5 microseconds to 100 milliseconds (para [0108]).

Regarding claim 62, Krespi discloses the method of claim 58, wherein the electric pulse is produced by a DC power source (para [0060]).

Regarding claim 63, Krespi discloses the method of claim 58, wherein the electric pulse is produced by an AC power source (para [0060]).

(see continuation of citations and explanations in fourth supplemental box)

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**Supplemental Box**

In case **the space in any of the preceding boxes is not sufficient.**
Continuation of:
citations and explanations from third supplemental box

Regarding claim 64, Donovan discloses the method of claim 44, wherein the energy applied to the target region is ultrasonic (para [0081]).

Regarding claim 65, Krespi does not expressly disclose the method of claim 44, wherein the energy applied to the targeted region is an x-ray beam, but discloses using electromagnetic energy (para [0037]. Since x-rays are a form of electromagnetic energy, it would have been obvious to one of ordinary skill in the art wherein the energy applied to the targeted region is an x-ray beam.

Regarding claim 66, Donovan discloses the method of claim 44, wherein the energy applied to the target region is ultrasonic (para [0081]) but does not expressly disclose focused ultrasound. However, it would have been obvious to one of ordinary skill in the art wherein the ultrasound used in the method is focused ultrasound.

Regarding claim 67, Krespi discloses the method of claim 44, wherein the energy applied to the targeted region is microwave (para [0115]).

Claims 68-78 lack an inventive step under PCT Article 33(3) as being obvious over Sanders in view of Donovan and further in view of Muni.

Regarding claim 68, neither Sanders nor Donovan discloses the method of claim 44, wherein the toxin is introduced to the target region through a catheter. However, Muni discloses wherein the toxin is introduced to the target region through a catheter (para [0095]). It would have been obvious to one of ordinary skill in the art to combine the disclosure of Muni with the combination of Sanders and Donovan because Muni states that the substance delivered by its apparatus may be any feasible drug (para [0077]) and Sanders discloses botulinum toxin used as a drug (col 2, ln 34-38).

Regarding claim 69, Muni discloses the method of claim 68, wherein the toxin is introduced through a balloon on the catheter (para [0095]).

Regarding claim 70, Muni discloses the method of claim 69, wherein the balloon is porous and the toxin is introduced through the balloon (para [0095]).

Regarding claim 71, Muni discloses the method of claim 68, wherein the toxin is introduced through a needle on the catheter (para [0014]).

Regarding claim 72, neither Sanders nor Donovan discloses the method of claim 68, wherein the toxin is introduced to the target region through a catheter. However, Muni discloses a catheter (para [0095]) and Sanders suggests aerosolizing the toxin (col 2, ln 45). Therefore it would have been obvious to one of ordinary skill in the art wherein the toxin is aerosolized from the catheter. It would have been obvious to one of ordinary skill in the art to combine the disclosure of Muni with the combination of Sanders and Donovan because Muni states that the substance delivered by its apparatus may be any feasible drug (para [0077]) and Sanders discloses botulinum toxin used as a drug (col 2, ln 34-38).

Regarding claim 73, neither Sanders nor Donovan discloses the method of claim 68, wherein energy is applied from a source on the catheter. However, Donovan suggests applying energy from a source close to the source for introducing the toxin (para [0081]). Muni discloses wherein the source for introducing the toxin is a catheter (para [0095]). Therefore it would have been obvious to one of ordinary skill in the art wherein energy is applied from a source on the catheter. It would have been obvious to one of ordinary skill in the art to combine the disclosure of Muni with the combination of Sanders and Donovan because Muni states that the substance delivered by its apparatus may be any feasible drug (para [0077]) and Sanders discloses botulinum toxin used as a drug (col 2, ln 34-38).

Regarding claim 74, neither Sanders nor Donovan discloses the method of claim 73, wherein acoustic energy is applied from a transducer on the catheter. However, Donovan suggests applying energy from a source close to the source for introducing the toxin (para [0081]) and also discloses wherein the energy is in the form of ultrasound (para [0081]). Muni discloses wherein the source for introducing the toxin is a catheter (para [0095]). Therefore it would have been obvious to one of ordinary skill in the art wherein acoustic energy is applied from a transducer on the catheter. It would have been obvious to one of ordinary skill in the art to combine the disclosure of Muni with the combination of Sanders and Donovan because Muni states that the substance delivered by its apparatus may be any feasible drug (para [0077]) and Sanders discloses botulinum toxin used as a drug (col 2, ln 34-38).

Regarding claim 75, neither Sanders nor Donovan discloses the method of claim 74, wherein electrical energy is applied from an electrode on the catheter. However, Donovan suggests applying energy from a source close to the source for introducing the toxin (para [0081]) and also discloses wherein the energy is in the form of electricity (para [0083]). Muni discloses wherein the source for introducing the toxin is a catheter (para [0095]). Therefore it would have been obvious to one of ordinary skill in the art wherein electrical energy is applied from an electrode on the catheter. It would have been obvious to one of ordinary skill in the art to combine the disclosure of Muni with the combination of Sanders and Donovan because Muni states that the substance delivered by its apparatus may be any feasible drug (para [0077]) and Sanders discloses botulinum toxin used as a drug (col 2, ln 34-38).

Regarding claim 76, Donovan discloses the method of claim 44, wherein the energy is delivered from a source external to the patient (para [0082] - 'to the skin').

