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Application Number: 16842209 Document Date: 04/07/2020

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Document Description: TrackOne Request

PTO/AIA/424 (04-14)

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)(1) and the prioritized examination fee set forth in 37 CFR 1.17(c) have been filed with the request. The publication fee requirement is met because that fee, set forth in 37 CFR 1.18(d), is currently $0. The basic filing fee, search fee, and examination fee are filed with the request or have been already been paid. I understand that any required excess claims fees or application size fee must be paid for the application.

2. I understand that the application may not contain, or be amended to contain, more than four independent claims, more than thirty total claims, or any multiple dependent claims, and that any request for an extension of time will cause an outstanding Track I request to be dismissed.

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 inventor's oath or declaration under 37 CFR 1.63 or 37 CFR 1.64 for each inventor, **or** the application data sheet meeting the conditions specified in 37 CFR 1.53(f)(3)(i) 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 04/07/2020
Name (Print/Typed) Daidre L. Burgess	Practitioner Registration Number 60389

Note: *This form must be signed in accordance with 37 CFR 1.33. See 37 CFR 1.4(d) for signature requirements and certifications. Submit multiple forms if more than one signature is required.**

☐ *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	5187.01US02AP
	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	

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	5187.01US02AP
	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	5187.01US02AP	**Small Entity Status Claimed**	☒
Application Type	Nonprovisional		
Subject Matter			
Total Number of Drawing Sheets (if any)	14	**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	5187.01US02AP
	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	16/659893	2019-10-22
Prior Application Status	Pending		Remove
Application Number	Continuity Type	Prior Application Number	Filing or 371(c) Date (YYYY-MM-DD)
16/659893	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

Application Data Sheet 37 CFR 1.76	Attorney Docket Number	5187.01US02AP
	Application Number	
Title of Invention	SYSTEMS AND METHODS FOR DELIVERY OF A THERAPEUTIC AGENT	

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

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	5187.01US02AP
	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	5187.01US02AP
	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	5187.01US02AP
	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)	2020-04-07
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	5187.01US02AP
	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.

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. Apparatus for treatment of a nasal condition comprising:

a hand-held elongate body having proximal and distal portions, the distal portion being configured for positioning in a nasopharyngeal passage of a patient with the proximal portion positioned outside the nasopharyngeal passage;

an energy transmission element in the distal portion configured to deliver energy to target tissue in the nasopharyngeal passage; and

an energy source operatively coupled to the energy transmission element for supplying energy thereto according to one or more parameters selected so as to alter nasopharyngeal cells in the target tissue such that nasal congestion is reduced.

2. The apparatus of claim 1, wherein the energy transmission element comprises at least one electrode.

3. The apparatus of claim 1, wherein the energy transmission element comprises an ultrasound transducer.

4. The apparatus of claim 1, wherein the energy transmission element comprises a microwave antenna.

5. The apparatus of claim 1, wherein the energy supplying means comprises an RF generator.

6. The apparatus of claim 1, wherein the energy supplying means comprises an ultrasound generator.

7. The apparatus of claim 1, wherein the energy supplying means comprises an AC or DC current source.

8. The apparatus of claim 1, wherein the energy transmission element is movable relative to the distal portion of the body.

9. The apparatus of claim 8, wherein the energy transmission element is configured to deliver energy laterally relative to the distal portion of the body.

10. The apparatus of clam 9, wherein the energy transmission element is configured to extend laterally from the distal portion of the body.

11. The apparatus of claim 8, wherein the energy transmission element is configured to penetrate the nasal tissue.

12. The apparatus of claim 1, further comprising: a sensing element on the distal portion of the body.

13. The apparatus of claim 12, wherein the sensing element comprises a temperature sensor.

14. The apparatus of claim 12, further comprising: a monitoring system operatively coupled to the sensing element for indicating a degree of treatment of the target tissue.

15. The apparatus of claim 1, further comprising: an agent delivery element in the distal portion of the body configured to deliver a therapeutic agent to the target tissue.

16. The apparatus of claim 15, wherein the agent delivery element comprises a porous member through which the agent may be delivered.

17. The apparatus of claim 16, wherein the agent delivery element comprises an inflatable member.

18. The apparatus of claim 16, wherein the agent delivery element comprises an injection element configured to penetrate the target tissue.

19. The apparatus of claim 15, further comprising: a source of therapeutic agent coupled to the proximal portion of the body.

20. The apparatus of claim 19, wherein the therapeutic agent comprises a neurotoxin.

21. The apparatus of claim 1, wherein the energy source and the energy transmission element are configured to deliver the energy so as to disable adrenergic cells in the target tissue.

22. The apparatus of claim 21, wherein the energy is delivered so as to block or disrupt acetycholine release in the adrenergic cells.

23. Apparatus for treatment of a nasal condition comprising:

a hand-held elongate body having proximal and distal portions, the distal portion being configured for positioning in a nasopharyngeal passage of a patient with the proximal portion positioned outside the nasopharyngeal passage; and

a transmission element in the distal portion configured to change the temperature of target tissue in the nasopharyngeal passage so as to disrupt neural activity in the target tissue such that nasal congestion is reduced.

24. The apparatus of claim 23, wherein the transmission element is configured to transfer thermal energy between the transmission element and the target tissue.

25. The apparatus of claim 23, wherein the transmission element is configured to change the temperature of the target tissue so as to disable adrenergic cells therein.

26. The apparatus of claim 23, wherein the transmission element is configured to change the temperature of the target tissue so as to block or disrupt acetycholine production in nasopharyngeal cells.

27. The apparatus of claim 23, wherein the transmission element is configured to contain a fluid to change the temperature of the target tissue.

28. The apparatus of claim 27, wherein the transmission element comprises an injection device configured to direct the fluid to the target tissue.

29. The apparatus of claim 28, wherein the fluid is heated.

SYSTEMS AND METHODS FOR DELIVERY OF A THERAPEUTIC AGENT

RELATED APPLICATIONS

This application is a continuation of Application No. 16/659,893 filed October 22, 2019, which in turn 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.

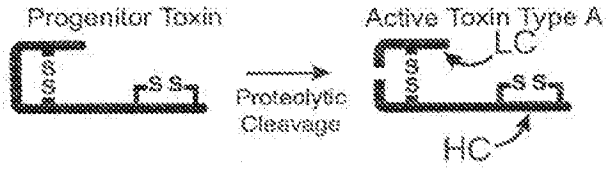

Progenitor Toxin
Active Toxin Type A
LC
HC
Proteolytic Cleavage

FIG. 1

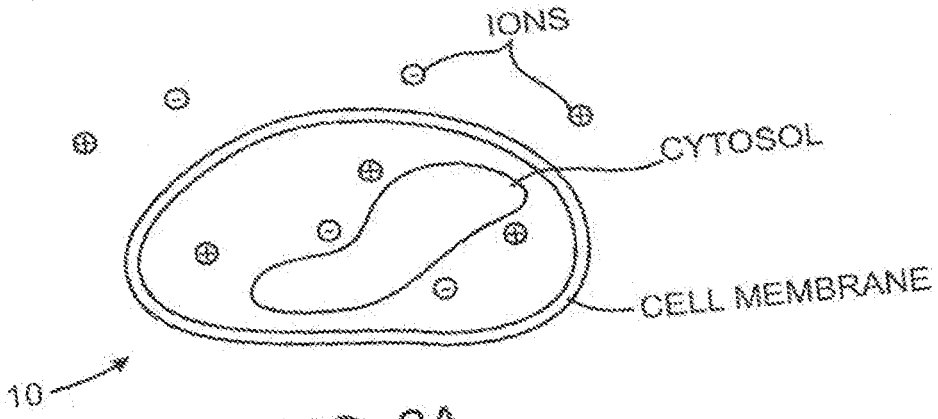


FIG. 2A

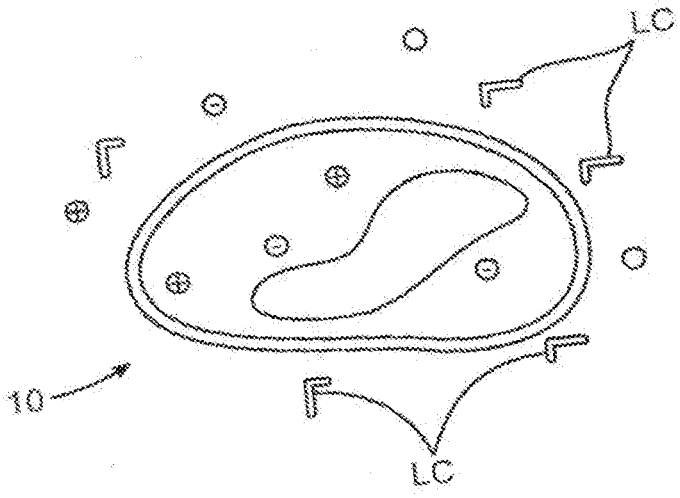


FIG. 2B

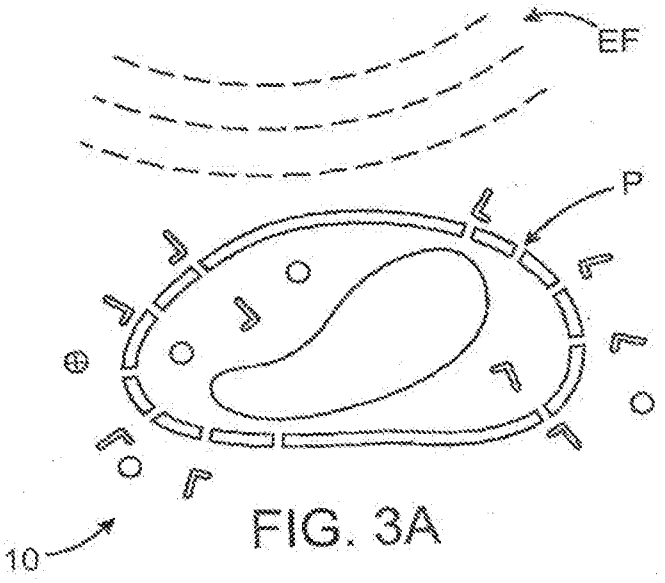


FIG. 3A

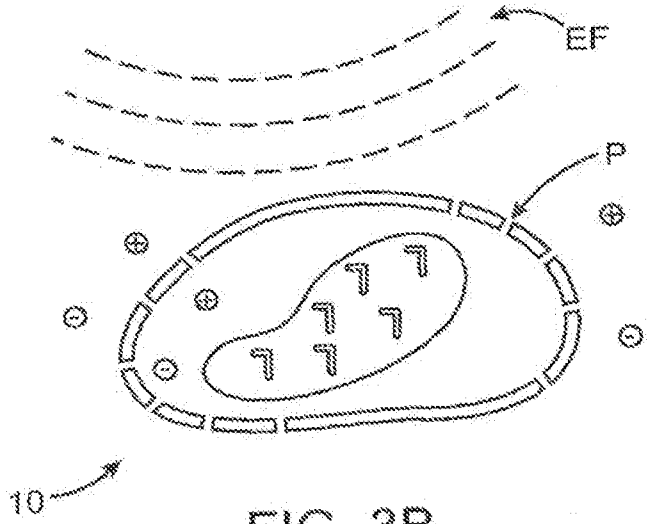


FIG. 3B

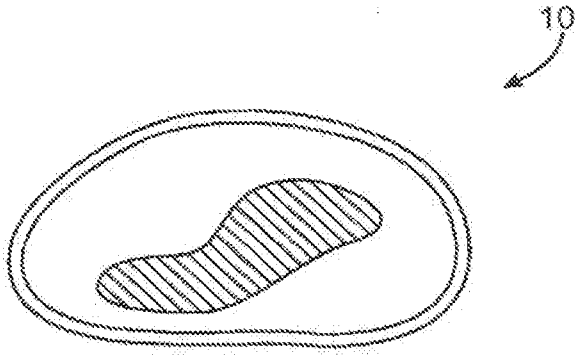


FIG. 4

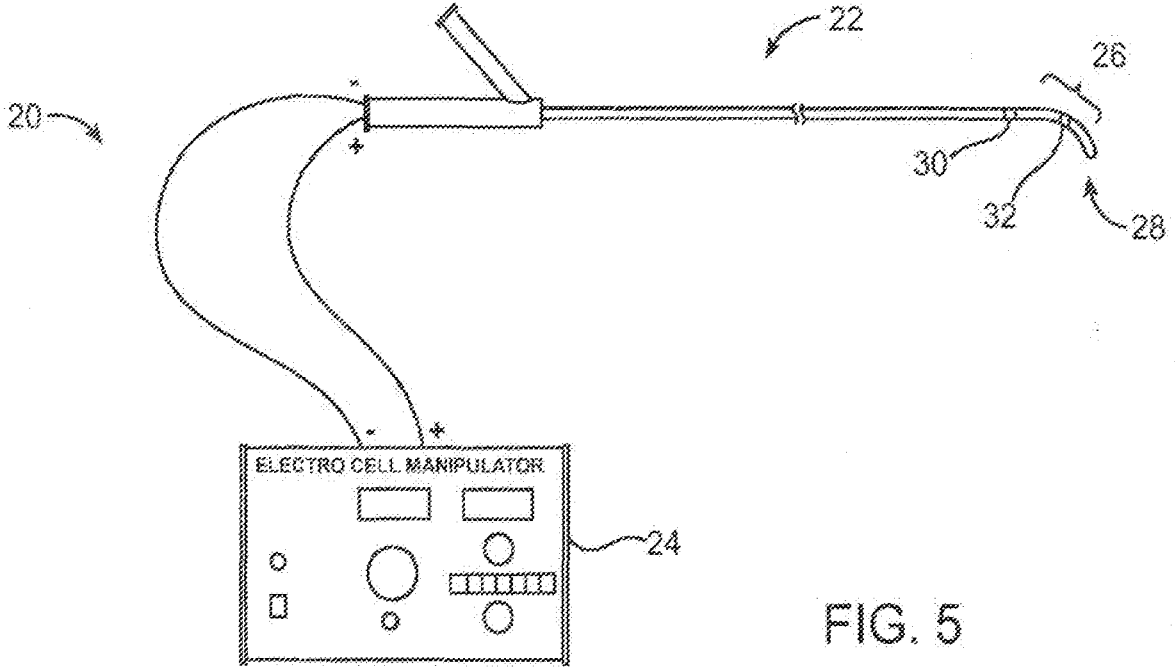


FIG. 5

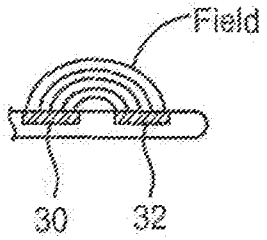


FIG. 5A

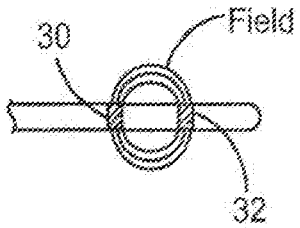


FIG. 5B

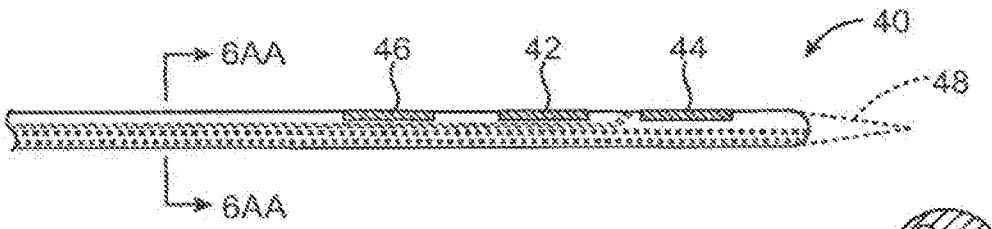


FIG. 6A

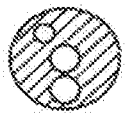


FIG. 6AA

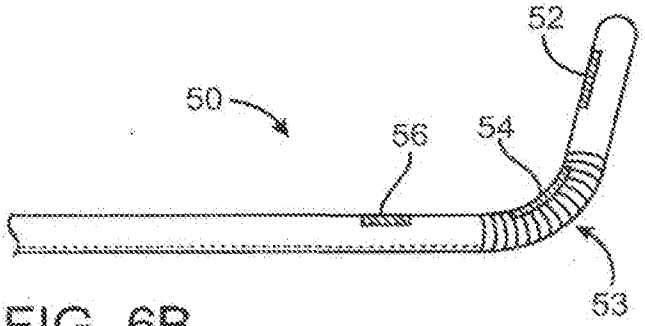


FIG. 6B

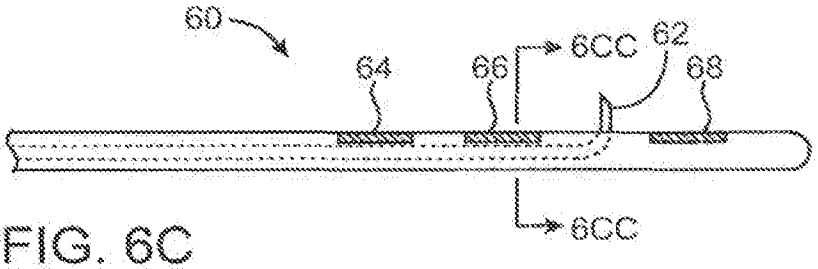


FIG. 6C

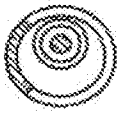


FIG. 6CC

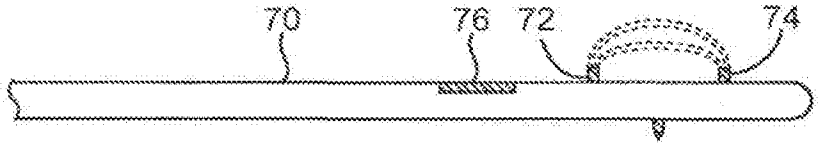


FIG. 6D

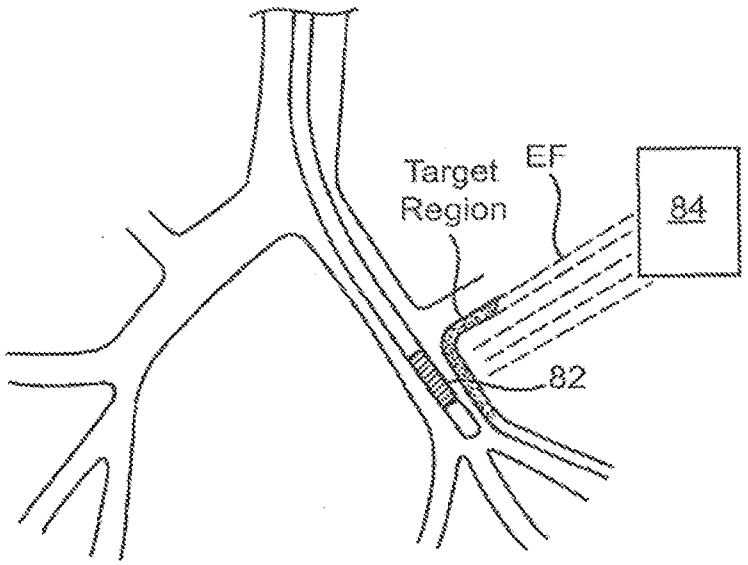


FIG. 7

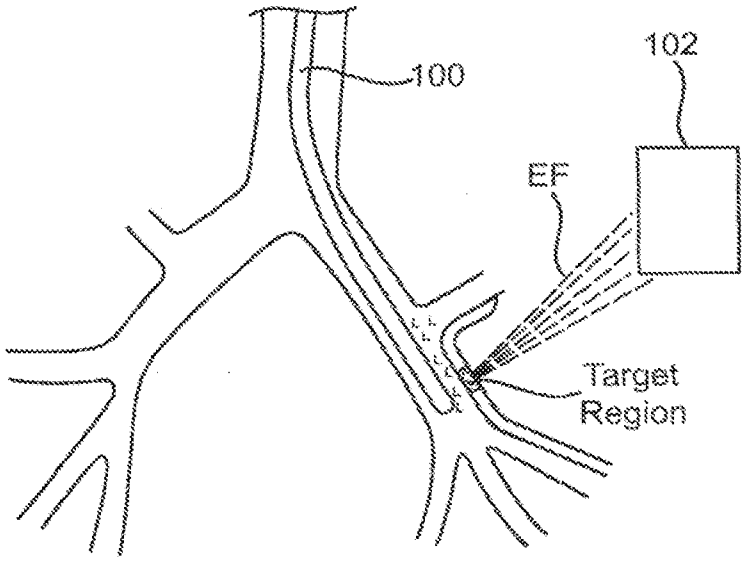


FIG. 13

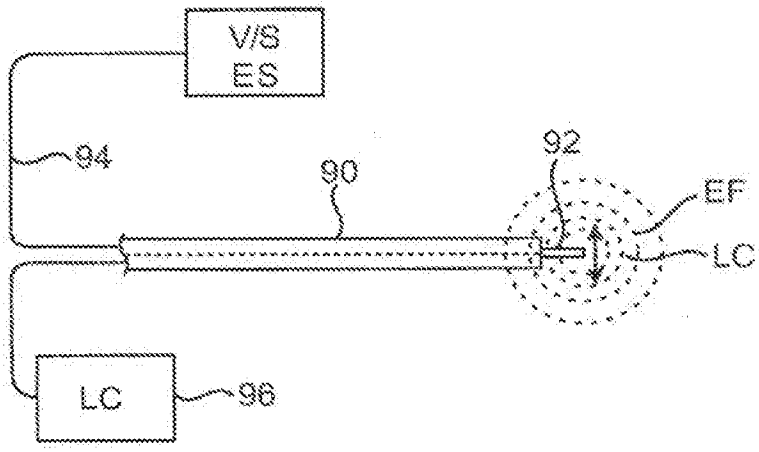


FIG. 8

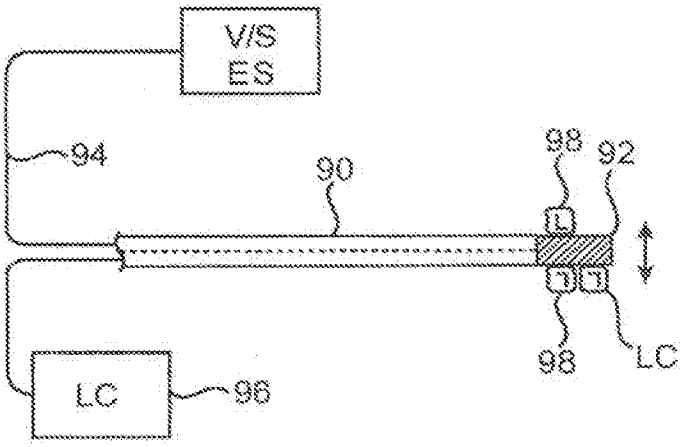


FIG. 11

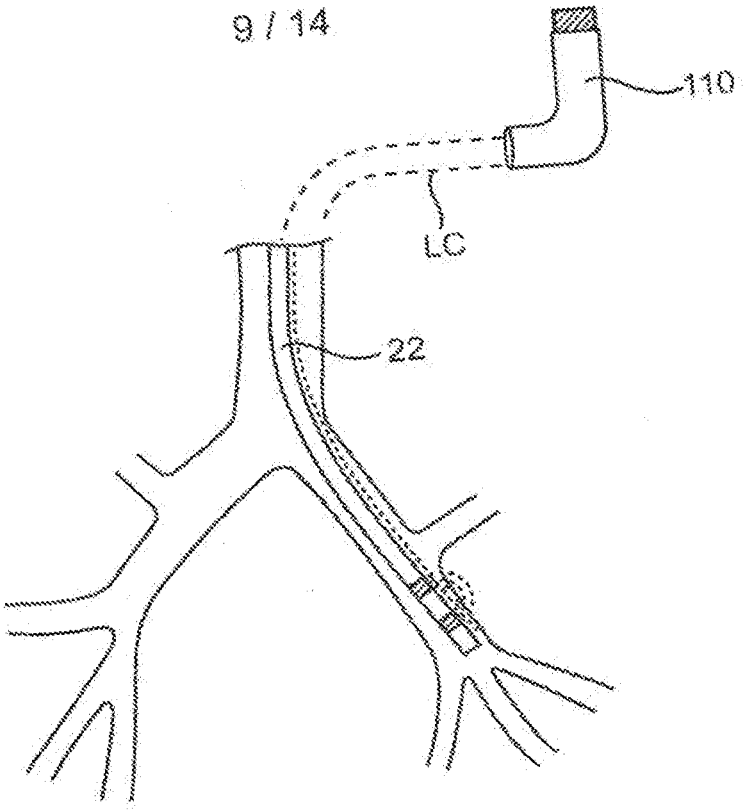


FIG. 9

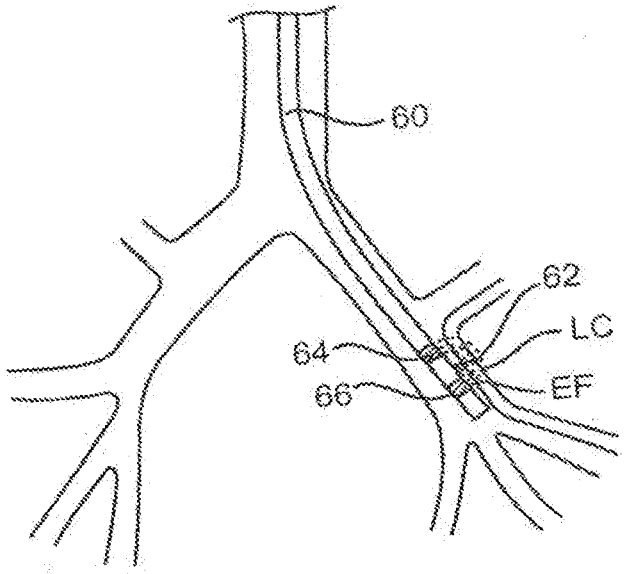


FIG. 10

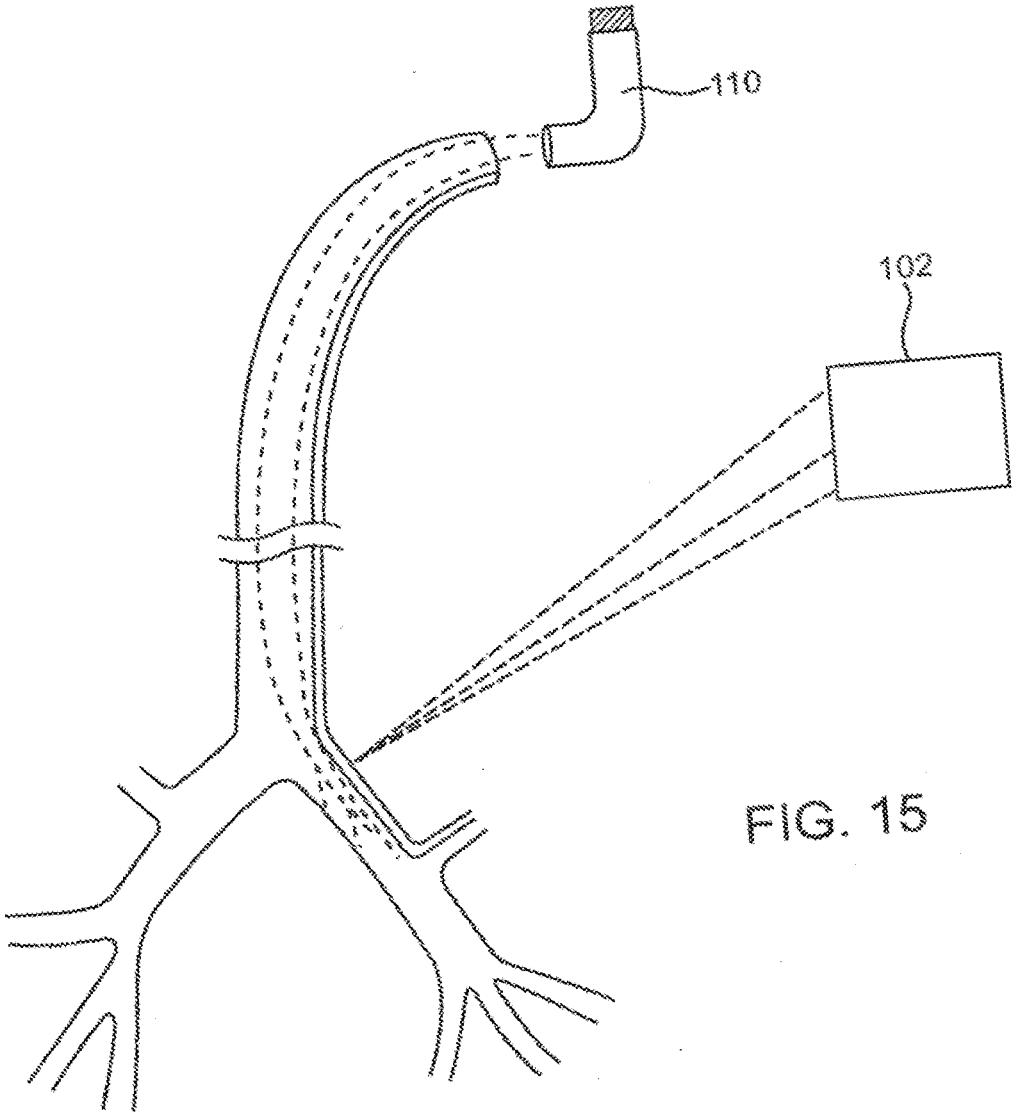


FIG. 15

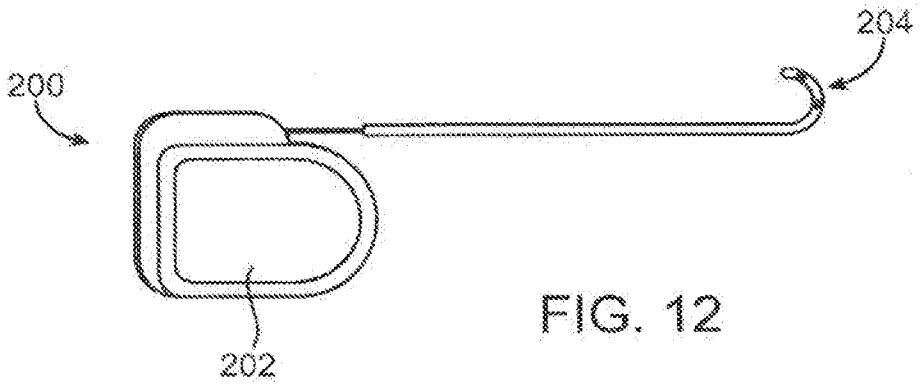


FIG. 12

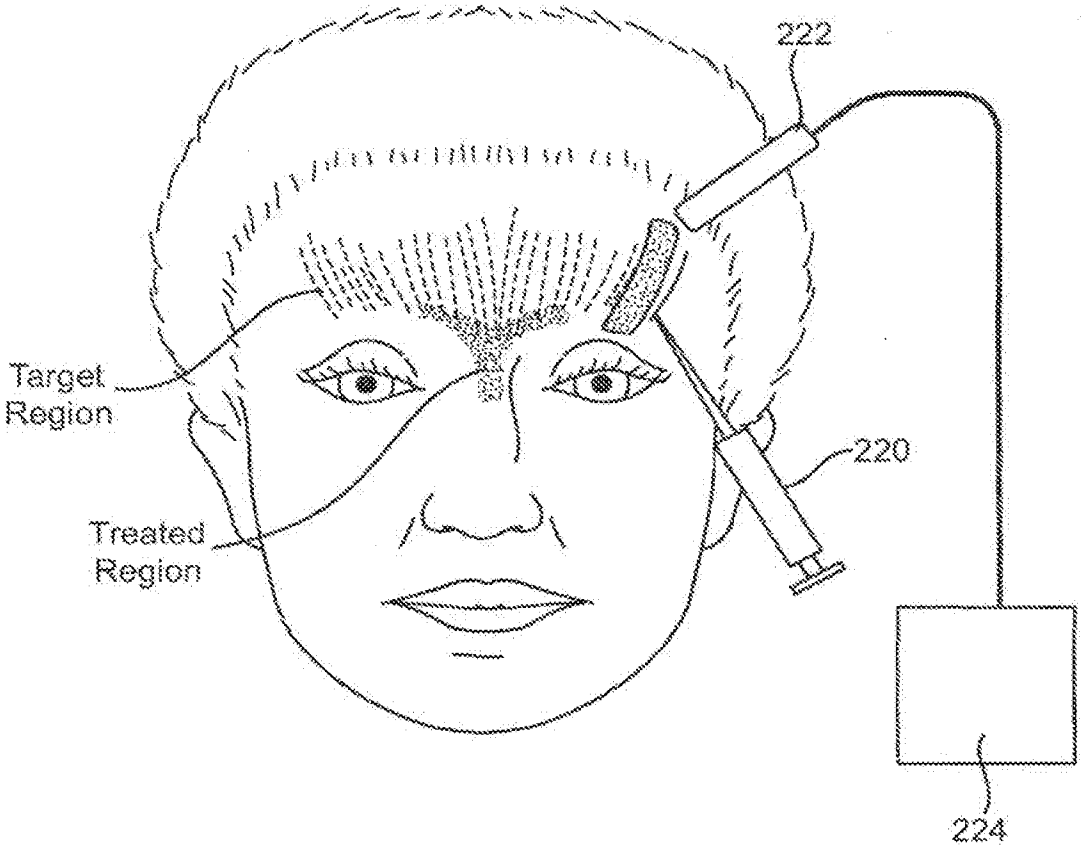


FIG. 14

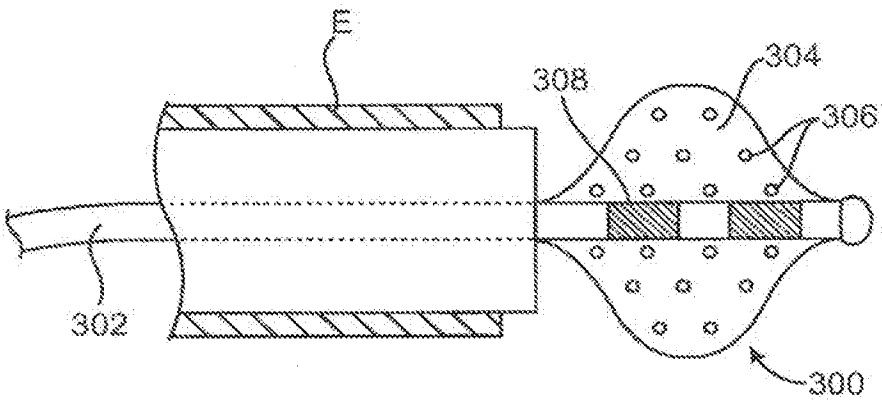


FIG. 15A

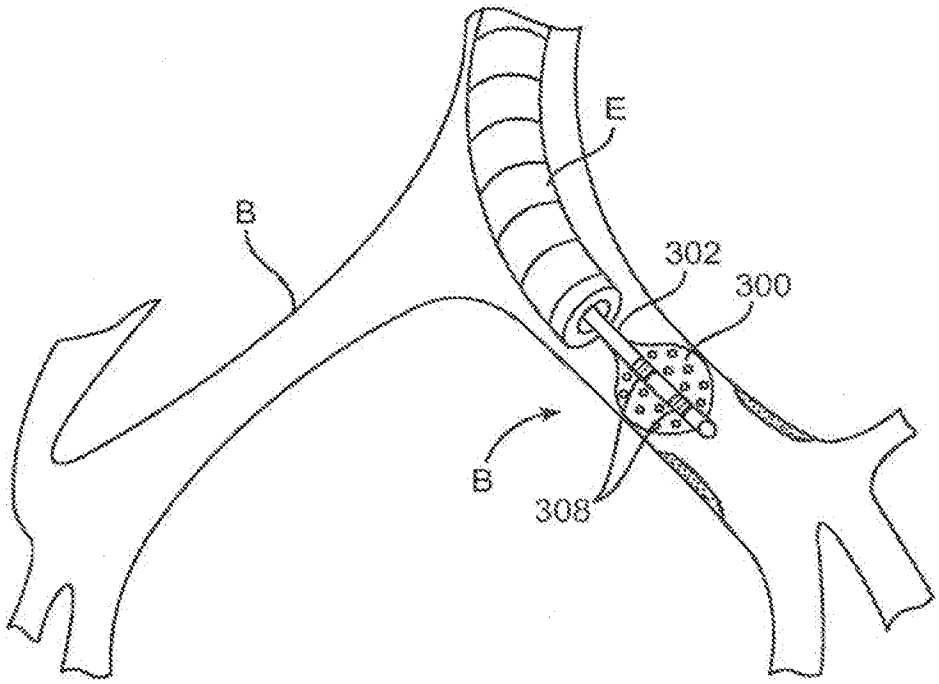


FIG. 15B

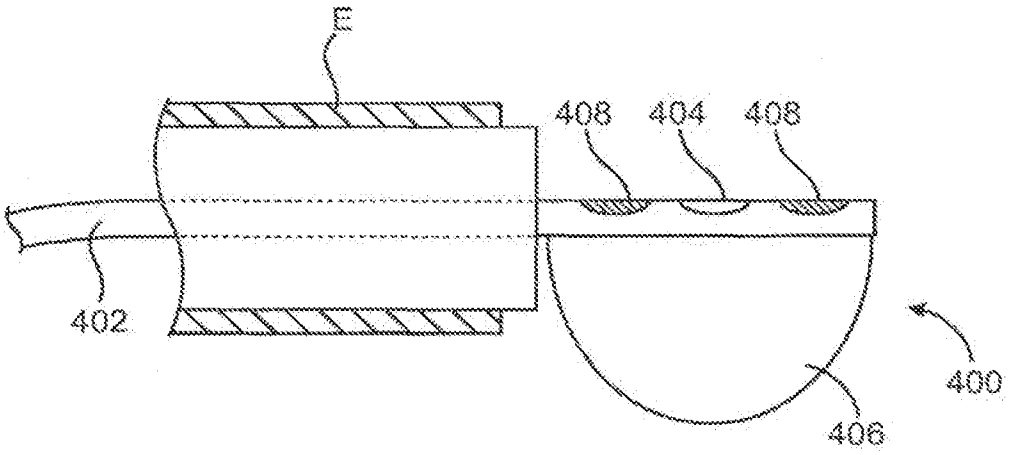


FIG. 16A

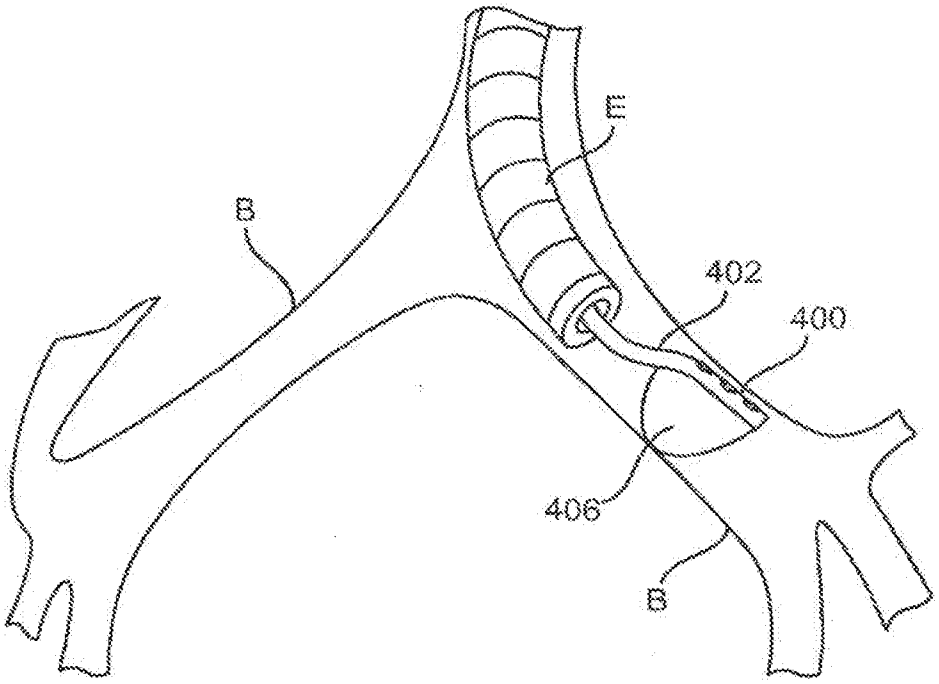


FIG. 16B

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

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:	5187.01US02AP

Filed as Small Entity

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

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Basic Filing:				
UTILITY FILING FEE (ELECTRONIC FILING)	4011	1	75	75
UTILITY SEARCH FEE	2111	1	330	330
UTILITY EXAMINATION FEE	2311	1	380	380
REQUEST FOR PRIORITIZED EXAMINATION	2817	1	2000	2000
Pages:				
Claims:				
CLAIMS IN EXCESS OF 20	2202	9	50	450
Miscellaneous-Filing:				

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
PUBL. FEE- EARLY, VOLUNTARY, OR NORMAL	1504	1	0	0
PROCESSING FEE, EXCEPT PROV. APPLS.	2830	1	70	70

Petition:	
Patent-Appeals-and-Interference:	
Post-Allowance-and-Post-Issuance:	
Extension-of-Time:	
Miscellaneous:	
Total in USD ($)	**3305**

Electronic Acknowledgement Receipt

EFS ID:	39087585
Application Number:	16842209
International Application Number:	
Confirmation Number:	2844
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:	5187.01US02AP
Receipt Date:	07-APR-2020
Filing Date:	
Time Stamp:	15:38:58
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	yes
Payment Type	CARD
Payment was successfully received in RAM	$3305
RAM confirmation Number	E202047F40144345
Deposit Account	160631
Authorized User	Valerie Mitchell

The Director of the USPTO is hereby authorized to charge indicated fees and credit any overpayment as follows:

37 CFR 1.16 (National application filing, search, and examination fees)

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	TrackOne Request	5187_01US02AP_Track_One_Request.pdf	134171 fbacc06355814b9a6d84bcaa3a357b5ce542826d	no	2
Warnings:					
Information:					
2	Application Data Sheet	5187_01US02AP_ADS.pdf	1256909 376b6a0eddab078253f4bd6ccb965fb762c8c026	no	9
Warnings:					
Information:					
3		5187_01US02AP_APP.pdf	202656 b4bb1215435ae2d663fd202153c8e7d7b72333c9	yes	60

Multipart Description/PDF files in .zip description

Document Description	Start	End
Abstract	60	60
Claims	55	59
Specification	1	54

Warnings:					
Information:					
4	Drawings-only black and white line drawings	5187_01US02AP_DRW.pdf	1177610 6a01094f126c373b4c2933a94a914c51680c8e62	no	14
Warnings:					
Information:					
5	Oath or Declaration filed	5187_01US02AP_Declaration.pdf	317507 d37c8f6e66602e36b29c7df7ab1b4963a563e18b	no	1

Warnings:					
Information:					
6	Fee Worksheet (SB06)	fee-info.pdf	41552 6566f6109bb4b454d1e98f8b7ed9b6d1e3bf7715	no	2
Warnings:					
Information:					
			Total Files Size (in bytes):	3130405	

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.

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

PTO/AIA/82B (07-13)
Approved for use through 11/30/2014. OMB 0651-0031
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

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	[signature]	Date (Optional)	2/12/13
Name	[illegible]		
Title	[illegible]		

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.

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	16/842,209
Filing Date	4/7/2020
First Named Inventor	Mark E. Deem
Title	SYSTEMS AND METHODS FOR DELIVERY OF A THERAPEUTIC AGENT
Art Unit	
Examiner Name	
Attorney Docket Number	5187.01US02AP

SIGNATURE of Applicant or Patent Practitioner

Signature	/Daidre L. Burgess/	Date (Optional)	4/10/2020
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.

Electronic Acknowledgement Receipt

EFS ID:	39130547
Application Number:	16842209
International Application Number:	
Confirmation Number:	2844
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:	5187.01US02AP
Receipt Date:	10-APR-2020
Filing Date:	
Time Stamp:	18:25:55
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_01US02AP_Power_of_Atty.pdf	1268845 af96915fa7f6bf476a88b331e09b04cc3fa4ac1f	yes	2

	Multipart Description/PDF files in .zip description		
	Document Description	**Start**	**End**
	Power of Attorney	2	2
	Transmittal Letter	1	1
Warnings:			
Information:			
	Total Files Size (in bytes):	1268845	

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.

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 NUMBER	FILING OR 371(C) DATE	FIRST NAMED APPLICANT	ATTY. DOCKET NO./TITLE
16/842,209	04/07/2020	Mark E. Deem	5187.01US02AP

CONFIRMATION NO. 2844

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

FORMALITIES LETTER

OC00000116245013

Date Mailed: 04/16/2020

NOTICE OF OMITTED ITEM(S) IN A NONPROVISIONAL APPLICATION

FILED UNDER 37 CFR 1.53(b)

A filing date has been accorded to the above-identified nonprovisional application papers; however, the following item(s) appear to have been omitted from the application:

- Figure(s) **17 - 40** described in the specification.

Applicant must reply to this notice within the time period set forth in this notice to avoid abandonment of this application. Applicant must select one of the three following options and the reply must comply with the requirements set forth in the selected option and any other requirements set forth in this notice. **The reply should also indicate which option applicant has selected.**

I. Petition for date of deposit: Should applicant contend that the above-noted omitted item(s) was in fact deposited in the U.S. Patent and Trademark Office (USPTO) with the nonprovisional application papers, a copy of this Notice and a petition (and the petition fee set forth in 37 CFR 1.17(f) with evidence of such deposit must be filed within **TWO MONTHS** of the date of this Notice. The petition fee will be refunded if it is determined that the item(s) was received by the USPTO. THIS TWO MONTH PERIOD IS EXTENDABLE UNDER 37 CFR 1.136(a) or (b).

Applicant should review their application file and determine whether their file differs from USPTO's records. In some situations there may be a mislabeling of the drawings and/or a failure to describe in the brief description each of the figures as labeled. See 37 CFR 1.74, 1.77(b)(9), and 1.84(u)(1).

The brief description of the drawings in the specification must correspond with the figures and the figures must be labeled in accordance with 37 CFR 1.84(u)(1). For example, if the brief description describes Figure 1 and Figure 2 only, but the drawings show Fig. 1 and Fig. 2A and Fig. 2B, then the specification must be amended to refer to Figure 2A and Figure 2B and delete the reference to Figure 2 and a substitute specification in compliance with 37 CFR 1.52, 1.121(b)(3), and 1.125, is required. As another example, if a drawing is labeled Figure 2, but there are actually multiple figures within the labeled Figure 2 having labels A, B, and C, then the drawings must be relabeled in accordance with 37 CFR 1.84(u)(1) (e.g., Fig. 2A, Fig. 2B, and Fig. 2C). If the specification does not refer to the figures as relabeled, then the specification must be amended to refer to the relabeled figures (e.g., Fig. 2A, Fig. 2B, and Fig. 2C) and a substitute specification in compliance with 37 CFR 1.52, 1.121(b)(3), and 1.125, is required. A petition for date of deposit under option I should NOT be filed in either situation or in similar situations where there is simply a mislabeling of the drawings and/or a failure to describe in the brief description each of the figures. Instead, applicant should file a reply under option III.A below (including replacement drawing sheets and/or a substitute specification as required in III.A.2).

A petition for date of deposit under option I should NOT be filed in situations where there is simply a mislabeling of the drawings and/or a failure to describe in the brief description each of the figures. Instead, applicant should file a reply under option III(A) below (including replacement drawing sheets and/or a substitute specification as described).

II. Petition for later filing date: Should applicant desire to supply the omitted item(s) and accept the date that such omitted item(s) was filed in the USPTO as the filing date of the above-identified application, a copy of this Notice, the omitted item(s), and a petition under 37 CFR 1.182 with the petition fee set forth in 37 CFR 1.17(f) requesting the later filing date must be filed within **TWO MONTHS** of the date of this Notice. THIS TWO MONTH PERIOD IS EXTENDABLE UNDER 37 CFR 1.136(a) or (b).

Applicant is advised that generally the filing fee required for an application is the filing fee in effect on the filing date accorded the application and that payment of the requisite basic filing fee on a date later than the filing date of the application requires payment of a surcharge (37 CFR 1.16(f)). To avoid processing delays and payment of a surcharge, applicant should submit any balance due for the requisite filing fee based on the later filing date being requested when submitting the omitted item(s) and the petition (and petition fee) requesting the later filing date.

III. Acceptance of application as deposited: Applicant may accept the application as deposited in the USPTO by filing an appropriate amendment as set forth in either (A) or (B) below within **TWO MONTHS** of the date of this Notice. THIS TWO MONTH PERIOD IS EXTENDABLE UNDER 37 CFR 1.136(a) or (b) . The application will maintain a filing date as of the date of deposit of the application papers in the USPTO, and original application papers (i.e., the original disclosure of the invention) will include only those application papers present in the USPTO on the date of deposit. A petition is not required for this option.