Regarding claims 77 and 78, Donovan discloses the method of claim 76, wherein the energy is ultrasound (para [0081]-[0082]), therefore it would have been obvious to one of ordinary skill in the art wherein the source is an acoustic energy transducer and wherein the acoustic energy transducer is a focused ultrasound transducer.

(see continuation of citations and explanations in fourth supplemental box)

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**Supplemental Box**

In case **the space in any of the preceding boxes is not sufficient.**
Continuation of:
citations and explanations from third supplemental box

Claims 24-25 lack an inventive step under PCT Article 33(3) as being obvious over Muni in view of Sanders and in view of Kahl and further in view of Voet.

Regarding claim 24, Sanders discloses the apparatus of claim 22, wherein the toxin comprises botulinum toxin (col 10, ln 18). Muni, Kahl and Sanders fail to expressly disclose wherein the toxin is a fragment of botulinum toxin. However, Voet discloses wherein the toxin is a fragment of botulinum toxin (para [0065]). It would have been obvious to one of ordinary skill in the art to combine the disclosure of Voet with the combination of Muni, Kahl and Sanders because Voet expressly references Sanders (para [0043]).

Regarding claim 25, Voet discloses the apparatus of claim 24, wherein the fragment is a light chain fragment of botulinum toxin (para [0065] and [0013]-[0014]).

Claims 26-28 and 30 lack an inventive step under PCT Article 33(3) as being obvious over Muni in view of Sanders and in view of Kahl and in view of Voet and further in view of Donovan.

Regarding claim 26, Kahl discloses the apparatus of claim 25, further comprising an energy delivery applicator configured for delivering energy to the region of nasal tissue (col 1, ln 22-35). Kahl does not expressly disclose wherein the delivery of energy enhances delivery of the toxin. However, Donovan discloses wherein the delivery of energy enhances delivery of the toxin (para [0081]-[0083]). It would have been obvious to one of ordinary skill in the art to combine the disclosure of Donovan with the combination of Muni, Kahl, Sanders and Voet because Kahl discloses delivery of energy to nasal tissues (col 1, ln 22-35) and Donovan discloses an advantage of that energy delivery (para [0081]-[0083]).

Regarding claim 27, Donovan discloses the apparatus of claim 27, wherein the energy delivery applicator is adapted to deliver energy under conditions which cause poration of at least one cell in the region of nasal tissue (para [0081] - 'permeablilizes the skin').

Regarding claim 28, Donovan discloses the apparatus of claim 26, wherein the energy delivery applicator is adapted to deliver an electric pulse (para [0083]).

Regarding claim 30, Donovan discloses the apparatus of claim 26, wherein the energy delivery is adapted to deliver ultrasound energy (para [0081]-[0082]).

Claim 29 lacks an inventive step under PCT Article 33(3) as being obvious over Muni in view of Sanders and in view of Kahl and in view of Voet and in view of Donovan and further in view of Krespi.

Regarding claim 29, Donovan discloses the apparatus of claim 28, wherein the energy delivery applicator is adapted to deliver an electric pulse (para [0083]). Donovan does not expressly disclose wherein the pulse is an RF signal. However, Krespi discloses wherein the pulse is an RF signal (para [0115]). It would have been obvious to one of ordinary skill in the art to combine the disclosure of Krespi with the combination of Kahl, Sanders, Voet and Donovan because Sanders suggests delivering botulinum toxin to the nasal passages (col 2, ln 34 -36), Donovan describes an improved method for delivering botulinum toxin that uses application of energy (para [0083]), and Krespi discloses application of energy to the nasal passages (para [0037]).

Claims 1-78 have industrial applicability as defined by PCT Article 33(4) because the subject matter can be made or used in industry.

# Electronic Acknowledgement Receipt

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|---|---|
| **EFS ID:** | 23972557 |
| **Application Number:** | 14841514 |
| **International Application Number:** | |
| **Confirmation Number:** | 6656 |
| **Title of Invention:** | METHODS AND SYSTEMS FOR TOXIN DELIVERY TO THE NASAL CAVITY |
| **First Named Inventor/Applicant Name:** | Mark E. Deem |
| **Customer Number:** | 21971 |
| **Filer:** | Darby Jing-Da Chan/Collin Szeto |
| **Filer Authorized By:** | Darby Jing-Da Chan |
| **Attorney Docket Number:** | 38077-714.303 |
| **Receipt Date:** | 03-NOV-2015 |
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| **Application Type:** | Utility under 35 USC 111(a) |

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## File Listing:

| Document Number | Document Description | File Name | File Size(Bytes)/ Message Digest | Multi Part /.zip | Pages (if appl.) |
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| 1 | | IDS38077-714-303-11-03-2015.pdf | 377051<br>b5bad3e729e2a6ba4cff7a078a86108346156ec0 | yes | 20 |

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|---|---|---|---|---|---|
| | Document Description | | Start | End | |
| | Transmittal Letter | | 1 | 4 | |
| | Information Disclosure Statement (IDS) Form (SB08) | | 5 | 20 | |
| **Warnings:** | | | | | |
| **Information:** | | | | | |
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| **Warnings:** | | | | | |
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**New Applications Under 35 U.S.C. 111**

**If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.**

**National Stage of an International Application under 35 U.S.C. 371**

**If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.**

**New International Application Filed with the USPTO as a Receiving Office**

**If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.**

Espacenet

# Bibliographic data: DE19848472 (A1) — 2000-04-27

## Coloring brush for hair, such as eyelashes has two bars with applicator brushes, which form round profile when connected for easier storage


**Inventor(s):** DUMLER NORBERT [DE] ± (DUMLER, NORBERT)

**Applicant(s):** GEKA BRUSH GEORG KARL GMBH [DE] ± (GEORG KARL GEKA-BRUSH GMBH, ; GEKA GMBH)



**Classification:** **- international:** ***A45D34/04; A45D40/28; A46B9/02;*** (IPC1-7): A45D34/04; A45D40/26; A46B11/00; A46B9/02; B65D53/00

**- cooperative:** **A45D34/046**; **A45D40/28**; **A46B9/023**

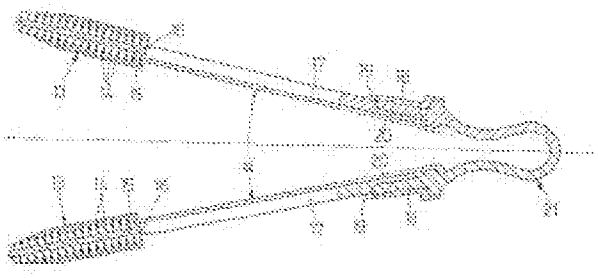
**Application number:** DE1998148472 19981021

**Priority number (s):** DE1998148472 19981021

**Also published as:** DE19848472 (B4)


## Abstract of DE19848472 (A1)


Brush has color container and applicator with two connected bars having applicator brushes (13) at the ends. The bars (17) have profiles, which form a circle when they are placed against each other. They are elastically connected via a loop (21) so that they point away from each other when not under load. The container has a neck with outer thread and a rotating stripper element.

(19) BUNDESREPUBLIK DEUTSCHLAND

DEUTSCHES PATENT- UND MARKENAMT

(12) **Offenlegungsschrift**

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(51) Int. Cl.[7]:
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A 46 B 9/02
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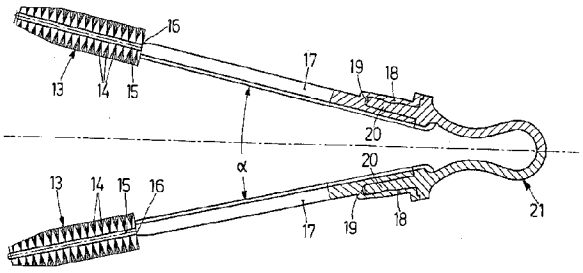
(56) Für die Beurteilung der Patentfähigkeit in Betracht zu ziehende Druckschriften:

US 50 07 442
EP 09 00 534 A1

**Die folgenden Angaben sind den vom Anmelder eingereichten Unterlagen entnommen**

(54) Einrichtung zum Färben von Haaren, wie Kopfhaaren oder Augenwimpern

(57) Bei einer Einrichtung zum Färben von Haaren, wie Kopfhaaren oder Augenwimpern, umfassend einen Behälter für das Färbemittel mit einer verschließbaren Öffnung, eine durch die Öffnung in den Innenraum des Behälters einführbare Applikatoreinheit, wobei die Applikatoreinheit zwei Schenkel bzw. Stiele aufweist, welche pinzettenartig elastisch miteinander verbunden sind und an ihren freien Enden Applikatoren, insbesondere Bürstchen, aufweist, ist vorgesehen, daß die Stiele bzw. Schenkel (17) einen derartigen Querschnitt aufweisen, daß sie sich im aneinandergelegten Zustand zu einem annähernd kreisförmigen Querschnitt ergänzen.




DE 198 48 472 A 1



BUNDESDRUCKEREI 03.00 002 017/323/1

## Beschreibung

Die Erfindung richtet sich auf eine Einrichtung zum Färben von Haaren, wie Kopfhaaren oder Augenwimpern, umfassend einen Behälter für das Färbemittel mit einer verschließbaren Öffnung, eine durch die Öffnung in den Innenraum des Behälters einführbare Applikatoreinheit, wobei die Applikatoreinheit zwei Schenkel bzw. Stiele aufweist, welche pinzettenartig elastisch miteinander verbunden sind und an ihren freien Enden Applikatoren, insbesondere Bürstchen, aufweisen. Eine derartige Einrichtung ist in Form einer Mascara-Einheit bekannt aus WO 95/12 332.

Eine Einrichtung der in Betracht stehenden Alt weist den Vorteil auf, daß die zu färbenden Haare zwischen den Schenkeln bzw. Stielen der Applikatoreinheit beim Auftragen des Färbemittels eingeschlossen werden können, so daß eine intensive Übertragung und Durchdringung der Haare mit dem Färbemittel gewährleistet ist. Bei der bekannten Einrichtung taucht jeder Schenkel bzw. Stiel in eine gesonderte Öffnung des Behälters ein und ihm ist jeweils eine gesondeite Abstreifeinrichtung zugeordnet. Diese Ausgestaltung ist konstruktiv aufwendig und ästhetisch nicht besonders ansprechend.

Hiervon ausgehend liegt der Erfindung die Aufgabe zugrunde, eine Einrichtung der gattungsgemäßen Alt so zu verbessern, daß ihr konstruktiver Aufbau vereinfacht und die Handhabung erleichtert wird.