(A) If applicant wants to accept the application as deposited without adding the subject matter that was in the omitted item, applicant is required to submit one or more of the following items without adding any new matter (see 35 U.S.C. 132(a)):

To remove a missing figure of the drawings or to correct the figure labeling,

- replacement drawing sheets in compliance with 37 CFR 1.121(d) to renumber the drawing figures consecutively (if necessary), and/or
- a substitute specification excluding claims in compliance with 37 CFR 1.121(b)(3) and 1.125 that amends the specification to cancel any references to any omitted drawing(s) and corrects the references in the specification to the drawing figures to correspond with any relabeled drawing figures,

A proper substitute specification in compliance with 37 CFR 1.121(b)(3) and 1.125 consists of:

- A copy of the previously-submitted specification, with deletions shown with strikethrough or brackets and insertions shown with underlining (marked-up version) unless it is indicated above that a marked-up version is not required for each of the correction(s).
- A copy of the amended specification without markings (clean version).
- A statement that the substitute specification contains no new matter, in compliance with 37 CFR 1.121(b)(3) and 1.125.

(B) Alternatively, if applicant wants to accept the application as deposited but wishes to add the subject matter in the omitted item by relying on an incorporation by reference under 37 CFR 1.57 or other portions of the original disclosure, applicant is required to submit the following without adding any new matter (see 35 U.S.C. 132(a)):

To add a missing figure of the drawings, new and replacement drawing sheets in compliance with 37 CFR 1.121(d);

If applicant is relying on an incorporation by reference under 37 CFR 1.57 to add the omitted subject matter, then applicant must also comply with the requirements of 37 CFR 1.57.

Applicant is cautioned that correction of the above items may cause the specification and drawings page count to exceed 100 pages. If the specification and drawings exceed 100 pages, applicant will need to submit the required application size fee.

Replies must be received in the USPTO within the set time period or must include a proper Certificate of Mailing or Transmission under 37 CFR 1.8 with a mailing or transmission date within the set time period. For more information and a suggested format, see Form PTO/SB/92 and MPEP 512.

Replies should be mailed to:

Mail Stop Missing Parts
Commissioner for Patents
P.O. Box 1450
Alexandria VA 22313-1450

Registered users of EFS-Web may alternatively submit their reply to this notice via EFS-Web, including a copy of this Notice and selecting the document description "Applicant response to Pre-Exam Formalities Notice". https://sportal.uspto.gov/authenticate/AuthenticateUserLocalEPF.html

For more information about EFS-Web please call the USPTO Electronic Business Center at 1-866-217-9197 or visit our website at http://www.uspto.gov/ebc.

If you are not using EFS-Web to submit your reply, you must include a copy of this notice.

Questions about the contents of this notice and the requirements it sets forth should be directed to the Office of Data Management, Application Assistance Unit, at **(571) 272-4000** or **(571) 272-4200** or **1-888-786-0101**.

/bnguyen/

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 NUMBER	FILING or 371(c) DATE	GRP ART UNIT	FIL FEE REC'D	ATTY.DOCKET.NO	TOT CLAIMS	IND CLAIMS
16/842,209	04/07/2020	1645	1235	5187.01US02AP	29	2

CONFIRMATION NO. 2844

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

FILING RECEIPT



Date Mailed: 04/16/2020

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 16/659,893 10/22/2019 PAT 10610675
which 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: 04/15/2020

The country code and number of your priority application, to be used for filing abroad under the Paris Convention, is **US 16/842,209**

Projected Publication Date: To Be Determined - pending completion of Omitted Items

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).

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Title 35, United States Code, Section 184

Title 37, Code of Federal Regulations, 5.11 & 5.15

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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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PATENT APPLICATION FEE DETERMINATION RECORD

Substitute for Form PTO-875

Application or Docket Number: 16/842,209

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))	29 minus 20 =	* 9	x 50 =	450	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	1235		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	SMALL ENTITY RATE($)	SMALL ENTITY ADDITIONAL FEE($)	OR	OTHER THAN SMALL ENTITY RATE($)	OTHER THAN SMALL ENTITY ADDITIONAL FEE($)
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.

PATENT APPLICATION

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re the application of:	Attorney Docket No.: 5187.01US02AP
Deem et al.	Confirmation No.: 2844
Application No.: 16/842,209	Examiner: Unknown
Filed: April 7, 2020	Group Art Unit: 1645

For: SYSTEMS AND METHODS FOR DELIVERY OF A THERAPEUTIC AGENT

RESPONSE TO NOTICE OF OMITTED ITEM(S) IN A NONPROVISIONAL APPLICATION

Mail Stop Missing Parts
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Commissioner:

In response to the Notice of Omitted Item(s) mailed April 16, 2020, attached are replacement drawings including omitted Figs. 17-40.

The Commissioner is hereby authorized to charge any underpayment or credit any overpayment to Deposit Account No. 16-0631.

Respectfully submitted,

/Daidre L. Burgess/

Daidre L. Burgess
Registration No. 60389

Customer No. 24113
Patterson Thuente Pedersen, P.A.
4800 IDS Center
80 South 8th Street
Minneapolis, Minnesota 55402-2100
Telephone: 612.252.1558

Please grant any extension of time necessary for entry; charge any fee due to Deposit Account No. 16-0631.

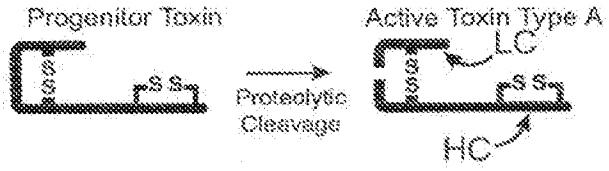

Progenitor Toxin
Active Toxin Type A
LC
HC
Proteolytic Cleavage
S S
S S

FIG. 1

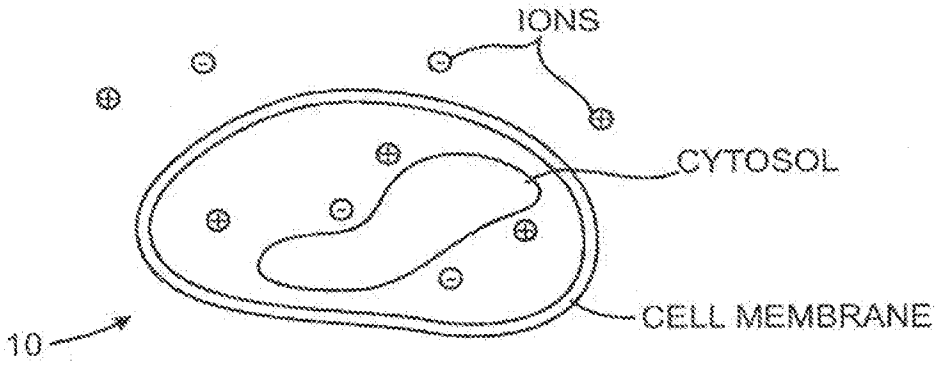


FIG. 2A

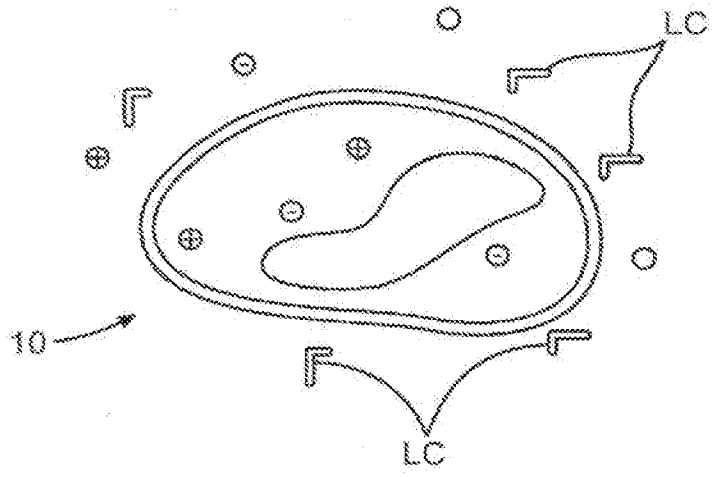


FIG. 2B

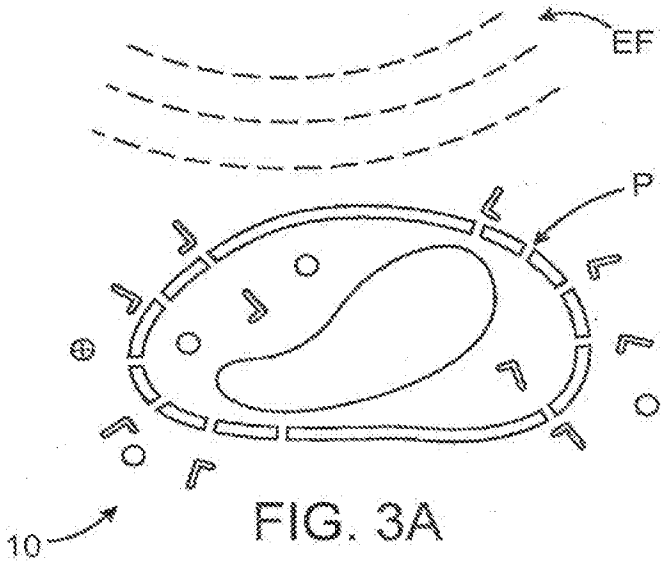


FIG. 3A

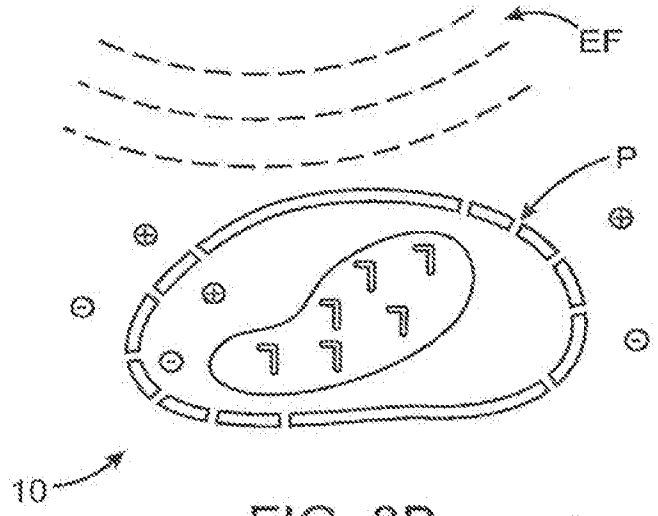


FIG. 3B

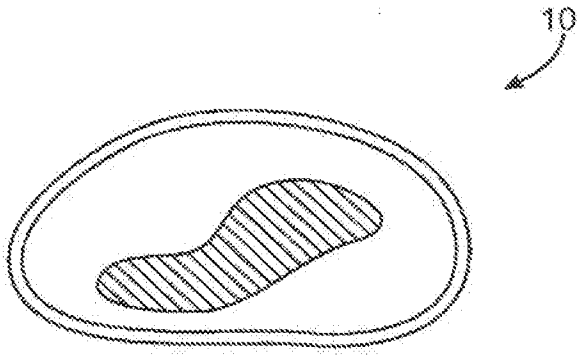


FIG. 4

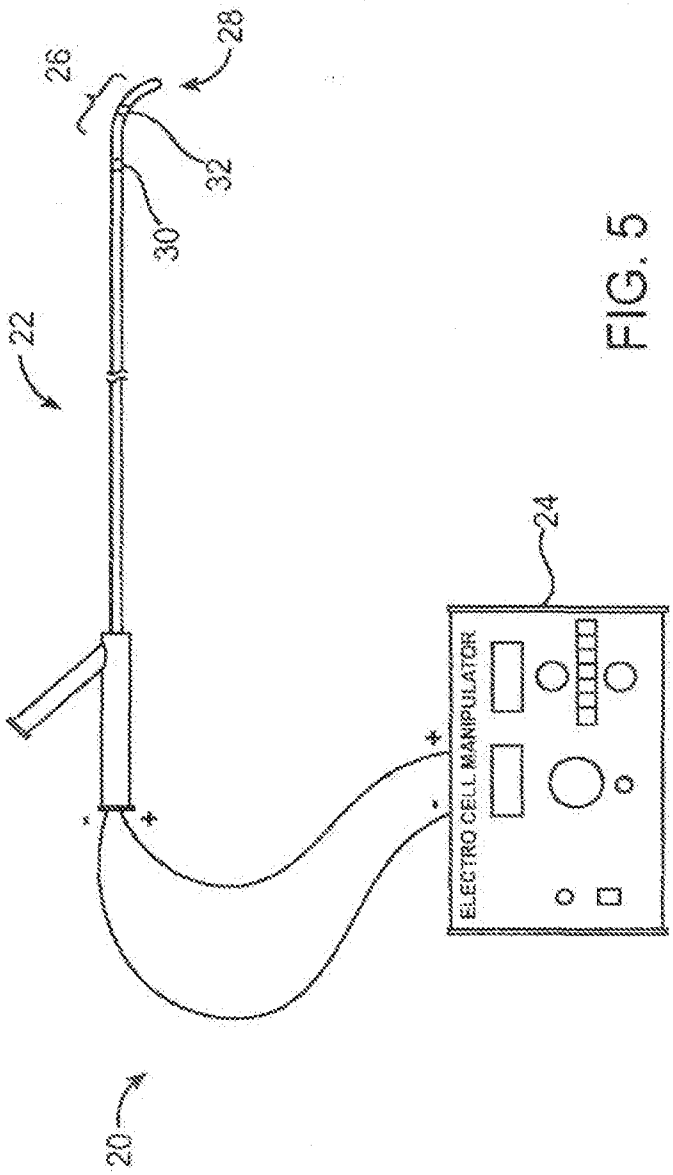


FIG. 5

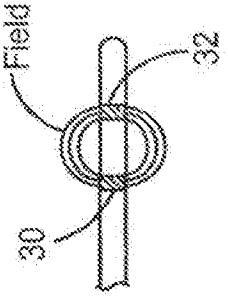


FIG. 5B

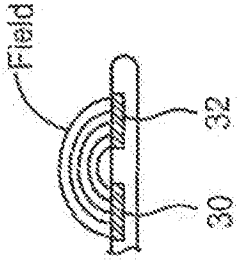


FIG. 5A

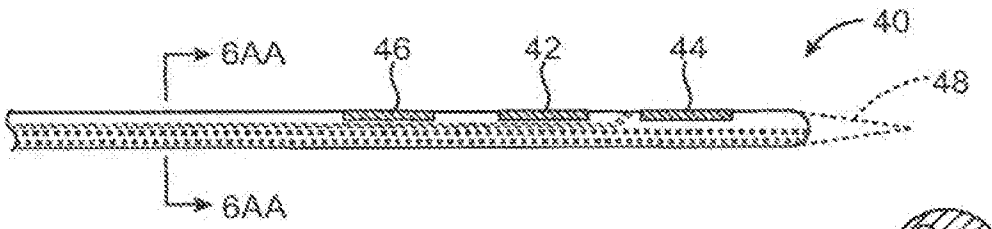


FIG. 6A

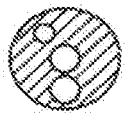


FIG. 6AA

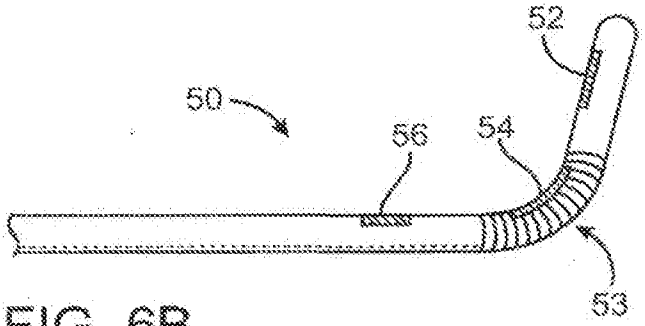


FIG. 6B

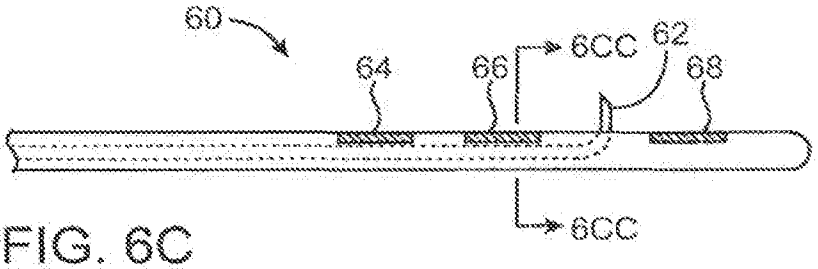


FIG. 6C

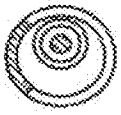


FIG. 6CC

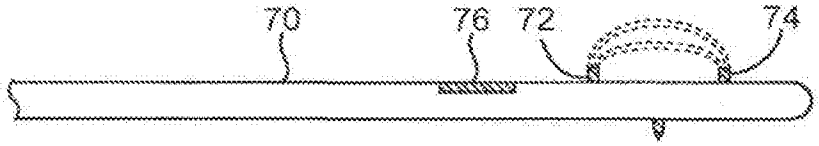


FIG. 6D

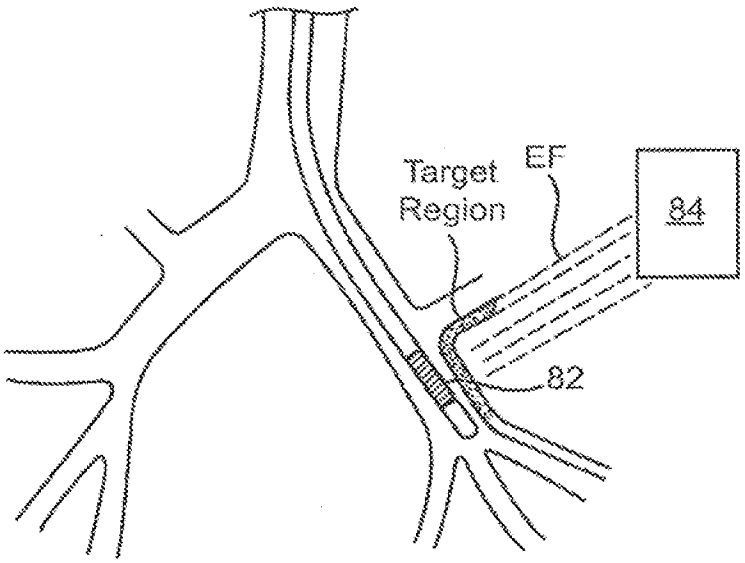


FIG. 7

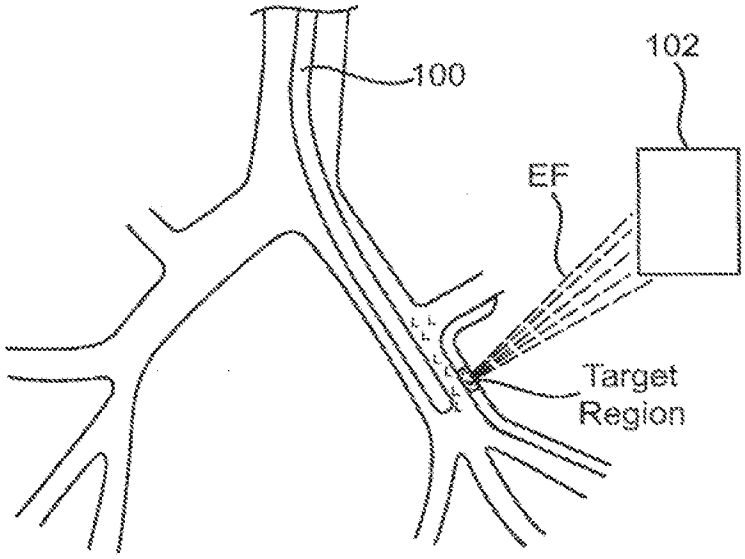


FIG. 13

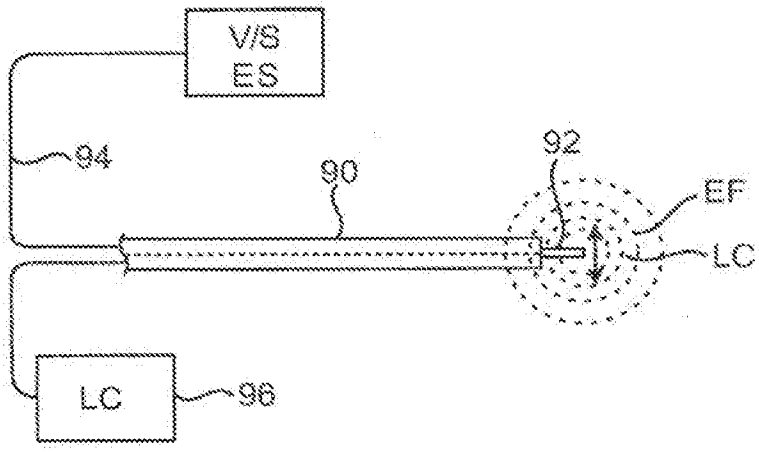


FIG. 8

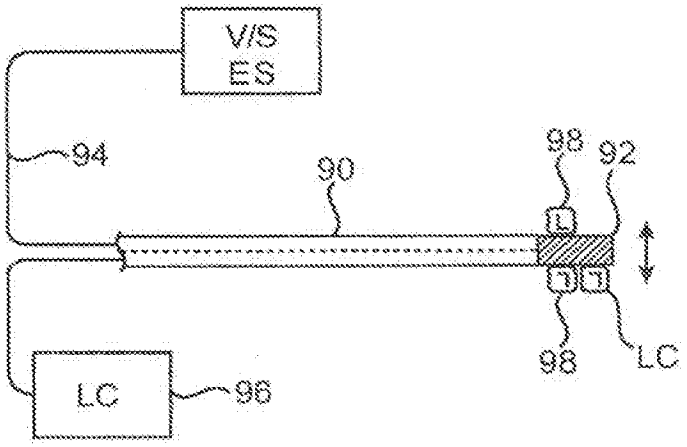


FIG. 11

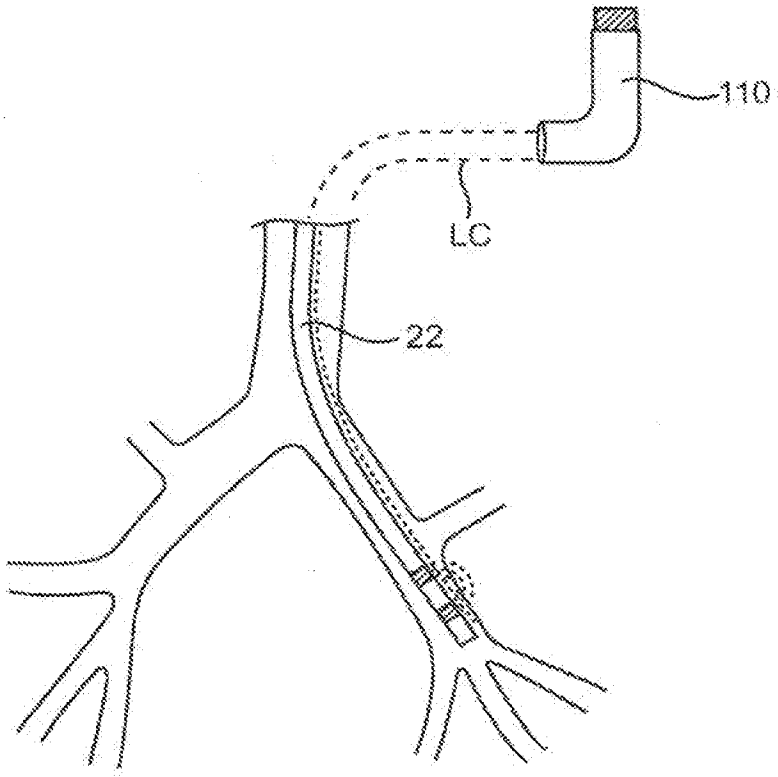


FIG. 9

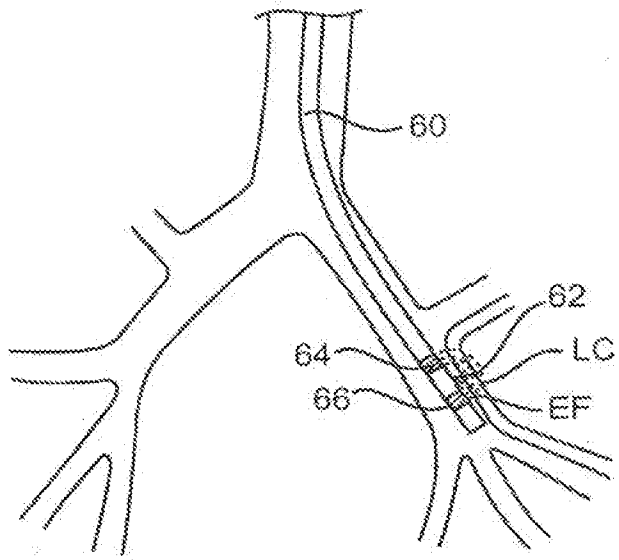


FIG. 10

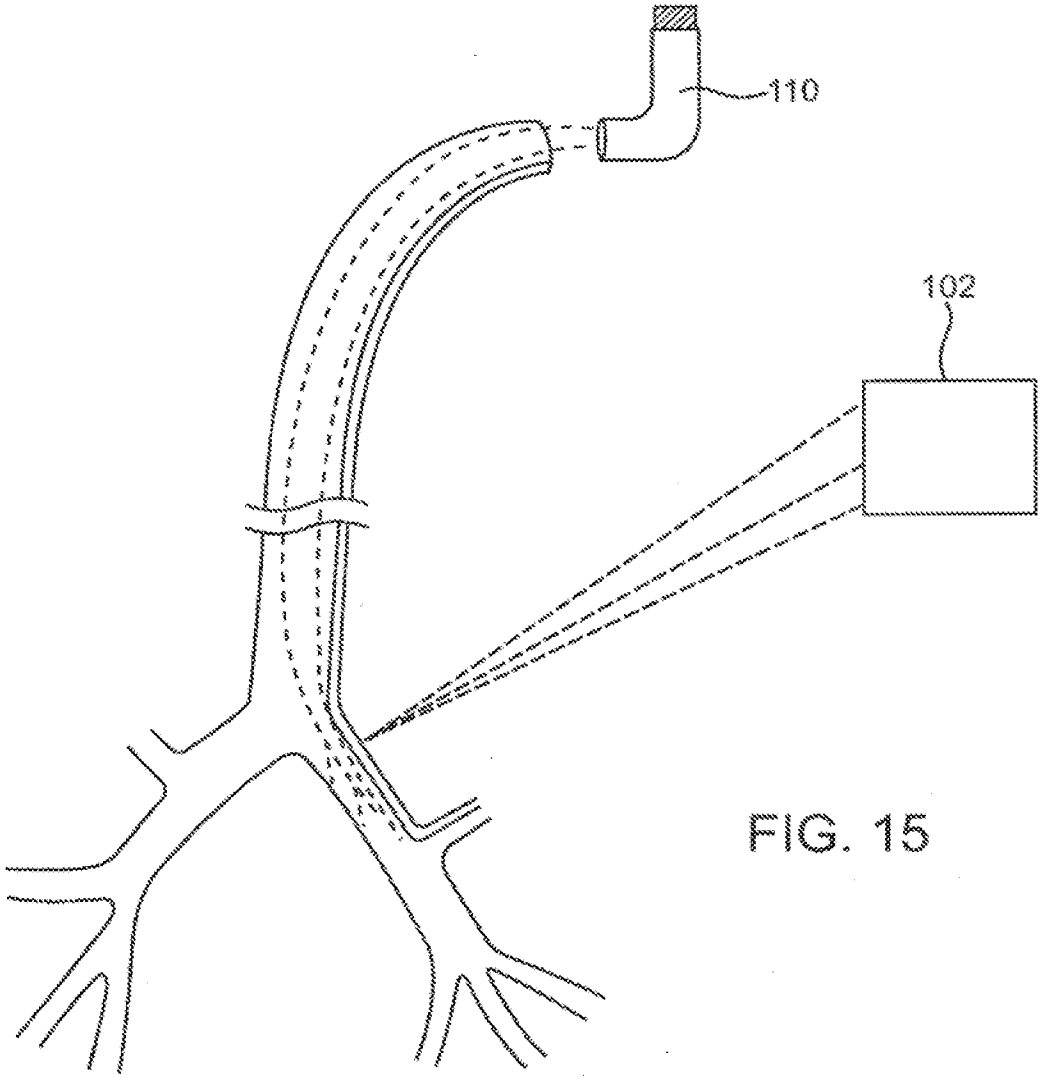


FIG. 15

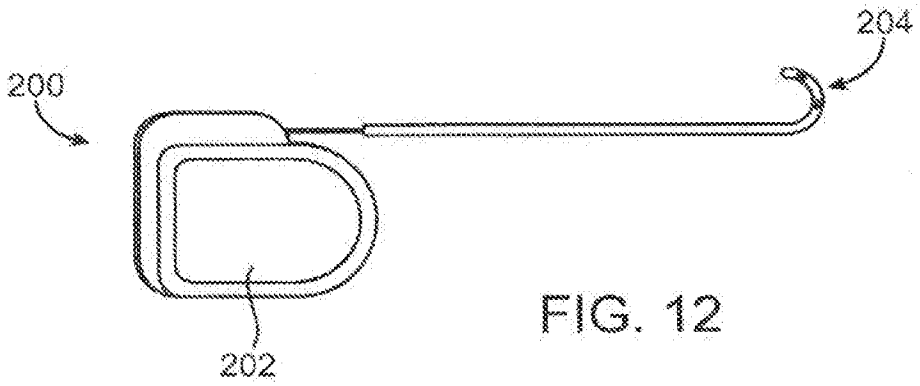


FIG. 12

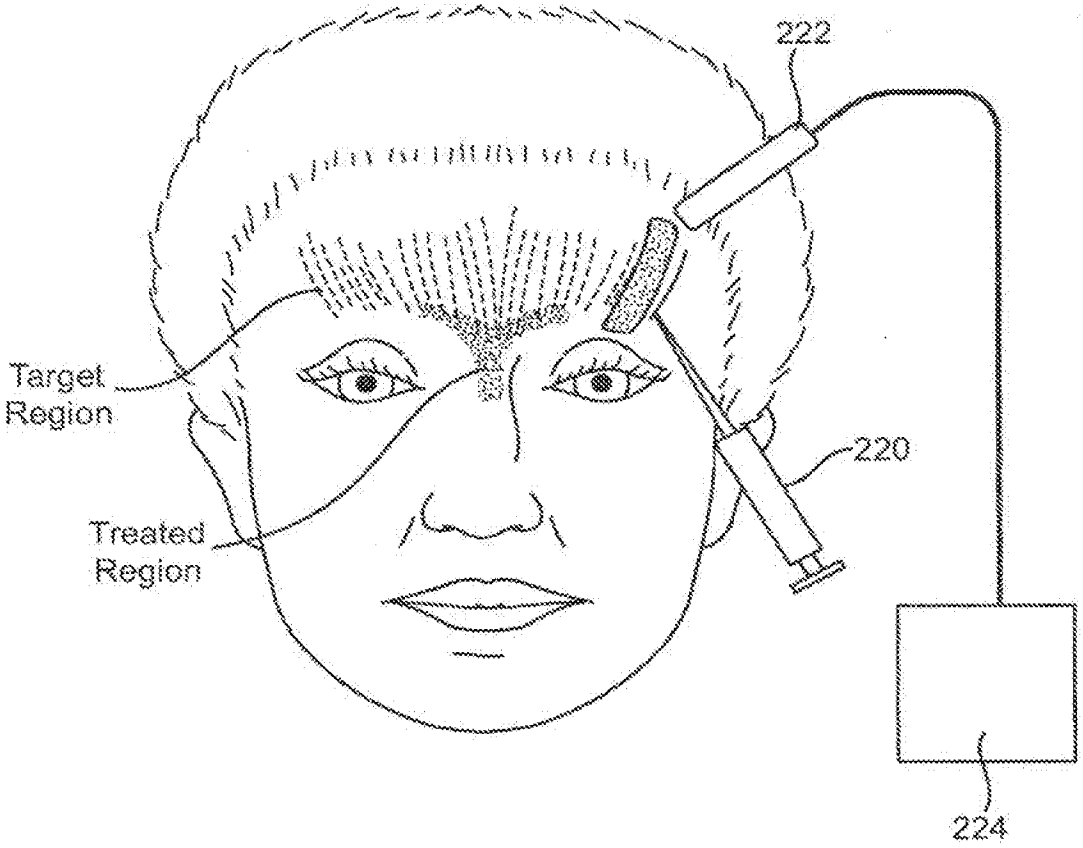


FIG. 14

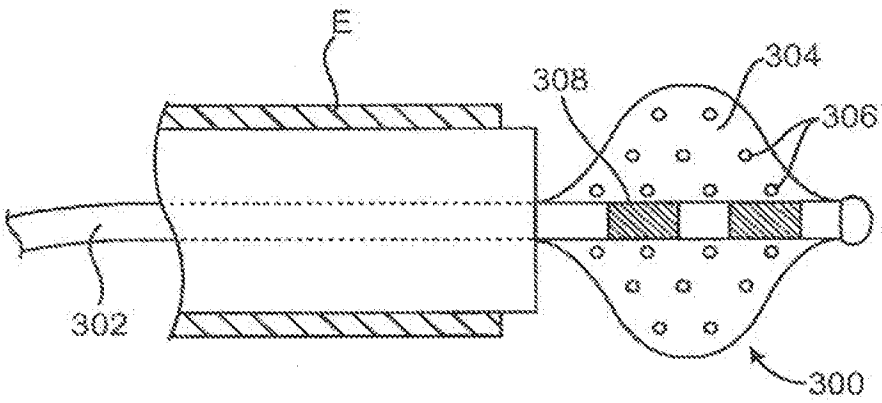


FIG. 15A

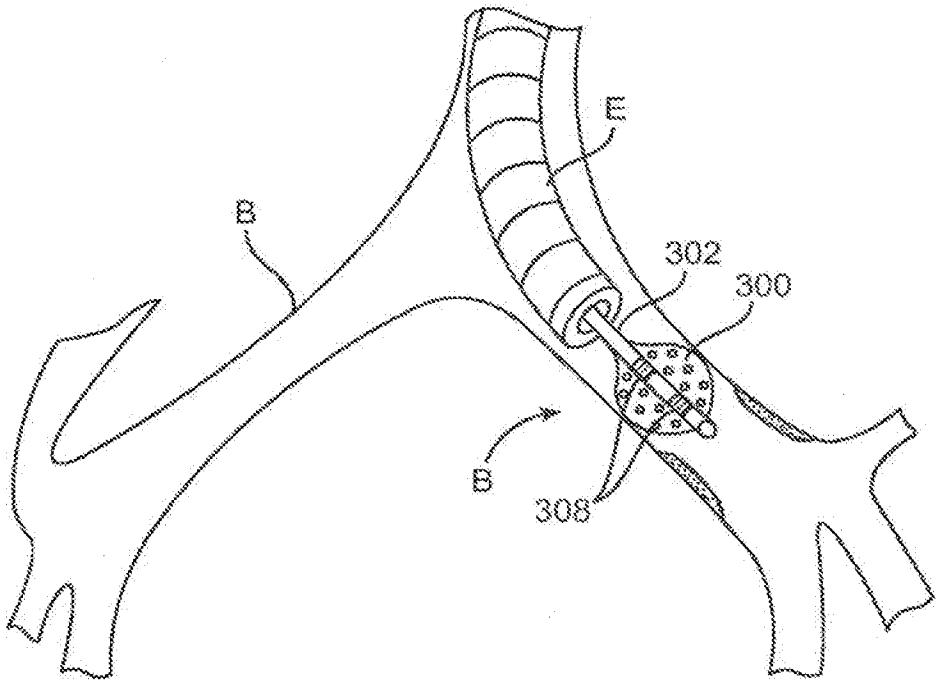


FIG. 15B

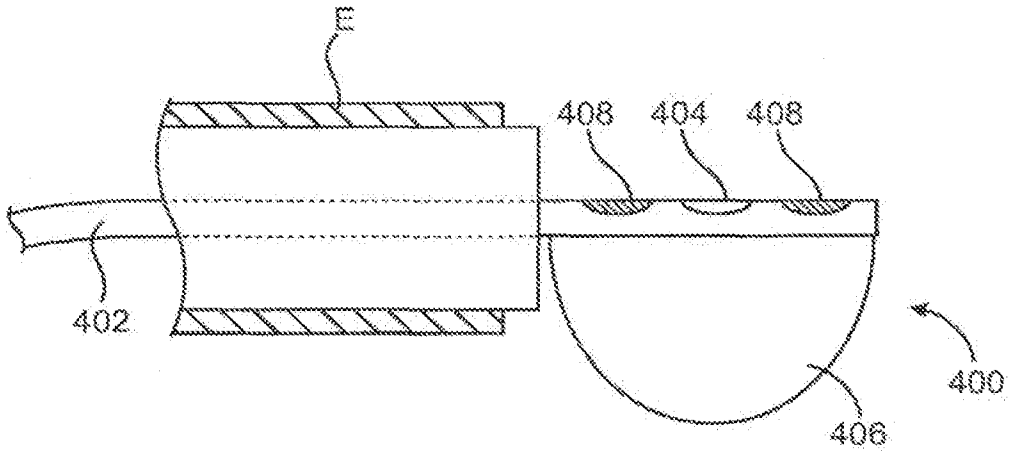


FIG. 16A

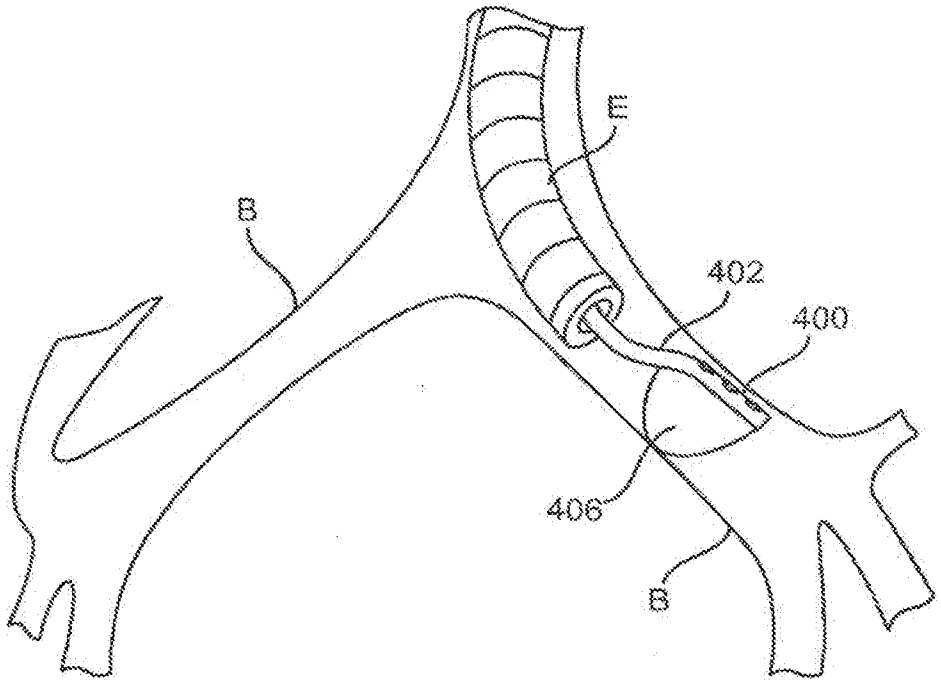


FIG. 16B

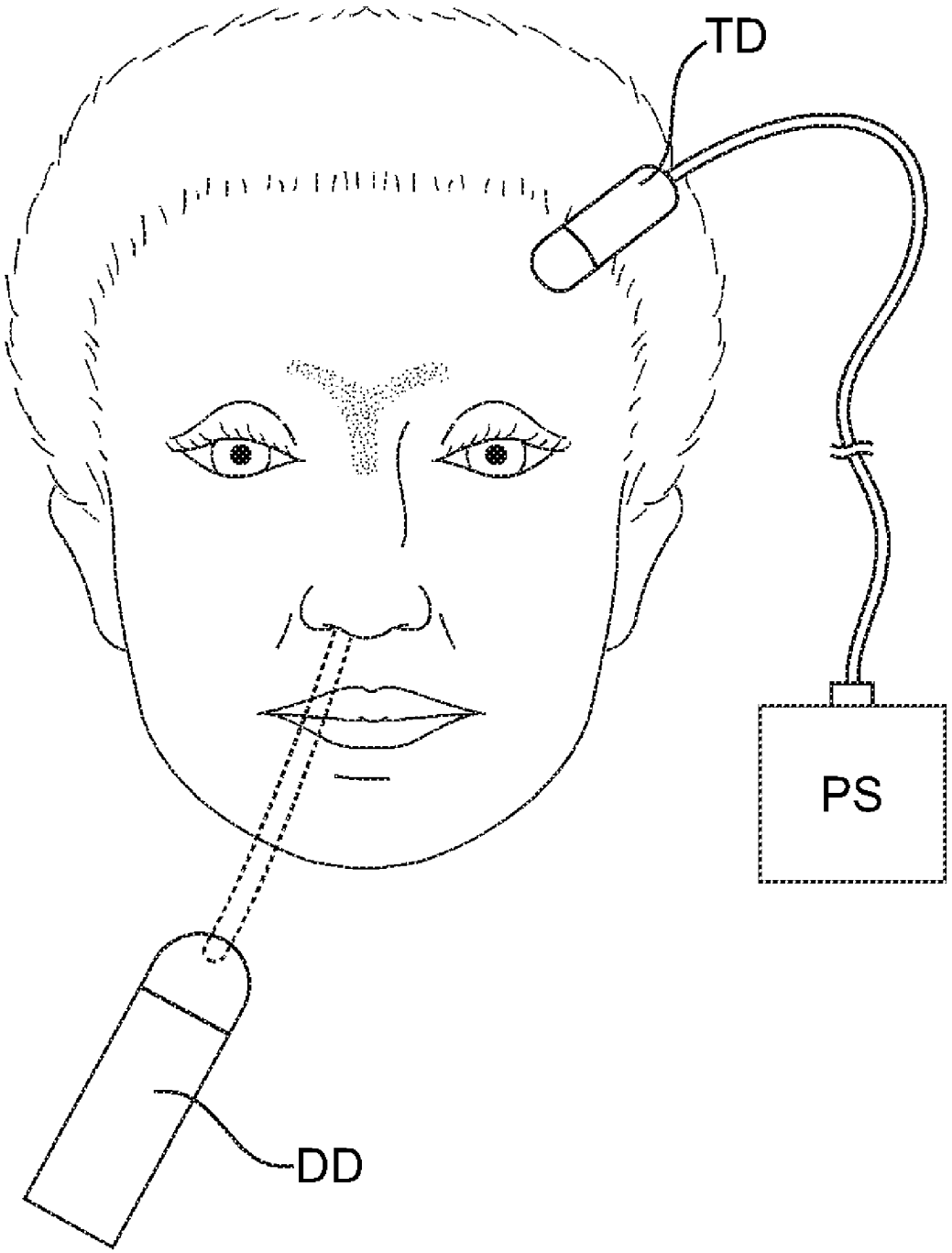


FIG. 17

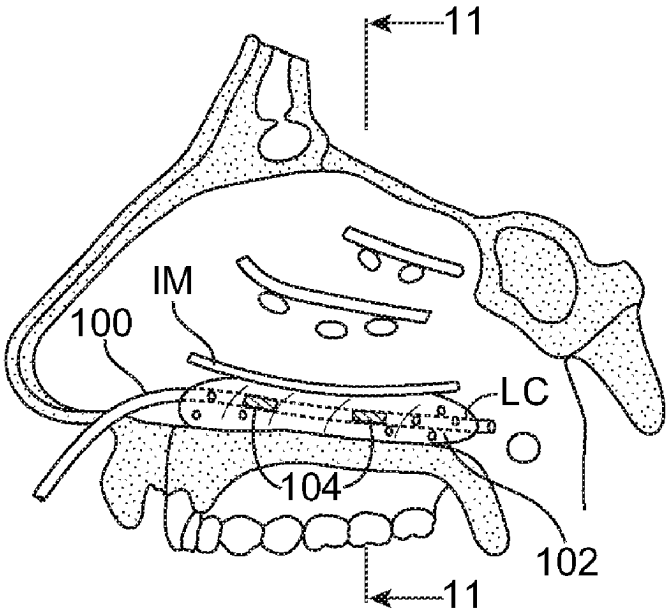


FIG. 18

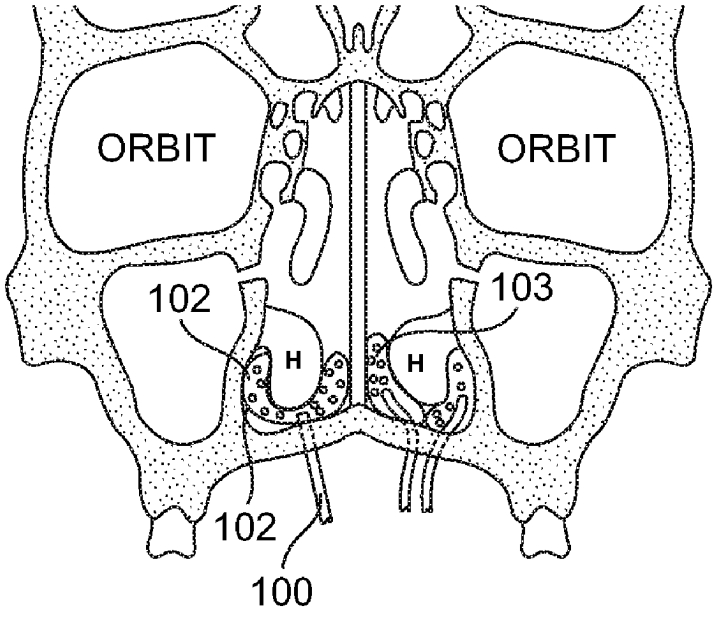


FIG. 19

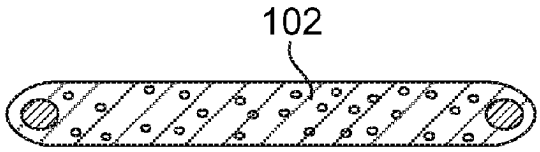


FIG. 20A

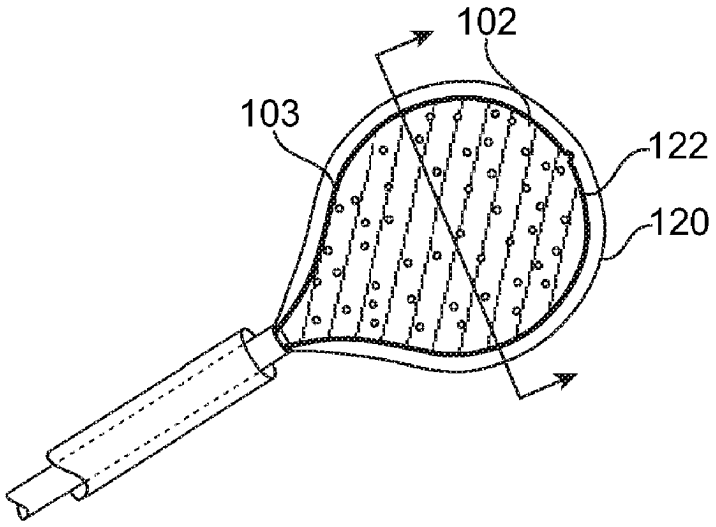


FIG. 20B

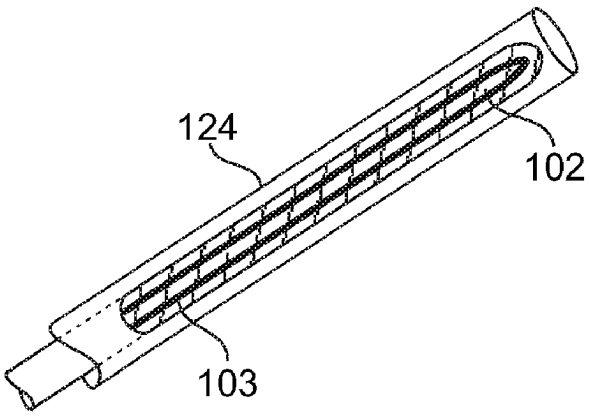


FIG. 20C

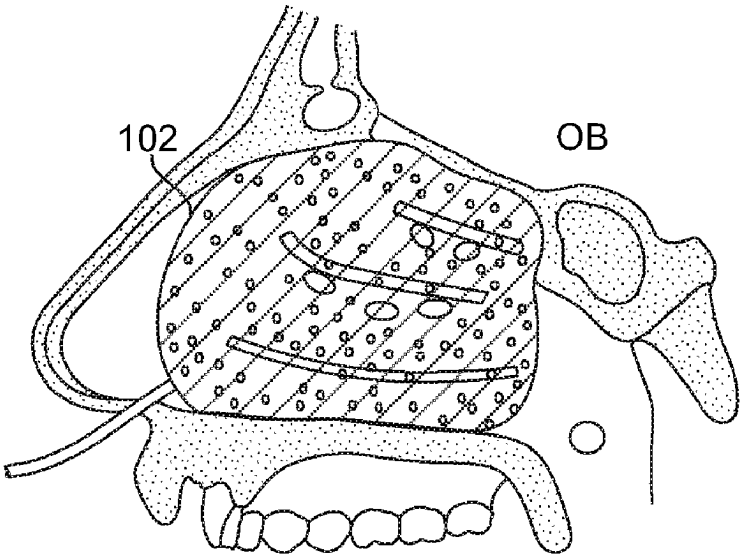


FIG. 21

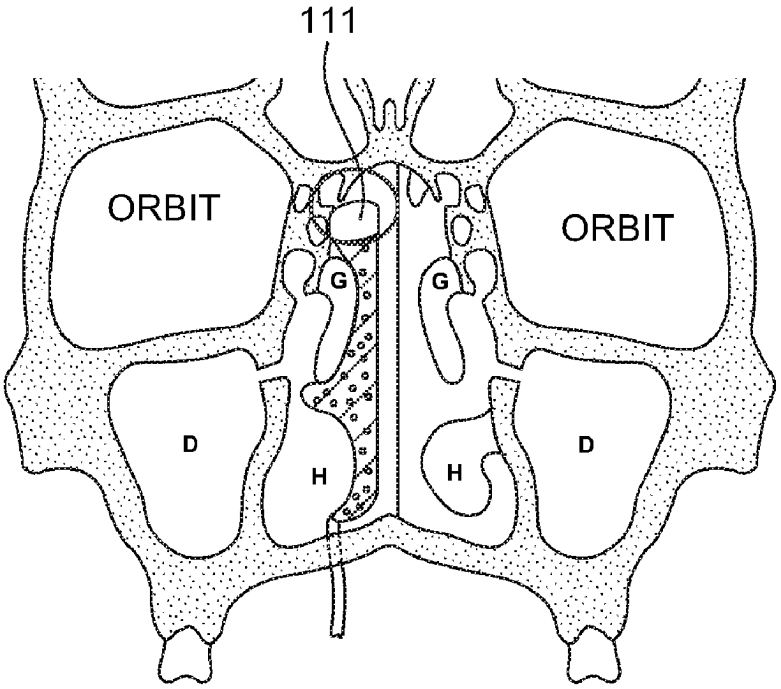


FIG. 22

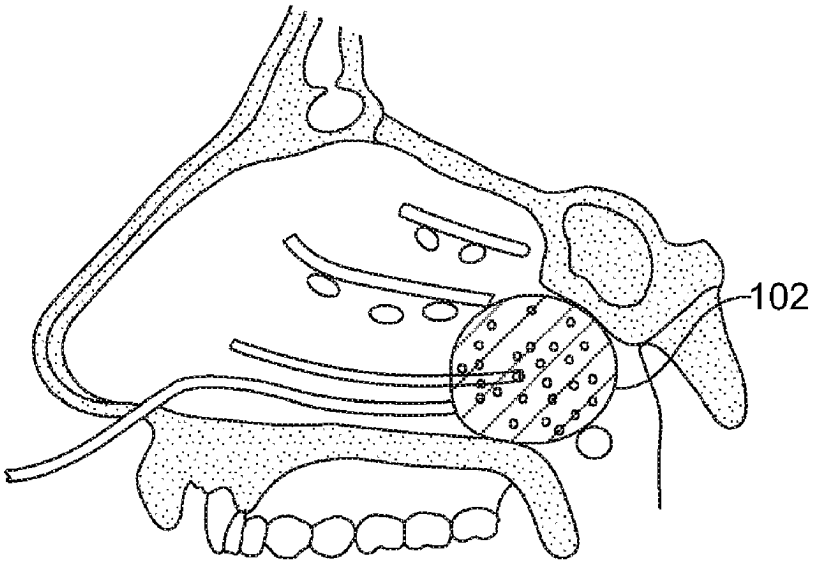


FIG. 23

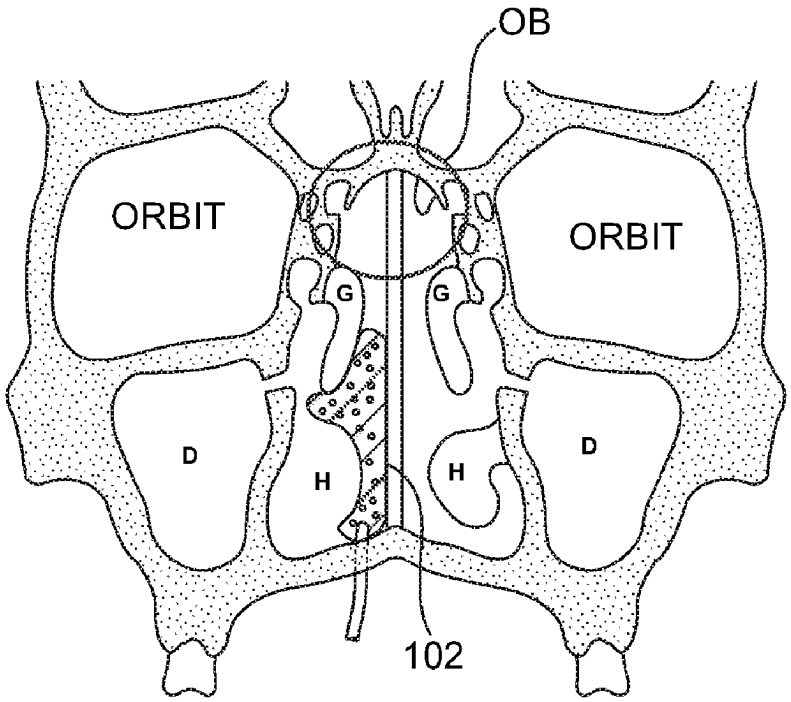


FIG. 24

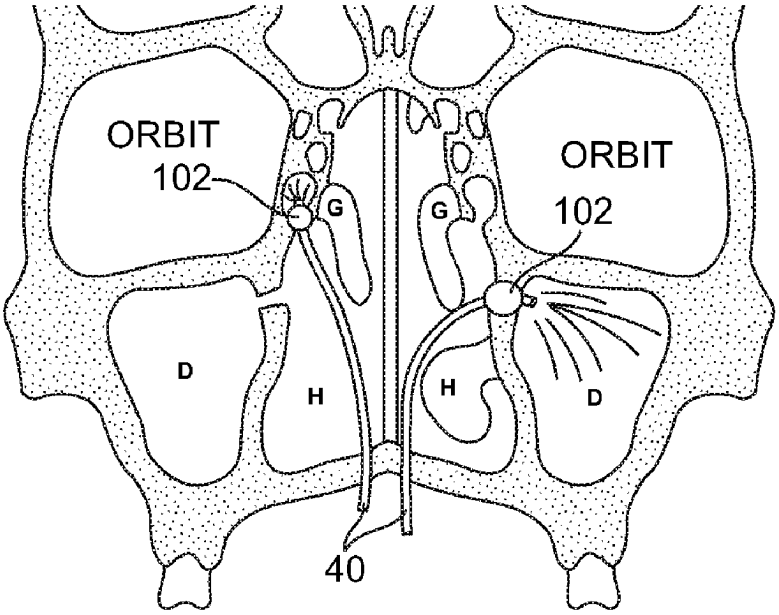


FIG. 25

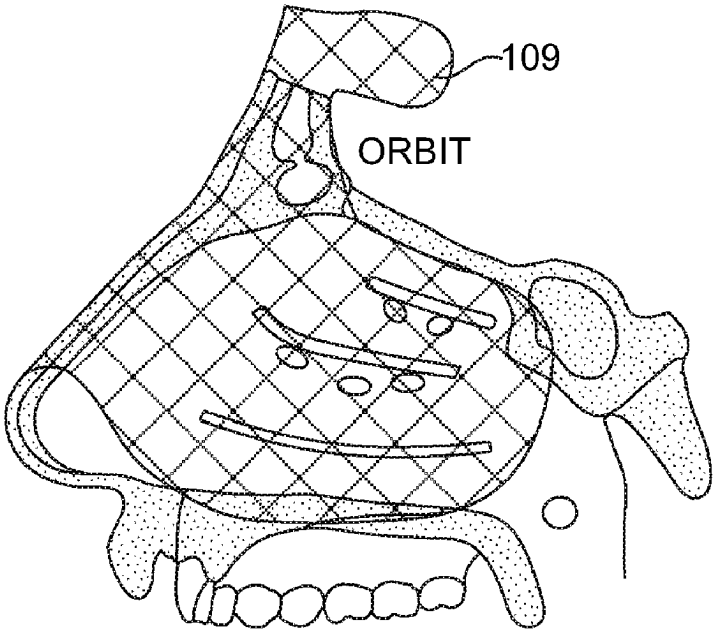


FIG. 26

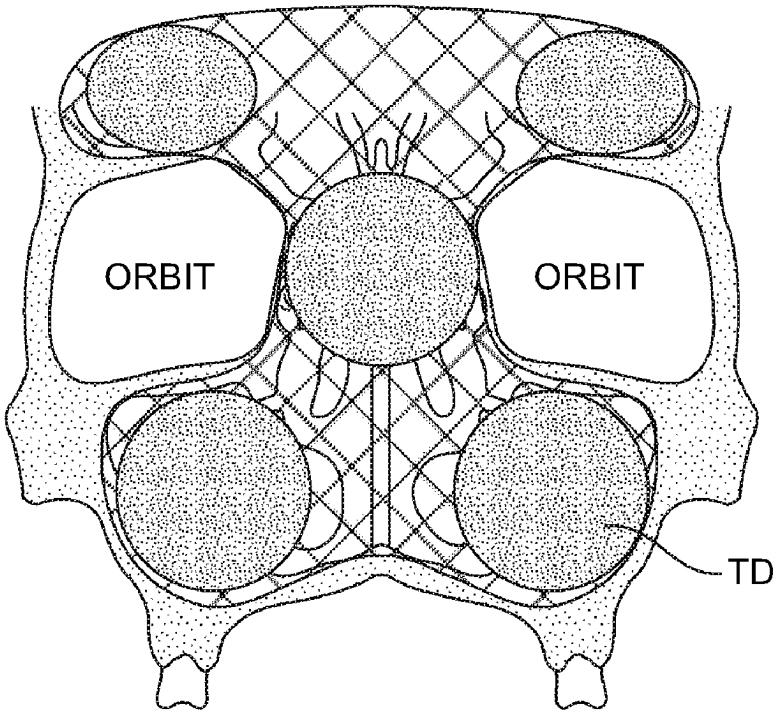


FIG. 27

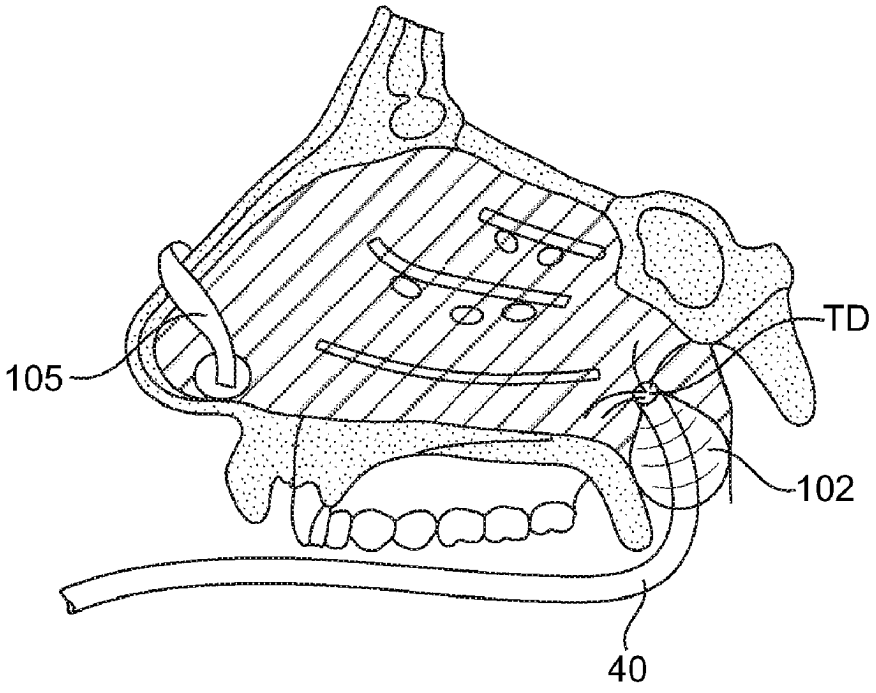


FIG. 28

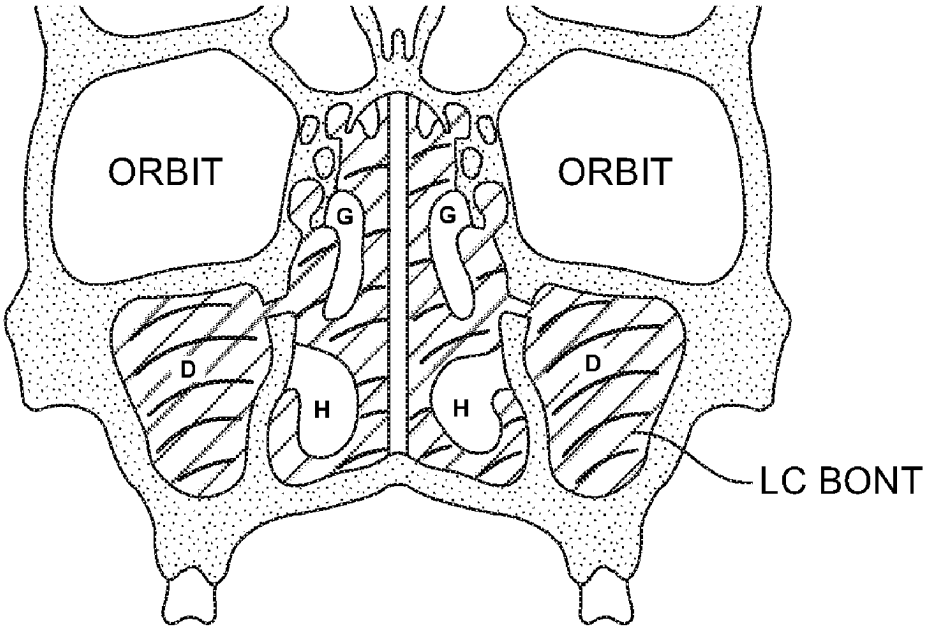


FIG. 29

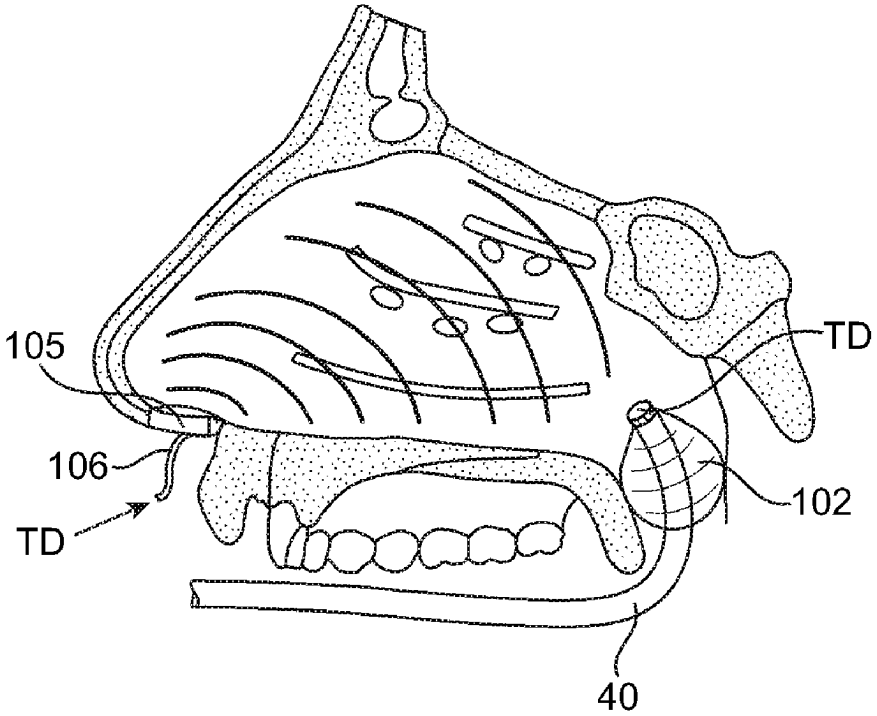


FIG. 30

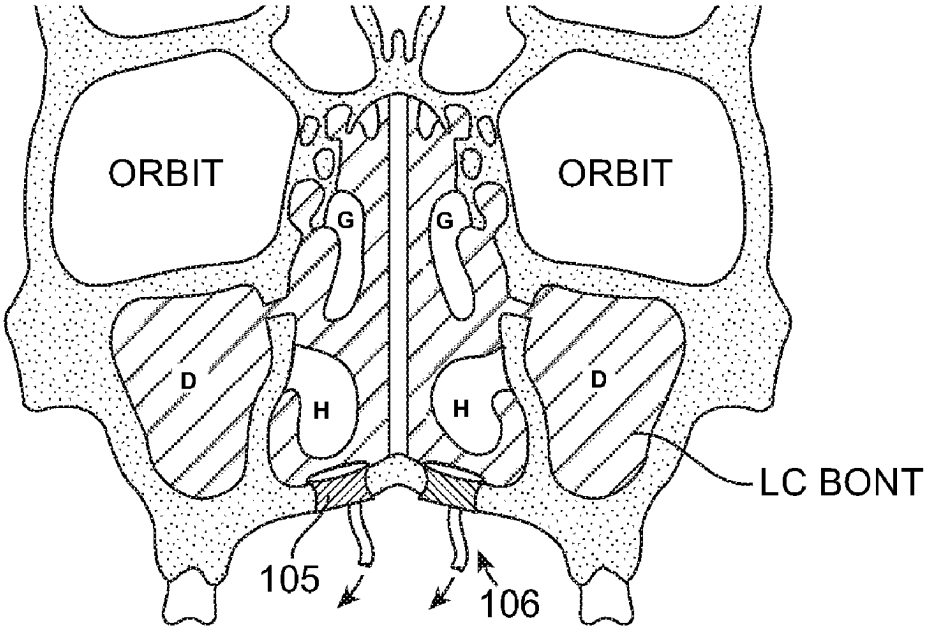


FIG. 31

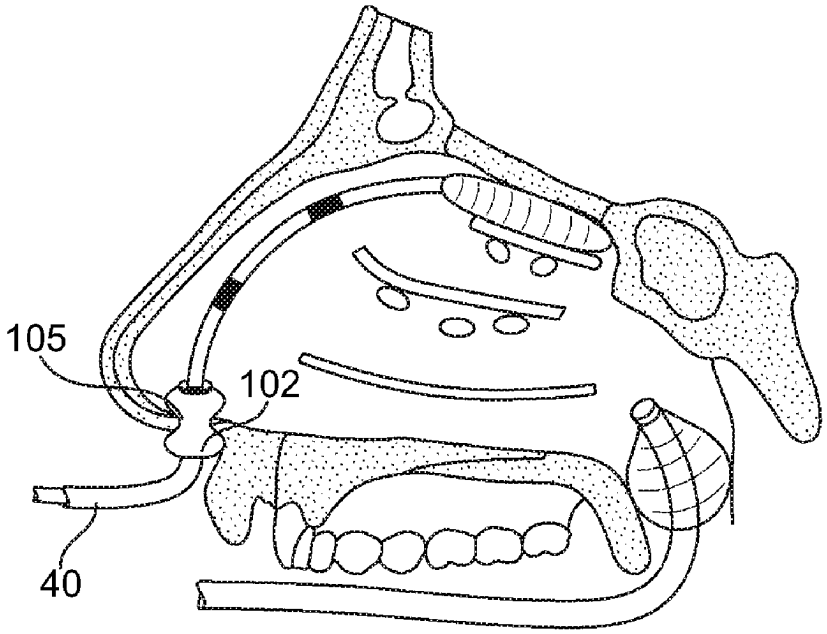


FIG. 32

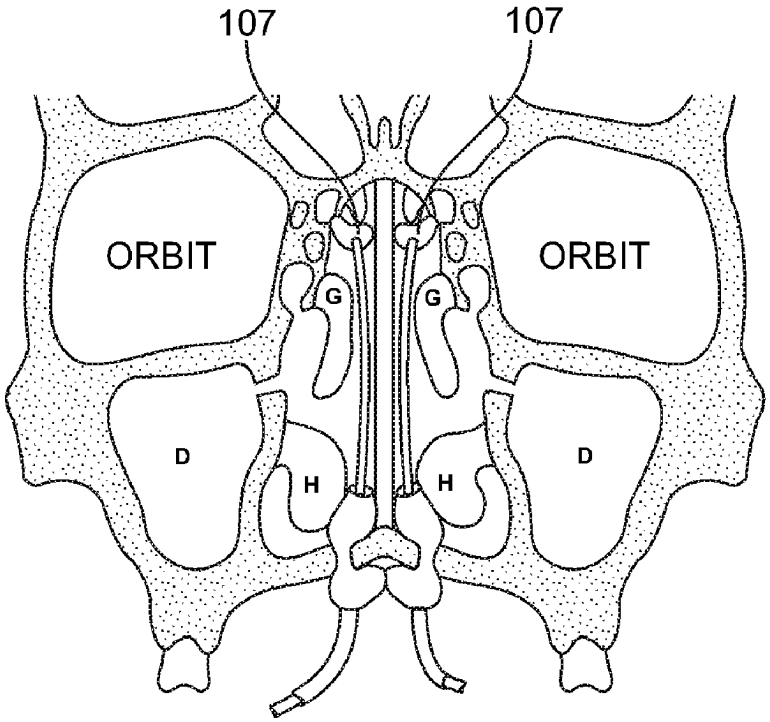


FIG. 33

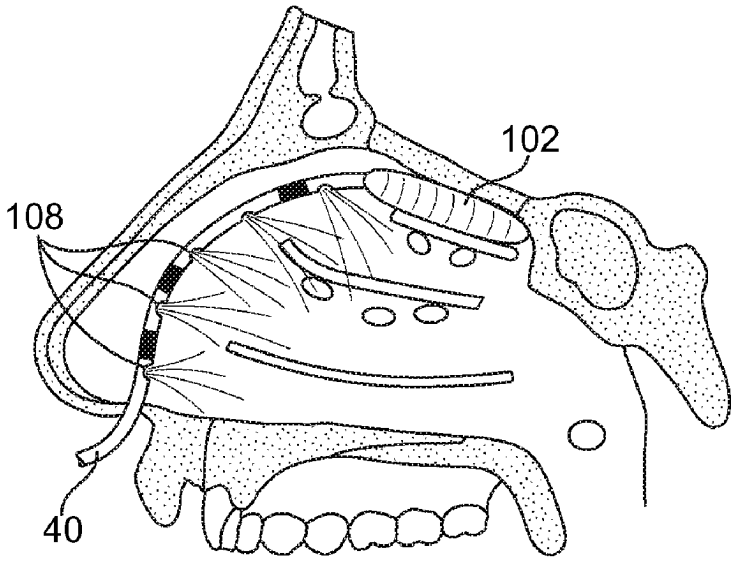


FIG. 34

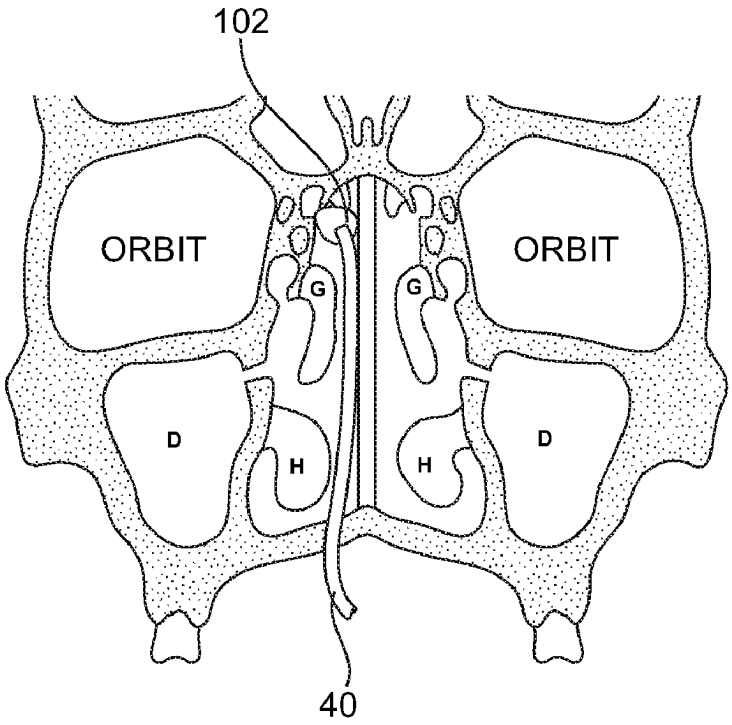


FIG. 35

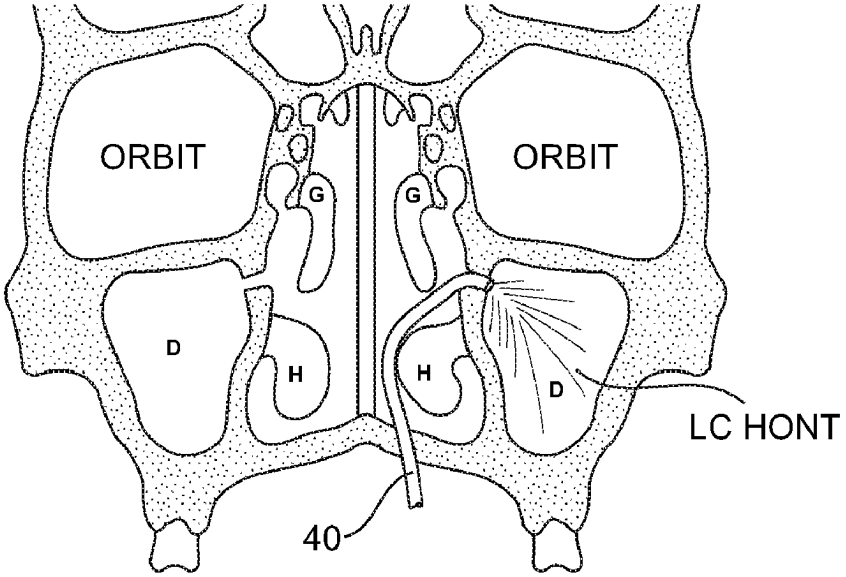


FIG. 36

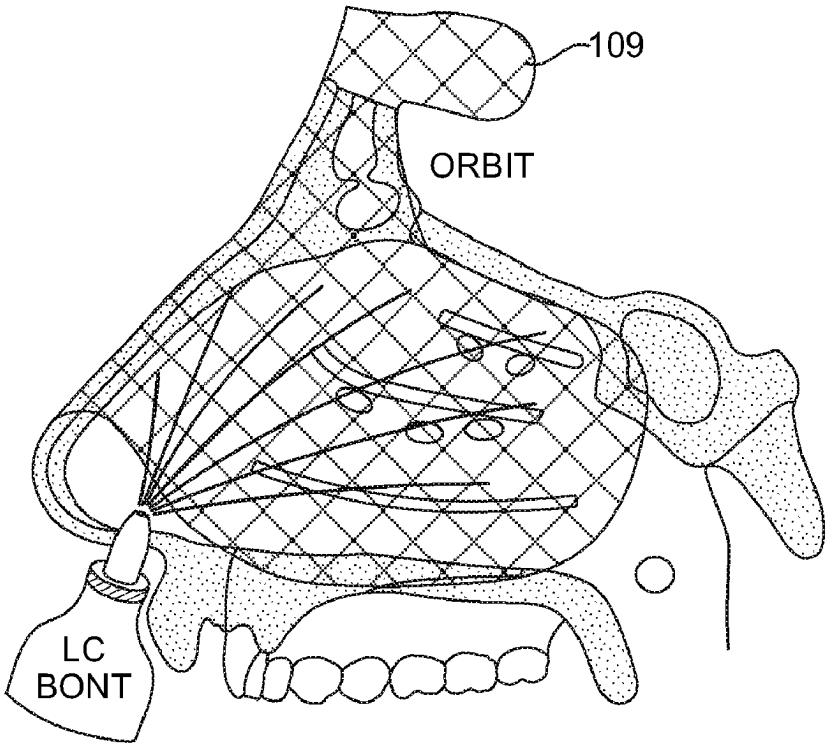


FIG. 37

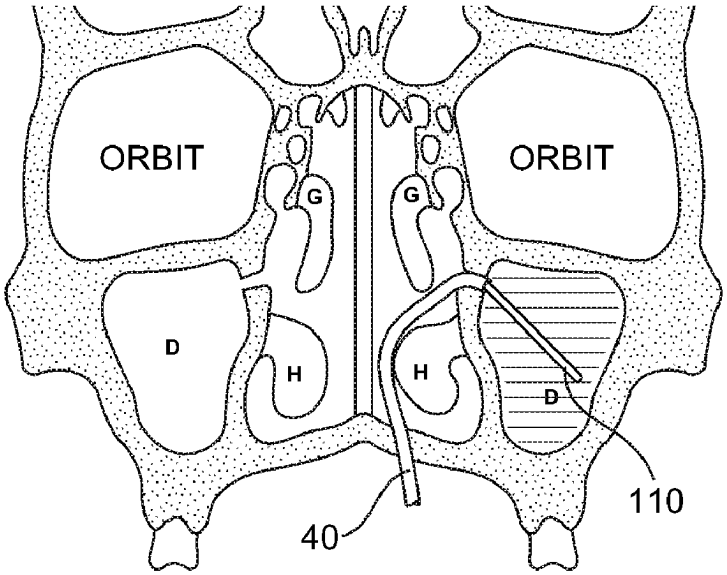


FIG. 38

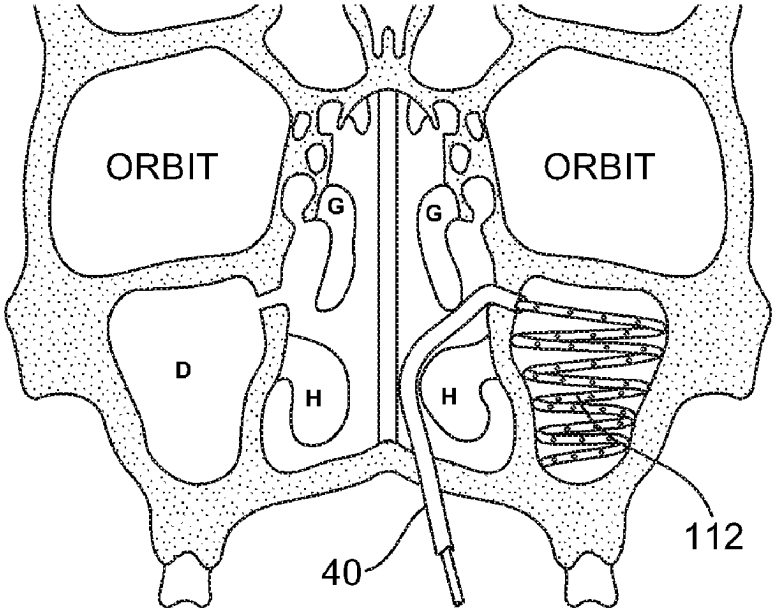


FIG. 39

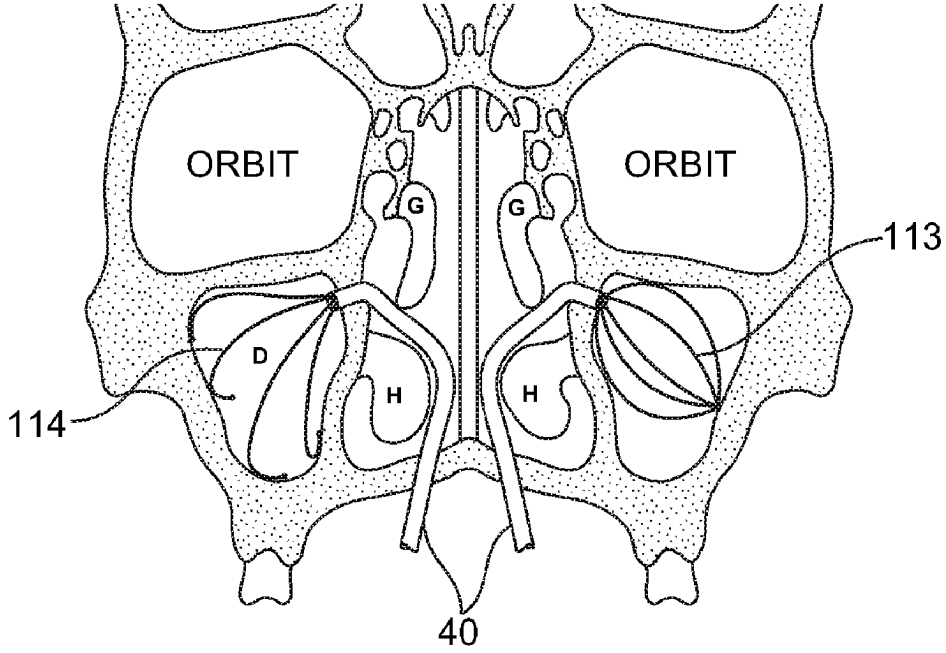


FIG. 40

Electronic Acknowledgement Receipt

EFS ID:	39207689
Application Number:	16842209
International Application Number:	
Confirmation Number:	2844
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:	5187.01US02AP
Receipt Date:	20-APR-2020
Filing Date:	07-APR-2020
Time Stamp:	15:54:59
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	Applicant Response to Pre-Exam Formalities Notice	5187_01US02AP_Reply_Omitted_Items.pdf	63968 47258dacf8e8c078a842122d1afa3454431d0081	no	1

Warnings:

Information:					
2	Drawings-only black and white line drawings	5187_01US02AP_Replacement_Drawings.pdf	2953689 691aa4e94739dc80c78e0e58366f8704743ff01d	no	27
Warnings:					
Information:					
			Total Files Size (in bytes):	3017657	

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.

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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
16/842,209	04/07/2020	Mark E. Deem	5187.01US02AP	2844

24113 7590 04/22/2020
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
04/22/2020	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.** 16/842,209	**Applicant(s)** Deem et al.	
	Examiner BRIAN W BROWN	**Art Unit** OPET	**AIA (FITF) Status** No

1. THE REQUEST FILED 07 April 2020 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 BRIAN BROWN at (571)272-5338. In his/her absence, calls may be directed to Petition Help Desk at (571) 272-3282.

/BRIAN W BROWN/ Petitions Examiner, OPET	

PATENT APPLICATION FEE DETERMINATION RECORD

Substitute for Form PTO-875

Application or Docket Number: 16/842,209

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))	29 minus 20 =	* 9	x 50 =	450	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	1235		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	SMALL ENTITY RATE($)	SMALL ENTITY ADDITIONAL FEE($)	OR	OTHER THAN SMALL ENTITY RATE($)	OTHER THAN SMALL ENTITY ADDITIONAL FEE($)
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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APPLICATION NUMBER	FILING or 371(c) DATE	GRP ART UNIT	FIL FEE REC'D	ATTY.DOCKET.NO	TOT CLAIMS	IND CLAIMS
16/842,209	04/07/2020	1645	1235	5187.01US02AP	29	2

CONFIRMATION NO. 2844

UPDATED FILING RECEIPT

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



Date Mailed: 04/22/2020

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 16/659,893 10/22/2019 PAT 10610675
which 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: 04/15/2020

The country code and number of your priority application, to be used for filing abroad under the Paris Convention, is **US 16/842,209**

Projected Publication Date: 07/30/2020

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

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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

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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
16/842,209	04/07/2020	Mark E. Deem	5187.01US02AP	2844

24113 7590 05/08/2020

PATTERSON THUENTE PEDERSEN, P.A.
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MINNEAPOLIS, MN 55402-2100

EXAMINER	
NAVARRO, ALBERT MARK	

ART UNIT	PAPER NUMBER
1645	

NOTIFICATION DATE	DELIVERY MODE
05/08/2020	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

Office Action Summary	Application No. 16/842,209	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 --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTHS FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

☐ A declaration(s)/affidavit(s) under **37 CFR 1.130(b)** was/were filed on _____.

2a)☐ This action is **FINAL.** 2b) ☑ This action is non-final.

3)☐ 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.

4)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims*

5) ☑ Claim(s) 1-29 is/are pending in the application.

5a) Of the above claim(s) _____ is/are withdrawn from consideration.

6) ☐ Claim(s) _____ is/are allowed.

7) ☑ Claim(s) 1-29 is/are rejected.

8) ☐ Claim(s) _____ is/are objected to.

9) ☐ Claim(s) _____ are subject to restriction and/or election requirement

* If any claims have been determined allowable, 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.**

Application Papers

10)☐ The specification is objected to by the Examiner.

11)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

Priority under 35 U.S.C. § 119

12)☐ 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)).

** See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☑ Notice of References Cited (PTO-892)

2) ☐ Information Disclosure Statement(s) (PTO/SB/08a and/or PTO/SB/08b) Paper No(s)/Mail Date _____.

3) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date _____.

4) ☐ Other: _____.

DETAILED ACTION

Notice of Pre-AIA or AIA Status

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

Claims 1-29 are pending in the instant application.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on nonstatutory double patenting provided the reference application or patent either is shown to be

commonly owned with the examined application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement. See MPEP § 717.02 for applications subject to examination under the first inventor to file provisions of the AIA as explained in MPEP § 2159. See MPEP §§ 706.02(l)(1) - 706.02(l)(3) for applications not subject to examination under the first inventor to file provisions of the AIA. A terminal disclaimer must be signed in compliance with 37 CFR 1.321(b).

The USPTO Internet website contains terminal disclaimer forms which may be used. Please visit www.uspto.gov/patent/patents-forms. The filing date of the application in which the form is filed determines what form (e.g., PTO/SB/25, PTO/SB/26, PTO/AIA/25, or PTO/AIA/26) should be used. A web-based eTerminal Disclaimer may be filled out completely online using web-screens. An eTerminal Disclaimer that meets all requirements is auto-processed and approved immediately upon submission. For more information about eTerminal Disclaimers, refer to www.uspto.gov/patents/process/file/efs/guidance/eTD-info-I.jsp.

1. Claims 1-29 are provisionally rejected on the ground of nonstatutory double patenting as being unpatentable over claims 21-40 of copending Application No. 16/036,381 (US Publication 2019/0083768; allowed but not issued); (reference application). Although the claims at issue are not identical, they are not patentably distinct from each other because the instantly filed claims directed to an apparatus for treatment comprising a hand held elongate body having proximal and distal portions, the distal portion being configured for positioning in a nasopharyngeal passage, an

energy transmission element, and an energy source are anticipated by the claims of 16/036,381, directed to devices for altering functions of a bronchial airway comprising a main catheter body configured to extend and at least one energy applicator which delivers energy in a lateral direction.

This is a provisional nonstatutory double patenting rejection because the patentably indistinct claims have not in fact been patented.

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 https://ppair-my.uspto.gov/pair/PrivatePair. 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
May 5, 2020

Notice of References Cited	Application/Control No. 16/842,209	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-20190083768-A1	03-2019	Deem; Mark E.	A61K38/164	1/1
	B					
	C					
	D					
	E					
	F					
	G					
	H					
	I					
	J					
	K					
	L					
	M					

FOREIGN PATENT DOCUMENTS

*		Document Number Country Code-Number-Kind Code	Date MM-YYYY	Country	Name	CPC Classification
	N					
	O					
	P					
	Q					
	R					
	S					
	T					

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.

Search Notes	Application/Control No.	Applicant(s)/Patent Under Reexamination
	16/842,209	Deem et al.
	Examiner	Art Unit
	Mark NAVARRO	1645

CPC - Searched*		
Symbol	Date	Examiner

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 16/659,893, 16/036,381, 15/358,187, 14/601,529, 13/660,629, 13/253,595, 12/559,278, 11/459,090	05/05/2020	MN

Interference Search			
US Class/CPC Symbol	US Subclass/CPC Group	Date	Examiner

Bibliographic Data

Application No: 16/842,209

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.
04/07/2020	424	1645	5187.01US02AP
RULE			

APPLICANTS

The Foundry, LLC, Menlo Park, CA,

INVENTORS

Mark E. Deem Mountain View, CA, UNITED STATES

Hanson Gifford Woodside, CA, UNITED STATES

CONTINUING DATA

This application is a CON of 16659893 10/22/2019 PAT 10610675

16659893 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**

04/15/2020

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STATE OR COUNTRY

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                  and Retrieval Quality
 NEWS  4  NOV 15  INPADOC Enhanced with More Current and Complete Japanese Legal
                  Status Information.
 NEWS  5  NOV 18  German Patent Full-Text Database DEFULL enhanced
 NEWS  6  NOV 25  CAS FORMULATIONS (TM) Enhanced on STNext
 NEWS  7  NOV 25  PatentPak(R) now available in USPATFULL/USPAT2 on STNext(R)
 NEWS  8  DEC 10  CAplus (SM) Now Provides Non-Conventional Patent Families
                  for Chinese Dual Filings
 NEWS  9  DEC 23  Derwent World Patents Index: Manual Code Revision 2020
 NEWS 10  FEB 13  Changes to Derwent WPI Update Numbering and Total
                  Number of Annual DWPI Updates
 NEWS 11  FEB 13  New Legal Event Data from Croatia, Italy, and Poland
                  in INPADOCDB and INPAFAMDB
 NEWS 12  MAR 10  2020 Version of MEDLINE Now Available on STN(R)
 NEWS 13  MAR 11  First 2020 Update to Emtree(TM) Now Available on STN(R)
 NEWS 14  MAR 26  STN Database Updates Continue as Usual
 NEWS 15  APR  6  Advanced German Patent Full-Text Database DEFULL
                  Replaces Patdpafull
 NEWS 16  APR  6  Announcements from Patent Offices Concerning
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=> s (apparatus? or device? or instrument?)

L1   21105875 (APPARATUS? OR DEVICE? OR INSTRUMENT?)

=> s l1 (300a) (nasophary?)

L2   3010 L1 (300A) (NASOPHARY?)

=> s l2 (300a) (energy? or electrod? or ultrasound? or microwave? or rf or ac or d
c)

L3   213 L2 (300A) (ENERGY? OR ELECTROD? OR ULTRASOUND? OR MICROWAVE?
               OR RF OR AC OR DC)

=> s l3 and (nasal? (30a) congest?)

L4   44 L3 AND (NASAL? (30A) CONGEST?)

=> dup rem l4

PROCESSING COMPLETED FOR L4
L5   44 DUP REM L4 (0 DUPLICATES REMOVED)

=> d ibib kwic 1-44

L5   ANSWER 1 OF 44 USPATFULL on STN
ACCESSION NUMBER: 2020:131305 USPATFULL
TITLE: DEVICES, SYSTEMS AND METHODS USEABLE FOR TREATING
                        SINUSITIS
INVENTOR(S):   Chang, John Y., Los Altos, CA, UNITED STATES
                        Makower, Joshua, Los Altos, CA, UNITED STATES
                        Vrany, Julia D., Los Altos, CA, UNITED STATES
                        Morriss, John H., Emerald Hills, CA, UNITED STATES
                        Muni, Ketan P., San Jose, CA, UNITED STATES
                        Kim, Isaac J., San Jose, CA, UNITED STATES
                        Ha, Hung V., San Jose, CA, UNITED STATES
                        Facteau, William M., Atherton, CA, UNITED STATES
                        Walke, Amrish J., Milpitas, CA, UNITED STATES
APPLICANT(S):   Acclarent, Inc., Irvine, CA, UNITED STATES

                             NUMBER   KIND   DATE
                        ---------------- ------ --------
PATENT INFORMATION: US 20200114132   A1   20200416
APPLICATION INFO.:   US 2019-16672702   A1   20191104 (16)
RELATED APPLN. INFO.:   Continuation of Ser. No. US 2017-15651101, filed on 17
                        Jul 2017, Pat. No. US 10500380 Continuation of Ser. No.
                        US 2014-14221550, filed on 21 Mar 2014, ABANDONED
                        Continuation of Ser. No. US 2007-928097, filed on 30
                        Oct 2007, Pat. No. US 8715169 Continuation of Ser. No.
                        US 2005-150847, filed on 10 Jun 2005, Pat. No. US
                        7803150 Continuation-in-part of Ser. No. US
                        2004-944270, filed on 17 Sep 2004, ABANDONED
                        Continuation-in-part of Ser. No. US 2004-829917, filed
                        on 21 Apr 2004, Pat. No. US 7654997
DOCUMENT TYPE: Utility
FILE SEGMENT: APPLICATION
NUMBER OF CLAIMS: 21
EXEMPLARY CLAIM: 1-19
NUMBER OF DRAWINGS: 41 Drawing Page(s)
LINE COUNT: 2545
CAS INDEXING IS AVAILABLE FOR THIS PATENT. Full-text
SUMM   Patients who suffer from sinusitis typically experience at least some of
       the following symptoms:

headaches or facial pain

nasal congestion or post-nasal drainage
difficulty breathing through one or both nostrils
bad breath
pain in the upper teeth Thus, one of the ways to treat sinusitis. . .
DETD Thereafter, in FIG. 2D, the working device 204 is used to perform a diagnostic or therapeutic procedure. In this particular example, the procedure is dilation of the. . . or modify any sinus ostium or other man-made or naturally occurring anatomical opening or passageway within the nose, paranasal sinuses, nasopharynx or adjacent areas. After the completion of the procedure, guide catheter 200, guidewire 202 and working device 204 are withdrawn and removed. As will be appreciated by those of skill in the art, in this or any. . . or imaging modalities including but not limited to fluoroscopic, X-ray radiographic, ultrasonic, radiofrequency localization, electromagnetic, magnetic, robotic and other radiative energy based modalities. In this regard, some of the figures show optional scopes SC is dotted lines. It is to be. . . types of rigid or flexible endoscopes and such optional scopes SC may be separate from or incorporated into the working devices and/or introduction devices of the present invention.

L5 ANSWER 2 OF 44 USPATFULL on STN

ACCESSION NUMBER:	2020:53186 USPATFULL		
TITLE:	SYSTEMS AND METHODS FOR DELIVERY OF A THERAPEUTIC AGENT		
INVENTOR(S):	Deem, Mark E., Mountain View, CA, UNITED STATES Gifford, Hanson, Woodside, CA, UNITED STATES		
APPLICANT(S):	The Foundry, LLC, Menlo Park, CA, UNITED STATES		
	NUMBER	KIND	DATE
PATENT INFORMATION:	US 20200046955	A1	20200213
	US 10610675	B2	20200407
APPLICATION INFO.:	US 2019-16659893	A1	20191022 (16)
RELATED APPLN. INFO.:	Continuation of Ser. No. US 2018-16036381, filed on 16 Jul 2018, PENDING Continuation of Ser. No. US 2016-15358187, filed on 22 Nov 2016, Pat. No. US 10022529 Continuation of Ser. No. US 2015-14601529, filed on 21 Jan 2015, Pat. No. US 9498283 Continuation of Ser. No. US 2012-13660629, filed on 25 Oct 2012, Pat. No. US 8961391 Continuation of Ser. No. US 2011-13253595, filed on 5 Oct 2011, Pat. No. US 8338164 Continuation of Ser. No. US 2009-559278, filed on 14 Sep 2009, Pat. No. US 8133497 Division of Ser. No. US 2006-459090, filed on 21 Jul 2006, Pat. No. US 7608275		
	NUMBER		DATE
PRIORITY INFORMATION:	US 2005-60702077		20050722 (60)
DOCUMENT TYPE:	Utility		
FILE SEGMENT:	APPLICATION		
NUMBER OF CLAIMS:	30		
EXEMPLARY CLAIM:	1		
NUMBER OF DRAWINGS:	27 Drawing Page(s)		
LINE COUNT:	1712		

CAS INDEXING IS AVAILABLE FOR THIS PATENT. Full-text
SUMM . . . 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.
SUMM . . . 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. . . 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. . .
SUMM 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. . .
DETD . . . 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.. . . 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.
CLM 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.

CLM What is claimed is:
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.

L5 ANSWER 3 OF 44 USPATFULL on STN
ACCESSION NUMBER: 2020:25852 USPATFULL
TITLE: DEVICES, SYSTEMS AND METHODS FOR DIAGNOSING AND TREATING SINUSITIS AND OTHER DISORDERS OF THE EARS, NOSE AND/OR THROAT
INVENTOR(S): Chang, John Y., Los Altos, CA, UNITED STATES
Makower, Joshua, Los Altos, CA, UNITED STATES
APPLICANT(S): Acclarent, Inc., Irvine, CA, UNITED STATES

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 20200022717	A1	20200123
APPLICATION INFO.:	US 2019-16532678	A1	20190806 (16)

RELATED APPLN. INFO.: Continuation of Ser. No. US 2017-15443319, filed on 27 Feb 2017, Pat. No. US 10492810 Continuation of Ser. No. US 2016-15363002, filed on 29 Nov 2016, ABANDONED Continuation of Ser. No. US 2013-13867972, filed on 22 Apr 2013, ABANDONED Continuation of Ser. No. US 2009-649050, filed on 29 Dec 2009, Pat. No. US 8425457 Continuation of Ser. No. US 2004-829917, filed on 21 Apr 2004, Pat. No. US 7654997
DOCUMENT TYPE: Utility
FILE SEGMENT: APPLICATION
NUMBER OF CLAIMS: 21
EXEMPLARY CLAIM: 1-18
NUMBER OF DRAWINGS: 41 Drawing Page(s)
LINE COUNT: 2875
CAS INDEXING IS AVAILABLE FOR THIS PATENT. Full-text
AB . . . nose and throat are diagnosed and/or treated using minimally invasive approaches and, in many cases, flexible catheters as opposed to instruments having rigid shafts. Various diagnostic procedures and devices are used to perform imaging studies, mucus flow studies, air/gas flow studies, anatomic dimension studies, endoscopic studies and transillumination studies. Access and occluder devices may be used to establish fluid tight seals in the anterior or posterior nasal cavities/nasopharynx and to facilitate insertion of working devices (e.g., scopes, guidewires, catheters, tissue cutting or remodeling

devices, electrosurgical devices, energy emitting devices, devices for injecting diagnostic or therapeutic agents, devices for implanting devices such as stents, substance eluting devices, substance delivery implants, etc.