Diese Aufgabe wird erfindungsgemäß dadurch gelöst, daß die Stiele bzw. Schenkel einen derartigen Querschnitt aufweisen, daß sie sich im aneinandergelegten Zustand zu einem annähernd kreisförmigen Querschnitt ergänzen. Dies bedeutet mit anderen Worten, daß im Aufbewahrungszustand, wenn also die Applikatoren in den Behälter eintauchen, ein nach außen zumindestens annähernd rotationssymmetrisches Gebilde geschaffen wird.

Dabei ist günstigerweise vorgesehen, daß die Schenkel bzw. Stiele über ein Schlaufenelement mit einer derartigen federelastischen Eigensteifigkeit verbunden sind, daß sich im unbelasteten Zustand eine Spreizung der Schenkel einstellt. Dementsprechend können die Schenkel dann zum Auftragen ähnlich wie bei einer Pinzette zwischen Daumen und Zeigefinger einer Hand zusammengedrückt werden.

Die annähernd rotationssymmetrische Ausgestaltung der Applikatoreinheit ermöglicht es, erfindungsgemäß vorzusehen, daß der Behälter einen Behälter-Hals mit einem Außengewinde aufweist, in den eine rotationssymmetrische Abstreifeinrichtung eingesetzt ist. Es kann also eine vergleichsweise einfache, günstig herstellbare Abstreifeinrichtung eingesetzt werden, was bei bekannten Einrichtungen dieser Art nicht möglich war oder zumindestens zwei Abstreifeinrichtungen erforderlich machte.

Günstigerweise kann weiterhin vorgesehen sein, daß die Abstreifeinrichtung eine Schulter aufweist, die im eingesetzten Zustand die Stirnseite des Halses übergreift und gegenüber einer aufschraubbaren Verschlußkappe als Dichtung wirkt, wenn eine innere Ringschulter der Verschlußkappe hieran zur Anlage kommt. Hierdurch wird ein gesondertes Dichtungselement erspart.

Bei einer bevorzugten Ausführungsform ist vorgesehen, daß an dem einen freien Ende der Schenkel bzw. Stiele ein Bürstchen und an dem anderen Ende ein Kunststoff-Formteil angeordnet ist, welches insbesondere als Widerlager für das Bürstchen konfiguriert sein kann.

Bei einer anderen Ausführungsform kann vorgesehen sein, daß an beiden Enden der Schenkel bzw. Stiele Applikatoren in Form von Bürstchen angebracht sind, wobei die Bürstchen einen unterschiedlichen Durchmesser aufweisen.

Neben einem unterschiedlichen Durchmesser können die Bürstchen auch mit einem unterschiedlichen Besatz versehen sein, so daß beispielsweise eines der Bürstchen aufgrund steiferer Borsten eine ausgeprägte Kämmwirkung besitzt, während das andere Bürstchen aufgrund weicherer Borsten besonderes günstige Auftragseigenschaften aufweist.

Weiterhin kann eines der Bürstchen mit einer konkaven Ausnehmung im Zuschnitt der Borsten derart versehen sein, daß die konvexe Hüllfläche der Borsten des jeweils anderen Bürstchens in diese Ausnehmung eingreift.

Zur Vereinfachung der Handhabung können schließlich noch die Schenkel bzw. Stiele Griffmulden aufweisen.

Nachfolgend wird die Erfindung anhand eines bevorzugten Ausführungsbeispiels in Verbindung mit der Zeichnung näher erläutert. Dabei zeigen:

**Fig.** 1 einen Längsschnitt durch eine erfindungsgemäße Anordnung im geschlossenen Zustand,

**Fig.** 2 einen Längsschnitt durch den Behälter bei herausgezogenem Applikator,

**Fig.** 3 einen Schnitt durch den Applikator und

**Fig.** 4 einen Schnitt durch die Verschlußkappe des in **Fig.** 2 dargestellten Behälters.

Eine in der Zeichnung dargestellte erfindungsgemäße Einrichtung umfaßt einen Behälter **1** mit einem Innenraum **2** zur Aufnahme eines Färbemittels, wie beispielsweise eines Haarfärbemittels oder einer Mascaraflüssigkeit für die Wimpern. Der Behälter **1** weist einen gegenüber dem Grundkörper **3** zurückspringenden Hals **4** geringeren Außendurchmessers mit einem Außengewinde **5** auf, wobei auf den Hals **4** bzw. das Gewinde **5** eine Verschlußkappe **6** mit einem Innengewinde **7** so aufschraubbar ist, daß die Außenwand **8** der Verschlußkappe **6** mit der Außenwand des Grundkörpers **3** des Behälters **1** fluchtet. In den Behälterhals **4** ist eine rotationssymmetrische Abstreifeinrichtung **9** mit einer Durchlaßöffnung **10** und einer Ringschulter **11** eingesetzt, die die Stirnseite des Halses **4** übergreift und mit diesem außen fluchtet. Der Behälter **1** weist zum Hals **4** hin eine Öffnung **12** auf, durch welche ein in **Fig.** 3 dargestelltes Paar von Applikatoren **13** in den Innenraum **2** des Behälters **1** einführbar ist.