SUMM nasal congestion or postnasal drainage

DETD . . . 9A-9C show a procedure for installation of a cochlear implant in accordance with the present invention. In this procedure, the nasopharyngeal opening into the Eustachian tube ET is located and a guidewire is initially advanced into the Eustachian tube ET. A. . . catheter 900 is in or near the tympanic cavity TC of the middle ear. Thereafter, if deemed necessary, a forceps device 790 and/or other devices are advanced through the catheter 900 and used to remove the small bones of the sear (i.e., the malleus, incus. . . This optional removal of the bones of the middle ear may be done under endoscopic visualization using an endoscope equipped device such as the endoscope equipped forceps device 790 shown in FIG. 5T and described above. As shown in FIG. 9B, a cochlear guide catheter 904 having a. . . tympanic membrane. In other applications, the cochlear guide catheter 904 may be positioned adjacent to the cochlea and a cochleostomy device (e.g., a penetrator such as a drill, needle or cutter) may be advanced through or formed or positioned on the. . . cochleostomy through which the distal end of the guide catheter 904 is advanced into the cochlea C. Thereafter, a cochlear electrode array 906 is advanced through the cochlear guide catheter 904 and into the cochlea, as seen in FIG. 9B. One example of a commercially available cochlear electrode array is the Nucleus 24 Countour device manufactured by Cochlear Corporation.

L5 ANSWER 4 OF 44 USPATFULL on STN

ACCESSION NUMBER:	2019:449166 USPATFULL		
TITLE:	DEVICES, SYSTEMS AND METHODS FOR DIAGNOSING AND TREATING SINUSITIS AND OTHER DISORDERS OF THE EARS, NOSE AND/OR THROAT		
INVENTOR(S):	Chang, John Y., Los Altos, CA, UNITED STATES Makower, Joshua, Los Altos, CA, UNITED STATES		
APPLICANT(S):	Acclarent, Inc., Irvine, CA, UNITED STATES		
	NUMBER	KIND	DATE
PATENT INFORMATION:	US 20190388113	A1	20191226
APPLICATION INFO.:	US 2019-16424728	A1	20190529 (16)
RELATED APPLN. INFO.:	Continuation of Ser. No. US 2017-15443319, filed on 27 Feb 2017, PENDING Continuation of Ser. No. US 2016-15363002, filed on 29 Nov 2016, ABANDONED Continuation of Ser. No. US 2013-13867972, filed on 22 Apr 2013, ABANDONED Continuation of Ser. No. US 2009-649050, filed on 29 Dec 2009, Pat. No. US 8425457 Continuation of Ser. No. US 2004-829917, filed on 21 Apr 2004, Pat. No. US 7654997		
DOCUMENT TYPE:	Utility		
FILE SEGMENT:	APPLICATION		
NUMBER OF CLAIMS:	21		
EXEMPLARY CLAIM:	1-18		
NUMBER OF DRAWINGS:	41 Drawing Page(s)		
LINE COUNT:	2882		

CAS INDEXING IS AVAILABLE FOR THIS PATENT. Full-text

AB . . . nose and throat are diagnosed and/or treated using minimally invasive approaches and, in many cases, flexible catheters as opposed to instruments having rigid shafts. Various diagnostic procedures and devices are used to perform imaging studies, mucus flow studies, air/gas flow studies, anatomic dimension studies, endoscopic studies and transillumination studies. Access and occluder devices may be used to establish fluid tight seals in the anterior or posterior nasal cavities/nasopharynx and to facilitate insertion of working devices (e.g., scopes, guidewires, catheters, tissue cutting or remodeling devices, electrosurgical devices, energy emitting devices, devices for injecting diagnostic or therapeutic agents, devices for implanting devices such as stents, substance eluting devices, substance delivery implants, etc.

SUMM Patients who suffer from sinusitis typically experience at least some of the following symptoms:

headaches or facial pain

nasal congestion or post-nasal drainage
difficulty breathing through one or both nostrils
bad breath
pain in the upper teeth
DETD . . . 9A-9C show a procedure for installation of a cochlear implant in accordance with the present invention. In this procedure, the nasopharyngeal opening into the Eustachian tube ET is located and a guidewire is initially advanced into the Eustachian tube ET. A. . . catheter 900 is in or near the tympanic cavity TC of the middle ear. Thereafter, if deemed necessary, a forceps device 790 and/or other devices are advanced through the catheter 900 and used to remove the small bones of the sear (i.e., the malleus, incus. . . This optional removal of the bones of the middle ear may be done under endoscopic visualization using an endoscope equipped device such as the endoscope equipped forceps device 790 shown in FIG. 5T and described above. As shown in FIG. 9B, a cochlear guide catheter 904 having a. . . tympanic membrane. In other applications, the cochlear guide catheter 904 may be positioned adjacent to the cochlea and a cochleostomy device (e.g., a penetrator such as a drill, needle or cutter) may be advanced through or formed or positioned on the. . . cochleostomy through which the distal end of the guide catheter 904 is advanced into the cochlea C. Thereafter, a cochlear electrode array 906 is advanced through the cochlear guide catheter 904 and into the cochlea, as seen in FIG. 9B. One example of a commercially available cochlear electrode array is the Nucleus 24 Countour device manufactured by Cochlear Corporation.

L5 ANSWER 5 OF 44 USPATFULL on STN
ACCESSION NUMBER: 2019:362669 USPATFULL
TITLE: APPARATUS AND METHODS FOR DILATING AND MODIFYING OSTIA OF PARANASAL SINUSES AND OTHER INTRANASAL OR PARANASAL STRUCTURES
INVENTOR(S): Chang, John Y., Los Altos, CA, UNITED STATES
Makower, Joshua, Los Altos, CA, UNITED STATES
Vrany, Julia D., Los Altos, CA, UNITED STATES
Walke, Amrish J., Milpitas, CA, UNITED STATES
APPLICANT(S): Acclarent, Inc., Irvine, CA, UNITED STATES

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 20190314620	A1	20191017
APPLICATION INFO.:	US 2019-16424735	A1	20190529 (16)

RELATED APPLN. INFO.: Continuation of Ser. No. US 2017-15624111, filed on 15 Jun 2017, PENDING Continuation of Ser. No. US 2014-14566845, filed on 11 Dec 2014, Pat. No. US 9713700 Continuation of Ser. No. US 2010-768963, filed on 28 Apr 2010, Pat. No. US 8945088 Continuation of Ser. No. US 2007-928346, filed on 30 Oct 2007, Pat. No. US 8172828 Continuation of Ser. No. US 2004-944270, filed on 17 Sep 2004, ABANDONED Continuation-in-part of Ser. No. US 2004-829917, filed on 21 Apr 2004, Pat. No. US 7654997
DOCUMENT TYPE: Utility
FILE SEGMENT: APPLICATION
NUMBER OF CLAIMS: 21
EXEMPLARY CLAIM: 1-10
NUMBER OF DRAWINGS: 35 Drawing Page(s)
LINE COUNT: 1520
CAS INDEXING IS AVAILABLE FOR THIS PATENT. Full-text
SUMM Patients who suffer from sinusitis typically experience at least some of the following symptoms:

headaches or facial pain

nasal congestion or post-nasal drainage
difficulty breathing through one or both nostrils
bad breath
pain in the upper teeth

DETD . . . conductive coatings, radiopaque coatings, echogenic coatings, thrombogenicity reducing coatings and coatings that release drugs. In FIG. 2B, a second introduction device comprising a guidewire 202 is introduced through the first introduction device (i.e., the guide catheter 200) so that the guidewire 202 enters the sphenoid sinus SS through the ostium SSO. Guidewire 202 may be constructed and coated as is common in the art of cardiology. In FIG. 2C, a working device 204 for example a balloon catheter is introduced over guidewire 202 into the sphenoid sinus SS. Thereafter, in FIG. 2D, the working device 204 is used to perform a diagnostic or therapeutic procedure. In this particular example, the procedure is dilation of the. . . or modify any sinus ostium or other man-made or naturally occurring anatomical opening or passageway within the nose, paranasal sinuses, nasopharynx or adjacent areas. After the completion of the procedure, guide catheter 200, guidewire 202 and working device 204 are withdrawn and removed. As will be appreciated by those of skill in the art, in this or any. . . or imaging modalities including but not limited to fluoroscopic, X-ray radiographic, ultrasonic, radiofrequency localization, electromagnetic, magnetic, robotic and other radiative energy based modalities. In this regard, some of the figures show optional scopes SC is dotted lines. It is to be. . . types of rigid or flexible endoscopes and such optional scopes SC may be separate from or incorporated into the working devices and/or introduction devices of the present invention.

L5 ANSWER 6 OF 44 USPATFULL on STN

ACCESSION NUMBER:	2019:316387 USPATFULL		
TITLE:	EAR THERAPEUTIC DEVICE		
INVENTOR(S):	AVNI, Yuval, Tel-Aviv, ISRAEL		
APPLICANT(S):	Vincent Yuval R&,D Limited, Hug Hom, Kowloon, HONG KONG		
	NUMBER	KIND	DATE
PATENT INFORMATION:	US 20190274917	A1	20190912
APPLICATION INFO.:	US 2019-16345912	A1	20171029 (16)
	WO 2017-IL51176		20171029
			20190429 PCT 371 date
	NUMBER		DATE
PRIORITY INFORMATION:	US 2016-62414735		20161030 (62)
DOCUMENT TYPE:	Utility		
FILE SEGMENT:	APPLICATION		
NUMBER OF CLAIMS:	21		
EXEMPLARY CLAIM:	1-40		
NUMBER OF DRAWINGS:	14 Drawing Page(s)		
LINE COUNT:	2569 Full-text		

SUMM . . . ear is the external portion of the ear, which consists of the pinna and external auditory meatus. It gathers sound energy and focuses it on the eardrum. From the pinna the sound pressure waves move into the ear canal, also known. . . also been called the tympanic cavity, or cavum tympani. The Eustachian tube joins the tympanic cavity with the nasal cavity (nasopharynx), allowing pressure to equalize between the middle ear and throat. The Eustachian tube originates in the rear of the nose. . . middle ear space. The middle ear space is the hollowed out portion of the skull bone that contains the hearing apparatus and is covered on one side by the eardrum. The inner ear (auris interna) is the innermost part of the. . .

SUMM Factors that may increase your chance of getting ETD include: age (children), nasal congestion from an allergy, cold other upper respiratory infection, ear or sinus infections, environmental allergies, children with large adenoids, activities with. . .

L5 ANSWER 7 OF 44 USPATFULL on STN

ACCESSION NUMBER:	2018:2306 USPATFULL
TITLE:	DEVICES, SYSTEMS AND METHODS USEABLE FOR TREATING SINUSITIS
INVENTOR(S):	Chang, John Y., Los Altos, CA, UNITED STATES Makower, Joshua, Los Altos, CA, UNITED STATES

Vrany, Julia D., Los Altos, CA, UNITED STATES
Morriss, John H., Emerald Hills, CA, UNITED STATES
Muni, Ketan P., San Jose, CA, UNITED STATES
Kim, Isaac J., San Jose, CA, UNITED STATES
Ha, Hung V., San Jose, CA, UNITED STATES
Facteau, William M., Atherton, CA, UNITED STATES
Walke, Amrish J., Milpitas, CA, UNITED STATES
APPLICANT(S): Acclarent, Inc., Irvine, CA, UNITED STATES

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 20180001065	A1	20180104
	US 10500380	B2	20191210
APPLICATION INFO.:	US 2017-15651101	A1	20170717 (15)

RELATED APPLN. INFO.: Continuation of Ser. No. US 2014-14221550, filed on 21 Mar 2014, ABANDONED Continuation of Ser. No. US 2007-928097, filed on 30 Oct 2007, Pat. No. US 8715169 Continuation of Ser. No. US 2005-150847, filed on 10 Jun 2005, Pat. No. US 7803150 Continuation-in-part of Ser. No. US 2004-944270, filed on 17 Sep 2004, ABANDONED Continuation-in-part of Ser. No. US 2004-829917, filed on 21 Apr 2004, Pat. No. US 7654997
DOCUMENT TYPE: Utility
FILE SEGMENT: APPLICATION
NUMBER OF CLAIMS: 21
EXEMPLARY CLAIM: 1-19
NUMBER OF DRAWINGS: 41 Drawing Page(s)
LINE COUNT: 2530
CAS INDEXING IS AVAILABLE FOR THIS PATENT. Full-text
SUMM Patients who suffer from sinusitis typically experience at least some of the following symptoms:

headaches or facial pain

nasal congestion or post-nasal drainage
difficulty breathing through one or both nostrils
bad breath
pain in the upper teeth Thus, one of the ways to treat sinusitis. . .
DETD Thereafter, in FIG. 2D, the working device 204 is used to perform a diagnostic or therapeutic procedure. In this particular example, the procedure is dilation of the. . . or modify any sinus ostium or other man-made or naturally occurring anatomical opening or passageway within the nose, paranasal sinuses, nasopharynx or adjacent areas. After the completion of the procedure, guide catheter 200, guidewire 202 and working device 204 are withdrawn and removed. As will be appreciated by those of skill in the art, in this or any. . . or imaging modalities including but not limited to fluoroscopic, X-ray radiographic, ultrasonic, radiofrequency localization, electromagnetic, magnetic, robotic and other radiative energy based modalities. In this regard, some of the figures show optional scopes SC is dotted lines. It is to be. . . types of rigid or flexible endoscopes and such optional scopes SC may be separate from or incorporated into the working devices and/or introduction devices of the present invention.

L5 ANSWER 8 OF 44 USPATFULL on STN
ACCESSION NUMBER: 2017:400941 USPATFULL
TITLE: APPARATUS AND METHODS FOR DILATING AND MODIFYING OSTIA OF PARANASAL SINUSES AND OTHER INTRANASAL OR PARANASAL STRUCTURES
INVENTOR(S): Chang, John Y., Los Altos, CA, UNITED STATES
Makower, Joshua, Los Altos, CA, UNITED STATES
Vrany, Julia D., Los Altos, CA, UNITED STATES
Walke, Amrish J., Milpitas, CA, UNITED STATES
APPLICANT(S): Acclarent, Inc., Irvine, CA, UNITED STATES

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 20170348516	A1	20171207
APPLICATION INFO.:	US 2017-15624111	A1	20170615 (15)

RELATED APPLN. INFO.: Continuation of Ser. No. US 2014-14566845, filed on 11 Dec 2014, Pat. No. US 9713700 Continuation of Ser. No.

US 2010-768963, filed on 28 Apr 2010, Pat. No. US 8945088 Continuation of Ser. No. US 2007-928346, filed on 30 Oct 2007, Pat. No. US 8172828 Continuation of Ser. No. US 2004-944270, filed on 17 Sep 2004, ABANDONED Continuation-in-part of Ser. No. US 2004-829917, filed on 21 Apr 2004, Pat. No. US 7654997
DOCUMENT TYPE: Utility
FILE SEGMENT: APPLICATION
NUMBER OF CLAIMS: 21
EXEMPLARY CLAIM: 1-20
NUMBER OF DRAWINGS: 35 Drawing Page(s)
LINE COUNT: 1575
CAS INDEXING IS AVAILABLE FOR THIS PATENT. Full-text
SUMM Patients who suffer from sinusitis typically experience at least some of the following symptoms:
headaches or facial pain

nasal congestion or post-nasal drainage
difficulty breathing through one or both nostrils
bad breath
pain in the upper teeth
DETD . . . conductive coatings, radiopaque coatings, echogenic coatings, thrombogenicity reducing coatings and coatings that release drugs. In FIG. 2B, a second introduction device comprising a guidewire 202 is introduced through the first introduction device (i.e., the guide catheter 200) so that the guidewire 202 enters the sphenoid sinus SS through the ostium SSO. Guidewire 202 may be constructed and coated as is common in the art of cardiology. In FIG. 2C, a working device 204 for example a balloon catheter is introduced over guidewire 202 into the sphenoid sinus SS. Thereafter, in FIG. 2D, the working device 204 is used to perform a diagnostic or therapeutic procedure. In this particular example, the procedure is dilation of the. . . or modify any sinus ostium or other man-made or naturally occurring anatomical opening or passageway within the nose, paranasal sinuses, nasopharynx or adjacent areas. After the completion of the procedure, guide catheter 200, guidewire 202 and working device 204 are withdrawn and removed. As will be appreciated by those of skill in the art, in this or any. . . or imaging modalities including but not limited to fluoroscopic, X-ray radiographic, ultrasonic, radiofrequency localization, electromagnetic, magnetic, robotic and other radiative energy based modalities. In this regard, some of the figures show optional scopes SC is dotted lines. It is to be. . . types of rigid or flexible endoscopes and such optional scopes SC may be separate from or incorporated into the working devices and/or introduction devices of the present invention.

L5 ANSWER 9 OF 44 USPATFULL on STN
ACCESSION NUMBER: 2017:306785 USPATFULL
TITLE: METHODS AND SYSTEMS FOR TOXIN DELIVERY TO THE NASAL CAVITY
INVENTOR(S): Deem, Mark E., Mountain View, CA, UNITED STATES
Gifford, Hanson, Woodside, CA, UNITED STATES
APPLICANT(S): The Foundry, LLC, Menlo Park, CA, UNITED STATES

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 20170266422	A1	20170921
	US 10052465	B2	20180821
APPLICATION INFO.:	US 2017-15615344	A1	20170606 (15)

RELATED APPLN. INFO.: Continuation of Ser. No. US 2015-14841514, filed on 31 Aug 2015, Pat. No. US 9700707 Continuation of Ser. No. US 2013-14139710, filed on 23 Dec 2013, ABANDONED Continuation of Ser. No. US 2011-13328203, filed on 16 Dec 2011, Pat. No. US 8636684 Continuation of Ser. No. US 2009-636477, filed on 11 Dec 2009, Pat. No. US 8105817 Division of Ser. No. US 2007-750963, filed on 18 May 2007, Pat. No. US 7655243 Continuation-in-part of Ser. No. US 2006-459090, filed on 21 Jul 2006, Pat. No. US 7608275

NUMBER	DATE

PRIORITY INFORMATION:	US 2006-60747771	20060519 (60)
	US 2005-60702077	20050722 (60)
DOCUMENT TYPE:	Utility	
FILE SEGMENT:	APPLICATION	
NUMBER OF CLAIMS:	35	
EXEMPLARY CLAIM:	1	
NUMBER OF DRAWINGS:	24 Drawing Page(s)	
LINE COUNT:	1394	

CAS INDEXING IS AVAILABLE FOR THIS PATENT. Full-text

SUMM . . . 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.

SUMM 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. . .

DETD . . . 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.. . . 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.

L5 ANSWER 10 OF 44 USPATFULL on STN

ACCESSION NUMBER:	2017:190421 USPATFULL		
TITLE:	DEVICES, SYSTEMS AND METHODS FOR DIAGNOSING AND TREATING SINUSITIS AND OTHER DISORDERS OF THE EARS, NOSE AND/OR THROAT		
INVENTOR(S):	Chang, John Y., Los Altos, CA, UNITED STATES Makower, Joshua, Los Altos, CA, UNITED STATES		
APPLICANT(S):	Acclarent, Inc., Irvine, CA, UNITED STATES		
	NUMBER	KIND	DATE
PATENT INFORMATION:	US 20170164965	A1	20170615
	US 10492810	B2	20191203
APPLICATION INFO.:	US 2017-15443319	A1	20170227 (15)
RELATED APPLN. INFO.:	Continuation of Ser. No. US 2016-15363002, filed on 29 Nov 2016, PENDING Continuation of Ser. No. US 2013-13867972, filed on 22 Apr 2013, PENDING Continuation of Ser. No. US 2009-649050, filed on 29 Dec 2009, Pat. No. US 8425457 Continuation of Ser. No. US 2004-829917, filed on 21 Apr 2004, Pat. No. US 7654997		
DOCUMENT TYPE:	Utility		
FILE SEGMENT:	APPLICATION		
NUMBER OF CLAIMS:	21		
EXEMPLARY CLAIM:	1-20		
NUMBER OF DRAWINGS:	41 Drawing Page(s)		
LINE COUNT:	2867		

CAS INDEXING IS AVAILABLE FOR THIS PATENT. Full-text

AB . . . nose and throat are diagnosed and/or treated using minimally invasive approaches and, in many cases, flexible catheters as opposed to instruments having rigid shafts. Various diagnostic procedures and devices are used to perform imaging studies, mucus flow studies, air/gas flow studies, anatomic dimension studies, endoscopic studies and transillumination studies. Access and occluder devices may be used to establish fluid tight seals in the anterior or posterior nasal cavities/nasopharynx and to facilitate insertion of working devices (e.g., scopes, guidewires, catheters, tissue cutting or remodeling devices, electrosurgical devices, energy emitting devices, devices for injecting diagnostic or therapeutic agents, devices for implanting devices such as stents, substance eluting devices, substance delivery implants, etc.

SUMM nasal congestion or postnasal drainage

DETD . . . 9A-9C show a procedure for installation of a cochlear implant in accordance with the present invention. In this procedure, the nasopharyngeal opening into the Eustachian tube ET is located and a guidewire is initially advanced into the Eustachian tube ET. A. . . catheter 900 is in or near the tympanic cavity TC of the middle ear. Thereafter, if deemed necessary, a forceps device 790 and/or other devices are advanced through the catheter 900 and used to remove the small bones of the sear (i.e., the malleus, incus. . . This optional removal of the bones of the middle ear may be done under endoscopic visualization using an endoscope equipped device such as the endoscope equipped forceps device 790 shown in FIG. 5T and described above. As shown in FIG. 9B, a cochlear guide catheter 904 having a. . . tympanic membrane. In other applications, the cochlear guide catheter 904 may be positioned adjacent to the cochlea and a cochleostomy device (e.g., a penetrator such as a drill, needle or cutter) may be advanced through or formed or positioned on the. . . cochleostomy through which the distal end of the guide catheter 904 is advanced into the cochlea C. Thereafter, a cochlear electrode array 906 is advanced through the cochlear guide catheter 904 and into the cochlea, as seen in FIG. 9B. One example of a commercially available cochlear electrode array is the Nucleus 24 Countour device manufactured by Cochlear Corporation.

L5 ANSWER 11 OF 44 USPATFULL on STN

ACCESSION NUMBER:	2017:82561 USPATFULL
TITLE:	DEVICES, SYSTEMS AND METHODS FOR DIAGNOSING AND TREATING SINUSITIS AND OTHER DISORDERS OF THE EARS, NOSE AND/OR THROAT
INVENTOR(S):	Chang, John Y., Los Altos, CA, UNITED STATES Makower, Joshua, Los Altos, CA, UNITED STATES
APPLICANT(S):	Acclarent, Inc., Irvine, CA, UNITED STATES

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 20170071625	A1	20170316
APPLICATION INFO.:	US 2016-15363002	A1	20161129 (15)

RELATED APPLN. INFO.:	Continuation of Ser. No. US 2013-13867972, filed on 22 Apr 2013, PENDING Continuation of Ser. No. US 2009-649050, filed on 29 Dec 2009, Pat. No. US 8425457 Continuation of Ser. No. US 2004-829917, filed on 21 Apr 2004, Pat. No. US 7654997
DOCUMENT TYPE:	Utility
FILE SEGMENT:	APPLICATION
NUMBER OF CLAIMS:	18
EXEMPLARY CLAIM:	1
NUMBER OF DRAWINGS:	41 Drawing Page(s)
LINE COUNT:	2825 Full-text

AB . . . nose and throat are diagnosed and/or treated using minimally invasive approaches and, in many cases, flexible catheters as opposed to instruments having rigid shafts. Various diagnostic procedures and devices are used to perform imaging studies, mucus flow studies, air/gas flow studies, anatomic dimension studies, endoscopic studies and transillumination studies. Access and occluder devices may be used to establish fluid tight seals in the anterior or posterior nasal cavities/nasopharynx and to facilitate insertion of working devices (e.g., scopes, guidewires, catheters, tissue cutting or remodeling devices, electrosurgical devices, energy emitting devices, devices for injecting diagnostic or therapeutic agents, devices for implanting devices such as stents, substance eluting devices, substance delivery implants, etc.

SUMM Patients who suffer from sinusitis typically experience at least some of the following symptoms:

headaches or facial pain

nasal congestion or postnasal drainage
difficulty breathing through one or both nostrils
bad breath
pain in the upper teeth

DETD . . . 9A-9C show a procedure for installation of a cochlear implant in accordance with the present invention. In this procedure, the

nasopharyngeal opening into the Eustachian tube ET is located and a guidewire is initially advanced into the Eustachian tube ET. A. . . catheter 900 is in or near the tympanic cavity TC of the middle ear. Thereafter, if deemed necessary, a forceps device 790 and/or other devices are advanced through the catheter 900 and used to remove the small bones of the sear (i.e., the malleus, incus. . . This optional removal of the bones of the middle ear may be done under endoscopic visualization using an endoscope equipped device such as the endoscope equipped forceps device 790 shown in FIG. 5T and described above. As shown in FIG. 9B, a cochlear guide catheter 904 having a. . . tympanic membrane. In other applications, the cochlear guide catheter 904 may be positioned adjacent to the cochlea and a cochleostomy device (e.g., a penetrator such as a drill, needle or cutter) may be advanced through or formed or positioned on the. . . cochleostomy through which the distal end of the guide catheter 904 is advanced into the cochlea C. Thereafter, a cochlear electrode array 906 is advanced through the cochlear guide catheter 904 and into the cochlea, as seen in FIG. 9B. One example of a commercially available cochlear electrode array is the Nucleus 24 Countour device manufactured by Cochlear Corporation.

L5 ANSWER 12 OF 44 USPATFULL on STN
ACCESSION NUMBER: 2016:377141 USPATFULL
TITLE: DEVICES FOR THERAPEUTIC NASAL NEUROMODULATION AND ASSOCIATED METHODS AND SYSTEMS
INVENTOR(S): Townley, David, County Clare, IRELAND
Shields, Brian, Galway, IRELAND
Keogh, Ivan, Galway, IRELAND
Qi Zhan, Michele, Antioch, CA, UNITED STATES
Farrell, Conor, County Mayo, IRELAND
APPLICANT(S): National University of Ireland, Galway, Galway, IRELAND

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 20160331459	A1	20161117
APPLICATION INFO.:	US 2016-15153217	A1	20160512 (15)

	NUMBER	DATE
PRIORITY INFORMATION:	US 2015-62160289	20150512 (62)

DOCUMENT TYPE: Utility
FILE SEGMENT: APPLICATION
NUMBER OF CLAIMS: 103
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 26 Drawing Page(s)
LINE COUNT: 2859 Full-text
SUMM . . . group of conditions, including allergic rhinitis, non-allergic rhinitis, chronic rhinitis, chronic sinusitis, and medical resistant rhinitis. Symptoms of rhinosinusitis include nasal blockage, obstruction, congestion, nasal discharge (e.g., rhinorrhea and/or posterior nasal drip), facial pain, facial pressure, and/or reduction or loss of smell. Allergic rhinitis can include further symptoms, such as sneezing,. . .
CLM What is claimed is:
. . . human patient, the method comprising: intraluminally advancing a therapeutic assembly at a distal portion of a shaft of a therapeutic device to a target site within the nasal region, wherein the target site is proximate to parasympathetic nerves spanning across at least one of an accessory foramen or microforamina proximate to the sphenopalatine foramen; and applying energy, with the therapeutic assembly, to the target site to therapeutically modulate autonomic activity within at least one of a nasal cavity, a nasopharynx, or paranasal cavities.

CLM What is claimed is:
. . . nasal region, the method comprising: intraluminally advancing a therapeutic assembly at a distal portion of a shaft of a therapeutic device to a target site within a nasal region, wherein the target site is proximate to parasympathetic nerves proximate to the sphenopalatine foramen; detecting locations of the parasympathetic nerves at the target site; and applying energy, with the therapeutic assembly, to the target site based on the detected locations of the parasympathetic

nerves, wherein applying energy therapeutically modulates autonomic activity within at least one of a nasal cavity, a nasopharynx, or paranasal cavities.

L5 ANSWER 13 OF 44 USPATFULL on STN
ACCESSION NUMBER: 2016:9960 USPATFULL
TITLE: DEVICES, SYSTEMS AND METHODS FOR DIAGNOSING AND TREATING SINUSITIS AND OTHER DISORDERS OF THE EARS, NOSE, AND/OR THROAT
INVENTOR(S): Makower, Joshua, Los Altos, CA, UNITED STATES
Chang, John Y., Los Altos, CA, UNITED STATES
Goldfarb, Eric, Belmont, CA, UNITED STATES
Morriss, John H., Emerald Hills, CA, UNITED STATES
Facteau, William M., Atherton, CA, UNITED STATES
APPLICANT(S): Acclarent, Inc., Menlo Park, CA, UNITED STATES

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 20160008017	A1	20160114
APPLICATION INFO.:	US 2015-14793954	A1	20150708 (14)

RELATED APPLN. INFO.: Continuation of Ser. No. US 2009-355492, filed on 16 Jan 2009, Pat. No. US 9101384 Continuation-in-part of Ser. No. US 2004-829917, filed on 21 Apr 2004, Pat. No. US 7654997 Continuation-in-part of Ser. No. US 2006-522497, filed on 15 Sep 2006, Pat. No. US 7559925
DOCUMENT TYPE: Utility
FILE SEGMENT: APPLICATION
NUMBER OF CLAIMS: 1
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 51 Drawing Page(s)
LINE COUNT: 4386 Full-text
SUMM Patients who suffer from sinusitis typically experience at least some of the following symptoms:

headaches or facial pain

nasal congestion or post-nasal drainage
difficulty breathing through one or both nostrils
bad breath
pain in the upper teeth
SUMM . . . United States. Patients who suffer from sinusitis typically experience at least some of the following symptoms: headaches or facial pain; nasal congestion or post-nasal drainage; difficulty breathing through one or both nostrils; bad breath; and/or pain in the upper teeth.
DETD . . . 9A-9C show a procedure for installation of a cochlear implant in accordance with the present invention. In this procedure, the nasopharyngeal opening into the Eustachian tube ET is located and a guidewire is initially advanced into the Eustachian tube ET. A. . . catheter 900 is in or near the tympanic cavity TC of the middle ear. Thereafter, if deemed necessary, a forceps device 790 and/or other devices are advanced through the catheter 900 and used to remove the small bones of the sear (i.e., the malleus, incur. . . This optional removal of the bones of the middle ear may be done under endoscopic visualization using an endoscope equipped device such as the endoscope equipped forceps device 790 shown in FIG. 5T and described above. As shown in FIG. 9B, a cochlear guide catheter 904 having a. . . tympanic membrane. In other applications, the cochlear guide catheter 904 may be positioned adjacent to the cochlea and a cochleostomy device (e.g., a penetrator such as a drill, needle or cutter) may be advanced through or formed or positioned on the. . . cochleostomy through which the distal end of the guide catheter 904 is advanced into the cochlea C. Thereafter, a cochlear electrode array 906 is advanced through the cochlear guide catheter 904 and into the cochlea, as seen in FIG. 9B. One example of a commercially available cochlear electrode array is the Nucleus 24 Contour device manufactured by Cochlear Corporation.

L5 ANSWER 14 OF 44 USPATFULL on STN

ACCESSION NUMBER: 2015:413714 USPATFULL
TITLE: METHODS AND SYSTEMS FOR TOXIN DELIVERY TO THE NASAL CAVITY
INVENTOR(S): Deem, Mark E., Mountain View, CA, UNITED STATES
Gifford, Hanson, Woodside, CA, UNITED STATES
APPLICANT(S): The Foundry LLC, Menlo Park, CA, UNITED STATES

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 20150367115	A1	20151224
	US 20170021148	A9	20170126
	US 9700707	B2	20170711
APPLICATION INFO.:	US 2015-14841514	A1	20150831 (14)

RELATED APPLN. INFO.: Continuation of Ser. No. US 2013-14139710, filed on 23 Dec 2013, ABANDONED Continuation of Ser. No. US 2011-13328203, filed on 16 Dec 2011, Pat. No. US 8636684 Continuation of Ser. No. US 2009-636477, filed on 11 Dec 2009, Pat. No. US 8105817 Division of Ser. No. US 2007-750963, filed on 18 May 2007, Pat. No. US 7655243 Continuation-in-part of Ser. No. US 2006-459090, filed on 21 Jul 2006, Pat. No. US 7608275

	NUMBER	DATE
PRIORITY INFORMATION:	US 2005-60702077	20050722 (60)

DOCUMENT TYPE: Utility
FILE SEGMENT: APPLICATION
NUMBER OF CLAIMS: 24
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 24 Drawing Page(s)
LINE COUNT: 1360
CAS INDEXING IS AVAILABLE FOR THIS PATENT. Full-text
SUMM . . . 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.
SUMM 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. . .
DETD . . . 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.. . . 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.

L5 ANSWER 15 OF 44 USPATFULL on STN
ACCESSION NUMBER: 2015:235947 USPATFULL
TITLE: DEVICES, SYSTEMS AND METHODS USEABLE FOR TREATING SINUSITIS
INVENTOR(S): Chang, John Y., Los Altos, CA, UNITED STATES
Makower, Joshua, Los Altos, CA, UNITED STATES
Vrany, Julia D., Los Altos, CA, UNITED STATES
Morriss, John H., San Francisco, CA, UNITED STATES
Muni, Ketan P., San Jose, CA, UNITED STATES
Kim, Isaac J., San Jose, CA, UNITED STATES
Ha, Hung V., San Jose, CA, UNITED STATES
Facteau, William M., Atherton, CA, UNITED STATES
Walke, Amrish Jayprakash, Milpitas, CA, UNITED STATES
APPLICANT(S): Acclarent, Inc., Menlo Park, CA, UNITED STATES

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 20150209055	A1	20150730
	US 9370649	B2	20160621
APPLICATION INFO.:	US 2015-14614799	A1	20150205 (14)

RELATED APPLN. INFO.: Continuation of Ser. No. US 2010-729109, filed on 22 Mar 2010, Pat. No. US 9055965 Continuation of Ser. No. US 2007-928160, filed on 30 Oct 2007, Pat. No. US 7771409 Continuation of Ser. No. US 2005-150847, filed on 10 Jun 2005, Pat. No. US 7803150 Continuation-in-part of Ser. No. US 2004-944270, filed on 17 Sep 2004, ABANDONED Continuation-in-part of Ser. No. US 2004-829917, filed on 21 Apr 2004, Pat. No. US 7654997
DOCUMENT TYPE: Utility
FILE SEGMENT: APPLICATION
NUMBER OF CLAIMS: 21
EXEMPLARY CLAIM: 1-5
NUMBER OF DRAWINGS: 41 Drawing Page(s)
LINE COUNT: 2522 Full-text
SUMM Patients who suffer from sinusitis typically experience at least some of the following symptoms:

headaches or facial pain

nasal congestion or post-nasal drainage
difficulty breathing through one or both nostrils
bad breath
pain in the upper teeth
DETD . . . conductive coatings, radiopaque coatings, echogenic coatings, thrombogenicity reducing coatings and coatings that release drugs. In FIG. 2B, a second introduction device comprising a guidewire 202 is introduced through the first introduction device (i.e., the guide catheter 200) so that the guidewire 202 enters the sphenoid sinus SS through the ostium SSO. Guidewire 202 may be constructed and coated as is common in the art of cardiology. In FIG. 2C, a working device 204 for example a balloon catheter is introduced over guidewire 202 into the sphenoid sinus SS. Thereafter, in FIG. 2D, the working device 204 is used to perform a diagnostic or therapeutic procedure. In this particular example, the procedure is dilation of the. . . or modify any sinus ostium or other man-made or naturally occurring anatomical opening or passageway within the nose, paranasal sinuses, nasopharynx or adjacent areas. After the completion of the procedure, guide catheter 200, guidewire 202 and working device 204 are withdrawn and removed. As will be appreciated by those of skill in the art, in this or any. . . or imaging modalities including but not limited to fluoroscopic, X-ray radiographic, ultrasonic, radiofrequency localization, electromagnetic, magnetic, robotic and other radiative energy based modalities. In this regard, some of the figures show optional scopes SC is dotted lines. It is to be. . . types of rigid or flexible endoscopes and such optional scopes SC may be separate from or incorporated into the working devices and/or introduction devices of the present invention.

L5 ANSWER 16 OF 44 USPATFULL on STN
ACCESSION NUMBER: 2015:206061 USPATFULL
TITLE: APPARATUS AND METHODS FOR DILATING AND MODIFYING OSTIA OF PARANASAL SINUSES AND OTHER INTRANASAL OR PARANASAL STRUCTURES
INVENTOR(S): Chang, John Y., Los Altos, CA, UNITED STATES
Makower, Joshua, Los Altos, CA, UNITED STATES
Vrany, Julia D., Los Altos, CA, UNITED STATES
Walke, Amrish Jayprakash, Milpitas, CA, UNITED STATES
APPLICANT(S): Acclarent, Inc., Menlo Park, CA, UNITED STATES

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 20150182735	A1	20150702
	US 9713700	B2	20170725
APPLICATION INFO.:	US 2014-14566845	A1	20141211 (14)

RELATED APPLN. INFO.: Continuation of Ser. No. US 2010-768963, filed on 28 Apr 2010, Pat. No. US 8945088 Continuation of Ser. No. US 2007-928346, filed on 30 Oct 2007, Pat. No. US 8172828 Continuation of Ser. No. US 2004-944270, filed on 17 Sep 2004, ABANDONED Continuation-in-part of Ser. No. US 2004-829917, filed on 21 Apr 2004, Pat. No. US

7654997
DOCUMENT TYPE: Utility
FILE SEGMENT: APPLICATION
NUMBER OF CLAIMS: 21
EXEMPLARY CLAIM: 1-20
NUMBER OF DRAWINGS: 35 Drawing Page(s)
LINE COUNT: 1569
CAS INDEXING IS AVAILABLE FOR THIS PATENT. Full-text
SUMM Patients who suffer from sinusitis typically experience at least some of the following symptoms:

headaches or facial pain

nasal congestion or post-nasal drainage
difficulty breathing through one or both nostrils
bad breath
pain in the upper teeth
DETD . . . conductive coatings, radiopaque coatings, echogenic coatings, thrombogenicity reducing coatings and coatings that release drugs. In FIG. 2B, a second introduction device comprising a guidewire 202 is introduced through the first introduction device (i.e., the guide catheter 200) so that the guidewire 202 enters the sphenoid sinus SS through the ostium SSO. Guidewire 202 may be constructed and coated as is common in the art of cardiology. In FIG. 2C, a working device 204 for example a balloon catheter is introduced over guidewire 202 into the sphenoid sinus SS. Thereafter, in FIG. 2D, the working device 204 is used to perform a diagnostic or therapeutic procedure. In this particular example, the procedure is dilation of the. . . or modify any sinus ostium or other man-made or naturally occurring anatomical opening or passageway within the nose, paranasal sinuses, nasopharynx or adjacent areas. After the completion of the procedure, guide catheter 200, guidewire 202 and working device 204 are withdrawn and removed. As will be appreciated by those of skill in the art, in this or any. . . or imaging modalities including but not limited to fluoroscopic, X-ray radiographic, ultrasonic, radiofrequency localization, electromagnetic, magnetic, robotic and other radiative energy based modalities. In this regard, some of the figures show optional scopes SC is dotted lines. It is to be. . . types of rigid or flexible endoscopes and such optional scopes SC may be separate from or incorporated into the working devices and/or introduction devices of the present invention.

L5 ANSWER 17 OF 44 USPATFULL on STN
ACCESSION NUMBER: 2014:362360 USPATFULL
TITLE: DEVICES, SYSTEMS AND METHODS USEABLE FOR TREATING SINUSITIS
INVENTOR(S): Chang, John Y., Los Altos, CA, UNITED STATES
Makower, Joshua, Los Altos, CA, UNITED STATES
Vrany, Julia D., Los Altos, CA, UNITED STATES
Morriss, John H., San Francisco, CA, UNITED STATES
Muni, Ketan P., San Jose, CA, UNITED STATES
Kim, Isaac J., San Jose, CA, UNITED STATES
Ha, Hung V., San Jose, CA, UNITED STATES
Facteau, William M., Atherton, CA, UNITED STATES
Walke, Amrish Jayprakash, Milpitas, CA, UNITED STATES
PATENT ASSIGNEE(S): Acclarent, Inc., Menlo Park, CA, UNITED STATES (U.S. corporation)

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 20140324093	A1	20141030
	US 9220879	B2	20151229
APPLICATION INFO.:	US 2014-14266025	A1	20140430 (14)

RELATED APPLN. INFO.: Continuation of Ser. No. US 2009-543445, filed on 18 Aug 2009, Pat. No. US 8764726 Division of Ser. No. US 2005-150847, filed on 10 Jun 2005, Pat. No. US 7803150 Continuation-in-part of Ser. No. US 2004-944270, filed on 17 Sep 2004, ABANDONED Continuation-in-part of Ser. No. US 2004-829917, filed on 21 Apr 2004, Pat. No. US 7654997
DOCUMENT TYPE: Utility

FILE SEGMENT: APPLICATION
NUMBER OF CLAIMS: 21
EXEMPLARY CLAIM: 1-23
NUMBER OF DRAWINGS: 41 Drawing Page(s)
LINE COUNT: 2494 Full-text
SUMM Patients who suffer from sinusitis typically experience at least some of the following symptoms:

headaches or facial pain

nasal congestion or post-nasal drainage
difficulty breathing through one or both nostrils
bad breath
pain in the upper teeth
DETD . . . conductive coatings, radiopaque coatings, echogenic coatings, thrombogenicity reducing coatings and coatings that release drugs. In FIG. 2B, a second introduction device comprising a guidewire 202 is introduced through the first introduction device (i.e., the guide catheter 200) so that the guidewire 202 enters the sphenoid sinus SS through the ostium SSO. Guidewire 202 may be constructed and coated as is common in the art of cardiology. In FIG. 2C, a working device 204 for example a balloon catheter is introduced over guidewire 202 into the sphenoid sinus SS. Thereafter, in FIG. 2D, the working device 204 is used to perform a diagnostic or therapeutic procedure. In this particular example, the procedure is dilation of the. . . or modify any sinus ostium or other man-made or naturally occurring anatomical opening or passageway within the nose, paranasal sinuses, nasopharynx or adjacent areas. After the completion of the procedure, guide catheter 200, guidewire 202 and working device 204 are withdrawn and removed. As will be appreciated by those of skill in the art, in this or any. . . or imaging modalities including but not limited to fluoroscopic, X-ray radiographic, ultrasonic, radiofrequency localization, electromagnetic, magnetic, robotic and other radiative energy based modalities. In this regard, some of the figures show optional scopes SC is dotted lines. It is to be. . . types of rigid or flexible endoscopes and such optional scopes SC may be separate from or incorporated into the working devices and/or introduction devices of the present invention.

L5 ANSWER 18 OF 44 USPATFULL on STN
ACCESSION NUMBER: 2014:331427 USPATFULL
TITLE: DEVICES, SYSTEMS AND METHODS USEABLE FOR TREATING SINUSITIS
INVENTOR(S): Chang, John Y., Los Altos, CA, UNITED STATES
Makower, Joshua, Los Altos, CA, UNITED STATES
Vrany, Julia D., Los Altos, CA, UNITED STATES
Morriss, John H., San Francisco, CA, UNITED STATES
Muni, Ketan P., San Jose, CA, UNITED STATES
Kim, Isaac J., San Jose, CA, UNITED STATES
Ha, Hung V., San Jose, CA, UNITED STATES
Facteau, William M., Atherton, CA, UNITED STATES
Walke, Amrish Jayprakash, Milpitas, CA, UNITED STATES
PATENT ASSIGNEE(S): Acclarent, Inc., Menlo Park, CA, UNITED STATES (U.S. corporation)

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 20140296898	A1	20141002
APPLICATION INFO.:	US 2014-14221550	A1	20140321 (14)

RELATED APPLN. INFO.: Continuation of Ser. No. US 2007-928097, filed on 30 Oct 2007, Pat. No. US 8715169 Continuation of Ser. No. US 2005-150847, filed on 10 Jun 2005, Pat. No. US 7803150 Continuation-in-part of Ser. No. US 2004-944270, filed on 17 Sep 2004, ABANDONED Continuation-in-part of Ser. No. US 2004-829917, filed on 21 Apr 2004, Pat. No. US 7654997
DOCUMENT TYPE: Utility
FILE SEGMENT: APPLICATION
NUMBER OF CLAIMS: 19
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 41 Drawing Page(s)

LINE COUNT: 2483 Full-text
SUMM Patients who suffer from sinusitis typically experience at least some of the following symptoms:

headaches or facial pain

nasal congestion or post-nasal drainage
difficulty breathing through one or both nostrils
bad breath
pain in the upper teeth Thus, one of the ways to treat sinusitis. . .
DETD Thereafter, in FIG. 2D, the working device 204 is used to perform a diagnostic or therapeutic procedure. In this particular example, the procedure is dilation of the. . . or modify any sinus ostium or other man-made or naturally occurring anatomical opening or passageway within the nose, paranasal sinuses, nasopharynx or adjacent areas. After the completion of the procedure, guide catheter 200, guidewire 202 and working device 204 are withdrawn and removed. As will be appreciated by those of skill in the art, in this or any. . . or imaging modalities including but not limited to fluoroscopic, X-ray radiographic, ultrasonic, radiofrequency localization, electromagnetic, magnetic, robotic and other radiative energy based modalities. In this regard, some of the figures show optional scopes SC is dotted lines. It is to be. . . types of rigid or flexible endoscopes and such optional scopes SC may be separate from or incorporated into the working devices and/or introduction devices of the present invention.

L5 ANSWER 19 OF 44 USPATFULL on STN

ACCESSION NUMBER:	2014:127127 USPATFULL		
TITLE:	METHODS AND SYSTEMS FOR TOXIN DELIVERY TO THE NASAL CAVITY		
INVENTOR(S):	Deem, Mark E., Mountain View, CA, UNITED STATES Gifford, Hanson, Woodside, CA, UNITED STATES		
PATENT ASSIGNEE(S):	The Foundry, LLC, Menlo Park, CA, UNITED STATES (U.S. corporation)		
	NUMBER	KIND	DATE
PATENT INFORMATION:	US 20140114233	A1	20140424
APPLICATION INFO.:	US 2013-14139710	A1	20131223 (14)
RELATED APPLN. INFO.:	Continuation of Ser. No. US 2011-13328203, filed on 16 Dec 2011, Pat. No. US 8636684 Continuation of Ser. No. US 2009-636477, filed on 11 Dec 2009, Pat. No. US 8105817 Division of Ser. No. US 2007-750963, filed on 18 May 2007, Pat. No. US 7655243 Continuation-in-part of Ser. No. US 2006-459090, filed on 21 Jul 2006, Pat. No. US 7608275		
	NUMBER		DATE
PRIORITY INFORMATION:	US 2005-60702077		20050722 (60)
	US 2006-60747771		20060519 (60)
DOCUMENT TYPE:	Utility		
FILE SEGMENT:	APPLICATION		
NUMBER OF CLAIMS:	31		
EXEMPLARY CLAIM:	1		
NUMBER OF DRAWINGS:	24 Drawing Page(s)		
LINE COUNT:	1374		

CAS INDEXING IS AVAILABLE FOR THIS PATENT. Full-text
SUMM . . . 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.
SUMM 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. . .
DETD . . . 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.. . . 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.

L5 ANSWER 20 OF 44 USPATFULL on STN
ACCESSION NUMBER: 2013:365863 USPATFULL
TITLE: Apparatus and Methods for Dilating and Modifying Ostia of Paranasal Sinuses and Other Intranasel or Paranasal Structures
INVENTOR(S): Chang, John Y., Mountain View, CA, UNITED STATES
Makower, Joshua, Los Altos, CA, UNITED STATES
Vrany, Julia D., Sunnyvale, CA, UNITED STATES
Walke, Amrish Jayprakash, Mountain View, CA, UNITED STATES
PATENT ASSIGNEE(S): ACCLARENT, INC., Menlo Park, CA, UNITED STATES (U.S. corporation)

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 20130325052	A1	20131205
	US 8777926	B2	20140715
APPLICATION INFO.:	US 2013-13840430	A1	20130315 (13)

RELATED APPLN. INFO.: Continuation of Ser. No. US 2010-768963, filed on 28 Apr 2010, PENDING Continuation of Ser. No. US 2004-944270, filed on 17 Sep 2004, ABANDONED Continuation-in-part of Ser. No. US 2004-829917, filed on 21 Apr 2004, Pat. No. US 7654997
DOCUMENT TYPE: Utility
FILE SEGMENT: APPLICATION
NUMBER OF CLAIMS: 20
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 35 Drawing Page(s)
LINE COUNT: 1540
CAS INDEXING IS AVAILABLE FOR THIS PATENT. Full-text
SUMM . . . United States. Patients who suffer from sinusitis typically experience at least some of the following symptoms:

headaches or facial pain

nasal congestion or post-nasal drainage
difficulty breathing through one or both nostrils
bad breath
pain in the upper teeth
DETD . . . conductive coatings, radiopaque coatings, echogenic coatings, thrombogenicity reducing coatings and coatings that release drugs. In FIG. 2B, a second introduction device comprising a guidewire 202 is introduced through the first introduction device (i.e., the guide catheter 200) so that the guidewire 202 enters the sphenoid sinus SS through the ostium SSO. Guidewire 202 may be constructed and coated as is common in the art of cardiology. In FIG. 2C, a working device 204 for example a balloon catheter is introduced over guidewire 202 into the sphenoid sinus SS. Thereafter, in FIG. 2D, the working device 204 is used to perform a diagnostic or therapeutic procedure. In this particular example, the procedure is dilation of the. . . or modify any sinus ostium or other man-made or naturally occurring anatomical opening or passageway within the nose, paranasal sinuses, nasopharynx or adjacent areas. After the completion of the procedure, guide catheter 200, guidewire 202 and working device 204 are withdrawn and removed. As will be appreciated by those of skill in the art, in this or any. . . or imaging modalities including but not limited to fluoroscopic, X-ray radiographic, ultrasonic, radiofrequency localization, electromagnetic, magnetic, robotic and other radiative energy based modalities. In this regard, some of the figures show optional scopes SC is dotted lines. It is to be. . . types of rigid or flexible endoscopes and such optional scopes SC may be separate from or incorporated into the working devices and/or introduction devices of the present invention.

L5 ANSWER 21 OF 44 USPATFULL on STN
ACCESSION NUMBER: 2013:261028 USPATFULL
TITLE: DEVICES, SYSTEMS AND METHODS FOR DIAGNOSING AND TREATING SINUSITIS ANDOTHER DISORDERS OF THE EARS, NOSE AND/OR THROAT
INVENTOR(S): John, Chang Y., Mountain View, CA, UNITED STATES
Joshua, Makower, Los Altos, CA, UNITED STATES
PATENT ASSIGNEE(S): ACCLARENT, INC., Menlo Park, CA, UNITED STATES (U.S. corporation)

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 20130231529	A1	20130905
APPLICATION INFO.:	US 2013-13867972	A1	20130422 (13)

RELATED APPLN. INFO.: Continuation of Ser. No. US 2009-649050, filed on 29 Dec 2009, Pat. No. US 8425457 Continuation of Ser. No. US 2004-829917, filed on 21 Apr 2004, Pat. No. US 7654997
DOCUMENT TYPE: Utility
FILE SEGMENT: APPLICATION
NUMBER OF CLAIMS: 18
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 41 Drawing Page(s)
LINE COUNT: 2815 Full-text
AB . . . nose and throat are diagnosed and/or treated using minimally invasive approaches and, in many cases, flexible catheters as opposed to instruments having rigid shafts. Various diagnostic procedures and devices are used to perform imaging studies, mucus flow studies, air/gas flow studies, anatomic dimension studies, endoscopic studies and transillumination studies. Access and occluder devices may be used to establish fluid tight seals in the anterior or posterior nasal cavities/nasopharynx and to facilitate insertion of working devices (e.g., scopes, guidewires, catheters, tissue cutting or remodeling devices, electrosurgical devices, energy emitting devices, devices for injecting diagnostic or therapeutic agents, devices for implanting devices such as stents, substance eluting devices, substance delivery implants, etc.
SUMM nasal congestion or post-nasal drainage
DETD . . . 9A-9C show a procedure for installation of a cochlear implant in accordance with the present invention. In this procedure, the nasopharyngeal opening into the Eustachian tube ET is located and a guidewire is initially advanced into the Eustachian tube ET. A. . . catheter 900 is in or near the tympanic cavity TC of the middle ear. Thereafter, if deemed necessary, a forceps device 790 and/or other devices are advanced through the catheter 900 and used to remove the small bones of the sear (i.e., the malleus, incus. . . This optional removal of the bones of the middle ear may be done under endoscopic visualization using an endoscope equipped device such as the endoscope equipped forceps device 790 shown in FIG. 5T and described above. As shown in FIG. 9B, a cochlear guide catheter 904 having a. . . tympanic membrane. In other applications, the cochlear guide catheter 904 may be positioned adjacent to the cochlea and a cochleostomy device (e.g., a penetrator such as a drill, needle or cutter) may be advanced through or formed or positioned on the. . . cochleostomy through which the distal end of the guide catheter 904 is advanced into the cochlea C. Thereafter, a cochlear electrode array 906 is advanced through the cochlear guide catheter 904 and into the cochlea, as seen in FIG. 9B. One example of a commercially available cochlear electrode array is the Nucleus 24 Countour device manufactured by Cochlear Corporation.

L5 ANSWER 22 OF 44 USPATFULL on STN
ACCESSION NUMBER: 2012:275311 USPATFULL
TITLE: Devices, Systems and Methods For Diagnosing and Treating Sinusitis and Other Disorders of the Ears, Nose and/or Throat
INVENTOR(S): Makower, Joshua, Los Altos, CA, UNITED STATES
Chang, John Y., Mountain View, CA, UNITED STATES
PATENT ASSIGNEE(S): ACCLARENT, INC., Menlo Park, CA, UNITED STATES (U.S. corporation)

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 20120245419	A1	20120927
	US 8905922	B2	20141209
APPLICATION INFO.:	US 2012-13429857	A1	20120326 (13)

RELATED APPLN. INFO.: Continuation of Ser. No. US 2008-42221, filed on 4 Mar 2008, Pat. No. US 8142422 Continuation of Ser. No. US 2004-829917, filed on 21 Apr 2004, Pat. No. US 7654997
DOCUMENT TYPE: Utility
FILE SEGMENT: APPLICATION
NUMBER OF CLAIMS: 10
EXEMPLARY CLAIM: 1-22
NUMBER OF DRAWINGS: 41 Drawing Page(s)
LINE COUNT: 2787
CAS INDEXING IS AVAILABLE FOR THIS PATENT. Full-text
AB . . . nose and throat are diagnosed and/or treated using minimally invasive approaches and, in many cases, flexible catheters as opposed to instruments having rigid shafts. Various diagnostic procedures and devices are used to perform imaging studies, mucus flow studies, air/gas flow studies, anatomic dimension studies, endoscopic studies and transillumination studies. Access and occluder devices may be used to establish fluid tight seals in the anterior or posterior nasal cavities/nasopharynx and to facilitate insertion of working devices (e.g., scopes, guidewires, catheters, tissue cutting or remodeling devices, electrosurgical devices, energy emitting devices, devices for injecting diagnostic or therapeutic agents, devices for implanting devices such as stents, substance eluting devices, substance delivery implants, etc.
SUMM Patients who suffer from sinusitis typically experience at least some of the following symptoms:

headaches or facial pain

nasal congestion or post-nasal drainage
difficulty breathing through one or both nostrils
bad breath
pain in the upper teeth
DETD . . . 9A-9C show a procedure for installation of a cochlear implant in accordance with the present invention. In this procedure, the nasopharyngeal opening into the Eustachian tube ET is located and a guidewire is initially advanced into the Eustachian tube ET. A. . . catheter 900 is in or near the tympanic cavity TC of the middle ear. Thereafter, if deemed necessary, a forceps device 790 and/or other devices are advanced through the catheter 900 and used to remove the small bones of the sear (i.e., the malleus, incus. . . This optional removal of the bones of the middle ear may be done under endoscopic visualization using an endoscope equipped device such as the endoscope equipped forceps device 790 shown in FIG. 5T and described above. As shown in FIG. 9B, a cochlear guide catheter 904 having a. . . tympanic membrane. In other applications, the cochlear guide catheter 904 may be positioned adjacent to the cochlea and a cochleostomy device (e.g., a penetrator such as a drill, needle or cutter) may be advanced through or formed or positioned on the. . . cochleostomy through which the distal end of the guide catheter 904 is advanced into the cochlea C. Thereafter, a cochlear electrode array 906 is advanced through the cochlear guide catheter 904 and into the cochlea, as seen in FIG. 9B. One example of a commercially available cochlear electrode array is the Nucleus 24 Countour device manufactured by Cochlear Corporation.

L5 ANSWER 23 OF 44 USPATFULL on STN
ACCESSION NUMBER: 2012:207121 USPATFULL
TITLE: Apparatus and Methods for Dilating and Modifying Ostia of Paranasal Sinuses and Other Intranasal or Paranasal Structures
INVENTOR(S): Chang, John Y., Mountain View, CA, UNITED STATES
Makower, Joshua, Los Altos, CA, UNITED STATES
Vrany, Julia D., Sunnyvale, CA, UNITED STATES
Walke, Amrish Jayprakash, Mountain View, CA, UNITED STATES
PATENT ASSIGNEE(S): Acclarent, Inc., Menlo Park, CA, UNITED STATES (U.S.

corporation)

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 20120184983	A1	20120719
	US 8721591	B2	20140513
APPLICATION INFO.:	US 2012-13355758	A1	20120123 (13)

RELATED APPLN. INFO.: Continuation of Ser. No. US 2007-928346, filed on 30 Oct 2007, Pat. No. US 8172828 Continuation of Ser. No. US 2004-944270, filed on 17 Sep 2004, ABANDONED Continuation-in-part of Ser. No. US 2004-829917, filed on 21 Apr 2004, Pat. No. US 7654997
DOCUMENT TYPE: Utility
FILE SEGMENT: APPLICATION
NUMBER OF CLAIMS: 20
EXEMPLARY CLAIM: 1-10
NUMBER OF DRAWINGS: 35 Drawing Page(s)
LINE COUNT: 1519 Full-text
SUMM Patients who suffer from sinusitis typically experience at least some of the following symptoms:

headaches or facial pain

nasal congestion or post-nasal drainage
difficulty breathing through one or both nostrils
bad breath
pain in the upper teeth Thus, one of the ways to treat sinusitis. . .
DETD . . . conductive coatings, radiopaque coatings, echogenic coatings, thrombogenicity reducing coatings and coatings that release drugs. In FIG. 2B, a second introduction device comprising a guidewire 202 is introduced through the first introduction device (i.e., the guide catheter 200) so that the guidewire 202 enters the sphenoid sinus SS through the ostium SSO. Guidewire 202 may be constructed and coated as is common in the art of cardiology. In FIG. 2C, a working device 204 for example a balloon catheter is introduced over guidewire 202 into the sphenoid sinus SS. Thereafter, in FIG. 2D, the working device 204 is used to perform a diagnostic or therapeutic procedure. In this particular example, the procedure is dilation of the. . . or modify any sinus ostium or other man-made or naturally occurring anatomical opening or passageway within the nose, paranasal sinuses, nasopharynx or adjacent areas. After the completion of the procedure, guide catheter 200, guidewire 202 and working device 204 are withdrawn and removed. As will be appreciated by those of skill in the art, in this or any. . . or imaging modalities including but not limited to fluoroscopic, X-ray radiographic, ultrasonic, radiofrequency localization, electromagnetic, magnetic, robotic and other radiative energy based modalities. In this regard, some of the figures show optional scopes SC is dotted lines. It is to be. . . types of rigid or flexible endoscopes and such optional scopes SC may be separate from or incorporated into the working devices and/or introduction devices of the present invention.

L5 ANSWER 24 OF 44 USPATFULL on STN
ACCESSION NUMBER: 2012:99920 USPATFULL
TITLE: METHODS AND SYSTEMS FOR TOXIN DELIVERY TO THE NASAL CAVITY
INVENTOR(S): Deem, Mark E., Mountain View, CA, UNITED STATES
Gifford, Hanson, Woodside, CA, UNITED STATES
PATENT ASSIGNEE(S): The Foundry, LLC, Menlo Park, CA, UNITED STATES (U.S. corporation)

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 20120089078	A1	20120412
	US 8636684	B2	20140128
APPLICATION INFO.:	US 2011-13328203	A1	20111216 (13)

RELATED APPLN. INFO.: Continuation of Ser. No. US 2009-636477, filed on 11 Dec 2009, Pat. No. US 8105817 Division of Ser. No. US 2007-750963, filed on 18 May 2007, Pat. No. US 7655243 Continuation-in-part of Ser. No. US 2006-459090, filed on 21 Jul 2006, Pat. No. US 7608275

	NUMBER	DATE
PRIORITY INFORMATION:	US 2005-60702077	20050722 (60)
	US 2006-60747771	20060519 (60)

DOCUMENT TYPE: Utility
FILE SEGMENT: APPLICATION
NUMBER OF CLAIMS: 68
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 24 Drawing Page(s)
LINE COUNT: 1435
CAS INDEXING IS AVAILABLE FOR THIS PATENT. Full-text

SUMM . . . 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.

SUMM 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. . .

DETD . . . 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.. . . 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.

L5 ANSWER 25 OF 44 USPATFULL on STN
ACCESSION NUMBER: 2011:302345 USPATFULL
TITLE: MODULATING FUNCTION OF THE FACIAL NERVE SYSTEM OR RELATED NEURAL STRUCTURES VIA THE EAR
INVENTOR(S): Borsody, Mark Klingler, San Francisco, CA, UNITED STATES
PATENT ASSIGNEE(S): LAKE BIOSCIENCES, LLC, San Francisco, CA, UNITED STATES (U.S. corporation)

	NUMBER	KIND	DATE	
PATENT INFORMATION:	US 20110270361	A1	20111103	
	US 9339645	B2	20160517	
APPLICATION INFO.:	US 2011-13096889	A1	20110428	(13)

	NUMBER	DATE
PRIORITY INFORMATION:	US 2010-61397462	20100614 (61)
	US 2010-61330366	20100502 (61)

DOCUMENT TYPE: Utility
FILE SEGMENT: APPLICATION
NUMBER OF CLAIMS: 64
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 26 Drawing Page(s)
LINE COUNT: 1729
CAS INDEXING IS AVAILABLE FOR THIS PATENT. Full-text

DETD While FIGS. 1-4 show the insulating guide sheath 104 and electrode 102 being inserted into the ear via the ear canal 122, these components can be also configured for insertion into. . . of the subject. Various disease processes in the ear canal or upon the tympanic membrane may impair access of medical devices through the ear canal. To overcome limited access through the ear canal 122, an apparatus capable of accessing the middle ear through the Eustachian tube 120 can be employed. The Eustachian tube 120 connects the middle ear 116 with the nasopharynx, allowing for pressure equilibration between the middle ear 116 and the external environment and for drainage from the middle ear 116 to enter the throat. The insulating guide sheath 104 and electrode 102 can be inserted into the Eustachian tube 120 without direct visualization through transnasal positioning, under direct visualization transnasally, or under direct visualization transorally.

The insulating guide sheath 104 and electrode 102 can then be advanced along the Eustachian tube 120 and into the middle ear 116. In some embodiments, the. . . ear 116 through the Eustachian tube 120. Once placed in the middle ear 116 through the Eustachian tube 120, the apparatus 100 can then be used as explained above, i.e., to apply stimulus energy to one or more components of the facial nerve system for stroke treatment, etc.

DETD . . . on one or more physiological or pathophysiological responses of the subject to the stimulus energy (e.g., taste sensation; audition; lacrimation; nasal drainage; nasal congestion; salivation; sound sensitivity; face, head, or hand movements; speech production or arrest; sensation of body movement; eye movements; cranial blood. . .

CLM What is claimed is:

. . . responses of the subject to the stimulus energy, the responses selected from the group consisting of: taste sensation; audition; lacrimation; nasal drainage; nasal congestion; salivation; sound sensitivity; face, head, or hand movements; speech production or arrest; sensation of body movement; eye movements; cranial blood. . .

CLM What is claimed is:

. . . wherein the one or more physiological or pathophysiological responses are selected from the group consisting of: taste sensation; audition; lacrimation; nasal drainage; nasal congestion; salivation; sound sensitivity; face, head, or hand movements; speech production or arrest; sensation of body movement; eye movements; cerebral or. . .

L5 ANSWER 26 OF 44 USPATFULL on STN

ACCESSION NUMBER:	2010:335684 USPATFULL
TITLE:	Apparatus and Methods for Dilating and Modifying Ostia of Paranasal Sinuses and Other Intranasal or Paranasal Structures
INVENTOR(S):	Chang, John Y., Mountain View, CA, UNITED STATES Makower, Joshua, Los Altos, CA, UNITED STATES Vrany, Julia D., Sunnyvale, CA, UNITED STATES Walke, Amrish Jayprakash, Mountain View, CA, UNITED STATES
PATENT ASSIGNEE(S):	ACCLARENT, INC., Menlo Park, CA, UNITED STATES (U.S. corporation)

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 20100298862	A1	20101125
	US 8945088	B2	20150203
APPLICATION INFO.:	US 2010-768963	A1	20100428 (12)

RELATED APPLN. INFO.:	Continuation of Ser. No. US 2007-928346, filed on 30 Oct 2007, PENDING Continuation of Ser. No. US 2004-944270, filed on 17 Sep 2004, ABANDONED Continuation-in-part of Ser. No. US 2004-829917, filed on 21 Apr 2004, Pat. No. US 7654997
DOCUMENT TYPE:	Utility
FILE SEGMENT:	APPLICATION
LEGAL REPRESENTATIVE:	STEPTOE & JOHNSON - ACCLARENT, INC., 2121 AVENUE OF THE STARS, SUITE 2800, LOS ANGELES, CA, 90067, US
NUMBER OF CLAIMS:	9
EXEMPLARY CLAIM:	1-9
NUMBER OF DRAWINGS:	35 Drawing Page(s)
LINE COUNT:	1482

CAS INDEXING IS AVAILABLE FOR THIS PATENT. Full-text

SUMM nasal congestion or post-nasal drainage

DETD . . . conductive coatings, radiopaque coatings, echogenic coatings, thrombogenicity reducing coatings and coatings that release drugs. In FIG. 2B, a second introduction device comprising a guidewire 202 is introduced through the first introduction device (i.e., the guide catheter 200) so that the guidewire 202 enters the sphenoid sinus SS through the ostium SSO. Guidewire 202 may be constructed and coated as is common in the art of cardiology. In FIG. 2C, a working device 204 for example a balloon catheter is introduced over guidewire 202 into the sphenoid sinus SS. Thereafter, in FIG. 2D, the working device 204 is used to perform a diagnostic or therapeutic procedure. In this particular example, the procedure is dilation of the. . . or modify any sinus ostium or other man-made or naturally occurring anatomical opening or passageway within the nose, paranasal sinuses, nasopharynx

or adjacent areas. After the completion of the procedure, guide catheter 200, guidewire 202 and working device 204 are withdrawn and removed. As will be appreciated by those of skill in the art, in this or any. . . or imaging modalities including but not limited to fluoroscopic, X-ray radiographic, ultrasonic, radiofrequency localization, electromagnetic, magnetic, robotic and other radiative energy based modalities. In this regard, some of the figures show optional scopes SC is dotted lines. It is to be. . . types of rigid or flexible endoscopes and such optional scopes SC may be separate from or incorporated into the working devices and/or introduction devices of the present invention.

L5 ANSWER 27 OF 44 USPATFULL on STN

ACCESSION NUMBER:	2010:236802 USPATFULL
TITLE:	Devices, Systems and Methods For Diagnosing and Treating Sinusitis and Other Disorders of the Ears, Nose and/or Throat
INVENTOR(S):	Makower, Joshua, Los Altos, CA, UNITED STATES Chang, John Y., Mountain View, CA, UNITED STATES
PATENT ASSIGNEE(S):	Acclarent, inc., Menlo Park, CA, UNITED STATES (U.S. corporation)

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 20100210901	A1	20100819
	US 8870893	B2	20141028
APPLICATION INFO.:	US 2010-769915	A1	20100429 (12)

RELATED APPLN. INFO.:	Division of Ser. No. US 2007-924473, filed on 25 Oct 2007, Pat. No. US 7727186 Continuation of Ser. No. US 2004-829917, filed on 21 Apr 2004, Pat. No. US 7654997
DOCUMENT TYPE:	Utility
FILE SEGMENT:	APPLICATION
LEGAL REPRESENTATIVE:	STEPTOE & JOHNSON - ACCLARENT, INC., 2121 AVENUE OF THE STARS, SUITE 2800, LOS ANGELES, CA, 90067, US
NUMBER OF CLAIMS:	21
EXEMPLARY CLAIM:	1
NUMBER OF DRAWINGS:	41 Drawing Page(s)
LINE COUNT:	2828

CAS INDEXING IS AVAILABLE FOR THIS PATENT. Full-text

AB . . . nose and throat are diagnosed and/or treated using minimally invasive approaches and, in many cases, flexible catheters as opposed to instruments having rigid shafts. Various diagnostic procedures and devices are used to perform imaging studies, mucus flow studies, air/gas flow studies, anatomic dimension studies, endoscopic studies and transillumination studies. Access and occluder devices may be used to establish fluid tight seals in the anterior or posterior nasal cavities/nasopharynx and to facilitate insertion of working devices (e.g., scopes, guidewires, catheters, tissue cutting or remodeling devices, electrosurgical devices, energy emitting devices, devices for injecting diagnostic or therapeutic agents, devices for implanting devices such as stents, substance eluting devices, substance delivery implants, etc.

SUMM nasal congestion or post-nasal drainage

DETD . . . 9A-9C show a procedure for installation of a cochlear implant in accordance with the present invention. In this procedure, the nasopharyngeal opening into the Eustachian tube ET is located and a guidewire is initially advanced into the Eustachian tube ET. A. . . catheter 900 is in or near the tympanic cavity TC of the middle ear. Thereafter, if deemed necessary, a forceps device 790 and/or other devices are advanced through the catheter 900 and used to remove the small bones of the sear (i.e., the malleus, incus. . . This optional removal of the bones of the middle ear may be done under endoscopic visualization using an endoscope equipped device such as the endoscope equipped forceps device 790 shown in FIG. 5T and described above. As shown in FIG. 9B, a cochlear guide catheter 904 having a. . . tympanic membrane. In other applications, the cochlear guide catheter 904 may be positioned adjacent to the cochlea and a cochleostomy device (e.g., a penetrator such as a drill, needle or cutter) may be advanced through or formed or positioned on the. . . cochleostomy through which the distal end of the guide catheter 904 is advanced into the cochlea C. Thereafter, a cochlear electrode array 906 is advanced

through the cochlear guide catheter 904 and into the cochlea, as seen in FIG. 9B. One example of a commercially available cochlear electrode array is the Nucleus 24 Countour device manufactured by Cochlear Corporation.

L5 ANSWER 28 OF 44 USPATFULL on STN
ACCESSION NUMBER: 2010:195524 USPATFULL
TITLE: DEVICES, SYSTEMS AND METHODS USEABLE FOR TREATING SINUSITIS
INVENTOR(S): Chang, John Y., Mountain View, CA, UNITED STATES
Makower, Joshua, Los Altos, CA, UNITED STATES
Vrany, Julia D., Sunnyvale, CA, UNITED STATES
Morriss, John H., Portola Valley, CA, UNITED STATES
Muni, Ketan P., San Jose, CA, UNITED STATES
Kim, Isaac J., San Jose, CA, UNITED STATES
Ha, Hung, San Jose, CA, UNITED STATES
Facteau, William M., Mountain View, CA, UNITED STATES
Walke, Amrish Jayprakash, Mountain View, CA, UNITED STATES
PATENT ASSIGNEE(S): ACCLARENT, INC., Menlo Park, CA, UNITED STATES (U.S. corporation)

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 20100174308	A1	20100708
	US 8828041	B2	20140909
APPLICATION INFO.:	US 2010-727190	A1	20100318 (12)

RELATED APPLN. INFO.: Continuation of Ser. No. US 2005-150847, filed on 10 Jun 2005, PENDING Continuation-in-part of Ser. No. US 2004-944270, filed on 17 Sep 2004, PENDING Continuation-in-part of Ser. No. US 2004-829917, filed on 21 Apr 2004, Pat. No. US 7654997
DOCUMENT TYPE: Utility
FILE SEGMENT: APPLICATION
LEGAL REPRESENTATIVE: Robert D. Buyan, Stout, Uxa, Buyan & Mullins,, LLP/Acclarent, Inc., 4 Venture, Suite 300, Irvine, CA, 92618, US
NUMBER OF CLAIMS: 14
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 41 Drawing Page(s)
LINE COUNT: 2461 Full-text
SUMM Patients who suffer from sinusitis typically experience at least some of the following symptoms:

headaches or facial pain

nasal congestion or post-nasal drainage
difficulty breathing through one or both nostrils
bad breath
pain in the upper teeth
DETD . . . conductive coatings, radiopaque coatings, echogenic coatings, thrombogenicity reducing coatings and coatings that release drugs. In FIG. 2B, a second introduction device comprising a guidewire 202 is introduced through the first introduction device (i.e., the guide catheter 200) so that the guidewire 202 enters the sphenoid sinus SS through the ostium SSO. Guidewire 202 may be constructed and coated as is common in the art of cardiology. In FIG. 2C, a working device 204 for example a balloon catheter is introduced over guidewire 202 into the sphenoid sinus SS. Thereafter, in FIG. 2D, the working device 204 is used to perform a diagnostic or therapeutic procedure. In this particular example, the procedure is dilation of the. . . or modify any sinus ostium or other man-made or naturally occurring anatomical opening or passageway within the nose, paranasal sinuses, nasopharynx or adjacent areas. After the completion of the procedure, guide catheter 200, guidewire 202 and working device 204 are withdrawn and removed. As will be appreciated by those of skill in the art, in this or any. . . or imaging modalities including but not limited to fluoroscopic, X-ray radiographic, ultrasonic, radiofrequency localization, electromagnetic, magnetic, robotic and other radiative energy based modalities. In this regard, some of the figures show optional scopes SC is dotted lines. It is to be. . . types of rigid or flexible

endoscopes and such optional scopes SC may be separate from or incorporated into the working devices and/or introduction devices of the present invention.

L5 ANSWER 29 OF 44 USPATFULL on STN
ACCESSION NUMBER: 2010:195354 USPATFULL
TITLE: DEVICES, SYSTEMS AND METHODS USEABLE FOR TREATING SINUSITIS
INVENTOR(S): Chang, John Y., Mountain View, CA, UNITED STATES
Makower, Joshua, Los Altos, CA, UNITED STATES
Vrany, Julia D., Sunnyvale, CA, UNITED STATES
Morriss, John H., Portola Valley, CA, UNITED STATES
Muni, Ketan P., San Jose, CA, UNITED STATES
Kim, Isaac J., San Jose, CA, UNITED STATES
Ha, Hung, San Jose, CA, UNITED STATES
Facteau, William M., Mountain View, CA, UNITED STATES
Walke, Amrish Jayprakash, Mountain View, CA, UNITED STATES
PATENT ASSIGNEE(S): ACCLARENT, INC., Menlo Park, CA, UNITED STATES (U.S. corporation)

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 20100174138	A1	20100708
	US 9055965	B2	20150616
APPLICATION INFO.:	US 2010-729109	A1	20100322 (12)

RELATED APPLN. INFO.: Continuation of Ser. No. US 2007-928160, filed on 30 Oct 2007, PENDING Continuation of Ser. No. US 2005-150847, filed on 10 Jun 2005, PENDING Continuation-in-part of Ser. No. US 2004-944270, filed on 17 Sep 2004, PENDING Continuation-in-part of Ser. No. US 2004-829917, filed on 21 Apr 2004, Pat. No. US 7654997
DOCUMENT TYPE: Utility
FILE SEGMENT: APPLICATION
LEGAL REPRESENTATIVE: STEPTOE & JOHNSON - ACCLARENT, INC., 2121 AVENUE OF THE STARS, SUITE 2800, LOS ANGELES, CA, 90067, US
NUMBER OF CLAIMS: 5
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 41 Drawing Page(s)
LINE COUNT: 2425
CAS INDEXING IS AVAILABLE FOR THIS PATENT. Full-text
SUMM Patients who suffer from sinusitis typically experience at least some of the following symptoms:

headaches or facial pain

nasal congestion or post-nasal drainage
difficulty breathing through one or both nostrils
bad breath
pain in the upper teeth

DETD . . . conductive coatings, radiopaque coatings, echogenic coatings, thrombogenicity reducing coatings and coatings that release drugs. In FIG. 2B, a second introduction device comprising a guidewire 202 is introduced through the first introduction device (i.e., the guide catheter 200) so that the guidewire 202 enters the sphenoid sinus SS through the ostium SSO. Guidewire 202 may be constructed and coated as is common in the art of cardiology. In FIG. 2C, a working device 204 for example a balloon catheter is introduced over guidewire 202 into the sphenoid sinus SS. Thereafter, in FIG. 2D, the working device 204 is used to perform a diagnostic or therapeutic procedure. In this particular example, the procedure is dilation of the. . . or modify any sinus ostium or other man-made or naturally occurring anatomical opening or passageway within the nose, paranasal sinuses, nasopharynx or adjacent areas. After the completion of the procedure, guide catheter 200, guidewire 202 and working device 204 are withdrawn and removed. As will be appreciated by those of skill in the art, in this or any. . . or imaging modalities including but not limited to fluoroscopic, X-ray radiographic, ultrasonic, radiofrequency localization, electromagnetic, magnetic, robotic and other radiative energy based modalities. In this regard, some of the figures show optional scopes SC

is dotted lines. It is to be. . . types of rigid or flexible endoscopes and such optional scopes SC may be separate from or incorporated into the working devices and/or introduction devices of the present invention.

L5 ANSWER 30 OF 44 USPATFULL on STN

ACCESSION NUMBER:	2010:112427 USPATFULL
TITLE:	DEVICES, SYSTEMS AND METHODS FOR DIAGNOSING AND TREATING SINUSITUS ANDOTHER DISORDERS OF THE EARS, NOSE AND/OR THROAT
INVENTOR(S):	Makower, Joshua, Los Altos, CA, UNITED STATES Chang, John Y., Mountain View, CA, UNITED STATES
PATENT ASSIGNEE(S):	ACCLARENT, INC., Menlo Park, CA, UNITED STATES (U.S. corporation)

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 20100100181	A1	20100422
	US 8425457	B2	20130423
APPLICATION INFO.:	US 2009-649050	A1	20091229 (12)

RELATED APPLN. INFO.:	Continuation of Ser. No. US 2004-829917, filed on 21 Apr 2004, Pat. No. US 7654997
DOCUMENT TYPE:	Utility
FILE SEGMENT:	APPLICATION
LEGAL REPRESENTATIVE:	Robert D. Buyan, Stout, Uxa, Buyan & Mullins,, LLP/Acclarent, Inc., 4 Venture, Suite 300, Irvine, CA, 92618, US
NUMBER OF CLAIMS:	10
EXEMPLARY CLAIM:	1
NUMBER OF DRAWINGS:	41 Drawing Page(s)
LINE COUNT:	2847

CAS INDEXING IS AVAILABLE FOR THIS PATENT. Full-text

AB . . . nose and throat are diagnosed and/or treated using minimally invasive approaches and, in many cases, flexible catheters as opposed to instruments having rigid shafts. Various diagnostic procedures and devices are used to perform imaging studies, mucus flow studies, air/gas flow studies, anatomic dimension studies, endoscopic studies and transillumination studies. Access and occluder devices may be used to establish fluid tight seals in the anterior or posterior nasal cavities/nasopharynx and to facilitate insertion of working devices (e.g., scopes, guidewires, catheters, tissue cutting or remodeling devices, electrosurgical devices, energy emitting devices, devices for injecting diagnostic or therapeutic agents, devices for implanting devices such as stents, substance eluting devices, substance delivery implants, etc.

SUMM nasal congestion or post-nasal drainage

DETD . . . 9A-9C show a procedure for installation of a cochlear implant in accordance with the present invention. In this procedure, the nasopharyngeal opening into the Eustachian tube ET is located and a guidewire is initially advanced into the Eustachian tube ET. A. . . catheter 900 is in or near the tympanic cavity TC of the middle ear. Thereafter, if deemed necessary, a forceps device 790 and/or other devices are advanced through the catheter 900 and used to remove the small bones of the sear (i.e., the malleus, incus. . . This optional removal of the bones of the middle ear may be done under endoscopic visualization using an endoscope equipped device such as the endoscope equipped forceps device 790 shown in FIG. 5T and described above. As shown in FIG. 9B, a cochlear guide catheter 904 having a. . . tympanic membrane. In other applications, the cochlear guide catheter 904 may be positioned adjacent to the cochlea and a cochleostomy device (e.g., a penetrator such as a drill, needle or cutter) may be advanced through or formed or positioned on the. . . cochleostomy through which the distal end of the guide catheter 904 is advanced into the cochlea C. Thereafter, a cochlear electrode array 906 is advanced through the cochlear guide catheter 904 and into the cochlea, as seen in FIG. 9B. One example of a commercially available cochlear electrode array is the Nucleus 24 Countour device manufactured by Cochlear Corporation.

L5 ANSWER 31 OF 44 USPATFULL on STN

ACCESSION NUMBER: 2010:98403 USPATFULL
TITLE: METHODS AND SYSTEMS FOR TOXIN DELIVERY TO THE NASAL CAVITY
INVENTOR(S): DEEM, MARK E., MOUNTAIN VIEW, CA, UNITED STATES
GIFFORD, HANSON, WOODSIDE, CA, UNITED STATES
PATENT ASSIGNEE(S): THE FOUNDY, LLC, MENLO PARK, CA, UNITED STATES (U.S. corporation)

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 20100087775	A1	20100408
	US 8105817	B2	20120131
APPLICATION INFO.:	US 2009-636477	A1	20091211 (12)

RELATED APPLN. INFO.: Division of Ser. No. US 2007-750963, filed on 18 May 2007, Pat. No. US 7655243 Continuation-in-part of Ser. No. US 2006-459090, filed on 21 Jul 2006, Pat. No. US 7608275

	NUMBER	DATE
PRIORITY INFORMATION:	US 2006-60747771	20060519 (60)
	US 2005-60702077	20050722 (60)

DOCUMENT TYPE: Utility
FILE SEGMENT: APPLICATION
LEGAL REPRESENTATIVE: TOWNSEND AND TOWNSEND AND CREW, LLP, TWO EMBARCADERO CENTER, EIGHTH FLOOR, SAN FRANCISCO, CA, 94111-3834, US
NUMBER OF CLAIMS: 31
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 24 Drawing Page(s)
LINE COUNT: 1356
CAS INDEXING IS AVAILABLE FOR THIS PATENT. Full-text
SUMM . . . 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.
SUMM 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. . .
DETD . . . 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.. . . 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.

L5 ANSWER 32 OF 44 USPATFULL on STN
ACCESSION NUMBER: 2010:47155 USPATFULL
TITLE: DEVICES, SYSTEMS AND METHODS USEABLE FOR TREATING SINUSITIS
INVENTOR(S): Chang, John Y., Mountain View, CA, UNITED STATES
Makower, Joshua, Los Altos, CA, UNITED STATES
Vrany, Julia D., Sunnyvale, CA, UNITED STATES
Morriss, John H., Portola Valley, CA, UNITED STATES
Muni, Ketan P, San Jose, CA, UNITED STATES
Kim, Isaac J., San Jose, CA, UNITED STATES
Ha, Hung, San Jose, CA, UNITED STATES
Facteau, William M., Mountain View, CA, UNITED STATES
Walke, Amrish Jayprakash, Mountain View, CA, UNITED STATES
PATENT ASSIGNEE(S): ACCLARENT, INC., Menlo Park, CA, UNITED STATES (U.S. corporation)

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 20100042046	A1	20100218
	US 8764726	B2	20140701

APPLICATION INFO.: US 2009-543445 A1 20090818 (12)
RELATED APPLN. INFO.: Division of Ser. No. US 2005-150847, filed on 10 Jun 2005, PENDING Continuation-in-part of Ser. No. US 2004-944270, filed on 17 Sep 2004, PENDING Continuation-in-part of Ser. No. US 2004-829917, filed on 21 Apr 2004, PENDING
DOCUMENT TYPE: Utility
FILE SEGMENT: APPLICATION
LEGAL REPRESENTATIVE: STOUT, UXA, BUYAN & MULLINS LLP, 4 VENTURE, SUITE 300, IRVINE, CA, 92618, US
NUMBER OF CLAIMS: 23
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 41 Drawing Page(s)
LINE COUNT: 2474
CAS INDEXING IS AVAILABLE FOR THIS PATENT. Full-text
SUMM nasal congestion or post-nasal drainage
DETD . . . conductive coatings, radiopaque coatings, echogenic coatings, thrombogenicity reducing coatings and coatings that release drugs. In FIG. 2B, a second introduction device comprising a guidewire 202 is introduced through the first introduction device (i.e., the guide catheter 200) so that the guidewire 202 enters the sphenoid sinus SS through the ostium SSO. Guidewire 202 may be constructed and coated as is common in the art of cardiology. In FIG. 2C, a working device 204 for example a balloon catheter is introduced over guidewire 202 into the sphenoid sinus SS. Thereafter, in FIG. 2D, the working device 204 is used to perform a diagnostic or therapeutic procedure. In this particular example, the procedure is dilation of the. . . or modify any sinus ostium or other man-made or naturally occurring anatomical opening or passageway within the nose, paranasal sinuses, nasopharynx or adjacent areas. After the completion of the procedure, guide catheter 200, guidewire 202 and working device 204 are withdrawn and removed. As will be appreciated by those of skill in the art, in this or any. . . or imaging modalities including but not limited to fluoroscopic, X-ray radiographic, ultrasonic, radiofrequency localization, electromagnetic, magnetic, robotic and other radiative energy based modalities. In this regard, some of the figures show optional scopes SC is dotted lines. It is to be. . . types of rigid or flexible endoscopes and such optional scopes SC may be separate from or incorporated into the working devices and/or introduction devices of the present invention.

L5 ANSWER 33 OF 44 USPATFULL on STN
ACCESSION NUMBER: 2009:208156 USPATFULL
TITLE: Devices, Systems and Methods for Diagnosing and Treating Sinusitis and Other Disorders of the Ears, Nose, and/or Throat
INVENTOR(S): Makower, Joshua, Los Altos, CA, UNITED STATES
Chang, John Y., Mountain, VA, UNITED STATES
Goldfarb, Eric, Belmont, CA, UNITED STATES
Morriss, John, Portola Valley, CA, UNITED STATES
Facteau, William M., Mountain View, CA, UNITED STATES
PATENT ASSIGNEE(S): Acclarent, Inc., Mountain View, CA, UNITED STATES (U.S. corporation)

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 20090187098	A1	20090723
	US 9101384	B2	20150811
APPLICATION INFO.:	US 2009-355492	A1	20090116 (12)

RELATED APPLN. INFO.: Continuation-in-part of Ser. No. US 2004-829917, filed on 21 Apr 2004, PENDING Continuation-in-part of Ser. No. US 2006-522497, filed on 15 Sep 2006, PENDING
DOCUMENT TYPE: Utility
FILE SEGMENT: APPLICATION
LEGAL REPRESENTATIVE: Townsend and Townsend and Crew LLP, Acclarent, Inc. (73608), Two Embarcadero Center, San Francisco, CA, 94111-3834, US
NUMBER OF CLAIMS: 27
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 51 Drawing Page(s)
LINE COUNT: 4495

CAS INDEXING IS AVAILABLE FOR THIS PATENT. Full-text
SUMM Patients who suffer from sinusitis typically experience at least some of the following symptoms:

headaches or facial pain

nasal congestion or post-nasal drainage
difficulty breathing through one or both nostrils
bad breath
pain in the upper teeth
SUMM . . . United States. Patients who suffer from sinusitis typically experience at least some of the following symptoms: headaches or facial pain; nasal congestion or post-nasal drainage; difficulty breathing through one or both nostrils; bad breath; and/or pain in the upper teeth.
DETD . . . 9A-9C show a procedure for installation of a cochlear implant in accordance with the present invention. In this procedure, the nasopharyngeal opening into the Eustachian tube ET is located and a guidewire is initially advanced into the Eustachian tube ET. A. . . catheter 900 is in or near the tympanic cavity TC of the middle ear. Thereafter, if deemed necessary, a forceps device 790 and/or other devices are advanced through the catheter 900 and used to remove the small bones of the sear (i.e., the malleus, incur. . . This optional removal of the bones of the middle ear may be done under endoscopic visualization using an endoscope equipped device such as the endoscope equipped forceps device 790 shown in FIG. 5T and described above. As shown in FIG. 9B, a cochlear guide catheter 904 having a. . . tympanic membrane. In other applications, the cochlear guide catheter 904 may be positioned adjacent to the cochlea and a cochleostomy device (e.g., a penetrator such as a drill, needle or cutter) may be advanced through or formed or positioned on the. . . cochleostomy through which the distal end of the guide catheter 904 is advanced into the cochlea C. Thereafter, a cochlear electrode array 906 is advanced through the cochlear guide catheter 904 and into the cochlea, as seen in FIG. 9B. One example of a commercially available cochlear electrode array is the Nucleus 24 Contour device manufactured by Cochlear Corporation.

L5 ANSWER 34 OF 44 USPATFULL on STN
ACCESSION NUMBER: 2009:103767 USPATFULL
TITLE: Devices, Systems and Methods Useable for Treating Sinusitis
INVENTOR(S): Chang, John Y., Mountain View, CA, UNITED STATES
Makower, Joshua, Los Altos, CA, UNITED STATES
Vrany, Julia D., Sunnyvale, CA, UNITED STATES
Morriss, John H., Portola Valley, CA, UNITED STATES
Muni, Ketan P., San Jose, CA, UNITED STATES
Kim, Isaac J., San Jose, CA, UNITED STATES
Ha, Hung, San Jose, CA, UNITED STATES
Facteau, William M., Mountain View, CA, UNITED STATES
Walke, Amrish Jayprakash, Mountain View, CA, UNITED STATES
PATENT ASSIGNEE(S): Acclarent, Inc., Menlo Park, CA, UNITED STATES (U.S. corporation)

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 20090093823	A1	20090409
	US 7771409	B2	20100810
APPLICATION INFO.:	US 2007-928160	A1	20071030 (11)

RELATED APPLN. INFO.: Continuation of Ser. No. US 2005-150847, filed on 10 Jun 2005, PENDING Continuation-in-part of Ser. No. US 2004-944270, filed on 17 Sep 2004, PENDING Continuation-in-part of Ser. No. US 2004-829917, filed on 21 Apr 2004, PENDING
DOCUMENT TYPE: Utility
FILE SEGMENT: APPLICATION
LEGAL REPRESENTATIVE: STEPTOE & JOHNSON - ACCLARENT, INC., 2121 AVENUE OF THE STARS, SUITE 2800, LOS ANGELES, CA, 90067, US
NUMBER OF CLAIMS: 5
EXEMPLARY CLAIM: 1

NUMBER OF DRAWINGS: 41 Drawing Page(s)
LINE COUNT: 2422
CAS INDEXING IS AVAILABLE FOR THIS PATENT. Full-text
SUMM Patients who suffer from sinusitis typically experience at least some of the following symptoms:

headaches or facial pain

nasal congestion or post-nasal drainage
difficulty breathing through one or both nostrils
bad breath
pain in the upper teeth Thus, one of the ways to treat sinusitis. . .
DETD . . . conductive coatings, radiopaque coatings, echogenic coatings, thrombogenicity reducing coatings and coatings that release drugs. In FIG. 2B, a second introduction device comprising a guidewire 202 is introduced through the first introduction device (i.e., the guide catheter 200) so that the guidewire 202 enters the sphenoid sinus SS through the ostium SSO. Guidewire 202 may be constructed and coated as is common in the art of cardiology. In FIG. 2C, a working device 204 for example a balloon catheter is introduced over guidewire 202 into the sphenoid sinus SS. Thereafter, in FIG. 2D, the working device 204 is used to perform a diagnostic or therapeutic procedure. In this particular example, the procedure is dilation of the. . . or modify any sinus ostium or other man-made or naturally occurring anatomical opening or passageway within the nose, paranasal sinuses, nasopharynx or adjacent areas. After the completion of the procedure, guide catheter 200, guidewire 202 and working device 204 are withdrawn and removed. As will be appreciated by those of skill in the art, in this or any. . . or imaging modalities including but not limited to fluoroscopic, X-ray radiographic, ultrasonic, radiofrequency localization, electromagnetic, magnetic, robotic and other radiative energy based modalities. In this regard, some of the figures show optional scopes SC is dotted lines. It is to be. . . types of rigid or flexible endoscopes and such optional scopes SC may be separate from or incorporated into the working devices and/or introduction devices of the present invention.

L5 ANSWER 35 OF 44 USPATFULL on STN
ACCESSION NUMBER: 2008:176365 USPATFULL
TITLE: Devices, Systems and Methods For Diagnosing and Treating Sinusitis and Other Disorders of the Ears, Nose and/or Throat
INVENTOR(S): Makower, Joshua, Los Altos, CA, UNITED STATES
Chang, John Y., Mountain View, CA, UNITED STATES
PATENT ASSIGNEE(S): ACCLARENT, INC., Menlo Park, CA, UNITED STATES (U.S. corporation)

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 20080154250	A1	20080626
	US 8142422	B2	20120327
APPLICATION INFO.:	US 2008-42221	A1	20080304 (12)

RELATED APPLN. INFO.: Continuation of Ser. No. US 2004-829917, filed on 21 Apr 2004, PENDING
DOCUMENT TYPE: Utility
FILE SEGMENT: APPLICATION
LEGAL REPRESENTATIVE: STEPTOE & JOHNSON - ACCLARENT, INC., 2121 AVENUE OF THE STARS, SUITE 2800, LOS ANGELES, CA, 90067, US
NUMBER OF CLAIMS: 31
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 41 Drawing Page(s)
LINE COUNT: 2871 Full-text
AB . . . nose and throat are diagnosed and/or treated using minimally invasive approaches and, in many cases, flexible catheters as opposed to instruments having rigid shafts. Various diagnostic procedures and devices are used to perform imaging studies, mucus flow studies, air/gas flow studies, anatomic dimension studies, endoscopic studies and transillumination studies. Access and occluder devices may be used to establish fluid tight seals in the anterior or posterior nasal cavities/nasopharynx and to facilitate insertion of working devices (e.g., scopes, guidewires, catheters, tissue cutting or remodeling

devices, electrosurgical devices, energy emitting devices, devices for injecting diagnostic or therapeutic agents, devices for implanting devices such as stents, substance eluting devices, substance delivery implants, etc.

SUMM Patients who suffer from sinusitis typically experience at least some of the following symptoms:

headaches or facial pain

nasal congestion or post-nasal drainage
difficulty breathing through one or both nostrils
bad breath
pain in the upper teeth

DETD . . . 9A-9C show a procedure for installation of a cochlear implant in accordance with the present invention. In this procedure, the nasopharyngeal opening into the Eustachian tube ET is located and a guidewire is initially advanced into the Eustachian tube ET. A. . . catheter 900 is in or near the tympanic cavity TC of the middle ear. Thereafter, if deemed necessary, a forceps device 790 and/or other devices are advanced through the catheter 900 and used to remove the small bones of the sear (i.e., the malleus, incus. . . This optional removal of the bones of the middle ear may be done under endoscopic visualization using an endoscope equipped device such as the endoscope equipped forceps device 790 shown in FIG. 5T and described above. As shown in FIG. 9B, a cochlear guide catheter 904 having a. . . tympanic membrane. In other applications, the cochlear guide catheter 904 may be positioned adjacent to the cochlea and a cochleostomy device (e.g., a penetrator such as a drill, needle or cutter) may be advanced through or formed or positioned on the. . . cochleostomy through which the distal end of the guide catheter 904 is advanced into the cochlea C. Thereafter, a cochlear electrode array 906 is advanced through the cochlear guide catheter 904 and into the cochlea, as seen in FIG. 9B. One example of a commercially available cochlear electrode array is the Nucleus 24 Countour device manufactured by Cochlear Corporation.