Die Applikatoren **13** sind im Ausführungsbeispiel als Bürstchen ausgebildet, wobei die Borsten **14** des Bürstchens in einer Seele **15** aus verdrillten Drahtabschnitten gehalten sind. Diese Seele **15** ist an dem freien Ende **16** eines Stiels **17** befestigt. Die inneren Enden **18** der Stiele **17** sind mit einer Ausnehmung **19** versehen, in die jeweils ein Zapfen **20** einer Federanordnung **21** formschlüssig eingesetzt ist. Die Federanordnung **21** ist gebildet durch ein schlaufenförmiges, um 180° umbiegbares Kunststoffteil, wobei der Kunststoff eine derartige federelastische Eigensteifigkeit aufweist, daß die Stiele bzw. Schenkel **17** ohne Kraftbeaufschlagung einen Winkel $\alpha$ von etwa 24° einnehmen und sich andererseits in eine aneinander anliegende Parallellage bringen lassen, wie diese in **Fig.** 1 dargestellt ist.

Die Stiele bzw. Schenkel **17** sind im Querschnitt derart halbkreisförmig ausgebildet, daß sie sich in dem in **Fig.** 1 dargestellten zusammengedrückten, aneinander anliegenden Zustand zu einem Querschnitts-Vollkreis ergänzen, wobei die Borsten **14** der Applikatoren **13** in diesem Zustand ineinander dringen und nach außen hin ein annähernd zylinderförmiges Bürstchen ausbilden.

Auf diese Weise ist es möglich, eine herkömmliche, rotationssymmetrische Abstreifeinrichtung **9** zu verwenden, um beim Herausziehen der Applikatoreinheit ausgehend von der in **Fig.** 1 dargestellten Position ein zuverlässiges und gleichmäßiges Abstreifen der Färbeflüssigkeit aus dem Innenraum **2** des Behälters **1** zu gewährleisten. Die Ringschulter **11** der Abstreifeinrichtung **9** wirkt beim Aufsetzen der

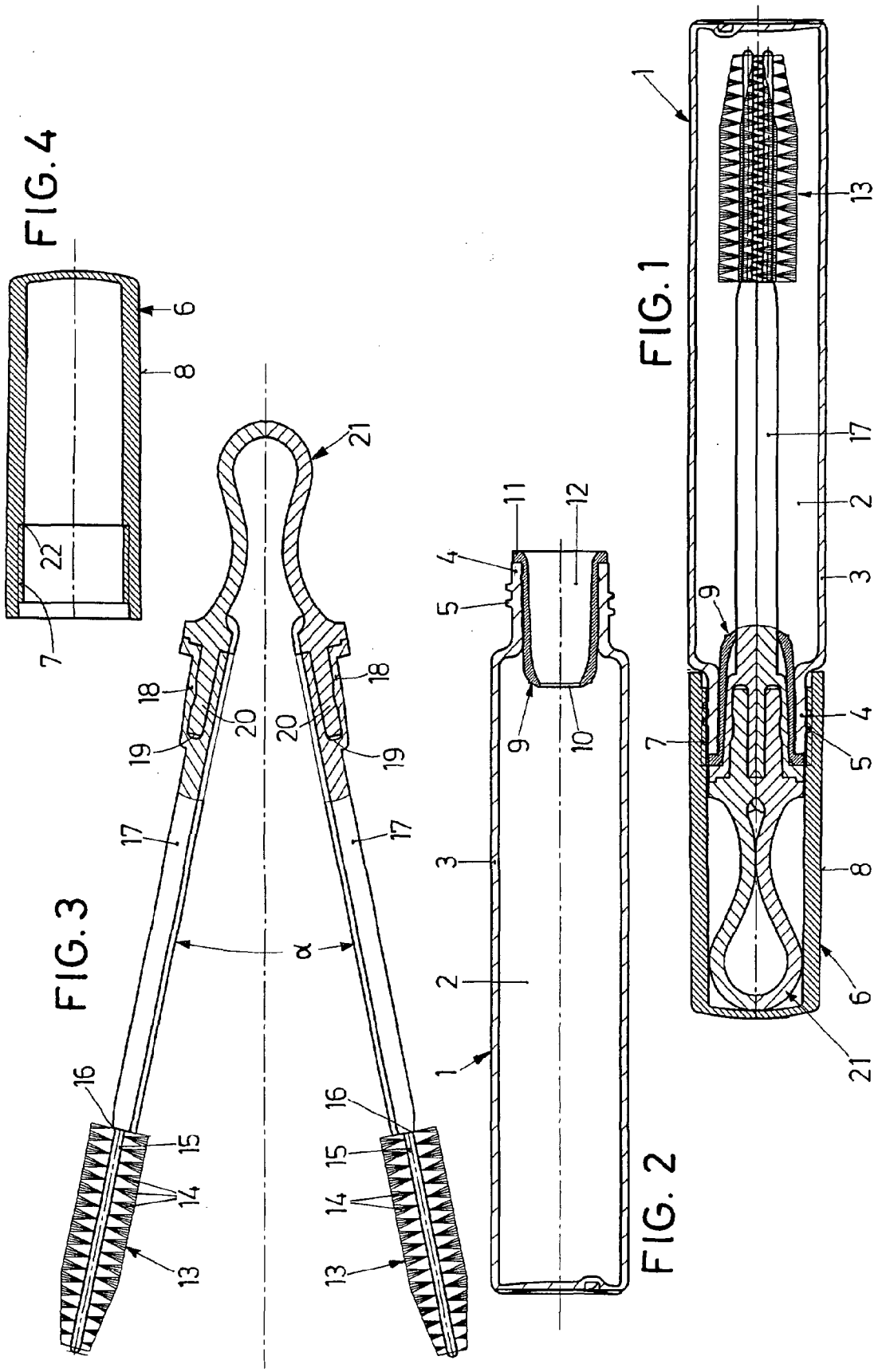
Schraubkappe **6** mit einer Ringschulter **22** an der Innenseite der Schraubkappe nach Art eines Dichtungselementes zusammen.