L5 ANSWER 36 OF 44 USPATFULL on STN

ACCESSION NUMBER:	2008:176352 USPATFULL
TITLE:	Apparatus and Methods for Dilating and Modifying Ostia of Paranasal Sinuses and Other Intranasal or Paranasal Structures
INVENTOR(S):	Chang, John Y., Mountain View, CA, UNITED STATES Makower, Joshua, Los Altos, CA, UNITED STATES Vrany, Julia D., Sunnyvale, CA, UNITED STATES Walke, Amrish Jayprakash, Mountain View, CA, UNITED STATES
PATENT ASSIGNEE(S):	Acclarent, Inc., Menlo Park, CA, UNITED STATES (U.S. corporation)

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 20080154237	A1	20080626
	US 8172828	B2	20120508
APPLICATION INFO.:	US 2007-928346	A1	20071030 (11)

RELATED APPLN. INFO.:	Continuation of Ser. No. US 2004-944270, filed on 17 Sep 2004, PENDING Continuation-in-part of Ser. No. US 2004-829917, filed on 21 Apr 2004, PENDING
DOCUMENT TYPE:	Utility
FILE SEGMENT:	APPLICATION
LEGAL REPRESENTATIVE:	STEPTOE & JOHNSON - ACCLARENT, INC., 2121 AVENUE OF THE STARS, SUITE 2800, LOS ANGELES, CA, 90067, US
NUMBER OF CLAIMS:	10
EXEMPLARY CLAIM:	1
NUMBER OF DRAWINGS:	35 Drawing Page(s)
LINE COUNT:	1517

CAS INDEXING IS AVAILABLE FOR THIS PATENT. Full-text

SUMM nasal congestion or post-nasal drainage

DETD . . . conductive coatings, radiopaque coatings, echogenic coatings, thrombogenicity reducing coatings and coatings that release drugs. In FIG. 2B, a second introduction device comprising a guidewire 202 is introduced through the first introduction device (i.e., the guide

catheter 200) so that the guidewire 202 enters the sphenoid sinus SS through the ostium SSO. Guidewire 202 may be constructed and coated as is common in the art of cardiology. In FIG. 2C, a working device 204 for example a balloon catheter is introduced over guidewire 202 into the sphenoid sinus SS. Thereafter, in FIG. 2D, the working device 204 is used to perform a diagnostic or therapeutic procedure. In this particular example, the procedure is dilation of the. . . or modify any sinus ostium or other man-made or naturally occurring anatomical opening or passageway within the nose, paranasal sinuses, nasopharynx or adjacent areas. After the completion of the procedure, guide catheter 200, guidewire 202 and working device 204 are withdrawn and removed. As will be appreciated by those of skill in the art, in this or any. . . or imaging modalities including but not limited to fluoroscopic, X-ray radiographic, ultrasonic, radiofrequency localization, electromagnetic, magnetic, robotic and other radiative energy based modalities. In this regard, some of the figures show optional scopes SC is dotted lines. It is to be. . . types of rigid or flexible endoscopes and such optional scopes SC may be separate from or incorporated into the working devices and/or introduction devices of the present invention.

L5 ANSWER 37 OF 44 USPATFULL on STN
ACCESSION NUMBER: 2008:144388 USPATFULL
TITLE: Devices, Systems and Methods Useable for Treating Sinusitis
INVENTOR(S): Chang, John Y., Mountain View, CA, UNITED STATES
Makower, Joshua, Los Altos, CA, UNITED STATES
Vrany, Julia D., Sunnyvale, CA, UNITED STATES
Morriss, John H., Portola Valley, CA, UNITED STATES
Muni, Ketan P., San Jose, CA, UNITED STATES
Kim, Isaac J., San Jose, CA, UNITED STATES
Ha, Hung, San Jose, CA, UNITED STATES
Facteau, William M., Mountain View, CA, UNITED STATES
Walke, Amrish Jayprakash, Mountain View, CA, UNITED STATES
PATENT ASSIGNEE(S): Acclarent, Inc., Menlo Park, CA, UNITED STATES (U.S. corporation)

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 20080125626	A1	20080529
	US 8715169	B2	20140506
APPLICATION INFO.:	US 2007-928097	A1	20071030 (11)

RELATED APPLN. INFO.: Continuation of Ser. No. US 2005-150847, filed on 10 Jun 2005, PENDING Continuation-in-part of Ser. No. US 2004-944270, filed on 17 Sep 2004, PENDING Continuation-in-part of Ser. No. US 2004-829917, filed on 21 Apr 2004, PENDING
DOCUMENT TYPE: Utility
FILE SEGMENT: APPLICATION
LEGAL REPRESENTATIVE: STOUT, UXA, BUYAN & MULLINS LLP, 4 VENTURE, SUITE 300, IRVINE, CA, 92618, US
NUMBER OF CLAIMS: 19
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 41 Drawing Page(s)
LINE COUNT: 2484
CAS INDEXING IS AVAILABLE FOR THIS PATENT. Full-text
SUMM Patients who suffer from sinusitis typically experience at least some of the following symptoms:

headaches or facial pain

nasal congestion or post-nasal drainage
difficulty breathing through one or both nostrils
bad breath
pain in the upper teeth Thus, one of the ways to treat sinusitis. . .
DETD Thereafter, in FIG. 2D, the working device 204 is used to perform a diagnostic or therapeutic procedure. In this particular example, the procedure is dilation of the. . . or modify any sinus ostium or other man-made or naturally occurring anatomical opening or passageway within the nose, paranasal sinuses, nasopharynx or adjacent areas. After the

completion of the procedure, guide catheter 200, guidewire 202 and working device 204 are withdrawn and removed. As will be appreciated by those of skill in the art, in this or any. . . or imaging modalities including but not limited to fluoroscopic, X-ray radiographic, ultrasonic, radiofrequency localization, electromagnetic, magnetic, robotic and other radiative energy based modalities. In this regard, some of the figures show optional scopes SC is dotted lines. It is to be. . . types of rigid or flexible endoscopes and such optional scopes SC may be separate from or incorporated into the working devices and/or introduction devices of the present invention.

L5 ANSWER 38 OF 44 USPATFULL on STN

ACCESSION NUMBER:	2008:111741 USPATFULL
TITLE:	DEVICES, SYSTEMS AND METHODS FOR DIAGNOSING AND TREATING SINUSITIS AND OTHER DISORDERS OF THE EARS, NOSE AND/OR THROAT
INVENTOR(S):	Makower, Joshua, Los Altos, CA, UNITED STATES Chang, John Y., Mountain View, CA, UNITED STATES
PATENT ASSIGNEE(S):	Acclarent, Inc., Menlo Park, CA, UNITED STATES, 940025 (U.S. corporation)

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 20080097295	A1	20080424
	US 7727186	B2	20100601
APPLICATION INFO.:	US 2007-924473	A1	20071025 (11)

RELATED APPLN. INFO.:	Continuation of Ser. No. US 2004-829917, filed on 21 Apr 2004, PENDING
DOCUMENT TYPE:	Utility
FILE SEGMENT:	APPLICATION
LEGAL REPRESENTATIVE:	STEPTOE & JOHNSON - ACCLARENT, INC., 2121 AVENUE OF THE STARS, SUITE 2800, LOS ANGELES, CA, 90067, US
NUMBER OF CLAIMS:	25
EXEMPLARY CLAIM:	1
NUMBER OF DRAWINGS:	41 Drawing Page(s)
LINE COUNT:	2875

CAS INDEXING IS AVAILABLE FOR THIS PATENT. Full-text

AB . . . nose and throat are diagnosed and/or treated using minimally invasive approaches and, in many cases, flexible catheters as opposed to instruments having rigid shafts. Various diagnostic procedures and devices are used to perform imaging studies, mucus flow studies, air/gas flow studies, anatomic dimension studies, endoscopic studies and transillumination studies. Access and occluder devices may be used to establish fluid tight seals in the anterior or posterior nasal cavities/nasopharynx and to facilitate insertion of working devices (e.g., scopes, guidewires, catheters, tissue cutting or remodeling devices, electrosurgical devices, energy emitting devices, devices for injecting diagnostic or therapeutic agents, devices for implanting devices such as stents, substance eluting devices, substance delivery implants, etc.

SUMM nasal congestion or post-nasal drainage

DETD . . . 9A-9C show a procedure for installation of a cochlear implant in accordance with the present invention. In this procedure, the nasopharyngeal opening into the Eustachian tube ET is located and a guidewire is initially advanced into the Eustachian tube ET. A. . . catheter 900 is in or near the tympanic cavity TC of the middle ear. Thereafter, if deemed necessary, a forceps device 790 and/or other devices are advanced through the catheter 900 and used to remove the small bones of the sear (i.e., the malleus, incus. . . This optional removal of the bones of the middle ear may be done under endoscopic visualization using an endoscope equipped device such as the endoscope equipped forceps device 790 shown in FIG. 5T and described above. As shown in FIG. 9B, a cochlear guide catheter 904 having a. . . tympanic membrane. In other applications, the cochlear guide catheter 904 may be positioned adjacent to the cochlea and a cochleostomy device (e.g., a penetrator such as a drill, needle or cutter) may be advanced through or formed or positioned on the. . . cochleostomy through which the distal end of the guide catheter 904 is advanced into the cochlea C. Thereafter, a cochlear electrode array 906 is advanced through the cochlear guide catheter 904 and into the cochlea, as seen in FIG. 9B. One example of a commercially available cochlear electrode

array is the Nucleus 24 Countour device manufactured by Cochlear Corporation.

L5 ANSWER 39 OF 44 USPATFULL on STN

ACCESSION NUMBER:	2008:24188 USPATFULL
TITLE:	METHODS AND SYSTEMS FOR TOXIN DELIVERY TO THE NASAL CAVITY
INVENTOR(S):	Deem, Mark E., Mountain View, CA, UNITED STATES Gifford, Hanson, Woodside, CA, UNITED STATES
PATENT ASSIGNEE(S):	The Foundry Inc., Menlo Park, CA, UNITED STATES (U.S. corporation)

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 20080021369	A1	20080124
	US 7655243	B2	20100202
APPLICATION INFO.:	US 2007-750963	A1	20070518 (11)

RELATED APPLN. INFO.: Continuation-in-part of Ser. No. US 2006-459090, filed on 21 Jul 2006, PENDING

	NUMBER	DATE
PRIORITY INFORMATION:	US 2006-60747771	20060519 (60)
	US 2005-60702077	20050722 (60)

DOCUMENT TYPE:	Utility
FILE SEGMENT:	APPLICATION
LEGAL REPRESENTATIVE:	TOWNSEND AND TOWNSEND AND CREW, LLP, TWO EMBARCADERO CENTER, EIGHTH FLOOR, SAN FRANCISCO, CA, 94111-3834, US
NUMBER OF CLAIMS:	69
EXEMPLARY CLAIM:	1
NUMBER OF DRAWINGS:	24 Drawing Page(s)
LINE COUNT:	1438

CAS INDEXING IS AVAILABLE FOR THIS PATENT. Full-text

SUMM . . . 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.

SUMM 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. . .

DETD . . . 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.. . . 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.

L5 ANSWER 40 OF 44 USPATFULL on STN

ACCESSION NUMBER:	2007:305933 USPATFULL
TITLE:	APPARATUS FOR TOXIN DELIVERY TO THE NASAL CAVITY
INVENTOR(S):	Deem, Mark E., Mountain View, CA, UNITED STATES Gifford, Hanson, Woodside, CA, UNITED STATES Kim, Steven, Los Altos, CA, UNITED STATES Salamini, Alexey, San Francisco, CA, UNITED STATES
PATENT ASSIGNEE(S):	The Foundry Inc., Menlo Park, CA, UNITED STATES (U.S. corporation)

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 20070267011	A1	20071122
	US 9511210	B2	20161206
APPLICATION INFO.:	US 2007-750967	A1	20070518 (11)

	NUMBER	DATE

PRIORITY INFORMATION: US 2006-60747771 20060519 (60)
DOCUMENT TYPE: Utility
FILE SEGMENT: APPLICATION
LEGAL REPRESENTATIVE: TOWNSEND AND TOWNSEND AND CREW, LLP, TWO EMBARCADERO CENTER, EIGHTH FLOOR, SAN FRANCISCO, CA, 94111-3834, US
NUMBER OF CLAIMS: 43
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 24 Drawing Page(s)
LINE COUNT: 1513
CAS INDEXING IS AVAILABLE FOR THIS PATENT. Full-text
DETD . . . 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.
DETD 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. . .
DETD 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. . .
DETD . . . 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.. . . 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.

L5 ANSWER 41 OF 44 USPATFULL on STN
ACCESSION NUMBER: 2007:155569 USPATFULL
TITLE: Use of mechanical dilator devices to enlarge ostia of paranasal sinuses and other passages in the ear, nose, throat and paranasal sinuses
INVENTOR(S): Chang, John Y., Mountain View, CA, UNITED STATES
Makower, Joshua, Los Altos, CA, UNITED STATES
Vrany, Julia D., Sunnyvale, CA, UNITED STATES
Morriss, John H., Portola Valley, CA, UNITED STATES
Muni, Ketan P., San Jose, CA, UNITED STATES
Kim, Isaac J., San Jose, CA, UNITED STATES
Ha, Hung, San Jose, CA, UNITED STATES
Facteau, William M., Mountain View, CA, UNITED STATES
Walke, Amrish Jayprakash, Mountain View, CA, UNITED STATES
PATENT ASSIGNEE(S): Acclarent, Inc., Menlo Park, CA, UNITED STATES (U.S. corporation)

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 20070135789	A1	20070614
	US 8858586	B2	20141014
APPLICATION INFO.:	US 2007-655794	A1	20070118 (11)

RELATED APPLN. INFO.: Continuation of Ser. No. US 2005-150847, filed on 10 Jun 2005, PENDING Continuation-in-part of Ser. No. US 2004-944270, filed on 17 Sep 2004, PENDING Continuation-in-part of Ser. No. US 2004-829917, filed on 21 Apr 2004, PENDING
DOCUMENT TYPE: Utility
FILE SEGMENT: APPLICATION
LEGAL REPRESENTATIVE: STOUT, UXA, BUYAN & MULLINS LLP, 4 VENTURE, SUITE 300, IRVINE, CA, 92618, US
NUMBER OF CLAIMS: 18
EXEMPLARY CLAIM: 1-197
NUMBER OF DRAWINGS: 41 Drawing Page(s)
LINE COUNT: 2462
CAS INDEXING IS AVAILABLE FOR THIS PATENT. Full-text
SUMM . . . who suffer from sinusitis typically experience at least some

of the following symptoms:

headaches or facial pain
nasal congestion or post-nasal drainage
difficulty breathing through one or both nostrils
bad breath
pain in the upper teeth Thus, one. . .

DETD . . . conductive coatings, radiopaque coatings, echogenic coatings, thrombogenicity reducing coatings and coatings that release drugs. In FIG. 2B, a second introduction device comprising a guidewire 202 is introduced through the first introduction device (i.e., the guide catheter 200) so that the guidewire 202 enters the sphenoid sinus SS through the ostium SSO. Guidewire 202 may be constructed and coated as is common in the art of cardiology. In FIG. 2C, a working device 204 for example a balloon catheter is introduced over guidewire 202 into the sphenoid sinus SS. Thereafter, in FIG. 2D, the working device 204 is used to perform a diagnostic or therapeutic procedure. In this particular example, the procedure is dilation of the. . . or modify any sinus ostium or other man-made or naturally occurring anatomical opening or passageway within the nose, paranasal sinuses, nasopharynx or adjacent areas. After the completion of the procedure, guide catheter 200, guidewire 202 and working device 204 are withdrawn and removed. As will be appreciated by those of skill in the art, in this or any. . . or imaging modalities including but not limited to fluoroscopic, X-ray radiographic, ultrasonic, radiofrequency localization, electromagnetic, magnetic, robotic and other radiative energy based modalities. In this regard, some of the figures show optional scopes SC is dotted lines. It is to be. . . types of rigid or flexible endoscopes and such optional scopes SC may be separate from or incorporated into the working devices and/or introduction devices of the present invention.

L5 ANSWER 42 OF 44 USPATFULL on STN

ACCESSION NUMBER:	2006:247216 USPATFULL
TITLE:	Devices, systems and methods useable for treating sinusitis
INVENTOR(S):	Chang, John Y., Mountain View, CA, UNITED STATES Makower, Joshua, Los Altos, CA, UNITED STATES Vrany, Julia D., Sunnyvale, CA, UNITED STATES Morriss, John H., Portola Valley, CA, UNITED STATES Muni, Ketan P., San Jose, CA, UNITED STATES Kim, Isaac J., San Jose, CA, UNITED STATES Ha, Hung, San Jose, CA, UNITED STATES Facteau, William M., Mountain View, CA, UNITED STATES Walke, Amrish Jayprakash, Mountain View, CA, UNITED STATES
PATENT ASSIGNEE(S):	Acclarent, Inc., Mountain View, CA, UNITED STATES (U.S. corporation)

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 20060210605	A1	20060921
	US 7803150	B2	20100928
APPLICATION INFO.:	US 2005-150847	A1	20050610 (11)

RELATED APPLN. INFO.:	Continuation-in-part of Ser. No. US 2004-944270, filed on 17 Sep 2004, PENDING Continuation-in-part of Ser. No. US 2004-829917, filed on 21 Apr 2004, PENDING
DOCUMENT TYPE:	Utility
FILE SEGMENT:	APPLICATION
LEGAL REPRESENTATIVE:	Robert D. Buyan, Stout, Uxa, Buyan & Mullins, LLP, Suite 300, 4 Venture, Irvine, CA, 92618, US
NUMBER OF CLAIMS:	97
EXEMPLARY CLAIM:	1
NUMBER OF DRAWINGS:	41 Drawing Page(s)
LINE COUNT:	2754

CAS INDEXING IS AVAILABLE FOR THIS PATENT. Full-text

SUMM nasal congestion or post-nasal drainage

DETD . . . conductive coatings, radiopaque coatings, echogenic coatings, thrombogenicity reducing coatings and coatings that release drugs. In FIG. 2B, a second introduction device comprising a guidewire 202 is introduced through the first introduction device (i.e., the guide

catheter 200) so that the guidewire 202 enters the sphenoid sinus SS through the ostium SSO. Guidewire 202 may be constructed and coated as is common in the art of cardiology. In FIG. 2C, a working device 204 for example a balloon catheter is introduced over guidewire 202 into the sphenoid sinus SS. Thereafter, in FIG. 2D, the working device 204 is used to perform a diagnostic or therapeutic procedure. In this particular example, the procedure is dilation of the. . . or modify any sinus ostium or other man-made or naturally occurring anatomical opening or passageway within the nose, paranasal sinuses, nasopharynx or adjacent areas. After the completion of the procedure, guide catheter 200, guidewire 202 and working device 204 are withdrawn and removed. As will be appreciated by those of skill in the art, in this or any. . . or imaging modalities including but not limited to fluoroscopic, X-ray radiographic, ultrasonic, radiofrequency localization, electromagnetic, magnetic, robotic and other radiative energy based modalities. In this regard, some of the figures show optional scopes SC is dotted lines. It is to be. . . types of rigid or flexible endoscopes and such optional scopes SC may be separate from or incorporated into the working devices and/or introduction devices of the present invention.

L5 ANSWER 43 OF 44 USPATFULL on STN

ACCESSION NUMBER:	2006:4863 USPATFULL
TITLE:	Apparatus and methods for dilating and modifying ostia of paranasal sinuses and other intranasal or paranasal structures
INVENTOR(S):	Chang, John Y., Mountain View, CA, UNITED STATES Makower, Joshua, Los Altos, CA, UNITED STATES Vrany, Julia D., Sunnyvale, CA, UNITED STATES Walke, Amrish Jayprakash, Mountain View, CA, UNITED STATES
PATENT ASSIGNEE(S):	ExploraMed NC1, Inc., Mountain View, CA, UNITED STATES (U.S. corporation)

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 20060004323	A1	20060105
APPLICATION INFO.:	US 2004-944270	A1	20040917 (10)

RELATED APPLN. INFO.:	Continuation-in-part of Ser. No. US 2004-829917, filed on 21 Apr 2004, PENDING
DOCUMENT TYPE:	Utility
FILE SEGMENT:	APPLICATION
LEGAL REPRESENTATIVE:	Robert D. Buyan, Stout, Uxa, Buyan & Mullins, LLP, Suite 300, 4 Venture, Irvine, CA, 92618, US
NUMBER OF CLAIMS:	114
EXEMPLARY CLAIM:	1
NUMBER OF DRAWINGS:	35 Drawing Page(s)
LINE COUNT:	2015 Full-text

SUMM . . . who suffer from sinusitis typically experience at least some of the following symptoms:

headaches or facial pain
nasal congestion or post-nasal drainage
difficulty breathing through one or both nostrils
bad breath
pain in the upper teeth Thus, one. . .

DETD . . . conductive coatings, radiopaque coatings, echogenic coatings, thrombogenicity reducing coatings and coatings that release drugs. In FIG. 2B, a second introduction device comprising a guidewire 202 is introduced through the first introduction device (i.e., the guide catheter 200) so that the guidewire 202 enters the sphenoid sinus SS through the ostium SSO. Guidewire 202 may be constructed and coated as is common in the art of cardiology. In FIG. 2C, a working device 204 for example a balloon catheter is introduced over guidewire 202 into the sphenoid sinus SS. Thereafter, in FIG. 2D, the working device 204 is used to perform a diagnostic or therapeutic procedure. In this particular example, the procedure is dilation of the. . . or modify any sinus ostium or other man-made or naturally occurring anatomical opening or passageway within the nose, paranasal sinuses, nasopharynx or adjacent areas. After the completion of the procedure, guide catheter 200, guidewire 202 and working device 204 are withdrawn and removed.

As will be appreciated by those of skill in the art, in this or any. . . or imaging modalities including but not limited to fluoroscopic, X-ray radiographic, ultrasonic, radiofrequency localization, electromagnetic, magnetic, robotic and other radiative energy based modalities. In this regard, some of the figures show optional scopes SC is dotted lines. It is to be. . . types of rigid or flexible endoscopes and such optional scopes SC may be separate from or incorporated into the working devices and/or introduction devices of the present invention.

CLM What is claimed is:

43. The system according to claim 33 wherein the working device is used to remodel or change the shape, size or configuration of a natural or artificially created passage way within the nose or nasopharynx using a device selected from the group consisting of balloon catheters, rotating cutters, rotating brushes, rotating drills, high frequency mechanical vibrators, sequential dilators, tapered dilators, swellable dilators, punches, radiofrequency ablation devices, microwave ablation devices, cutters, mechanically expandable members, dilating stents and devices that introduce diagnostic or therapeutic agents.

L5 ANSWER 44 OF 44 USPATFULL on STN

ACCESSION NUMBER:	2005:275582 USPATFULL
TITLE:	Devices, systems and methods for diagnosing and treating sinusitus and other disorders of the ears, nose and/or throat
INVENTOR(S):	Makower, Joshua, Los Altos, CA, UNITED STATES Chang, John Y., Mountain View, CA, UNITED STATES
PATENT ASSIGNEE(S):	ExploraMed II, Inc., Menlo Park, CA, UNITED STATES (U.S. corporation)

	NUMBER	KIND	DATE	
PATENT INFORMATION:	US 20050240147	A1	20051027	
	US 7654997	B2	20100202	
APPLICATION INFO.:	US 2004-829917	A1	20040421	(10)

DOCUMENT TYPE:	Utility
FILE SEGMENT:	APPLICATION
LEGAL REPRESENTATIVE:	Robert D. Buyan, Stout, Uxa, Buyan & Mullins, LLP, 4 Venture, Suite 300, Irvine, CA, 92618, US
NUMBER OF CLAIMS:	91
EXEMPLARY CLAIM:	1
NUMBER OF DRAWINGS:	41 Drawing Page(s)
LINE COUNT:	3253

CAS INDEXING IS AVAILABLE FOR THIS PATENT. Full-text

AB . . . nose and throat are diagnosed and/or treated using minimally invasive approaches and, in many cases, flexible catheters as opposed to instruments having rigid shafts. Various diagnostic procedures and devices are used to perform imaging studies, mucus flow studies, air/gas flow studies, anatomic dimension studies, endoscopic studies and transillumination studies. Access and occluder devices may be used to establish fluid tight seals in the anterior or posterior nasal cavities/nasopharynx and to facilitate insertion of working devices (e.g., scopes, guidewires, catheters, tissue cutting or remodeling devices, electrosurgical devices, energy emitting devices, devices for injecting diagnostic or therapeutic agents, devices for implanting devices such as stents, substance eluting devices, substance delivery implants, etc.

SUMM . . . who suffer from sinusitis typically experience at least some of the following symptoms:

headaches or facial pain
nasal congestion or post-nasal drainage
difficulty breathing through one or both nostrils
bad breath
pain in the upper teeth Proposed Mechanism. . .

DETD . . . 9A-9C show a procedure for installation of a cochlear implant in accordance with the present invention. In this procedure, the nasopharyngeal opening into the Eustachian tube ET is located and a guidewire is initially advanced into the Eustachian tube ET. A. . .

catheter 900 is in or near the tympanic cavity TC of the middle ear. Thereafter, if deemed necessary, a forceps device 790 and/or other devices are advanced through the catheter 900 and used to remove the small bones of the sear (i.e., the malleus, incus. . . This optional removal of the bones of the middle ear may be done under endoscopic visualization using an endoscope equipped device such as the endoscope equipped forceps device 790 shown in FIG. 5T and described above. As shown in FIG. 9B, a cochlear guide catheter 904 having a. . . tympanic membrane. In other applications, the cochlear guide catheter 904 may be positioned adjacent to the cochlea and a cochleostomy device (e.g., a penetrator such as a drill, needle or cutter) may be advanced through or formed or positioned on the. . . cochleostomy through which the distal end of the guide catheter 904 is advanced into the cochlea C. Thereafter, a cochlear electrode array 906 is advanced through the cochlear guide catheter 904 and into the cochlea, as seen in FIG. 9B. One example of a commercially available cochlear electrode array is the Nucleus 24 Countour device manufactured by Cochlear Corporation.

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=> e deem ma?/au

E1            1     DEEM M O/AU
E2           59     DEEM M W/AU
E3            0 --> DEEM MA?/AU
E4            7     DEEM MADELEINE C/AU
E5            1     DEEM MADELINE/AU
E6          294     DEEM MARK/AU
E7          371     DEEM MARK E/AU
E8            3     DEEM MARY L/AU
E9            6     DEEM MARY LEASE/AU
E10           1     DEEM MICHAEL/AU
E11           1     DEEM MICHAEL A/AU
E12           9     DEEM MICHAEL E/AU

=> s e6-7

L6          665 ("DEEM MARK"/AU OR "DEEM MARK E"/AU)

=> s l6 and nasal

L7           36 L6 AND NASAL

=> dup rem L7

PROCESSING COMPLETED FOR L7
L8            31 DUP REM L7 (5 DUPLICATES REMOVED)

=> d ibib kwic ab 1-31


L8   ANSWER 1 OF 31  USPATFULL on STN
ACCESSION NUMBER:       2020:53186  USPATFULL
TITLE:                  SYSTEMS AND METHODS FOR DELIVERY OF A THERAPEUTIC AGENT
INVENTOR(S):            Deem, Mark E., Mountain View, CA, UNITED STATES
                        Gifford, Hanson, Woodside, CA, UNITED STATES
APPLICANT(S):           The Foundry, LLC, Menlo Park, CA, UNITED STATES

                             NUMBER       KIND    DATE
                        ---------------- ------ --------
PATENT INFORMATION:     US 20200046955     A1   20200213
                        US 10610675        B2   20200407
APPLICATION INFO.:      US 2019-16659893   A1   20191022  (16)
RELATED APPLN. INFO.:   Continuation of Ser. No. US 2018-16036381, filed on 16
                        Jul 2018, PENDING Continuation of Ser. No. US
                        2016-15358187, filed on 22 Nov 2016, Pat. No. US
                        10022529 Continuation of Ser. No. US 2015-14601529,
                        filed on 21 Jan 2015, Pat. No. US 9498283 Continuation
                        of Ser. No. US 2012-13660629, filed on 25 Oct 2012,
                        Pat. No. US 8961391 Continuation of Ser. No. US
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2011-13253595, filed on 5 Oct 2011, Pat. No. US 8338164
Continuation of Ser. No. US 2009-559278, filed on 14
Sep 2009, Pat. No. US 8133497 Division of Ser. No. US
2006-459090, filed on 21 Jul 2006, Pat. No. US 7608275

	NUMBER	DATE
PRIORITY INFORMATION:	US 2005-60702077	20050722 (60)
DOCUMENT TYPE:	Utility	
FILE SEGMENT:	APPLICATION	
NUMBER OF CLAIMS:	30	
EXEMPLARY CLAIM:	1	
NUMBER OF DRAWINGS:	27 Drawing Page(s)	
LINE COUNT:	1712	

CAS INDEXING IS AVAILABLE FOR THIS PATENT. Full-text

IN Deem, Mark E., Mountain View, CA, UNITED STATES

SUMM . . . relates to methods and systems for delivering toxins, such as botulinum toxin light chain fragments, to target cells in a nasal cavity.

SUMM . . . 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. . . 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.

SUMM . . . 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.

SUMM . . . 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. . .

SUMM . . . 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,. . .

SUMM 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,. . . 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.

SUMM 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.. . .

SUMM . . . 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. . . 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. . .

SUMM . . . 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. . . 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. . .

SUMM . . . 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. . . 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. . .

SUMM . . . external ultrasonic transducers and/or ultrasound wave guides capable of delivering focused or unfocused ultrasound into the target tissues of the nasal cavity.

SUMM . . . 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. . . 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. . .

SUMM . . . 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.. . .

SUMM . . . 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. . .

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

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

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

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

DRWD . . . 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.

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

DETD . . . 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. . .

DETD . . . 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.

DETD . . . 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. . .

DETD Delivery to Nasal Cavity

DETD . . . 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,. . .

DETD 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. . . 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. . . 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. . .

DETD . . . 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. . .

DETD 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. . . 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. . .

DETD . . . 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. . .

DETD . . . 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,. . .

DETD 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. . . 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.

DETD . . . 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. . .

DETD . . . 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. . .

DETD 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. . .

DETD 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. . .

DETD 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. . .

CLM 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. . .

CLM What is claimed is:
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. . .

AB 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.

L8 ANSWER 2 OF 31 USPATFULL on STN

ACCESSION NUMBER: 2020:713 USPATFULL
TITLE: NASOLACRIMAL DRAINAGE SYSTEM IMPLANTS FOR DRUG THERAPY
INVENTOR(S): de Juan, JR., Eugene, San Francisco, CA, UNITED STATES
Boyd, Stephen, Murrieta, CA, UNITED STATES
Reich, Cary, Los Gatos, CA, UNITED STATES
Rapacki, Alan, Redwood, CA, UNITED STATES
Gifford, Hanson S., Woodside, CA, UNITED STATES
Deem, Mark, Mountain View, CA, UNITED STATES
PATENT ASSIGNEE(S): Mati Therapeutics Inc., Austin, TX, UNITED STATES (U.S. corporation)

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 20200000715	A1	20200102
APPLICATION INFO.:	US 2019-16544884	A1	20190819 (16)

RELATED APPLN. INFO.: Continuation of Ser. No. US 2017-15852619, filed on 22 Dec 2017, Pat. No. US 10383817 Continuation of Ser. No. US 2017-15405991, filed on 13 Jan 2017, Pat. No. US 9849082 Continuation of Ser. No. US 2015-14858555, filed on 18 Sep 2015, Pat. No. US 9549852 Continuation of Ser. No. US 2014-14265071, filed on 29 Apr 2014, Pat. No. US 9168222 Continuation of Ser. No. US 2011-13184690, filed on 18 Jul 2011, Pat. No. US 8747884 Continuation of Ser. No. US 2007-695545, filed on 2 Apr 2007, Pat. No. US 7998497

	NUMBER	DATE
PRIORITY INFORMATION:	US 2006-60871864	20061226 (60)
	US 2006-60787775	20060331 (60)

DOCUMENT TYPE: Utility
FILE SEGMENT: APPLICATION
NUMBER OF CLAIMS: 47
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 30 Drawing Page(s)
LINE COUNT: 1976
CAS INDEXING IS AVAILABLE FOR THIS PATENT. Full-text

IN Deem, Mark, Mountain View, CA, UNITED STATES
DETD . . . extend through the drug core 112 to permit tear flow through the lumen for the delivery of therapeutic agent for nasal and systemic applications of the therapeutic agent. In addition or in combination with channel 112C, retention structure 132 and core. . .
AB An implant for insertion through a punctum and into a canalicular lumen of a patient. The implant includes a matrix of material, a therapeutic agent dispersed in the matrix of material, a sheath disposed over a portion of the matrix of material and configured to inhibit the therapeutic agent from being released from the matrix of material into the canalicular lumen and to allow the therapeutic agent to be released from a surface of the matrix of material to a tear film, and a retention structure configured to retain the implant within the canalicular lumen.

L8 ANSWER 3 OF 31 USPATFULL on STN
ACCESSION NUMBER: 2019:61992 USPATFULL
TITLE: NASOLACRIMAL DRAINGAGE SYSTEM IMPLANTS FOR DRUG THERAPY
INVENTOR(S): de Juan, JR., Eugene, San Francisco, CA, UNITED STATES
Reich, Cary, Los Gatos, CA, UNITED STATES
Boyd, Stephen, Murrieta, CA, UNITED STATES
Gifford, Hanson S., Woodside, CA, UNITED STATES
Deem, Mark, Mountain View, CA, UNITED STATES
Rapacki, Alan, Redwood City, CA, UNITED STATES
PATENT ASSIGNEE(S): Mati Therapeutics Inc., Austin, TX, UNITED STATES (U.S. corporation)

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 20190054018	A1	20190221
	US 10300014	B2	20190528
APPLICATION INFO.:	US 2018-16168554	A1	20181023 (16)

RELATED APPLN. INFO.: Continuation of Ser. No. US 2017-15852619, filed on 22 Dec 2017, PENDING Continuation of Ser. No. US 2017-15405991, filed on 13 Jan 2017, Pat. No. US 9849082 Continuation of Ser. No. US 2015-14858555, filed on 18 Sep 2015, Pat. No. US 9549852 Continuation of Ser. No. US 2014-14265071, filed on 29 Apr 2014, Pat. No. US 9168222 Continuation of Ser. No. US 2011-13184690, filed on 18 Jul 2011, Pat. No. US 8747884 Continuation of Ser. No. US 2007-695545, filed on 2 Apr 2007, Pat. No. US 7998497

	NUMBER	DATE
PRIORITY INFORMATION:	US 2006-60871864	20061226 (60)
	US 2006-60787775	20060331 (60)

DOCUMENT TYPE: Utility
FILE SEGMENT: APPLICATION
NUMBER OF CLAIMS: 21
EXEMPLARY CLAIM: 1-47
NUMBER OF DRAWINGS: 30 Drawing Page(s)
LINE COUNT: 1846
CAS INDEXING IS AVAILABLE FOR THIS PATENT. Full-text
IN Deem, Mark, Mountain View, CA, UNITED STATES
DETD . . . extend through the drug core 112 to permit tear flow through the lumen for the delivery of therapeutic agent for nasal and systemic applications of the therapeutic agent. In addition or in combination with channel 112C, retention structure 132 and core. . .
AB An implant for insertion through a punctum and into a canalicular lumen of a patient. The implant includes a matrix of material, a therapeutic agent dispersed in the matrix of material, a sheath disposed over a portion of the matrix of material and configured to inhibit the therapeutic agent from being released from the matrix of material into the canalicular lumen and to allow the therapeutic agent to be released from a surface of the matrix of material to a tear film, and a retention structure configured to retain the implant within the canalicular lumen.

L8 ANSWER 4 OF 31 USPATFULL on STN
ACCESSION NUMBER: 2019:61991 USPATFULL
TITLE: DRUG DELIVERY METHODS, STRUCTURES, AND COMPOSITIONS FOR

NASOLACRIMAL SYSTEM
INVENTOR(S): de Juan, Eugene, San Francisco, CA, UNITED STATES
Reich, Cary, Los Gatos, CA, UNITED STATES
Boyd, Stephen, Murrieta, CA, UNITED STATES
Gifford, Hanson S., Woodside, CA, UNITED STATES
Deem, Mark, Mountain View, CA, UNITED STATES
PATENT ASSIGNEE(S): Mati Therapeutics Inc., Austin, TX, UNITED STATES (U.S. corporation)

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 20190054017	A1	20190221
APPLICATION INFO.:	US 2018-16168335	A1	20181023 (16)

RELATED APPLN. INFO.: Continuation of Ser. No. US 2014-14333349, filed on 16 Jul 2014, PENDING Continuation of Ser. No. US 2014-14180592, filed on 14 Feb 2014, Pat. No. US 9610194 Continuation of Ser. No. US 2012-13645261, filed on 4 Oct 2012, Pat. No. US 8691265 Continuation of Ser. No. US 2008-332219, filed on 10 Dec 2008, ABANDONED Continuation of Ser. No. US 2007-695537, filed on 2 Apr 2007, Pat. No. US 8795711

	NUMBER	DATE
PRIORITY INFORMATION:	US 2006-60787775	20060331 (60)
	US 2006-60871864	20061226 (60)

DOCUMENT TYPE: Utility
FILE SEGMENT: APPLICATION
NUMBER OF CLAIMS: 53
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 25 Drawing Page(s)
LINE COUNT: 1905
CAS INDEXING IS AVAILABLE FOR THIS PATENT. Full-text
IN Deem, Mark, Mountain View, CA, UNITED STATES
DETD . . . extend through the drug core 112 to permit tear flow through the lumen for the delivery of therapeutic agent for nasal and systemic applications of the therapeutic agent. In addition or in combination with channel 112C, retention structure 132 and core. . .
AB An implant for insertion into a punctum of a patient comprises a body. The body has a distal end, a proximal end, and an axis therebetween. The distal end of the body is insertable distally through the punctum into the canalicular lumen. The body comprises a therapeutic agent included within an agent matrix drug core. Exposure of the agent matrix to the tear fluid effects an effective therapeutic agent release into the tear fluid over a sustained period. The body has a sheath disposed over the agent matrix to inhibit release of the agent away from the proximal end. The body also has an outer surface configured to engage luminal wall tissues so as to inhibit expulsion when disposed therein. In specific embodiments, the agent matrix comprises a non-bioabsorbable polymer, for example silicone in a non-homogenous mixture with the agent.

L8 ANSWER 5 OF 31 BIOSIS COPYRIGHT (c) 2020 Clarivate Analytics on STN
ACCESSION NUMBER: 2018:777166 BIOSIS
DOCUMENT NUMBER: PREV201800777166
TITLE: Methods and systems for toxin delivery to the nasal cavity.
AUTHOR(S): Deem, Mark E. [Inventor]; Anonymous; Gifford, Hanson [Inventor]
CORPORATE SOURCE: Mountain View, CA USA
ASSIGNEE: The Foundry LLC
PATENT INFORMATION: US 10052465 20180821
SOURCE: Official Gazette of the United States Patent and Trademark Office Patents, (AUG 21 2018)
CODEN: OGUPE7. ISSN: 0098-1133.
DOCUMENT TYPE: Patent
LANGUAGE: English
ENTRY DATE: Entered STN: 26 Sep 2018
Last Updated on STN: 3 Oct 2018 Full-text
TI Methods and systems for toxin delivery to the nasal cavity.
AU Deem, Mark E. [Inventor]; Anonymous; Gifford, Hanson [Inventor]
AB 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. . .

IT . . .
and Techniques; Equipment Apparatus Devices and Instrumentation; Pulmonary Medicine (Human Medicine, Medical Sciences)

IT Parts, Structures, & Systems of Organisms
nasal cavity: respiratory system

IT Chemicals & Biochemicals
toxins: toxin

AB 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.

L8 ANSWER 6 OF 31 USPATFULL on STN

ACCESSION NUMBER: 2018:153972 USPATFULL
TITLE: NASOLACRIMAL DRAINAGE SYSTEM IMPLANTS FOR DRUG THERAPY
INVENTOR(S): de Juan, JR., Eugene, San Francisco, CA, UNITED STATES
Boyd, Stephen, Murrieta, CA, UNITED STATES
Reich, Cary, Los Gatos, CA, UNITED STATES
Rapacki, Alan, Redwood, CA, UNITED STATES
Gifford, Hanson S., Woodside, CA, UNITED STATES
Deem, Mark, Mountain View, CA, UNITED STATES
APPLICANT(S): Mati Therapeutics Inc., Austin, TX, UNITED STATES

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 20180133150	A1	20180517
	US 10383817	B2	20190820
APPLICATION INFO.:	US 2017-15852619	A1	20171222 (15)

RELATED APPLN. INFO.: Continuation of Ser. No. US 2017-15405991, filed on 13 Jan 2017, Pat. No. US 9849082 Continuation of Ser. No. US 2015-14858555, filed on 18 Sep 2015, Pat. No. US 9549852 Continuation of Ser. No. US 2014-14265071, filed on 29 Apr 2014, Pat. No. US 9168222 Continuation of Ser. No. US 2011-13184690, filed on 18 Jul 2011, Pat. No. US 8747884 Continuation of Ser. No. US 2007-695545, filed on 2 Apr 2007, Pat. No. US 7998497

	NUMBER	DATE
PRIORITY INFORMATION:	US 2006-60871864	20061226 (60)
	US 2006-60787775	20060331 (60)

DOCUMENT TYPE: Utility
FILE SEGMENT: APPLICATION
NUMBER OF CLAIMS: 47
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 30 Drawing Page(s)
LINE COUNT: 1976
CAS INDEXING IS AVAILABLE FOR THIS PATENT. Full-text
IN Deem, Mark, Mountain View, CA, UNITED STATES
DETD . . . extend through the drug core 112 to permit tear flow through the lumen for the delivery of therapeutic agent for nasal and systemic applications of the therapeutic agent. In addition or in combination with channel 112C, retention structure 132 and core. . .
AB An implant for insertion through a punctum and into a canalicular lumen of a patient. The implant includes a matrix of material, a therapeutic agent dispersed in the matrix of material, a sheath disposed over a portion of the matrix of material and configured to inhibit the therapeutic agent from being released from the matrix of material into the canalicular lumen and to allow the therapeutic agent to be released from a surface of the matrix of material to a tear film, and a retention structure configured to retain the implant within the canalicular lumen.

L8 ANSWER 7 OF 31 BIOSIS COPYRIGHT (c) 2020 Clarivate Analytics on STN
ACCESSION NUMBER: 2017:585488 BIOSIS
DOCUMENT NUMBER: PREV201700585488

TITLE: Methods and systems for toxin delivery to the nasal cavity.
AUTHOR(S): Deem, Mark E. [Inventor]; Anonymous; Gifford, Hanson [Inventor]
CORPORATE SOURCE: Mountain View, CA USA
ASSIGNEE: The Foundry LLC
PATENT INFORMATION: US 09700707 20170711
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DOCUMENT TYPE: Patent
LANGUAGE: English
ENTRY DATE: Entered STN: 2 Aug 2017
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TI Methods and systems for toxin delivery to the nasal cavity.
AU Deem, Mark E. [Inventor]; Anonymous; Gifford, Hanson [Inventor]
AB 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. . .
AB 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.

L8 ANSWER 8 OF 31 USPATFULL on STN
ACCESSION NUMBER: 2017:306785 USPATFULL
TITLE: METHODS AND SYSTEMS FOR TOXIN DELIVERY TO THE NASAL CAVITY
INVENTOR(S): Deem, Mark E., Mountain View, CA, UNITED STATES
Gifford, Hanson, Woodside, CA, UNITED STATES
APPLICANT(S): The Foundry, LLC, Menlo Park, CA, UNITED STATES

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 20170266422	A1	20170921
	US 10052465	B2	20180821
APPLICATION INFO.:	US 2017-15615344	A1	20170606 (15)

RELATED APPLN. INFO.: Continuation of Ser. No. US 2015-14841514, filed on 31 Aug 2015, Pat. No. US 9700707 Continuation of Ser. No. US 2013-14139710, filed on 23 Dec 2013, ABANDONED Continuation of Ser. No. US 2011-13328203, filed on 16 Dec 2011, Pat. No. US 8636684 Continuation of Ser. No. US 2009-636477, filed on 11 Dec 2009, Pat. No. US 8105817 Division of Ser. No. US 2007-750963, filed on 18 May 2007, Pat. No. US 7655243 Continuation-in-part of Ser. No. US 2006-459090, filed on 21 Jul 2006, Pat. No. US 7608275

	NUMBER	DATE
PRIORITY INFORMATION:	US 2006-60747771	20060519 (60)
	US 2005-60702077	20050722 (60)

DOCUMENT TYPE: Utility
FILE SEGMENT: APPLICATION
NUMBER OF CLAIMS: 35
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 24 Drawing Page(s)
LINE COUNT: 1394
CAS INDEXING IS AVAILABLE FOR THIS PATENT. Full-text
TI METHODS AND SYSTEMS FOR TOXIN DELIVERY TO THE NASAL CAVITY
IN Deem, Mark E., Mountain View, CA, UNITED STATES
AB 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. . .
SUMM . . . relates to methods and systems for delivering toxins, such as botulinum toxin light chain fragments, to target cells in a nasal cavity.

SUMM . . . 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. . . 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.

SUMM . . . 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.

SUMM . . . 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. . .

SUMM . . . 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.

SUMM 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,. . . 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.

SUMM 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.. . .

SUMM . . . 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. . . 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. . .

SUMM . . . 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. . . 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. . .

SUMM . . . 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. . . 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. . .

SUMM . . . external ultrasonic transducers and/or ultrasound wave guides capable of delivering focused or unfocused ultrasound into the target tissues of the nasal cavity.

SUMM . . . 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. . . 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. . .

SUMM . . . 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.. . .

SUMM . . . 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. . .

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

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

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

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

DRWD . . . 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.

DRWD FIG. 29 depicts toxin delivery using a nasal spray and energy delivery using a face mask.

DRWD FIG. 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.

DRWD FIG. 35 depicts the applicator device illustrated in FIG. 33 when placed within the nasal passageway.

DETD 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,. . .

DETD 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. . . 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. . . 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. . .

DETD . . . 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 FIG. 2A. Fragmented neurotoxin such as BoNT-LC (LC) is introduced into the vicinity of the. . .

DETD . . . 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.

DETD . . . 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. . .

DETD . . . of producing a porative effect at the cellular level, including electrodes, ultrasonic elements and the like, for treatment in the nasal passages.

DETD . . . the energy, or both, non-invasively. For example, as illustrated in FIG. 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. . .

DETD 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. 10, a balloon catheter 100 may be provided with a porous balloon 102. . . 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 FIG. 10, the toxin is being delivered to a lower. . .

DETD . . . 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. . .

DETD . . . 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,. . .

DETD Referring now to FIGS. 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. . . shown in FIG. 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 (FIG. 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.

DETD . . . 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. . .

DETD . . . 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. . .

DETD Referring to FIG. 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. . .

DETD FIGS. 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. . . 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 FIG. 35.

DETD 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 FIG. 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. . .

DETD . . . 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 FIG. 37A, the operator would apply inward pressure in the direction of the arrows to the. . . 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 FIG. 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.

DETD 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. . . 39A) and an expanded configuration when wet (FIG. 39B), wherein the sponge 121 is configured to fit securely within the nasal passageway.

DETD . . . 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 FIG. 36, the liquid can be infused into the applicator tip through. . .

DETD 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.. . .

DETD . . . 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 FIGS. 39A and 39B, a sponge and spring can. . .

DETD . . . 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.

DETD . . . 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.

DETD . . . 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. . . 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.

DETD . . . 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.

DETD 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,. . . open-faced chambers. The outer member may also comprise an array of microneedles to facilitate the passage of BoNT across the nasal membrane. 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. . . 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.

DETD . . . 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. . .

DETD 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.

DETD . . . 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.

DETD . . . this application, the device described with respect to FIGS. 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. . .

DETD 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. . .

DETD 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. . .

CLM What is claimed is:

1. A system for treating a nasal condition in a patient, said system comprising: an apparatus comprising an applicator tip and insertable into a nasal cavity of the patient, the applicator tip comprising an outer expandable member and an inner expandable member disposed within the outer expandable member and configured to expand within the nasal cavity, wherein expansion of the inner expandable member causes expansion of the outer expandable member such that the outer expandable member is placed in contact with a wall of the nasal cavity; and a toxin either: (i) carried by the outer expandable member or (ii) disposed in a space between the. . . and wherein the outer expandable member is configured to deliver the toxin to target cells in the wall of the nasal cavity.

CLM What is claimed is:

. . . system of claim 1, wherein the inner expandable member comprises a low volume configuration adapted to facilitate insertion into the nasal cavity and an expanded volume configuration adapted to place the outer expandable member in contact with the wall of the nasal cavity.

CLM What is claimed is:
. . . expandable member is configured to deliver the toxin from the porous portion to target cells in the wall of the nasal cavity.

CLM What is claimed is:
21. An apparatus for treating a nasal condition in a patient, said apparatus comprising: an applicator tip comprising an outer expandable member and an inner expandable member, wherein the applicator tip is configured to be inserted into a nasal cavity of the patient, wherein the inner expandable member is disposed within the outer expandable member and configured to expand within the nasal cavity, wherein expansion of the inner expandable member causes expansion of the outer expandable member such that the outer expandable member is placed in contact with a wall of the nasal cavity, wherein (i) the outer expandable member is configured to carry a toxin or (ii) the applicator tip comprises a. . . and wherein the outer expandable member in configured to deliver the toxin to target cells in the wall of the nasal cavity.

CLM What is claimed is:
. . . apparatus of claim 21, wherein the inner expandable member comprises a low volume configuration adapted to facilitate insertion into the nasal cavity and an expanded volume configuration adapted to place the outer expandable member in contact with the wall of the nasal cavity.

CLM What is claimed is:
. . . expandable member is configured to deliver the toxin from the porous portion to target cells in the wall of the nasal cavity.

AB 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.

L8 ANSWER 9 OF 31 USPATFULL on STN

ACCESSION NUMBER:	2017:148318 USPATFULL		
TITLE:	NASOLACRIMAL DRAINAGE SYSTEM IMPLANTS FOR DRUG THERAPY		
INVENTOR(S):	de Juan, Jr., Eugene, San Francisco, CA, UNITED STATES Boyd, Stephen, Murrieta, CA, UNITED STATES Reich, Cary, Los Gatos, CA, UNITED STATES Rapacki, Alan, Redwood, CA, UNITED STATES Gifford, Hanson S, Woodside, CA, UNITED STATES Deem, Mark, Mountain View, CA, UNITED STATES		
APPLICANT(S):	Mati Therapeutics Inc., Austin, TX, UNITED STATES		
	NUMBER	KIND	DATE
PATENT INFORMATION:	US 20170128361	A1	20170511
	US 9849082	B2	20171226
APPLICATION INFO.:	US 2017-15405991	A1	20170113 (15)
RELATED APPLN. INFO.:	Continuation of Ser. No. US 2015-14858555, filed on 18 Sep 2015, Pat. No. US 9549852 Continuation of Ser. No. US 2014-14265071, filed on 29 Apr 2014, Pat. No. US 9168222 Continuation of Ser. No. US 2011-13184690, filed on 18 Jul 2011, Pat. No. US 8747884 Continuation of Ser. No. US 2007-695545, filed on 2 Apr 2007, Pat. No. US 7998497		
	NUMBER		DATE
PRIORITY INFORMATION:	US 2006-60787775		20060331 (60)
	US 2006-60871864		20061226 (60)
DOCUMENT TYPE:	Utility		
FILE SEGMENT:	APPLICATION		
NUMBER OF CLAIMS:	25		
EXEMPLARY CLAIM:	1		
NUMBER OF DRAWINGS:	30 Drawing Page(s)		

LINE COUNT: 1862
CAS INDEXING IS AVAILABLE FOR THIS PATENT. Full-text
IN Deem, Mark, Mountain View, CA, UNITED STATES
DETD . . . extend through the drug core 112 to permit tear flow through the lumen for the delivery of therapeutic agent for nasal and systemic applications of the therapeutic agent. In addition or in combination with channel 112C, retention structure 132 and core. . .
AB An implant for insertion through a punctum and into a canalicular lumen of a patient. The implant includes a matrix of material, a therapeutic agent dispersed in the matrix of material, a sheath disposed over a portion of the matrix of material and configured to inhibit the therapeutic agent from being released from the matrix of material into the canalicular lumen and to allow the therapeutic agent to be released from a surface of the matrix of material to a tear film, and a retention structure configured to retain the implant within the canalicular lumen.

L8 ANSWER 10 OF 31 BIOSIS COPYRIGHT (c) 2020 Clarivate Analytics on STN
DUPLICATE 1
ACCESSION NUMBER: 2017:53857 BIOSIS
DOCUMENT NUMBER: PREV201700053857
TITLE: Apparatus for toxin delivery to the nasal cavity.
AUTHOR(S): Deem, Mark E. [Inventor]; Anonymous; Gifford, Hanson [Inventor]; Kim, Steven [Inventor]; Salamini, Alexey [Inventor]
CORPORATE SOURCE: Mountain View, CA USA
ASSIGNEE: THE FOUNDRY LLC
PATENT INFORMATION: US 09511210 20161206
SOURCE: Official Gazette of the United States Patent and Trademark Office Patents, (DEC 6 2016)
CODEN: OGUPE7. ISSN: 0098-1133.
DOCUMENT TYPE: Patent
LANGUAGE: English
ENTRY DATE: Entered STN: 28 Dec 2016
Last Updated on STN: 1 Mar 2017 Full-text
TI Apparatus for toxin delivery to the nasal cavity.
AU Deem, Mark E. [Inventor]; Anonymous; Gifford, Hanson [Inventor]; Kim, Steven [Inventor]; Salamini, Alexey [Inventor]
AB Apparatus 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. . .
AB Apparatus 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.

L8 ANSWER 11 OF 31 USPATFULL on STN
ACCESSION NUMBER: 2016:10112 USPATFULL
TITLE: NASOLACRIMAL DRAINAGE SYSTEM IMPLANTS FOR DRUG THERAPY
INVENTOR(S): de Juan, JR., Eugene, San Francisco, CA, UNITED STATES
Boyd, Stephen, Murrieta, CA, UNITED STATES
Reich, Cary, Los Gatos, CA, UNITED STATES
Rapacki, Alan, Redwood, CA, UNITED STATES
Gifford, Hanson S., Woodside, CA, UNITED STATES
Deem, Mark, Mountain View, CA, UNITED STATES
APPLICANT(S): Mati Therapeutics Inc, Austin, TX, UNITED STATES

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 20160008171	A1	20160114
	US 9549852	B2	20170124
APPLICATION INFO.:	US 2015-14858555	A1	20150918 (14)

RELATED APPLN. INFO.: Continuation of Ser. No. US 2014-14265071, filed on 29 Apr 2014, Pat. No. US 9168222 Continuation of Ser. No. US 2011-13184690, filed on 18 Jul 2011, Pat. No. US 8747884 Continuation of Ser. No. US 2007-695545, filed on 2 Apr 2007, Pat. No. US 7998497

NUMBER	DATE

PRIORITY INFORMATION: US 2006-60871864 20061226 (60)
US 2006-60787775 20060331 (60)
US 2006-60871864 20061226 (60)
DOCUMENT TYPE: Utility
FILE SEGMENT: APPLICATION
NUMBER OF CLAIMS: 14
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 30 Drawing Page(s)
LINE COUNT: 1850
CAS INDEXING IS AVAILABLE FOR THIS PATENT. Full-text
IN Deem, Mark, Mountain View, CA, UNITED STATES
DETD . . . extend through the drug core 112 to permit tear flow through the lumen for the delivery of therapeutic agent for nasal and systemic applications of the therapeutic agent. In addition or in combination with channel 112C, retention structure 132 and core. . .
AB An implant for insertion through a punctum and into a canalicular lumen of a patient. The implant includes a matrix of material, a therapeutic agent dispersed in the matrix of material, a sheath disposed over a portion of the matrix of material and configured to inhibit the therapeutic agent from being released from the matrix of material into the canalicular lumen and to allow the therapeutic agent to be released from a surface of the matrix of material to a tear film, and a retention structure configured to retain the implant within the canalicular lumen.

L8 ANSWER 12 OF 31 USPATFULL on STN
ACCESSION NUMBER: 2015:413714 USPATFULL
TITLE: METHODS AND SYSTEMS FOR TOXIN DELIVERY TO THE NASAL CAVITY
INVENTOR(S): Deem, Mark E., Mountain View, CA, UNITED STATES
Gifford, Hanson, Woodside, CA, UNITED STATES
APPLICANT(S): The Foundry LLC, Menlo Park, CA, UNITED STATES

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 20150367115	A1	20151224
	US 20170021148	A9	20170126
	US 9700707	B2	20170711
APPLICATION INFO.:	US 2015-14841514	A1	20150831 (14)

RELATED APPLN. INFO.: Continuation of Ser. No. US 2013-14139710, filed on 23 Dec 2013, ABANDONED Continuation of Ser. No. US 2011-13328203, filed on 16 Dec 2011, Pat. No. US 8636684 Continuation of Ser. No. US 2009-636477, filed on 11 Dec 2009, Pat. No. US 8105817 Division of Ser. No. US 2007-750963, filed on 18 May 2007, Pat. No. US 7655243 Continuation-in-part of Ser. No. US 2006-459090, filed on 21 Jul 2006, Pat. No. US 7608275

	NUMBER	DATE
PRIORITY INFORMATION:	US 2005-60702077	20050722 (60)

DOCUMENT TYPE: Utility
FILE SEGMENT: APPLICATION
NUMBER OF CLAIMS: 24
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 24 Drawing Page(s)
LINE COUNT: 1360
CAS INDEXING IS AVAILABLE FOR THIS PATENT. Full-text
TI METHODS AND SYSTEMS FOR TOXIN DELIVERY TO THE NASAL CAVITY
IN Deem, Mark E., Mountain View, CA, UNITED STATES
AB 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. . .
SUMM . . . relates to methods and systems for delivering toxins, such as botulinum toxin light chain fragments, to target cells in a nasal cavity.
SUMM . . . 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. . . 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.

SUMM . . . 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.

SUMM . . . 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. . .

SUMM . . . 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.

SUMM 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,. . . 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.

SUMM 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.. . .

SUMM . . . 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. . . 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. . .

SUMM . . . 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. . . 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. . .

SUMM . . . 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. . . 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. . .

SUMM . . . external ultrasonic transducers and/or ultrasound wave guides capable of delivering focused or unfocused ultrasound into the target tissues of the nasal cavity.

SUMM . . . 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. . . 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. . .

SUMM . . . 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.. . .

SUMM . . . 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. . .

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

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

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

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

DRWD . . . 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.

DRWD FIG. 29 depicts toxin delivery using a nasal spray and energy delivery using a face mask.

DRWD FIG. 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.

DRWD FIG. 35 depicts the applicator device illustrated in FIG. 33 when placed within the nasal passageway.

DETD 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,. . .

DETD 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. . . 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. . . 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. . .

DETD . . . 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 FIG. 2A. Fragmented neurotoxin such as BoNT-LC (LC) is introduced into the vicinity of the. . .

DETD . . . 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.

DETD . . . 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. . .

DETD . . . of producing a porative effect at the cellular level, including electrodes, ultrasonic elements and the like, for treatment in the nasal passages.

DETD . . . the energy, or both, non-invasively. For example, as illustrated in FIG. 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. . .

DETD 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. 10, a balloon catheter 100 may be provided with a porous balloon 102. . . 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 FIG. 10, the toxin is being delivered to a lower. . .

DETD . . . 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. . .

DETD . . . 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,. . .

DETD Referring now to FIGS. 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. . . shown in FIG. 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 (FIG. 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.

DETD . . . 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. . .

DETD . . . 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. . .

DETD Referring to FIG. 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. . .

DETD FIGS. 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. . . 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 FIG. 35.

DETD 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 FIG. 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. . .

DETD . . . 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 FIG. 37A, the operator would apply inward pressure in the direction of the arrows to the. . . 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 FIG. 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.

DETD 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. . . 39A) and an expanded configuration when wet (FIG. 39B), wherein the sponge 121 is configured to fit securely within the nasal passageway.

DETD . . . 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 FIG. 36, the liquid can be infused into the applicator tip through. . .

DETD 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.. . .

DETD . . . 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 FIGS. 39A and 39B, a sponge and spring can. . .

DETD . . . 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.

DETD . . . 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.

DETD . . . 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. . . 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.

DETD . . . 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.

DETD 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,. . . open-faced chambers. The outer member may also comprise an array of microneedles to facilitate the passage of BoNT across the nasal membrane. 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. . . 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.

DETD . . . 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. . .

DETD 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.

DETD . . . 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.

DETD . . . this application, the device described with respect to FIGS. 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. . .

DETD 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. . .

DETD 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. . .

CLM What is claimed is:

1. A method for treating a nasal condition in a patient, said method comprising: inserting an applicator tip of an apparatus through a nostril of the patient and into a nasal cavity of the patient, wherein the applicator tip comprises an inner expandable member and an outer expandable member extending around the inner expandable member, wherein the inner expandable member is expanded in the nasal cavity thereby causing the outer expandable member to expand and contact a wall of the nasal cavity, and wherein a toxin is delivered from the expanded outer expandable member to target cells in the wall of the nasal cavity.

CLM What is claimed is:

12. The method of claim 1, wherein the inner expandable member substantially fills the nasal cavity when expanded, thereby inhibiting release of the toxin into portions of the nasal cavity other than the wall.

CLM What is claimed is:

. . . The method of claim 12, wherein the toxin is delivered by delivering a therapeutic dose to the wall of the nasal cavity while inhibiting release of the toxin into other portions of the nasal cavity.

CLM What is claimed is:

15. The method of claim 14, wherein the applicator tip is inserted into

the nasal cavity with the handle in the compressed configuration.

CLM What is claimed is:
. . . the handle is biased to be in the expanded configuration such that when the applicator tip is inserted into the nasal cavity, the applicator tip is pressed against a nasal turbinate of the nasal cavity.

CLM What is claimed is:
. . . of claim 1, wherein the toxin is delivered at a rate proportionate with a rate of toxin absorption across a nasal membrane of the patient.

CLM What is claimed is:
. . . wherein the outer expandable member when expanded is configured to match a shape of at least a portion of the nasal cavity.

CLM What is claimed is:
24. A method for treating a nasal condition in a patient, said method comprising: inserting a first applicator tip and a second applicator tip of an apparatus respectively through a first nostril and a second nostril of the patient and into a nasal cavity of the patient with a handle of the apparatus, wherein the first applicator tip and the second applicator tip. . . and an outer expandable member extending around the inner expandable member, wherein the inner expandable members are expanded in the nasal cavity thereby causing the outer expandable member to expand and contact a wall of the nasal cavity, and wherein a toxin is delivered from the expanded outer expandable members to target cells in the wall of the nasal cavity.

AB 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.

L8 ANSWER 13 OF 31 USPATFULL on STN

ACCESSION NUMBER:	2015:253031 USPATFULL
TITLE:	Drug Delivery Methods, Structures, and Compositions for Nasolacrimal Systems
INVENTOR(S):	de Juan, JR., Eugene, San Francisco, CA, UNITED STATES Boyd, Stephen, Murrieta, CA, UNITED STATES Gifford, III, Hanson S., Woodside, CA, UNITED STATES Deem, Mark, Mountain View, CA, UNITED STATES Reich, Cary, Los Gatos, CA, UNITED STATES
PATENT ASSIGNEE(S):	Mati Therapeutics Inc., Austin, TX, UNITED STATES (U.S. corporation)

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 20150224200	A1	20150813
APPLICATION INFO.:	US 2015-14598262	A1	20150116 (14)

RELATED APPLN. INFO.: Continuation of Ser. No. US 2014-14180592, filed on 14 Feb 2014, PENDING Continuation of Ser. No. US 2012-13645261, filed on 4 Oct 2012, Pat. No. US 8691265 Continuation of Ser. No. US 2008-332219, filed on 10 Dec 2008, ABANDONED Continuation of Ser. No. US 2007-695537, filed on 2 Apr 2007, Pat. No. US 8795711

	NUMBER	DATE
PRIORITY INFORMATION:	US 2006-60787775	20060331 (60)
	US 2006-60871864	20061226 (60)

DOCUMENT TYPE:	Utility
FILE SEGMENT:	APPLICATION
NUMBER OF CLAIMS:	21
EXEMPLARY CLAIM:	1-53
NUMBER OF DRAWINGS:	25 Drawing Page(s)
LINE COUNT:	1807

CAS INDEXING IS AVAILABLE FOR THIS PATENT. Full-text

IN Deem, Mark, Mountain View, CA, UNITED STATES

DETD . . . extend through the drug core 112 to permit tear flow through the lumen for the delivery of therapeutic agent for nasal and systemic applications of the therapeutic agent. In addition or in combination with channel 112C, retention structure 132 and core. . .

AB An implant for insertion into a punctum of a patient comprises a body. The body has a distal end, a proximal end, and an axis therebetween. The distal end of the body is insertable distally through the punctum into the canalicular lumen. The body comprises a therapeutic agent included within an agent matrix drug core. Exposure of the agent matrix to the tear fluid effects an effective therapeutic agent release into the tear fluid over a sustained period. The body has a sheath disposed over the agent matrix to inhibit release of the agent away from the proximal end. The body also has an outer surface configured to engage luminal wall tissues so as to inhibit expulsion when disposed therein. In specific embodiments, the agent matrix comprises a non-bioabsorbable polymer, for example silicone in a non-homogenous mixture with the agent.

L8 ANSWER 14 OF 31 BIOSIS COPYRIGHT (c) 2020 Clarivate Analytics on STN
ACCESSION NUMBER: 2014:257758 BIOSIS
DOCUMENT NUMBER: PREV201400257758
TITLE: Methods and systems for toxin delivery to the nasal cavity.
AUTHOR(S): Deem, Mark E. [Inventor]; Anonymous; Gifford, Hanson [Inventor]
CORPORATE SOURCE: Mountain View, CA USA
ASSIGNEE: The Foundry LLC
PATENT INFORMATION: US 08636684 20140128
SOURCE: Official Gazette of the United States Patent and Trademark Office Patents, (JAN 28 2014)
CODEN: OGUPE7. ISSN: 0098-1133.
DOCUMENT TYPE: Patent
LANGUAGE: English
ENTRY DATE: Entered STN: 19 Mar 2014
Last Updated on STN: 19 Mar 2014 Full-text

TI Methods and systems for toxin delivery to the nasal cavity.
AU Deem, Mark E. [Inventor]; Anonymous; Gifford, Hanson [Inventor]
AB 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. . .
IT Methods & Equipment
nasal cavity providing toxin delivery system: medical equipment;
nasal cavity providing toxin delivery method: clinical techniques
AB 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.

L8 ANSWER 15 OF 31 USPATFULL on STN
ACCESSION NUMBER: 2014:368120 USPATFULL
TITLE: DRUG DELIVERY METHODS, STRUCTURES, AND COMPOSITIONS FOR NASOLACRIMAL SYSTEM
INVENTOR(S): de Juan, JR., Eugene, San Francisco, CA, UNITED STATES
Reich, Cary, Los Gatos, CA, UNITED STATES
Boyd, Stephen, Murrieta, CA, UNITED STATES
Gifford, Hanson S., Woodside, CA, UNITED STATES
Deem, Mark, Mountain View, CA, UNITED STATES
APPLICANT(S): Mati Therapeutics, Austin, TX, UNITED STATES

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 20140328894	A1	20141106
APPLICATION INFO.:	US 2014-14333349	A1	20140716 (14)

RELATED APPLN. INFO.: Continuation of Ser. No. US 2007-695537, filed on 2 Apr 2007, Pat. No. US 8795711

NUMBER	DATE

PRIORITY INFORMATION: US 2006-60787775 20060331 (60)
US 2006-60871864 20061226 (60)
DOCUMENT TYPE: Utility
FILE SEGMENT: APPLICATION
NUMBER OF CLAIMS: 53
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 25 Drawing Page(s)
LINE COUNT: 1908
CAS INDEXING IS AVAILABLE FOR THIS PATENT. Full-text
IN Deem, Mark, Mountain View, CA, UNITED STATES
DETD . . . extend through the drug core 112 to permit tear flow through the lumen for the delivery of therapeutic agent for nasal and systemic applications of the therapeutic agent. In addition or in combination with channel 112C, retention structure 132 and core. . .
AB An implant for insertion into a punctum of a patient comprises a body. The body has a distal end, a proximal end, and an axis therebetween. The distal end of the body is insertable distally through the punctum into the canalicular lumen. The body comprises a therapeutic agent included within an agent matrix drug core. Exposure of the agent matrix to the tear fluid effects an effective therapeutic agent release into the tear fluid over a sustained period. The body has a sheath disposed over the agent matrix to inhibit release of the agent away from the proximal end. The body also has an outer surface configured to engage luminal wall tissues so as to inhibit expulsion when disposed therein. In specific embodiments, the agent matrix comprises a non-bioabsorbable polymer, for example silicone in a non-homogenous mixture with the agent.

L8 ANSWER 16 OF 31 USPATFULL on STN
ACCESSION NUMBER: 2014:265257 USPATFULL
TITLE: NASOLACRIMAL DRAINAGE SYSTEM IMPLANTS FOR DRUG THERAPY
INVENTOR(S): De Juan, JR., Eugene, San Francisco, CA, UNITED STATES
Boyd, Stephen, Murrieta, CA, UNITED STATES
Reich, Cary, Los Gatos, CA, UNITED STATES
Rapacki, Alan, Redwood, CA, UNITED STATES
Gifford, Hanson S., Woodside, CA, UNITED STATES
Deem, Mark, Mountain View, CA, UNITED STATES
PATENT ASSIGNEE(S): Mati Therapeutics Inc., Austin, TX, UNITED STATES (U.S. corporation)

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 20140236293	A1	20140821
	US 9168222	B2	20151027
APPLICATION INFO.:	US 2014-14265071	A1	20140429 (14)

RELATED APPLN. INFO.: Continuation of Ser. No. US 2011-13184690, filed on 18 Jul 2011, Pat. No. US 8747884 Continuation of Ser. No. US 2007-695545, filed on 2 Apr 2007, Pat. No. US 7998497

	NUMBER	DATE
PRIORITY INFORMATION:	US 2006-60871864	20061226 (60)
	US 2006-60787775	20060331 (60)

DOCUMENT TYPE: Utility
FILE SEGMENT: APPLICATION
NUMBER OF CLAIMS: 21
EXEMPLARY CLAIM: 1-20
NUMBER OF DRAWINGS: 30 Drawing Page(s)
LINE COUNT: 1848
CAS INDEXING IS AVAILABLE FOR THIS PATENT. Full-text
IN Deem, Mark, Mountain View, CA, UNITED STATES
DETD . . . extend through the drug core 112 to permit tear flow through the lumen for the delivery of therapeutic agent for nasal and systemic applications of the therapeutic agent. In addition or in combination with channel 112C, retention structure 132 and core. . .
AB An implant for insertion through a punctum and into a canalicular lumen of a patient. The implant includes a matrix of material, a therapeutic agent dispersed in the matrix of material, a sheath disposed over a portion of the matrix of material and configured to inhibit the therapeutic agent from being released from the matrix of material into the canalicular lumen and to allow the therapeutic agent to be released

from a surface of the matrix of material to a tear film, and a retention structure configured to retain the implant within the canalicular lumen.

L8 ANSWER 17 OF 31 USPATFULL on STN
ACCESSION NUMBER: 2014:181695 USPATFULL
TITLE: DRUG DELIVERY METHODS, STRUCTURES, AND COMPOSITIONS FOR NASOLACRIMAL SYSTEM
INVENTOR(S): De Juan, JR., Eugene, San Francisco, CA, UNITED STATES
Boyd, Stephen, Murrieta, CA, UNITED STATES
Gifford, III, Hanson S., Woodside, CA, UNITED STATES
Deem, Mark, Mountain View, CA, UNITED STATES
Reich, Cary J., Los Gatos, CA, UNITED STATES
PATENT ASSIGNEE(S): Mati Therapeutics, Inc., Austin, TX, UNITED STATES (U.S. corporation)

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 20140161863	A1	20140612
	US 9610194	B2	20170404
APPLICATION INFO.:	US 2014-14180592	A1	20140214 (14)

RELATED APPLN. INFO.: Continuation of Ser. No. US 2012-13645261, filed on 4 Oct 2012, Pat. No. US 8691265 Continuation of Ser. No. US 2008-332219, filed on 10 Dec 2008, ABANDONED Continuation of Ser. No. US 2007-695537, filed on 2 Apr 2007, PENDING

	NUMBER	DATE
PRIORITY INFORMATION:	US 2006-60871864	20061226 (60)

DOCUMENT TYPE: Utility
FILE SEGMENT: APPLICATION
NUMBER OF CLAIMS: 21
EXEMPLARY CLAIM: 1-89
NUMBER OF DRAWINGS: 25 Drawing Page(s)
LINE COUNT: 1815
CAS INDEXING IS AVAILABLE FOR THIS PATENT. Full-text
IN Deem, Mark, Mountain View, CA, UNITED STATES
DETD . . . extend through the drug core 112 to permit tear flow through the lumen for the delivery of therapeutic agent for nasal and systemic applications of the therapeutic agent. In addition or in combination with channel 112C, retention structure 132 and core. . .
AB A drug insert is configured for use with an implant. The implant is configured for insertion into a lacrimal canaliculus. The drug insert includes a drug core comprising a therapeutic agent and a polymer; and a sheath body comprising material substantially impermeable to the therapeutic agent, wherein the drug core is positioned within the sheath body. The sheath body is configured to provide an exposed end of the drug core that releases therapeutic agent to an eye when the drug insert is disposed within the implant and the implant is positioned in the lacrimal canaliculus. A distal end of the drug core is sealed with a medical-grade adhesive.

L8 ANSWER 18 OF 31 USPATFULL on STN
ACCESSION NUMBER: 2014:127127 USPATFULL
TITLE: METHODS AND SYSTEMS FOR TOXIN DELIVERY TO THE NASAL CAVITY
INVENTOR(S): Deem, Mark E., Mountain View, CA, UNITED STATES
Gifford, Hanson, Woodside, CA, UNITED STATES
PATENT ASSIGNEE(S): The Foundry, LLC, Menlo Park, CA, UNITED STATES (U.S. corporation)

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 20140114233	A1	20140424
APPLICATION INFO.:	US 2013-14139710	A1	20131223 (14)

RELATED APPLN. INFO.: Continuation of Ser. No. US 2011-13328203, filed on 16 Dec 2011, Pat. No. US 8636684 Continuation of Ser. No. US 2009-636477, filed on 11 Dec 2009, Pat. No. US 8105817 Division of Ser. No. US 2007-750963, filed on 18 May 2007, Pat. No. US 7655243 Continuation-in-part

of Ser. No. US 2006-459090, filed on 21 Jul 2006, Pat. No. US 7608275

	NUMBER	DATE
PRIORITY INFORMATION:	US 2005-60702077	20050722 (60)
	US 2006-60747771	20060519 (60)

DOCUMENT TYPE: Utility
FILE SEGMENT: APPLICATION
NUMBER OF CLAIMS: 31
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 24 Drawing Page(s)
LINE COUNT: 1374
CAS INDEXING IS AVAILABLE FOR THIS PATENT. Full-text
TI METHODS AND SYSTEMS FOR TOXIN DELIVERY TO THE NASAL CAVITY
IN Deem, Mark E., Mountain View, CA, UNITED STATES
AB 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. . .
SUMM . . . relates to methods and systems for delivering toxins, such as botulinum toxin light chain fragments, to target cells in a nasal cavity.
SUMM . . . 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. . . 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.
SUMM . . . 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.
SUMM . . . 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. . .
SUMM . . . 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.
SUMM 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,. . . 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.
SUMM 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.. . .
SUMM . . . 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. . . 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. . .

SUMM . . . 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. . . 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. . .

SUMM . . . 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. . . 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. . .

SUMM . . . external ultrasonic transducers and/or ultrasound wave guides capable of delivering focused or unfocused ultrasound into the target tissues of the nasal cavity.

SUMM . . . 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. . . 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. . .

SUMM . . . 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.. . .

SUMM . . . 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. . .

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

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

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

DRWD FIGS. 22 and 23--depict nose plugs for occluding and optionally delivery

poration energy to the nasal cavity.

DRWD . . . 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.

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

DRWD FIG. 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.

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

DETD 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,. . .

DETD 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. . . 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. . . 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. . .

DETD . . . 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 FIG. 2A. Fragmented neurotoxin such as BoNT-LC (LC) is introduced into the vicinity of the. . .

DETD . . . 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.

DETD . . . 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. . .

DETD . . . of producing a porative effect at the cellular level, including electrodes, ultrasonic elements and the like, for treatment in the nasal passages.

DETD . . . the energy, or both, non-invasively. For example, as illustrated in FIG. 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. . .

DETD 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. 10, a balloon catheter 100 may be provided with a porous balloon 102. . . 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 FIG. 10, the toxin is being delivered to a lower. . .

DETD . . . 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. . .

DETD . . . 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,. . .

DETD Referring now to FIGS. 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. . . shown in FIG. 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 (FIG. 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.

DETD . . . 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. . .

DETD . . . 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. . .

DETD Referring to FIG. 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. . .

DETD FIGS. 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. . . 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 FIG. 35.

DETD 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 FIG. 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. . .

DETD . . . 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 FIG. 37A, the operator would apply inward pressure in the direction of the arrows to the. . . 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 FIG. 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.

DETD 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. . . 39A) and an expanded configuration when wet (FIG. 39B), wherein

the sponge 121 is configured to fit securely within the nasal passageway.

DETD . . . 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 FIG. 36, the liquid can be infused into the applicator tip through. . .

DETD 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.. . .

DETD . . . 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 FIGS. 39A and 39B, a sponge and spring can. . .

DETD . . . 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.

DETD . . . 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.

DETD . . . 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. . . 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.

DETD . . . 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.

DETD 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,. . . open-faced chambers. The outer member may also comprise an array of microneedles to facilitate the passage of BoNT across the nasal membrane. 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. . . 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.

DETD . . . 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. . .

DETD 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.

DETD . . . 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.

DETD . . . this application, the device described with respect to FIGS. 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. . .

DETD 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. . .

DETD 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. . .

CLM What is claimed is:
1. A system for treating a nasal condition in a patient, said system comprising: an apparatus insertable into a nasal cavity of the patient, the apparatus comprising an outer expandable member and an inner expandable member disposed within the outer expandable member and configured to expand within the nasal cavity, wherein expansion of the inner expandable member causes expansion of the outer expandable member such that the outer expandable member is placed in contact with a wall of the nasal cavity; and a toxin either: (i) carried by the outer expandable member or (ii) disposed in a space between the. . . members, wherein the outer expandable member is configured to deliver the toxin to target cells in the wall of the nasal cavity.

CLM What is claimed is:
. . . system of claim 1, wherein the inner expandable member comprises a low volume configuration adapted to facilitate insertion into the nasal cavity and an expanded volume configuration adapted to place the outer expandable member in contact with the wall of the nasal cavity.

CLM What is claimed is:
19. A method for treating a nasal condition in a patient, said method comprising: inserting an apparatus into a nasal cavity of the patient, wherein the apparatus comprises an inner and an outer expandable member; expanding the inner expandable member thereby causing the outer expandable member to expand and contact a wall of the nasal cavity; and delivering a toxin from the outer expandable member to target cells in the wall of the nasal cavity.

CLM What is claimed is:
30. The method of claim 19, wherein expanding the inner balloon substantially fills the nasal cavity, thereby inhibiting release of the toxin into portions of the nasal cavity other than the wall.

CLM What is claimed is:
. . . 31. The method of claim 30, wherein delivering the toxin comprises delivering a therapeutic dose to the wall of the nasal cavity while inhibiting release of the toxin into other portions of the nasal cavity.

AB 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.

L8 ANSWER 19 OF 31 USPATFULL on STN

ACCESSION NUMBER:	2013:115390 USPATFULL
TITLE:	DRUG DELIVERY METHODS, STRUCTURES, AND COMPOSITIONS FOR NASOLACRIMAL SYSTEM
INVENTOR(S):	de Juan, JR., Eugene, San Francisco, CA, UNITED STATES Boyd, Stephen, Murrieta, CA, UNITED STATES Gifford, III, Hanson S., Woodside, CA, UNITED STATES Deem, Mark, Mountain View, CA, UNITED STATES Reich, Cary J., Los Gatos, CA, UNITED STATES
PATENT ASSIGNEE(S):	QLT INC., Vancouver, CANADA (non-U.S. corporation)

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 20130101658	A1	20130425
	US 8691265	B2	20140408
APPLICATION INFO.:	US 2012-13645261	A1	20121004 (13)

RELATED APPLN. INFO.: Continuation of Ser. No. US 2008-332219, filed on 10 Dec 2008, ABANDONED Continuation of Ser. No. US 2007-695537, filed on 2 Apr 2007, PENDING

	NUMBER	DATE
PRIORITY INFORMATION:	US 2006-60871864	20061226 (60)

US 2006-60787775 20060331 (60)
DOCUMENT TYPE: Utility
FILE SEGMENT: APPLICATION
NUMBER OF CLAIMS: 21
EXEMPLARY CLAIM: 1-89
NUMBER OF DRAWINGS: 25 Drawing Page(s)
LINE COUNT: 1826
CAS INDEXING IS AVAILABLE FOR THIS PATENT. Full-text
IN Deem, Mark, Mountain View, CA, UNITED STATES
DETD . . . extend through the drug core 112 to permit tear flow through the lumen for the delivery of therapeutic agent for nasal and systemic applications of the therapeutic agent. In addition or in combination with channel 112C, retention structure 132 and core. . .
AB A drug insert is configured for use with an implant. The implant is configured for insertion into a lacrimal canaliculus. The drug insert includes a drug core comprising a therapeutic agent and a polymer; and a sheath body comprising material substantially impermeable to the therapeutic agent, wherein the drug core is positioned within the sheath body. The sheath body is configured to provide an exposed end of the drug core that releases therapeutic agent to an eye when the drug insert is disposed within the implant and the implant is positioned in the lacrimal canaliculus. A distal end of the drug core is sealed with a medical-grade adhesive.

L8 ANSWER 20 OF 31 BIOSIS COPYRIGHT (c) 2020 Clarivate Analytics on STN
ACCESSION NUMBER: 2012:369512 BIOSIS
DOCUMENT NUMBER: PREV201200369512
TITLE: Methods and systems for toxin delivery to the nasal cavity.
AUTHOR(S): Deem, Mark E. [Inventor]; Anonymous; Gifford, Hanson [Inventor]
CORPORATE SOURCE: Mountain View, CA USA
ASSIGNEE: The Foundry LLC
PATENT INFORMATION: US 08105817 20120131
SOURCE: Official Gazette of the United States Patent and Trademark Office Patents, (JAN 31 2012)
CODEN: OGUPE7. ISSN: 0098-1133.
DOCUMENT TYPE: Patent
LANGUAGE: English
ENTRY DATE: Entered STN: 9 May 2012
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TI Methods and systems for toxin delivery to the nasal cavity.
AU Deem, Mark E. [Inventor]; Anonymous; Gifford, Hanson [Inventor]
AB 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. . .
IT Methods & Equipment
nasal cavity targeted toxin/toxin fragment delivery method: therapeutic and prophylactic techniques, clinical techniques; nasal cavity targeted toxin/toxin fragment delivery system: drug delivery device
AB 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.

L8 ANSWER 21 OF 31 USPATFULL on STN
ACCESSION NUMBER: 2012:99920 USPATFULL
TITLE: METHODS AND SYSTEMS FOR TOXIN DELIVERY TO THE NASAL CAVITY
INVENTOR(S): Deem, Mark E., Mountain View, CA, UNITED STATES
Gifford, Hanson, Woodside, CA, UNITED STATES
PATENT ASSIGNEE(S): The Foundry, LLC, Menlo Park, CA, UNITED STATES (U.S. corporation)

NUMBER	KIND	DATE

PATENT INFORMATION: US 20120089078 A1 20120412
US 8636684 B2 20140128
APPLICATION INFO.: US 2011-13328203 A1 20111216 (13)
RELATED APPLN. INFO.: Continuation of Ser. No. US 2009-636477, filed on 11 Dec 2009, Pat. No. US 8105817 Division of Ser. No. US 2007-750963, filed on 18 May 2007, Pat. No. US 7655243 Continuation-in-part of Ser. No. US 2006-459090, filed on 21 Jul 2006, Pat. No. US 7608275

	NUMBER	DATE
PRIORITY INFORMATION:	US 2005-60702077	20050722 (60)
	US 2006-60747771	20060519 (60)

DOCUMENT TYPE: Utility
FILE SEGMENT: APPLICATION
NUMBER OF CLAIMS: 68
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 24 Drawing Page(s)
LINE COUNT: 1435
CAS INDEXING IS AVAILABLE FOR THIS PATENT. Full-text
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IN Deem, Mark E., Mountain View, CA, UNITED STATES
AB 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. . .
SUMM . . . relates to methods and systems for delivering toxins, such as botulinum toxin light chain fragments, to target cells in a nasal cavity.
SUMM . . . 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. . . 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.
SUMM . . . 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.
SUMM . . . 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. . .
SUMM . . . 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.
SUMM 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,. . . 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

SUMM 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.. . .

SUMM . . . 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. . . 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. . .

SUMM . . . 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. . . 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. . .

SUMM . . . 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. . . 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. . .

SUMM . . . external ultrasonic transducers and/or ultrasound wave guides capable of delivering focused or unfocused ultrasound into the target tissues of the nasal cavity.

SUMM . . . 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. . . 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. . .

SUMM . . . 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.. . .

SUMM . . . 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. . .

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

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

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

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

DRWD . . . 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.

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

DRWD FIG. 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.

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

DETD 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,. . .

DETD 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. . . 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. . . 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. . .

DETD . . . 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 FIG. 2A. Fragmented neurotoxin such as BoNT-LC (LC) is introduced into the vicinity of the. . .

DETD . . . 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.

DETD . . . 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. . .

DETD . . . of producing a porative effect at the cellular level, including electrodes, ultrasonic elements and the like, for treatment in the nasal passages.

DETD . . . the energy, or both, non-invasively. For example, as illustrated in FIG. 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. . .

DETD 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. 10, a balloon catheter 100 may be provided with a porous balloon 102. . . 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 FIG. 10, the toxin is being delivered to a lower. . .

DETD . . . 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. . .

DETD . . . 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,. . .

DETD Referring now to FIGS. 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. . . shown in FIG. 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

(FIG. 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.

DETD . . . 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. . .

DETD . . . 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. . .

DETD Referring to FIG. 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. . .

DETD FIGS. 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. . . 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 FIG. 35.

DETD 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 FIG. 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. . .

DETD . . . 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 FIG. 37A, the operator would apply inward pressure in the direction of the arrows to the. . . 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 FIG. 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.

DETD 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. . . 39A) and an expanded configuration when wet (FIG. 39B), wherein the sponge 121 is configured to fit securely within the nasal

passageway.

DETD . . . 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 FIG. 36, the liquid can be infused into the applicator tip through. . .

DETD 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.. . .

DETD . . . 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 FIGS. 39A and 39B, a sponge and spring can. . .

DETD . . . 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.

DETD . . . 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

DETD . . . 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. . . 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.

DETD . . . 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.

DETD 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,. . . open-faced chambers. The outer member may also comprise an array of microneedles to facilitate the passage of BoNT across the nasal membrane. 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. . . 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.

DETD . . . 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. . .

DETD 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

DETD . . . 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.

DETD . . . this application, the device described with respect to FIGS. 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. . .

DETD 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. . .

DETD 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. . .

CLM What is claimed is:
2. A method of treating a nasal condition comprising: positioning one or more occlusion devices in a nasal cavity to fluidly isolate a treatment region therein from a remaining portion of the nasal cavity, the treatment region containing target cells; and introducing a toxin to the treatment region while the one or more occlusion devices block the toxin from entering the remaining portion of the nasal cavity, wherein the toxin inhibits mucous secretion in the target.

CLM What is claimed is:
. . . method of claim 2, wherein the one or more occlusion devices comprise one or more plugs positioned to block a nasal passage of the patient.

CLM What is claimed is:
27. The method of claim 2, wherein the treatment region comprises at least one paranasal sinus, a main nasal passage, or a nasal turbinate.

CLM What is claimed is:
28. The method of claim 2, wherein the treatment region comprises substantially the entire nasal cavity.

CLM What is claimed is:
34. A method of treating a nasal condition in a patient, said method comprising: introducing a gel or foam carrier comprising a toxin to a treatment region in a nasal cavity containing target cells, wherein the toxin is delivered from the gel or foam carrier to the target cells so. . .

CLM What is claimed is:
39. The method of claim 34, further comprising filling a targeted airway of the nasal cavity of the patient with the gel or foam carrier.

CLM What is claimed is:
40. The method of claim 39, further comprising fluidly isolating a treatment region of the nasal cavity, wherein the toxin is introduced into the treatment region.

CLM What is claimed is:
41. The method of claim 34, wherein the gel or foam carrier remains in place in the nasal cavity following introduction while the toxin is delivered to the target cells.

CLM What is claimed is:
62. The method of claim 34, wherein the treatment region comprises at least one paranasal sinus, a main nasal passage, or a nasal turbinate.

CLM What is claimed is:
63. The method of claim 34, wherein the treatment region comprises substantially the entire nasal cavity.

AB 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.

L8 ANSWER 22 OF 31 USPATFULL on STN
ACCESSION NUMBER: 2011:337379 USPATFULL
TITLE: SYSTEM AND METHOD FOR PULMONARY TREATMENT
INVENTOR(S): Deem, Mark, Mountain View, CA, UNITED STATES
Shenoy, Vivek, Redwood City, CA, UNITED STATES

Mayse, Martin L., University City, MO, UNITED STATES
PATENT ASSIGNEE(S): Innovative Pulmonary Solutions, Inc., Bellevue, WA, UNITED STATES (U.S. corporation)

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 20110301587	A1	20111208
APPLICATION INFO.:	US 2011-13081406	A1	20110406 (13)

	NUMBER	DATE
PRIORITY INFORMATION:	US 2010-61321346	20100406 (61)

DOCUMENT TYPE: Utility
FILE SEGMENT: APPLICATION
NUMBER OF CLAIMS: 33
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 49 Drawing Page(s)
LINE COUNT: 2412 Full-text
IN Deem, Mark, Mountain View, CA, UNITED STATES
DETD . . . protection device is inserted into the esophagus 30. This device can be inserted through the mouth, or preferably, trans-nasally. The trans-nasal placement keeps the device separated from the manipulations of the device, to be placed in the trachea.
AB An apparatus and method for pulmonary treatment by denervation is provided. The apparatus includes an elongate member configured for insertion into the trachea to a position adjacent a pulmonary plexus. The apparatus further includes at least one energy delivery element disposed on the elongate member. The energy delivery element is positionable to target at least one nerve in the tracheal wall when the elongate member is positioned in the trachea. Energy from the energy delivery element is delivered to the at least one nerve to treat pulmonary symptoms, conditions, and/or diseases, such as asthma, COPD, obstructive lung diseases, or other pulmonary diseases.

L8 ANSWER 23 OF 31 USPATFULL on STN
ACCESSION NUMBER: 2011:308844 USPATFULL
TITLE: NASOLACRIMAL DRAINAGE SYSTEM IMPLANTS FOR DRUG THERAPY
INVENTOR(S): de Juan, JR., Eugene, San Francisco, CA, UNITED STATES
Boyd, Stephen, Murrieta, CA, UNITED STATES
Reich, Cary, Los Gatos, CA, UNITED STATES
Rapacki, Alan, Redwood City, CA, UNITED STATES
Gifford, III, Hanson S., Woodside, CA, UNITED STATES
Deem, Mark, Mountain View, CA, UNITED STATES
PATENT ASSIGNEE(S): QLT INC., Vancouver, CANADA (non-U.S. corporation)

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 20110276131	A1	20111110
	US 8747884	B2	20140610
APPLICATION INFO.:	US 2011-13184690	A1	20110718 (13)

RELATED APPLN. INFO.: Continuation of Ser. No. US 2007-695545, filed on 2 Apr 2007, Pat. No. US 7998497

	NUMBER	DATE
PRIORITY INFORMATION:	US 2006-60787775	20060331 (60)
	US 2006-60871864	20061226 (60)

DOCUMENT TYPE: Utility
FILE SEGMENT: APPLICATION
NUMBER OF CLAIMS: 20
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 30 Drawing Page(s)
LINE COUNT: 1843
CAS INDEXING IS AVAILABLE FOR THIS PATENT. Full-text
IN Deem, Mark, Mountain View, CA, UNITED STATES
DETD . . . extend through the drug core 112 to permit tear flow through the lumen for the delivery of therapeutic agent for nasal and systemic applications of the therapeutic agent. In addition or in combination with channel 112C, retention structure 132 and core. . .
AB An implant for insertion through a punctum and into a canalicular lumen of a patient. The implant includes a matrix of material, a therapeutic

agent dispersed in the matrix of material, a sheath disposed over a portion of the matrix of material and configured to inhibit the therapeutic agent from being released from the matrix of material into the canalicular lumen and to allow the therapeutic agent to be released from a surface of the matrix of material to a tear film, and a retention structure configured to retain the implant within the canalicular lumen.

L8 ANSWER 24 OF 31 BIOSIS COPYRIGHT (c) 2020 Clarivate Analytics on STN
ACCESSION NUMBER: 2010:122525 BIOSIS
DOCUMENT NUMBER: PREV201000122525
TITLE: Methods and systems for toxin delivery to the nasal cavity.
AUTHOR(S): Deem, Mark E. [Inventor]; Anonymous; Gifford, Hanson [Inventor]
CORPORATE SOURCE: Mountain View, CA USA
ASSIGNEE: The Foundry LLC
PATENT INFORMATION: US 07655243 20100202
SOURCE: Official Gazette of the United States Patent and Trademark Office Patents, (FEB 2 2010)
CODEN: OGUPE7. ISSN: 0098-1133.
DOCUMENT TYPE: Patent
LANGUAGE: English
ENTRY DATE: Entered STN: 24 Feb 2010
Last Updated on STN: 24 Feb 2010 Full-text
TI Methods and systems for toxin delivery to the nasal cavity.
AU Deem, Mark E. [Inventor]; Anonymous; Gifford, Hanson [Inventor]
AB 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. . .
IT Methods & Equipment
nasal cavity based toxin delivery system: drug delivery device
AB 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.

L8 ANSWER 25 OF 31 USPATFULL on STN
ACCESSION NUMBER: 2010:98403 USPATFULL
TITLE: METHODS AND SYSTEMS FOR TOXIN DELIVERY TO THE NASAL CAVITY
INVENTOR(S): DEEM, MARK E., MOUNTAIN VIEW, CA, UNITED STATES
GIFFORD, HANSON, WOODSIDE, CA, UNITED STATES
PATENT ASSIGNEE(S): THE FOUNDY, LLC, MENLO PARK, CA, UNITED STATES (U.S. corporation)

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 20100087775	A1	20100408
	US 8105817	B2	20120131
APPLICATION INFO.:	US 2009-636477	A1	20091211 (12)

RELATED APPLN. INFO.: Division of Ser. No. US 2007-750963, filed on 18 May 2007, Pat. No. US 7655243 Continuation-in-part of Ser. No. US 2006-459090, filed on 21 Jul 2006, Pat. No. US 7608275

	NUMBER	DATE
PRIORITY INFORMATION:	US 2006-60747771	20060519 (60)
	US 2005-60702077	20050722 (60)

DOCUMENT TYPE: Utility
FILE SEGMENT: APPLICATION
LEGAL REPRESENTATIVE: TOWNSEND AND TOWNSEND AND CREW, LLP, TWO EMBARCADERO CENTER, EIGHTH FLOOR, SAN FRANCISCO, CA, 94111-3834, US
NUMBER OF CLAIMS: 31
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 24 Drawing Page(s)
LINE COUNT: 1356

CAS INDEXING IS AVAILABLE FOR THIS PATENT. Full-text
TI METHODS AND SYSTEMS FOR TOXIN DELIVERY TO THE NASAL CAVITY
IN DEEM, MARK E., MOUNTAIN VIEW, CA, UNITED STATES
AB 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. . .
SUMM . . . relates to methods and systems for delivering toxins, such as botulinum toxin light chain fragments, to target cells in a nasal cavity.
SUMM . . . 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. . . 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.
SUMM . . . 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.
SUMM . . . 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. . .
SUMM . . . 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.
SUMM 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,. . . 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.
SUMM 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.. . .
SUMM . . . 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. . . 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. . .
SUMM . . . 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. . . 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. . .

SUMM . . . 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. . . 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. . .

SUMM . . . external ultrasonic transducers and/or ultrasound wave guides capable of delivering focused or unfocused ultrasound into the target tissues of the nasal cavity.

SUMM . . . 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. . . 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. . .

SUMM . . . 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.. . .

SUMM . . . 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. . .

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

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

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

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

DRWD . . . 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.

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

DRWD FIG. 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.

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

DETD 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,. . .

DETD 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. . . 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. . . 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. . .

DETD . . . 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 FIG. 2A. Fragmented neurotoxin such as BoNT-LC (LC)is introduced into the vicinity of the targeted. . .

DETD . . . 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.

DETD . . . 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. . .

DETD . . . of producing a porative effect at the cellular level, including electrodes, ultrasonic elements and the like, for treatment in the nasal passages.

DETD . . . the energy, or both, non-invasively. For example, as illustrated in FIG. 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. . .

DETD 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. 10, a balloon catheter 100 may be provided with a porous balloon 102. . . 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 FIG. 10, the toxin is being delivered to a lower. . .

DETD . . . 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. . .

DETD . . . 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,. . .

DETD Referring now to FIGS. 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. . . shown in FIG. 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 (FIG. 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.

DETD . . . 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. . .

DETD . . . 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. . .

DETD Referring to FIG. 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. . .

DETD FIGS. 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. . . 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 FIG. 35.

DETD 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 FIG. 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. . .

DETD . . . 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 FIG. 37A, the operator would apply inward pressure in the direction of the arrows to the. . . 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 FIG. 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.

DETD 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. . . 39A) and an expanded configuration when wet (FIG. 39B), wherein

the sponge 121 is configured to fit securely within the nasal passageway.

DETD . . . 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 FIG. 36, the liquid can be infused into the applicator tip through. . .

DETD 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.. . .

DETD . . . 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 FIGS. 39A and 39B, a sponge and spring can. . .

DETD . . . 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.

DETD . . . 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.

DETD . . . 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. . . 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.

DETD . . . 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.

DETD 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,. . . open-faced chambers. The outer member may also comprise an array of microneedles to facilitate the passage of BoNT across the nasal membrane. 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. . . 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.

DETD . . . 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. . .

DETD 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.

DETD . . . 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.

DETD . . . this application, the device described with respect to FIGS. 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. . .

DETD 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. . .

DETD 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. . .

CLM What is claimed is:

1. 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. . .

CLM What is claimed is:

. . . A system as in claim 1, wherein the energy applicator comprises a wave guide configured to be positioned within a nasal passageway.

CLM What is claimed is:

30. A system as in claim 17, wherein the balloon is configured to be positioned within a nasal passageway.

AB 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.