## Patentansprüche

1. Einrichtung zum Färben von Haaren, wie Kopfhaaren oder Augenwimpern, umfassend einen Behälter für das Färbemittel mit einer verschließbaren Öffnung, eine durch die Öffnung in den Innenraum des Behälters einführbare Applikatoreinheit, wobei die Applikatoreinheit zwei Schenkel bzw. Stiele aufweist, welche pinzettenartig elastisch miteinander verbunden sind und an ihren freien Enden Applikatoren, insbesondere Bürstchen, aufweisen, **dadurch gekennzeichnet**, daß die Stiele bzw. Schenkel (**17**) einen derartigen Querschnitt aufweisen, daß sie sich im aneinandergelegten Zustand zu einem annähernd kreisförmigen Querschnitt ergänzen.
2. Einrichtung nach Anspruch 1, dadurch gekennzeichnet, daß die Schenkel bzw. Stiele (**17**) über ein Schlaufenelement (**21**) mit einer derartigen federelastischen Eigensteifigkeit verbunden sind, daß sich im unbelasteten Zustand eine Spreizung der Stiele bzw. Schenkel (**17**) einstellt.
3. Einrichtung nach Anspruch 1, dadurch gekennzeichnet, daß der Behälter (**1**) einen Behälter-Hals (**4**) mit einem Außengewinde (**5**) aufweist, in den eine rotationssymmetrische Abstreifeinrichtung (**9**) eingesetzt ist.
4. Einrichtung nach Anspruch 3, dadurch gekennzeichnet daß die Abstreifeinrichtung (**5**) eine Schulter (**11**) aufweist, die im eingesetzten Zustand die Stirnseite des Halses (**4**) übergreift und gegenüber einer aufschraubbaren Verschlußkappe (**6**) als Dichtung wirkt, wenn eine innere Ringschulter (**22**) der Verschlußkappe (**6**) hieran zur Anlage kommt.
5. Einrichtung nach Anspruch 1, dadurch gekennzeichnet daß an dem einen freien Ende (**16**) der Schenkel bzw. Stiele (**17**) ein Bürstchen (**13**) und an dem anderen Ende ein Kunststoff-Formteil angeordnet ist.
6. Einrichtung nach Anspruch 1, dadurch gekennzeichnet daß an beiden Enden (**16**) der Schenkel bzw. Stiele (**17**) Applikatoren in Form von Bürstchen (**13**) angebracht sind, wobei die Bürstchen einen unterschiedlichen Durchmesser aufweisen.
7. Einrichtung nach Anspruch 1, dadurch gekennzeichnet daß an den Enden der Schenkel bzw. Stiele (**17**) Bürstchen (**13**) mit unterschiedlichem Besatz angebracht sind.
8. Einrichtung nach Anspruch 7, dadurch gekennzeichnet daß eines der Bürstchen (**13**) mit einer konkaven Ausnehmung im Zuschnitt der Borsten (**14**) derart vorgesehen ist, daß die konvexe Hüllfläche der Borsten (**14**) des jeweils anderen Bürstchens (**13**) in diese Ausnehmung eingreift.
9. Einrichtung nach Anspruch 1, dadurch gekennzeichnet daß an den Schenkel bzw. Stielen (**17**) Griffmulden ausgebildet sind.

Hierzu 1 Seite(n) Zeichnungen

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| NAVARRO, ALBERT MARK | |

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Applicants IDS submitted January 21, 2020 has been considered. A signed copy is enclosed.

/ALBERT M NAVARRO/
Primary Examiner, Art Unit 1645

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| First Named Inventor | MARK; E. Deem |
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| Examiner Name | Albert Mark Navarro |
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| Application Number | 16659893 |
| Filing Date | 10-22-2019 |
| First Named Inventor | MARK; E. Deem |
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| Examiner Name | Albert Mark Navarro |
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# INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(Use as many sheets as necessary)

Sheet 5 of 17

| Complete if Known | |
|---|---|
| Application Number | 16659893 |
| Filing Date | 10-22-2019 |
| First Named Inventor | MARK; E. Deem |
| Art Unit | 1645 |
| Examiner Name | Albert Mark Navarro |
| Attorney Docket Number | 5187.01US01AP |

| Examiner Initials* | Cite No.[1] | Document Number<br>Number-Kind Code[2] (if known) | Publication Date MM-DD-YYYY | Name of Patentee or Applicant of Cited Document |
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Sheet 6 of 17

| Complete if Known | |
|---|---|
| Application Number | 16659893 |
| Filing Date | 10-22-2019 |
| First Named Inventor | MARK; E. Deem |
| Art Unit | 1645 |
| Examiner Name | Albert Mark Navarro |
| Attorney Docket Number | 5187.01US01AP |

| Examiner Initials* | Cite No.[1] | Document Number<br>Number-Kind Code[2] (if known) | Publication Date MM-DD-YYYY | Name of Patentee or Applicant of Cited Document |
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# INFORMATION DISCLOSURE STATEMENT BY APPLICANT

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Sheet 7 of 17

| Complete if Known | |
|---|---|
| Application Number | 16659893 |
| Filing Date | 10-22-2019 |
| First Named Inventor | MARK; E. Deem |
| Art Unit | 1645 |
| Examiner Name | Albert Mark Navarro |
| Attorney Docket Number | 5187.01US01AP |

| Examiner Initials* | Cite No.[1] | Document Number<br>Number-Kind Code[2] (if known) | Publication Date MM-DD-YYYY | Name of Patentee or Applicant of Cited Document |
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Sheet 8 of 17

| Complete if Known | |
|---|---|
| Application Number | 16659893 |
| Filing Date | 10-22-2019 |
| First Named Inventor | MARK; E. Deem |
| Art Unit | 1645 |
| Examiner Name | Albert Mark Navarro |
| Attorney Docket Number | 5187.01US01AP |

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Sheet 9 of 17

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| Application Number | 16659893 |
| Filing Date | 10-22-2019 |
| First Named Inventor | MARK; E. Deem |
| Art Unit | 1645 |
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| Complete if Known | |
|---|---|
| Application Number | 16659893 |
| Filing Date | 10-22-2019 |
| First Named Inventor | MARK; E. Deem |
| Art Unit | 1645 |
| Examiner Name | Albert Mark Navarro |
| Attorney Docket Number | 5187.01US01AP |

| Examiner Initials* | Cite No.[1] | Foreign Patent Document<br>Country Code[3]–Number[4]–Kind Code[5] (if known) | Publication Date MM-DD-YYYY | Name of Patentee or Applicant of Cited Document | T[6] |
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| Examiner Signature | /ALBERT M NAVARRO/ | Date Considered | 02/06/2020 |
|---|---|---|---|

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant. 1 Applicant's unique citation designation number (optional). 2 Applicant is to place a check mark here if English language Translation is attached. This collection of information is required by 37 CFR 1.98. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 2 hours to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

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ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /A.M.N/

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| APPLICATION NUMBER | FILING OR 371(C) DATE | FIRST NAMED APPLICANT | ATTY. DOCKET NO./TITLE |
|---|---|---|---|
| 16/659,893 | 10/22/2019 | Mark E. Deem | 5187.01US01AP |

**CONFIRMATION NO. 4259**

24113
PATTERSON THUENTE PEDERSEN, P.A.
80 SOUTH 8TH STREET
4800 IDS CENTER
MINNEAPOLIS, MN 55402-2100

**PUBLICATION NOTICE**

*OC000000114703280*

**Title:**SYSTEMS AND METHODS FOR DELIVERY OF A THERAPEUTIC AGENT

**Publication No.**US-2020-0046955-A1
**Publication Date:**02/13/2020

## NOTICE OF PUBLICATION OF APPLICATION

The above-identified application will be electronically published as a patent application publication pursuant to 37 CFR 1.211, et seq. The patent application publication number and publication date are set forth above.

The publication may be accessed through the USPTO's publically available Searchable Databases via the Internet at www.uspto.gov. The direct link to access the publication is currently http://www.uspto.gov/patft/.

The publication process established by the Office does not provide for mailing a copy of the publication to applicant. A copy of the publication may be obtained from the Office upon payment of the appropriate fee set forth in 37 CFR 1.19(a)(1). Orders for copies of patent application publications are handled by the USPTO's Public Records Division. The Public Records Division can be reached by telephone at (571) 272-3150 or (800) 972-6382, by facsimile at (571) 273-3250, by mail addressed to the United States Patent and Trademark Office, Public Records Division, Alexandria, VA 22313-1450 or via the Internet.

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Office of Data Managment, Application Assistance Unit (571) 272-4000, or (571) 272-4200, or 1-888-786-0101

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Note: A certificate of mailing can only be used for domestic mailings of the Fee(s) Transmittal. This certificate cannot be used for any other accompanying papers. Each additional paper, such as an assignment or formal drawing, must have its own certificate of mailing or transmission.

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I hereby certify that this Fee(s) Transmittal is being deposited with the United States Postal Service with sufficient postage for first class mail in an envelope addressed to the Mail Stop ISSUE FEE address above, or being transmitted to the USPTO via EFS-Web or by facsimile to (571) 273-2885, on the date below.

| |
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| (Typed or printed name) |
| (Signature) |
| (Date) |

| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
|---|---|---|---|---|
| 16/659,893 | 10/22/2019 | Mark E. Deem | 5187.01US01AP | 4259 |

TITLE OF INVENTION: SYSTEMS AND METHODS FOR DELIVERY OF A THERAPEUTIC AGENT

| APPLN. TYPE | ENTITY STATUS | ISSUE FEE DUE | PUBLICATION FEE DUE | PREV. PAID ISSUE FEE | TOTAL FEE(S) DUE | DATE DUE |
|---|---|---|---|---|---|---|
| nonprovisional | SMALL | $500 | $0.00 | $0.00 | $500 | 02/24/2020 |

| EXAMINER | ART UNIT | CLASS-SUBCLASS |
|---|---|---|
| NAVARRO, ALBERT MARK | 1645 | 424-190100 |

1. Change of correspondence address or indication of "Fee Address" (37 CFR 1.363).

☐ Change of correspondence address (or Change of Correspondence Address form PTO/SB/122) attached.

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2. For printing on the patent front page, list
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1 Patterson Thuente Pedersen, P.A.
2
3

3. ASSIGNEE NAME AND RESIDENCE DATA TO BE PRINTED ON THE PATENT (print or type)

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(A) NAME OF ASSIGNEE: The Foundry, LLC

(B) RESIDENCE: (CITY and STATE OR COUNTRY): Menlo Park, California

Please check the appropriate assignee category or categories (will not be printed on the patent) : ☐ Individual ☒ Corporation or other private group entity ☐ Government

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Authorized Signature _____ Date 2/24/2020

Typed or printed name Daidre L. Burgess Registration No. 60389

# Electronic Patent Application Fee Transmittal

| | |
|---|---|
| **Application Number:** | 16659893 |
| **Filing Date:** | 22-Oct-2019 |
| **Title of Invention:** | SYSTEMS AND METHODS FOR DELIVERY OF A THERAPEUTIC AGENT |
| **First Named Inventor/Applicant Name:** | Mark E. Deem |
| **Filer:** | Daidre L. Burgess/Valerie Mitchell |
| **Attorney Docket Number:** | 5187.01US01AP |

Filed as Small Entity

**Filing Fees for Utility under 35 USC 111(a)**

| Description | Fee Code | Quantity | Amount | Sub-Total in USD($) |
|---|---|---|---|---|
| **Basic Filing:** | | | | |
| **Pages:** | | | | |
| **Claims:** | | | | |
| **Miscellaneous-Filing:** | | | | |
| **Petition:** | | | | |
| **Patent-Appeals-and-Interference:** | | | | |
| **Post-Allowance-and-Post-Issuance:** | | | | |
| UTILITY APPL ISSUE FEE | 2501 | 1 | 500 | 500 |

| Description | Fee Code | Quantity | Amount | Sub-Total in USD($) |
|---|---|---|---|---|
| **Extension-of-Time:** | | | | |
| **Miscellaneous:** | | | | |
| | | | **Total in USD ($)** | **500** |

# Electronic Acknowledgement Receipt

| | |
|---|---|
| **EFS ID:** | 38669683 |
| **Application Number:** | 16659893 |
| **International Application Number:** | |
| **Confirmation Number:** | 4259 |
| **Title of Invention:** | SYSTEMS AND METHODS FOR DELIVERY OF A THERAPEUTIC AGENT |
| **First Named Inventor/Applicant Name:** | Mark E. Deem |
| **Customer Number:** | 24113 |
| **Filer:** | Daidre L. Burgess/Valerie Mitchell |
| **Filer Authorized By:** | Daidre L. Burgess |
| **Attorney Docket Number:** | 5187.01US01AP |
| **Receipt Date:** | 24-FEB-2020 |
| **Filing Date:** | 22-OCT-2019 |
| **Time Stamp:** | 13:49:53 |
| **Application Type:** | Utility under 35 USC 111(a) |

## Payment information:

| | |
|---|---|
| Submitted with Payment | yes |
| Payment Type | CARD |
| Payment was successfully received in RAM | $500 |
| RAM confirmation Number | E20202ND50254886 |
| Deposit Account | 160631 |
| Authorized User | Valerie Mitchell |

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37 CFR 1.17 (Patent application and reexamination processing fees)

37 CFR 1.19 (Document supply fees)

37 CFR 1.20 (Post Issuance fees)

37 CFR 1.21 (Miscellaneous fees and charges)

## File Listing:

| Document Number | Document Description | File Name | File Size(Bytes)/ Message Digest | Multi Part /.zip | Pages (if appl.) |
|---|---|---|---|---|---|
| 1 | Issue Fee Payment (PTO-85B) | 5187_01US01AP_ISSUE_FEE.pdf | 114875<br>d0a7dc63b5ac6bb59988b762e9f249be56f225e6 | no | 1 |
| **Warnings:** | | | | | |
| **Information:** | | | | | |
| 2 | Fee Worksheet (SB06) | fee-info.pdf | 30376<br>d1f92d581915c4f54d9708a00a57b28663b36deb | no | 2 |
| **Warnings:** | | | | | |
| **Information:** | | | | | |
| | | **Total Files Size (in bytes):** | 145251 | | |

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**New International Application Filed with the USPTO as a Receiving Office**

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| APPLICATION NO. | ISSUE DATE | PATENT NO. | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
|---|---|---|---|---|
| 16/659,893 | 04/07/2020 | 10610675 | 5187.01US01AP | 4259 |

24113 7590 03/18/2020

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# ISSUE NOTIFICATION

The projected patent number and issue date are specified above.

**Determination of Patent Term Adjustment under 35 U.S.C. 154 (b)**
(application filed on or after May 29, 2000)

The Patent Term Adjustment is 0 day(s). Any patent to issue from the above-identified application will include an indication of the adjustment on the front page.

If a Continued Prosecution Application (CPA) was filed in the above-identified application, the filing date that determines Patent Term Adjustment is the filing date of the most recent CPA.

Applicant will be able to obtain more detailed information by accessing the Patent Application Information Retrieval (PAIR) WEB site (http://pair.uspto.gov).

Any questions regarding the Patent Term Extension or Adjustment determination should be directed to the Office of Patent Legal Administration at (571)-272-7702. Questions relating to issue and publication fee payments should be directed to the Application Assistance Unit (AAU) of the Office of Data Management (ODM) at (571)-272-4200.

APPLICANT(s) (Please see PAIR WEB site http://pair.uspto.gov for additional applicants):

Mark E. Deem, Mountain View, CA;
The Foundry, LLC, Menlo Park, CA
Hanson Gifford, Woodside, CA;

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