L8 ANSWER 26 OF 31 USPATFULL on STN
ACCESSION NUMBER: 2009:102600 USPATFULL
TITLE: Drug Delivery Methods, Structures, and Compositions for Nasolacrimal System
INVENTOR(S): de Juan, JR., Eugene, San Francisco, CA, UNITED STATES
Reich, Cary, Los Gatos, CA, UNITED STATES
Boyd, Stephen, Murrieta, CA, UNITED STATES
Gifford, III, Hanson G., Woodside, CA, UNITED STATES
Deem, Mark, Mountain View, CA, UNITED STATES
PATENT ASSIGNEE(S): QLT Plug Delivery, Inc., Menlo Park, CA, UNITED STATES (U.S. corporation)
ForSight Labs, LLC., a California corporation, Menlo Park, CA, UNITED STATES (U.S. corporation)

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 20090092654	A1	20090409
APPLICATION INFO.:	US 2008-332219	A1	20081210 (12)

RELATED APPLN. INFO.: Continuation of Ser. No. US 2007-695537, filed on 2 Apr 2007, PENDING

	NUMBER	DATE
PRIORITY INFORMATION:	US 2006-60787775	20060331 (60)
	US 2006-60871864	20061226 (60)

DOCUMENT TYPE: Utility
FILE SEGMENT: APPLICATION
LEGAL REPRESENTATIVE: SCHWEGMAN, LUNDBERG & WOESSNER, P.A., P.O. BOX 2938, MINNEAPOLIS, MN, 55402, US
NUMBER OF CLAIMS: 77
EXEMPLARY CLAIM: 1-53
NUMBER OF DRAWINGS: 25 Drawing Page(s)
LINE COUNT: 2031
CAS INDEXING IS AVAILABLE FOR THIS PATENT. Full-text
IN Deem, Mark, Mountain View, CA, UNITED STATES
DETD . . . extend through the drug core 112 to permit tear flow through the lumen for the delivery of therapeutic agent for nasal and systemic applications of the therapeutic agent. In addition or in combination with channel 112C, retention structure 132 and core. . .
AB An implant for insertion into a punctum of a patient comprises a body. The body has a distal end, a proximal end, and an axis therebetween. The distal end of the body is insertable distally through the punctum into the canalicular lumen. The body comprises a therapeutic agent included within an agent matrix drug core. Exposure of the agent matrix to the tear fluid effects an effective therapeutic agent release into the tear fluid over a sustained period. The body has a sheath disposed over the agent matrix to inhibit release of the agent away from the proximal end. The body also has an outer surface configured to engage luminal wall tissues so as to inhibit expulsion when disposed therein. In specific embodiments, the agent matrix comprises a non-bioabsorbable polymer, for example silicone in a non-homogenous mixture with the agent.

L8 ANSWER 27 OF 31 CA COPYRIGHT 2020 ACS on STN DUPLICATE 2
ACCESSION NUMBER: 148:175883 CA
TITLE: Methods and systems for toxin delivery to the nasal cavity
INVENTOR(S): Deem, Mark E.; Gifford, Hanson
PATENT ASSIGNEE(S): The Foundry Inc., USA
SOURCE: U.S. Pat. Appl. Publ., 38pp., Cont.-in-part of U. S. Ser. No. 459,090.

CODEN: USXXCO
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 4
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 20080021369	A1	20080124	US 2007-750963	20070518
US 7655243	B2	20100202		
US 20070025919	A1	20070201	US 2006-459090	20060721
US 7608275	B2	20091027		
WO 2007137235	A2	20071129	WO 2007-US69391	20070521
WO 2007137235	A3	20080522		
EP 2021022	A2	20090211	EP 2007-784000	20070521
EP 2021022	B1	20170412		
JP 2009538641	T	20091112	JP 2009-511262	20070521
JP 5183627	B2	20130417		
EP 3248612	A1	20171129	EP 2017-165407	20070521
US 20100003282	A1	20100107	US 2009-559278	20090914
US 8133497	B2	20120313		
US 20100087775	A1	20100408	US 2009-636477	20091211
US 8105817	B2	20120131		
US 20120029261	A1	20120202	US 2011-13253595	20111005
US 8338164	B2	20121225		
US 20120089078	A1	20120412	US 2011-13328203	20111216
US 8636684	B2	20140128		
US 8961391	B2	20150224	US 2012-13660629	20121025
US 20140114233	A1	20140424	US 2013-14139710	20131223
US 20150150625	A1	20150604	US 2015-14601529	20150121
US 9498283	B2	20161122		
JP 2015186597	A	20151029	JP 2015-120827	20150616
JP 6290139	B2	20180307		
US 20150367115	A1	20151224	US 2015-14841514	20150831
US 20170021148	A9	20170126		
US 9700707	B2	20170711		
US 20170072176	A1	20170316	US 2016-15358187	20161122
US 10022529	B2	20180717		
JP 2017038963	A	20170223	JP 2016-227703	20161124
US 20170266422	A1	20170921	US 2017-15615344	20170606
US 10052465	B2	20180821		
US 20190083768	A1	20190321	US 2018-16036381	20180716
US 20200046955	A1	20200213	US 2019-16659893	20191022
US 10610675	B2	20200407		

PRIORITY APPLN. INFO.:		
US 2005-60702077	P	20050722
US 2006-60747771	P	20060519
US 2006-459090	A2	20060721
JP 2008-522980	A3	20060721
US 2007-750963	A	20070518
US 2007-750967	A	20070518
EP 2007-784000	A3	20070521
WO 2007-US69391	W	20070521
US 2009-559278	A1	20090914
US 2009-636477	A1	20091211
US 2011-13253595	A1	20111005
US 2011-13328203	A1	20111216
US 2012-13660629	A1	20121025
US 2013-14139710	A1	20131223
US 2015-14601529	A1	20150121
JP 2015-120827	A3	20150616
US 2015-14841514	A1	20150831
US 2016-15358187	A1	20161122
US 2018-16036381	A1	20180716

ASSIGNMENT HISTORY FOR US PATENT AVAILABLE IN LSUS DISPLAY FORMAT Full-text
TI Methods and systems for toxin delivery to the nasal cavity
IN Deem, Mark E.; Gifford, Hanson
AB 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. . .
ST system toxin delivery nasal cavity
IT Catheters

Epithelium
Headache
Human
Microwave
Migraine
Nasopharynx
Nose
Sound and Ultrasound
(methods and systems for toxin delivery to nasal cavity)

IT Toxins
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(methods and systems for toxin delivery to nasal cavity)

IT 93384-43-1, Botulin A 93384-44-2, Botulin B 93384-45-3, Botulin C 93384-46-4, Botulin D 93384-47-5, Botulin E 107231-12-9, Botulinum toxin 107231-15-2, Botulin F 107231-16-3, Botulin G
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(methods and systems for toxin delivery to nasal cavity)

AB 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. The use of balloon catheters for delivering toxins to the nasopharynx is depicted (no data).

OS.CITING REF COUNT: 16 THERE ARE 16 CAPLUS RECORDS THAT CITE THIS RECORD (26 CITINGS)
REFERENCE COUNT: 75 THERE ARE 75 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L8 ANSWER 28 OF 31 CA COPYRIGHT 2020 ACS on STN DUPLICATE 3
ACCESSION NUMBER: 147:548133 CA
TITLE: Apparatus, methods and systems for toxin delivery to the nasal cavity
INVENTOR(S): Deem, Mark E.; Gifford, Hanson; Kim, Steven; Salamini, Alexey
PATENT ASSIGNEE(S): The Foundry Inc., USA
SOURCE: PCT Int. Appl., 68 pp., Chemical Indexing Equivalent to 166:33837 (US)
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 4
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2007137235	A2	20071129	WO 2007-US69391	20070521
WO 2007137235	A3	20080522		
US 20080021369	A1	20080124	US 2007-750963	20070518
US 7655243	B2	20100202		
US 9511210	B2	20161206	US 2007-750967	20070518
US 20070267011	A1	20071122		
EP 2021022	A2	20090211	EP 2007-784000	20070521
EP 2021022	B1	20170412		
JP 2009538641	T	20091112	JP 2009-511262	20070521
JP 5183627	B2	20130417		
US 20120029261	A1	20120202	US 2011-13253595	20111005
US 8338164	B2	20121225		
US 8961391	B2	20150224	US 2012-13660629	20121025
US 20150150625	A1	20150604	US 2015-14601529	20150121
US 9498283	B2	20161122		
JP 2015186597	A	20151029	JP 2015-120827	20150616
JP 6290139	B2	20180307		
JP 2017038963	A	20170223	JP 2016-227703	20161124
PRIORITY APPLN. INFO.:			US 2006-60747771 P	20060519
			US 2007-750963 A	20070518
			US 2007-750967 A	20070518
			US 2005-60702077 P	20050722
			JP 2008-522980 A3	20060721
			US 2006-459090 A2	20060721
			WO 2007-US69391 W	20070521

	US 2009-559278	A1 20090914
	US 2011-13253595	A1 20111005
	US 2012-13660629	A1 20121025
	JP 2015-120827	A3 20150616

ASSIGNMENT HISTORY FOR US PATENT AVAILABLE IN LSUS DISPLAY FORMAT
OTHER SOURCE(S): CASFORMULTNS 2007:1363693 Full-text
TI Apparatus, methods and systems for toxin delivery to the nasal cavity
IN Deem, Mark E.; Gifford, Hanson; Kim, Steven; Salamini, Alexey
AB App., 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. . .
ST toxin delivery nasal cavity inflammation
IT Medical goods
(balloons; toxin delivery to the nasal cavity)
IT Coating materials
(bioresorbable; toxin delivery to the nasal cavity)
IT Medical goods
(springs; toxin delivery to the nasal cavity)
IT Anti-inflammatory agents
Inflammation
Medical sponges
Microwave
Nasal drug delivery systems
Nasal mucosa
Nose
Pulsed electric current
Sound and Ultrasound
Springs (mechanical)
X-ray
(toxin delivery to the nasal cavity)
IT Toxins
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(toxin delivery to the nasal cavity)
IT 93384-43-1, Botulin A 93384-44-2, Botulin B 93384-45-3, Botulin C 93384-46-4, Botulin D 93384-47-5, Botulin E 107231-15-2, Botulin F 107231-16-3, Botulin G
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(toxin delivery to the nasal cavity)
AB App., 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.

L8 ANSWER 29 OF 31 USPATFULL on STN
ACCESSION NUMBER: 2007:308397 USPATFULL
TITLE: Drug Delivery Methods, Structures, and Compositions for Nasolacrimal System
INVENTOR(S): de Juan, Eugene JR., San Francisco, CA, UNITED STATES
Reich, Cary, Los Gatos, CA, UNITED STATES
Boyd, Stephen, Murrieta, CA, UNITED STATES
Gifford, Hanson G. III, Woodside, CA, UNITED STATES
Deem, Mark, Mountain View, CA, UNITED STATES
PATENT ASSIGNEE(S): FORSIGHT LABS, LLC, Menlo Park, CA, UNITED STATES, 94025 (U.S. corporation)

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 20070269487	A1	20071122
	US 8795711	B2	20140805
APPLICATION INFO.:	US 2007-695537	A1	20070402 (11)

	NUMBER	DATE
PRIORITY INFORMATION:	US 2006-60787775	20060331 (60)
	US 2006-60871864	20061226 (60)

DOCUMENT TYPE: Utility
FILE SEGMENT: APPLICATION
LEGAL REPRESENTATIVE: TOWNSEND AND TOWNSEND AND CREW, LLP, TWO EMBARCADERO

CENTER, EIGHTH FLOOR, SAN FRANCISCO, CA, 94111-3834, US
NUMBER OF CLAIMS: 53
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 25 Drawing Page(s)
LINE COUNT: 1911
CAS INDEXING IS AVAILABLE FOR THIS PATENT. Full-text
IN Deem, Mark, Mountain View, CA, UNITED STATES
DETD . . . extend through the drug core 112 to permit tear flow through the lumen for the delivery of therapeutic agent for nasal and systemic applications of the therapeutic agent. In addition or in combination with channel 112C, retention structure 132 and core. . .
AB An implant for insertion into a punctum of a patient comprises a body. The body has a distal end, a proximal end, and an axis therebetween. The distal end of the body is insertable distally through the punctum into the canalicular lumen. The body comprises a therapeutic agent included within an agent matrix drug core. Exposure of the agent matrix to the tear fluid effects an effective therapeutic agent release into the tear fluid over a sustained period. The body has a sheath disposed over the agent matrix to inhibit release of the agent away from the proximal end. The body also has an outer surface configured to engage luminal wall tissues so as to inhibit expulsion when disposed therein. In specific embodiments, the agent matrix comprises a non-bioabsorbable polymer, for example silicone in a non-homogenous mixture with the agent.

L8 ANSWER 30 OF 31 USPATFULL on STN
ACCESSION NUMBER: 2007:305933 USPATFULL
TITLE: APPARATUS FOR TOXIN DELIVERY TO THE NASAL CAVITY
INVENTOR(S): Deem, Mark E., Mountain View, CA, UNITED STATES
Gifford, Hanson, Woodside, CA, UNITED STATES
Kim, Steven, Los Altos, CA, UNITED STATES
Salamini, Alexey, San Francisco, CA, UNITED STATES
PATENT ASSIGNEE(S): The Foundry Inc., Menlo Park, CA, UNITED STATES (U.S. corporation)

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 20070267011	A1	20071122
	US 9511210	B2	20161206
APPLICATION INFO.:	US 2007-750967	A1	20070518 (11)

	NUMBER	DATE
PRIORITY INFORMATION:	US 2006-60747771	20060519 (60)

DOCUMENT TYPE: Utility
FILE SEGMENT: APPLICATION
LEGAL REPRESENTATIVE: TOWNSEND AND TOWNSEND AND CREW, LLP, TWO EMBARCADERO CENTER, EIGHTH FLOOR, SAN FRANCISCO, CA, 94111-3834, US
NUMBER OF CLAIMS: 43
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 24 Drawing Page(s)
LINE COUNT: 1513
CAS INDEXING IS AVAILABLE FOR THIS PATENT. Full-text
TI APPARATUS FOR TOXIN DELIVERY TO THE NASAL CAVITY
IN Deem, Mark E., Mountain View, CA, UNITED STATES
AB Apparatus 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. . .
DRWD FIG. 9--depicts use on an external hand held transducer for enhancing cellular uptake of toxin delivered from a separate nasal aerosolizer.
DRWD FIG. 15--depicts sizing of a delivery balloon to control distribution of toxin released into the nasal cavity.
DRWD FIG. 17--depicts the use of multiple small balloons for selective toxin delivery into the nasal cavity.
DRWD FIGS. 22 and 23--depict nose plugs for occluding and optionally delivery poration energy to the nasal cavity.
DRWD . . . 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.
DRWD FIG. 29--depicts toxin delivery using a nasal spray and energy delivery using a face mask.
DRWD FIG. 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.

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

DETD . . . relates to methods and systems for delivering toxins, such as botulinum toxin light chain fragments, to target cells in a nasal cavity.

DETD . . . 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. . . 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.

DETD . . . 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.

DETD . . . 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. . .

DETD . . . 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.

DETD 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.

DETD 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,. . . 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.

DETD 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.. . .

DETD 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.

DETD . . . 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. The outward bias from this spring element can result in an expanded treatment configuration for delivering toxin to the nasal tissue.

DETD . . . 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. . .

DETD 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. . .

DETD . . . 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. . .

DETD . . . 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.

DETD . . . 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. . .

DETD 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,. . .

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.

DETD 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.. . .

DETD . . . 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. . . 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. . .

DETD . . . 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. . . 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. . .

DETD . . . 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. . . 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. . .

DETD . . . external ultrasonic transducers and/or ultrasound wave guides capable of delivering focused or unfocused ultrasound into the target tissues of the nasal cavity.

DETD . . . 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. . . 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. . .

DETD . . . 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.. . .

DETD . . . 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. . .

DETD 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,. . .

DETD 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. . . 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. . . 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. . .

DETD . . . 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 FIG. 2A. Fragmented neurotoxin such as BoNT-LC (LC) is introduced into the vicinity of the. . .

DETD . . . 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.

DETD . . . 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. . .

DETD . . . of producing a porative effect at the cellular level, including electrodes, ultrasonic elements and the like, for treatment in the nasal passages.

DETD . . . the energy, or both, non-invasively. For example, as illustrated in FIG. 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. . .

DETD 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. 10, a balloon catheter 100 may be provided with a porous balloon 102. . . 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 FIG. 10, the toxin is being delivered to a lower. . .

DETD . . . 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. . .

DETD . . . 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,. . .

DETD Referring now to FIGS. 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. . . shown in FIG. 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 (FIG. 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.

DETD . . . 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. . .

DETD . . . 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. . .

DETD Referring to FIG. 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. . .

DETD FIGS. 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. . . 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 FIG. 35.

DETD 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 FIG. 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. . .

DETD . . . 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 FIG. 37A, the operator would apply inward pressure in the direction of the arrows to the. . . 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 FIG. 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.

DETD 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. . . 39A) and an expanded configuration when wet (FIG. 39B), wherein

the sponge 121 is configured to fit securely within the nasal passageway.

DETD . . . 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 FIG. 36, the liquid can be infused into the applicator tip through. . .

DETD 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.. . .

DETD . . . 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 FIGS. 39A and 39B, a sponge and spring can. . .

DETD . . . 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.

DETD . . . 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.

DETD . . . 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. . . 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.

DETD . . . 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.

DETD 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,. . . 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. . . 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. . . 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.

DETD . . . 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. . .

DETD 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.

DETD . . . 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.

DETD . . . this application, the device described with respect to FIGS. 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. . .

DETD 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. . .

DETD 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. . .

CLM What is claimed is:
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. . . 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.

CLM What is claimed is:
4. 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 toxin to the region of nasal tissue.

CLM What is claimed is:
. . . 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.

CLM What is claimed is:
. . . 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.

CLM What is claimed is:
. . . 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.

CLM What is claimed is:
. . . apparatus of claim 17, wherein the applicator tips are configured to receive the toxin prior to being positioned in the nasal passageway.

CLM What is claimed is:
. . . The apparatus of claim 17, wherein the applicator tips are configured to receive the toxin after being positioned in the nasal passageway.

CLM What is claimed is:
. . . 26. The apparatus of claim 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.

CLM What is claimed is:
. . . applicator is adapted to deliver energy under conditions which cause poration of at least one cell in the region of nasal tissue.

CLM What is claimed is:
31. 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: 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.

CLM What is claimed is:
. . . 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.

CLM What is claimed is:
40. The apparatus of claim 39, wherein expansion of the inner member facilitates delivery of the toxin to the nasal tissue.

CLM What is claimed is:
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:. . . 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.

CLM What is claimed is:
. . . element is configured to provide the applicator tips with an outward bias when the applicator tips are placed within the nasal passageway.

CLM What is claimed is:
43. The apparatus of claim 42, wherein the outward bias presses each applicator tip against a turbinate in the nasal cavity.

AB Apparatus 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.

L8 ANSWER 31 OF 31 USPATFULL on STN
ACCESSION NUMBER: 2007:277801 USPATFULL
TITLE: Nasolacrimal Drainage System Implants for Drug Therapy
INVENTOR(S): de Juan, Eugene JR., San Francisco, CA, UNITED STATES
Boyd, Stephen, Murrieta, CA, UNITED STATES
Reich, Cary, Los Gatos, CA, UNITED STATES
Rapacki, Alan, Redwood City, CA, UNITED STATES
Gifford, Hanson S. III, Woodside, CA, UNITED STATES
Deem, Mark, Mountain View, CA, UNITED STATES
PATENT ASSIGNEE(S): ForSight Labs, LLC, Menlo Park, CA, UNITED STATES (U.S. corporation)

	NUMBER	KIND	DATE	
PATENT INFORMATION:	US 20070243230	A1	20071018	
	US 7998497	B2	20110816	
APPLICATION INFO.:	US 2007-695545	A1	20070402	(11)

	NUMBER	DATE	
PRIORITY INFORMATION:	US 2006-60787775	20060331	(60)

US 2006-60871864 20061226 (60)
DOCUMENT TYPE: Utility
FILE SEGMENT: APPLICATION
LEGAL REPRESENTATIVE: TOWNSEND AND TOWNSEND AND CREW, LLP, TWO EMBARCADERO CENTER, EIGHTH FLOOR, SAN FRANCISCO, CA, 94111-3834, US
NUMBER OF CLAIMS: 47
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 30 Drawing Page(s)
LINE COUNT: 1982
CAS INDEXING IS AVAILABLE FOR THIS PATENT. Full-text
IN Deem, Mark, Mountain View, CA, UNITED STATES
DETD . . . extend through the drug core 112 to permit tear flow through the lumen for the delivery of therapeutic agent for nasal and systemic applications of the therapeutic agent. In addition or in combination with channel 112C, retention structure 132 and core. . .
AB Implant devices, systems and methods for insertion into a punctum of a patient optionally comprises a drug core and a sheath body disposed over the drug core. The drug core includes a therapeutic agent deliverable into the eye, and the sheath defines at least one exposed surface of the drug core. The exposed surface(s) of the drug core may contact a tear or tear film fluid and release the therapeutic agent at therapeutic levels over a sustained period when the implant is implanted for use. The implant may include a retention element to retain the drug core and sheath body near the punctum, optionally comprising a shape memory alloy that can resiliently expand. An occlusive element may be attached to the retention element to at least partially occlude tear flow through the canalicular lumen.

=> e gifford h?/au

E1	4		GIFFORD H S/AU
E2	22		GIFFORD H S III/AU
E3	0	-->	GIFFORD H?/AU
E4	1		GIFFORD HAM H/AU
E5	1		GIFFORD HANSEN/AU
E6	204		GIFFORD HANSON/AU
E7	1		GIFFORD HANSON G/AU
E8	1		GIFFORD HANSON G III/AU
E9	38		GIFFORD HANSON III/AU
E10	259		GIFFORD HANSON S/AU
E11	1		GIFFORD HANSON S 3RD/AU
E12	191		GIFFORD HANSON S III/AU

=> e

E13	2	GIFFORD HAROLD/AU
E14	2	GIFFORD HAROLD JR/AU
E15	2	GIFFORD HAROLD S/AU
E16	1	GIFFORD HARRY D/AU
E17	2	GIFFORD HARRY E/AU
E18	2	GIFFORD HARRY P/AU
E19	1	GIFFORD HAYWARD W/AU
E20	63	GIFFORD HEATHER/AU
E21	1	GIFFORD HEATHER DR/AU
E22	7	GIFFORD HENRY/AU
E23	1	GIFFORD HENRY A/AU
E24	2	GIFFORD HOLLINGSWORTH CYNTHIA/AU

=> s e5-12

L9 696 ("GIFFORD HANSEN"/AU OR "GIFFORD HANSON"/AU OR "GIFFORD HANSON G"/AU OR "GIFFORD HANSON G III"/AU OR "GIFFORD HANSON III"/AU OR "GIFFORD HANSON S"/AU OR "GIFFORD HANSON S 3RD"/AU OR "GIFFORD HANSON S III"/AU)

=> s l9 and nasal

L10 47 L9 AND NASAL

=> dup rem L10

PROCESSING COMPLETED FOR L10
L11 39 DUP REM L10 (8 DUPLICATES REMOVED)

=> d ibib kwic ab 1-39

L11 ANSWER 1 OF 39 USPATFULL on STN
ACCESSION NUMBER: 2020:53186 USPATFULL
TITLE: SYSTEMS AND METHODS FOR DELIVERY OF A THERAPEUTIC AGENT
INVENTOR(S): Deem, Mark E., Mountain View, CA, UNITED STATES
Gifford, Hanson, Woodside, CA, UNITED STATES
APPLICANT(S): The Foundry, LLC, Menlo Park, CA, UNITED STATES

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 20200046955	A1	20200213
	US 10610675	B2	20200407
APPLICATION INFO.:	US 2019-16659893	A1	20191022 (16)

RELATED APPLN. INFO.: Continuation of Ser. No. US 2018-16036381, filed on 16 Jul 2018, PENDING Continuation of Ser. No. US 2016-15358187, filed on 22 Nov 2016, Pat. No. US 10022529 Continuation of Ser. No. US 2015-14601529, filed on 21 Jan 2015, Pat. No. US 9498283 Continuation of Ser. No. US 2012-13660629, filed on 25 Oct 2012, Pat. No. US 8961391 Continuation of Ser. No. US 2011-13253595, filed on 5 Oct 2011, Pat. No. US 8338164 Continuation of Ser. No. US 2009-559278, filed on 14 Sep 2009, Pat. No. US 8133497 Division of Ser. No. US 2006-459090, filed on 21 Jul 2006, Pat. No. US 7608275

	NUMBER	DATE
PRIORITY INFORMATION:	US 2005-60702077	20050722 (60)

DOCUMENT TYPE: Utility
FILE SEGMENT: APPLICATION
NUMBER OF CLAIMS: 30
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 27 Drawing Page(s)
LINE COUNT: 1712
CAS INDEXING IS AVAILABLE FOR THIS PATENT. Full-text
IN Gifford, Hanson, Woodside, CA, UNITED STATES
SUMM . . . relates to methods and systems for delivering toxins, such as botulinum toxin light chain fragments, to target cells in a nasal cavity.
SUMM . . . 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. . . 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.
SUMM . . . 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.
SUMM . . . 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. . .
SUMM . . . 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,. . .

SUMM 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,. . . 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.

SUMM 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.. . .

SUMM . . . 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. . . 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. . .

SUMM . . . 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. . . 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. . .

SUMM . . . 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. . . 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. . .

SUMM . . . external ultrasonic transducers and/or ultrasound wave guides capable of delivering focused or unfocused ultrasound into the target tissues of the nasal cavity.

SUMM . . . 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. . . 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. . .

SUMM . . . 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.. . .

SUMM . . . 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. . .

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

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

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

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

DRWD . . . 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.

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

DETD . . . 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. . .

DETD . . . 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.

DETD . . . 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. . .

DETD Delivery to Nasal Cavity

DETD . . . 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,. . .

DETD 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. . . 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. . . 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. . .

DETD . . . 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. . .

DETD 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. . . 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. . .

DETD . . . 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. . .

DETD . . . 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,. . .

DETD 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. . . 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.

DETD . . . 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. . .

DETD . . . 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. . .

DETD 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. . .

DETD 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. . .

DETD 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. . .

CLM 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. . .

CLM What is claimed is:
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. . .

AB 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.

L11 ANSWER 2 OF 39 USPATFULL on STN
ACCESSION NUMBER: 2020:713 USPATFULL
TITLE: NASOLACRIMAL DRAINAGE SYSTEM IMPLANTS FOR DRUG THERAPY
INVENTOR(S): de Juan, JR., Eugene, San Francisco, CA, UNITED STATES
Boyd, Stephen, Murrieta, CA, UNITED STATES
Reich, Cary, Los Gatos, CA, UNITED STATES
Rapacki, Alan, Redwood, CA, UNITED STATES
Gifford, Hanson S., Woodside, CA, UNITED STATES
Deem, Mark, Mountain View, CA, UNITED STATES
PATENT ASSIGNEE(S): Mati Therapeutics Inc., Austin, TX, UNITED STATES (U.S. corporation)

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 20200000715	A1	20200102
APPLICATION INFO.:	US 2019-16544884	A1	20190819 (16)

RELATED APPLN. INFO.: Continuation of Ser. No. US 2017-15852619, filed on 22 Dec 2017, Pat. No. US 10383817 Continuation of Ser. No. US 2017-15405991, filed on 13 Jan 2017, Pat. No. US 9849082 Continuation of Ser. No. US 2015-14858555, filed on 18 Sep 2015, Pat. No. US 9549852 Continuation of Ser. No. US 2014-14265071, filed on 29 Apr 2014, Pat. No. US 9168222 Continuation of Ser. No. US 2011-13184690, filed on 18 Jul 2011, Pat. No. US 8747884 Continuation of Ser. No. US 2007-695545, filed on 2 Apr 2007, Pat. No. US 7998497

	NUMBER	DATE
PRIORITY INFORMATION:	US 2006-60871864	20061226 (60)
	US 2006-60787775	20060331 (60)

DOCUMENT TYPE: Utility
FILE SEGMENT: APPLICATION
NUMBER OF CLAIMS: 47
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 30 Drawing Page(s)
LINE COUNT: 1976
CAS INDEXING IS AVAILABLE FOR THIS PATENT. Full-text
IN Gifford, Hanson S., Woodside, CA, UNITED STATES
DETD . . . extend through the drug core 112 to permit tear flow through the lumen for the delivery of therapeutic agent for nasal and systemic applications of the therapeutic agent. In addition or in combination with channel 112C, retention structure 132 and core. . .
AB An implant for insertion through a punctum and into a canalicular lumen of a patient. The implant includes a matrix of material, a therapeutic agent dispersed in the matrix of material, a sheath disposed over a portion of the matrix of material and configured to inhibit the therapeutic agent from being released from the matrix of material into the canalicular lumen and to allow the therapeutic agent to be released from a surface of the matrix of material to a tear film, and a retention structure configured to retain the implant within the canalicular lumen.

L11 ANSWER 3 OF 39 USPATFULL on STN
ACCESSION NUMBER: 2019:120958 USPATFULL
TITLE: DRUG CORES FOR SUSTAINED RELEASE OF THERAPEUTIC AGENTS
INVENTOR(S): Utkhede, JR., Deepank, Surrey, CANADA
Shimizu, Robert, Laguna Niguel, CA, UNITED STATES
Jain, Rachna, Milpitas, CA, UNITED STATES
Boyd, Stephen, Murrieta, CA, UNITED STATES
Gifford, Hanson S, Woodside, CA, UNITED STATES
De Juan, Eugene, San Francisco, CA, UNITED STATES
Reich, Cary, Los Gatos, CA, UNITED STATES
PATENT ASSIGNEE(S): Mati Therapeutics Inc., Austin, TX, UNITED STATES (U.S. corporation)

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 20190105265	A1	20190411
APPLICATION INFO.:	US 2018-16157712	A1	20181011 (16)

RELATED APPLN. INFO.: Continuation of Ser. No. US 2017-15598035, filed on 17 May 2017, PENDING Continuation of Ser. No. US 2008-231986, filed on 5 Sep 2008, ABANDONED

	NUMBER	DATE
PRIORITY INFORMATION:	US 2007-60970709	20070907 (60)
	US 2007-60970820	20070907 (60)
	US 2008-61049317	20080430 (61)
	US 2007-60970699	20070907 (60)

DOCUMENT TYPE: Utility
FILE SEGMENT: APPLICATION
NUMBER OF CLAIMS: 13

EXEMPLARY CLAIM: 1-41
NUMBER OF DRAWINGS: 50 Drawing Page(s)
LINE COUNT: 7186
CAS INDEXING IS AVAILABLE FOR THIS PATENT. Full-text
IN Gifford, Hanson S, Woodside, CA, UNITED STATES
DETD . . . therapeutic target, e.g., the eye, while blocking release to non-target tissue, such as the interior of the canaliculus, or the nasal sinus.
DETD . . . various embodiments, the drug cores can be used for sustained release of therapeutic agents into the ears and/or Eustachian tubes, nasal and/or sinus cavities, urethra, skin, gastrointestinal tract (including colon, bowel duct, and the like), and in or near joints such. . .
DETD . . . extend through the drug core 112 to permit tear flow through the lumen for the delivery of therapeutic agent for nasal and systemic applications of the therapeutic agent. In addition or in combination with channel 112C, retention structure 132 and core. . .
DETD . . . other therapeutic agent to an eye (e.g., to treat an infection, inflammation, glaucoma or other ocular disease or disorder), a nasal passage (e.g., to treat a sinus or allergy disorder) or an inner ear system (e.g., to treat dizziness or a. . .
DETD . . . insert can be disposed in the second cavity to provide a sustained drug or other therapeutic agent release to a nasal passage or inner ear system, for example. An implant body septum can be positioned between the first cavity and the. . .
DETD . . . having structures derived from the punctual implants described above may allow elution of one or more therapeutic agent into a nasal cavity. Modifications or differences between such nasal implants and the punctual implants described above may include providing a passage for controlled release of medicated tear fluid through the canilicular lumen. Alternative nasal tissue structures may be quite different in overall form, optionally including any of a variety of known nasal cavity drug release shapes, but optionally taking advantage of one or more aspects of the drug cores or other drug. . .
AB A solid drug core insert can be manufactured by injecting a liquid mixture comprising a therapeutic agent and a matrix precursor into a sheath body. The injection can be conducted at subambient temperatures. The mixture is cured to form a solid drug-matrix core. The therapeutic agent can be a liquid at about room temperature that forms a dispersion of droplets in the matrix material. A surface of the solid drug core is exposed, for example by cutting the tube, and the exposed surface of the solid drug core releases therapeutic quantities of the therapeutic agent when implanted into the patient. In some embodiments, the insert body inhibits release of the therapeutic agent, for example with a material substantially impermeable to the therapeutic agent, such that the therapeutic quantities are released through the exposed surface, thereby avoiding release of the therapeutic agent to non-target tissues.

L11 ANSWER 4 OF 39 USPATFULL on STN
ACCESSION NUMBER: 2019:61992 USPATFULL
TITLE: NASOLACRIMAL DRAINGAGE SYSTEM IMPLANTS FOR DRUG THERAPY
INVENTOR(S): de Juan, JR., Eugene, San Francisco, CA, UNITED STATES
Reich, Cary, Los Gatos, CA, UNITED STATES
Boyd, Stephen, Murrieta, CA, UNITED STATES
Gifford, Hanson S., Woodside, CA, UNITED STATES
Deem, Mark, Mountain View, CA, UNITED STATES
Rapacki, Alan, Redwood City, CA, UNITED STATES
PATENT ASSIGNEE(S): Mati Therapeutics Inc., Austin, TX, UNITED STATES (U.S. corporation)

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 20190054018	A1	20190221
	US 10300014	B2	20190528
APPLICATION INFO.:	US 2018-16168554	A1	20181023 (16)

RELATED APPLN. INFO.: Continuation of Ser. No. US 2017-15852619, filed on 22 Dec 2017, PENDING Continuation of Ser. No. US 2017-15405991, filed on 13 Jan 2017, Pat. No. US 9849082 Continuation of Ser. No. US 2015-14858555, filed on 18 Sep 2015, Pat. No. US 9549852 Continuation of Ser. No. US 2014-14265071, filed on 29 Apr 2014,

Pat. No. US 9168222 Continuation of Ser. No. US 2011-13184690, filed on 18 Jul 2011, Pat. No. US 8747884 Continuation of Ser. No. US 2007-695545, filed on 2 Apr 2007, Pat. No. US 7998497

	NUMBER	DATE
PRIORITY INFORMATION:	US 2006-60871864	20061226 (60)
	US 2006-60787775	20060331 (60)

DOCUMENT TYPE: Utility
FILE SEGMENT: APPLICATION
NUMBER OF CLAIMS: 21
EXEMPLARY CLAIM: 1-47
NUMBER OF DRAWINGS: 30 Drawing Page(s)
LINE COUNT: 1846
CAS INDEXING IS AVAILABLE FOR THIS PATENT. Full-text
IN Gifford, Hanson S., Woodside, CA, UNITED STATES
DETD . . . extend through the drug core 112 to permit tear flow through the lumen for the delivery of therapeutic agent for nasal and systemic applications of the therapeutic agent. In addition or in combination with channel 112C, retention structure 132 and core. . .
AB An implant for insertion through a punctum and into a canalicular lumen of a patient. The implant includes a matrix of material, a therapeutic agent dispersed in the matrix of material, a sheath disposed over a portion of the matrix of material and configured to inhibit the therapeutic agent from being released from the matrix of material into the canalicular lumen and to allow the therapeutic agent to be released from a surface of the matrix of material to a tear film, and a retention structure configured to retain the implant within the canalicular lumen.

L11 ANSWER 5 OF 39 USPATFULL on STN
ACCESSION NUMBER: 2019:61991 USPATFULL
TITLE: DRUG DELIVERY METHODS, STRUCTURES, AND COMPOSITIONS FOR NASOLACRIMAL SYSTEM
INVENTOR(S): de Juan, Eugene, San Francisco, CA, UNITED STATES
Reich, Cary, Los Gatos, CA, UNITED STATES
Boyd, Stephen, Murrieta, CA, UNITED STATES
Gifford, Hanson S., Woodside, CA, UNITED STATES
Deem, Mark, Mountain View, CA, UNITED STATES
PATENT ASSIGNEE(S): Mati Therapeutics Inc., Austin, TX, UNITED STATES (U.S. corporation)

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 20190054017	A1	20190221
APPLICATION INFO.:	US 2018-16168335	A1	20181023 (16)

RELATED APPLN. INFO.: Continuation of Ser. No. US 2014-14333349, filed on 16 Jul 2014, PENDING Continuation of Ser. No. US 2014-14180592, filed on 14 Feb 2014, Pat. No. US 9610194 Continuation of Ser. No. US 2012-13645261, filed on 4 Oct 2012, Pat. No. US 8691265 Continuation of Ser. No. US 2008-332219, filed on 10 Dec 2008, ABANDONED Continuation of Ser. No. US 2007-695537, filed on 2 Apr 2007, Pat. No. US 8795711

	NUMBER	DATE
PRIORITY INFORMATION:	US 2006-60787775	20060331 (60)
	US 2006-60871864	20061226 (60)

DOCUMENT TYPE: Utility
FILE SEGMENT: APPLICATION
NUMBER OF CLAIMS: 53
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 25 Drawing Page(s)
LINE COUNT: 1905
CAS INDEXING IS AVAILABLE FOR THIS PATENT. Full-text
IN Gifford, Hanson S., Woodside, CA, UNITED STATES
DETD . . . extend through the drug core 112 to permit tear flow through the lumen for the delivery of therapeutic agent for nasal and systemic applications of the therapeutic agent. In addition or in combination with channel 112C, retention structure 132 and core. . .

AB An implant for insertion into a punctum of a patient comprises a body. The body has a distal end, a proximal end, and an axis therebetween. The distal end of the body is insertable distally through the punctum into the canalicular lumen. The body comprises a therapeutic agent included within an agent matrix drug core. Exposure of the agent matrix to the tear fluid effects an effective therapeutic agent release into the tear fluid over a sustained period. The body has a sheath disposed over the agent matrix to inhibit release of the agent away from the proximal end. The body also has an outer surface configured to engage luminal wall tissues so as to inhibit expulsion when disposed therein. In specific embodiments, the agent matrix comprises a non-bioabsorbable polymer, for example silicone in a non-homogenous mixture with the agent.

L11 ANSWER 6 OF 39 BIOSIS COPYRIGHT (c) 2020 Clarivate Analytics on STN
ACCESSION NUMBER: 2018:777166 BIOSIS
DOCUMENT NUMBER: PREV201800777166
TITLE: Methods and systems for toxin delivery to the nasal cavity.
AUTHOR(S): Deem, Mark E. [Inventor]; Anonymous; Gifford, Hanson [Inventor]
CORPORATE SOURCE: Mountain View, CA USA
ASSIGNEE: The Foundry LLC
PATENT INFORMATION: US 10052465 20180821
SOURCE: Official Gazette of the United States Patent and Trademark Office Patents, (AUG 21 2018)
CODEN: OGUPE7. ISSN: 0098-1133.
DOCUMENT TYPE: Patent
LANGUAGE: English
ENTRY DATE: Entered STN: 26 Sep 2018
Last Updated on STN: 3 Oct 2018 Full-text
TI Methods and systems for toxin delivery to the nasal cavity.
AU Deem, Mark E. [Inventor]; Anonymous; Gifford, Hanson [Inventor]
AB 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. . .
IT . . .
and Techniques; Equipment Apparatus Devices and Instrumentation; Pulmonary Medicine (Human Medicine, Medical Sciences)
IT Parts, Structures, & Systems of Organisms
nasal cavity: respiratory system
IT Chemicals & Biochemicals
toxins: toxin
AB 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.

L11 ANSWER 7 OF 39 BIOSIS COPYRIGHT (c) 2020 Clarivate Analytics on STN
ACCESSION NUMBER: 2018:214452 BIOSIS
DOCUMENT NUMBER: PREV201800214452
TITLE: Delivery devices for nasopharyngeal mucosa targets.
AUTHOR(S): Morriss, John [Inventor]; Anonymous; Gifford, Hanson [Inventor]
CORPORATE SOURCE: San Francisco, CA USA
ASSIGNEE: The Foundry LLC
PATENT INFORMATION: US 09867972 20180116
SOURCE: Official Gazette of the United States Patent and Trademark Office Patents, (JAN 16 2018)
CODEN: OGUPE7. ISSN: 0098-1133.
DOCUMENT TYPE: Patent
LANGUAGE: English
ENTRY DATE: Entered STN: 14 Feb 2018
Last Updated on STN: 14 Feb 2018 Full-text
AU Morriss, John [Inventor]; Anonymous; Gifford, Hanson [Inventor]
AB. . . configuration to an expanded configuration. The expanded configuration is adapted to engage and conform to the mucosa tissue in a nasal cavity, and the contracted configuration has a size suitable for

introduction into the nasal cavity. The drug reservoir holds a therapeutic agent and is at least partially covered by the porous pad. The drug. . .

IT Major Concepts
Pharmacology; Otolaryngology (Human Medicine, Medical Sciences); Equipment Apparatus Devices and Instrumentation

IT Parts, Structures, & Systems of Organisms
nasal cavity: respiratory system; nasopharyngeal mucosa: respiratory system

AB A system for delivering a therapeutic agent to nasopharyngeal mucosa tissue has a shaft, a porous pad of compliant material coupled to the shaft near the distal end, and a drug reservoir. The porous pad is configured to expand from a contracted configuration to an expanded configuration. The expanded configuration is adapted to engage and conform to the mucosa tissue in a nasal cavity, and the contracted configuration has a size suitable for introduction into the nasal cavity. The drug reservoir holds a therapeutic agent and is at least partially covered by the porous pad. The drug reservoir is configured to release a fixed volume of the therapeutic agent into the porous pad within a period of less than about 120 minutes, and has a wall with a plurality of channels fluidly coupled with the porous pad.

L11 ANSWER 8 OF 39 USPATFULL on STN

ACCESSION NUMBER:	2018:303843 USPATFULL
TITLE:	METHODS AND APPARATUS FOR DELIVERING A THERAPEUTIC AGENT TO NASPHARYNGEAL MUCOSA TARGETS
INVENTOR(S):	MORRISS, John, San Francisco, CA, UNITED STATES REICH, Cary, Los Gatos, CA, UNITED STATES GIFFORD, Hanson, Woodside, CA, UNITED STATES
APPLICANT(S):	The Foundry, LLC, Menlo Park, CA, UNITED STATES

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 20180264092	A1	20180920
APPLICATION INFO.:	US 2018-15988801	A1	20180524 (15)

RELATED APPLN. INFO.: Division of Ser. No. US 2016-15089007, filed on 1 Apr 2016, Pat. No. US 10004789 Division of Ser. No. US 2014-14151767, filed on 9 Jan 2014, Pat. No. US 9327104 Continuation of Ser. No. WO 2012-US46089, filed on 10 Jul 2012, PENDING

	NUMBER	DATE
PRIORITY INFORMATION:	US 2011-61507417	20110713 (61)

DOCUMENT TYPE:	Utility
FILE SEGMENT:	APPLICATION
NUMBER OF CLAIMS:	25
EXEMPLARY CLAIM:	1-77
NUMBER OF DRAWINGS:	7 Drawing Page(s)
LINE COUNT:	829

CAS INDEXING IS AVAILABLE FOR THIS PATENT. Full-text

IN GIFFORD, Hanson, Woodside, CA, UNITED STATES

SUMM Rhinitis is commonly referred to as “stuffy nose,” and results from inflammation and swelling of the mucus membranes lining the nasal cavity. Rhinitis falls into two major categories—allergic and non-allergic (or vasomotor). Chronic rhinitis can result in chronic inflammation of the nasal passages resulting in sinusitis, an infection or inflammation of the paranasal sinuses. Rhinitis includes the symptoms of rhinorrhea which is commonly referred to as “runny nose.” Rhinorrhea describes 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,. . .

SUMM Allergic rhinitis is an immunologic response modulated by immunoglobulin E (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.. . .

SUMM . . . be caused by anatomic pathologies such as blockages, as seen in the case of sinusitis. Symptoms may include sneezing, itching, nasal congestion, and a runny nose. Non-allergic rhinitis is a diagnosis of rhinitis without any IgE mediation, as documented by allergen. . .

SUMM . . . 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 toxin 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. It has been published in the scientific literature that introduction of botulinum toxin into the nasal passages of canines can reduce mucus secretion by a significant amount. This work is further discussed in scientific and patent. . .

SUMM . . . 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 reported in the scientific literature, will have limited ability to uniformly and selectively deliver the botulinum to the. . .

SUMM . . . treatment site. Such improved methods and systems are preferably used to deliver a toxin, such as botulinum toxin to the nasal membrane of a patient, particularly in 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 an appropriate dose of the toxins to a 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, accurate and effective delivery of a proper dose 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.

SUMM Patents and publications related to delivery of a toxin to the nasal cavity include U.S. Pat. Nos. 5,766,605 and 6,974,578; and U.S. Patent Publication No. 2005/0281751. Related scientific literature includes Sharri et. . .

SUMM . . . therapeutic agent. The therapeutic agent may be a toxin or a non-toxin and in preferred embodiments is delivered to the nasal cavity. When toxins are used, the invention provides for the delivery of the 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.

SUMM The region where the toxin is introduced may comprise any portion of the nasal cavity, such as the turbinates, 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. . .

SUMM . . . and the toxin 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. . .

SUMM . . . invention further provides systems for delivering toxins to epithelial or goblet and other target cells as defined above in a nasal membrane.

DRWD FIG. 1 illustrates basic anatomy of the nasal cavity.

DRWD FIGS. 5A-5H illustrate an exemplary method of using foam to deliver a toxin to the nasal cavity.

DETD . . . directed to methods and systems for delivering therapeutic agents such as toxins or non-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,. . .

DETD 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 in accordance with the principles of the present invention. The. . . energy to permeablize or porate the cell membranes of the epithelial or goblet cells or other mucus-secreting cells of the nasal lining, may facilitate botulinum and other toxins to be preferentially delivered to the targeted

epithelial or goblet and other mucus-producing. . . 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. . .

DETD FIG. 1 illustrates the basic anatomy of the nasal cavity. The entrance to the nasal cavity is via the external naris. Long, narrow, and curled bone shelves line a portion of the nasal cavity. These bones are referred to as nasal concha or turbinates. An upper or superior turbinate, a middle turbinate, and an inferior turbinate divide the nasal airway into four channel-like air passages which direct inhaled air to flow in a steady, regular pattern around the largest. . . and climate controlling tissue. Various sinus cavities are also disposed within the bones of the face and skull adjacent the nasal cavity. These sinuses, such as the frontal sinus and the sphenoid sinus are mucosa lined airspaces that produce mucus. The nasal cavity communicates with the throat via the nasopharynx.

DETD FIGS. 5A-5H illustrate an exemplary method of using foam to deliver a toxin to the nasal cavity. A toxin such as botulinum toxin is contained in the pump dispenser 22 along with a liquid such as. . . shaft extending laterally outward from the pump dispenser. The nozzle may be used to help direct the foam into the nasal cavity or other target area. The surfactant reduces surface tension of the liquid

facilitating formation of foam, and actuation of. . . the foam. Additionally, any of the foam delivery devices disclosed herein may be used to deliver the foam into the nasal cavity.

DETD FIG. 5A is a cross-sectional model of the nasal cavity NC with a translucent top surface to allow the interior of the nose to be seen. The model includes the mouth M, nose N, nasal cavity NC, turbinates, and throat T. The three turbinates include the superior turbinate ST, middle turbinate MT, and inferior turbinate. . .

DETD . . . of the nose N. A first actuation of the pump dispenser 22 forces foam F containing the toxin into the nasal cavity NC. A second actuation of the pump dispenser 22 forces additional foam F into the nasal cavity NC as seen in FIG. 5C. A third, fourth, and fifth actuation of the pump dispenser 22 continue to deliver foam F into the nasal cavity as seen in FIGS. 5D-5F, until the nasal cavity is substantially filled with foam as seen in FIG. 5F. Continued introduction of foam into the nasal cavity can also direct foam into the sinuses via various ducts and apertures in the nasal wall. While the nasal cavity NC is substantially filled with foam, it is not overfilled with foam F so as to avoid the passage. . . therein is not delivered to an undesired location such as the lungs. The foam is permitted to reside in the nasal cavity for a predetermined time in order to allow the therapeutic agent that is dispersed therein to be delivered into. . .

DETD . . . also plug the nostril, to prevent the inadvertent inhalation of the foam. The plug will keep the foam in the nasal passage for the desired time, at which point the plug can be removed.

DETD After the foam F has resided in the nasal cavity for a sufficient time to allow an effective amount of the therapeutic agent to be delivered to the mucosa, the foam is removed from the nasal cavity, preferably by aspiration. Optionally, an anti-foaming agent such as simethicone may be delivered via a syringe 24 placed in. . . polyethylene glycol, polypropylene glycol copolymers, and dishwasher detergents. After a sufficient amount of the anti-foaming agent is delivered to the nasal cavity NC, the syringe 24 is removed from the nose, and the foam F continues to collapse, as seen in. . .

DETD While the exemplary embodiment above describes substantially filling the nasal cavity with the foam and toxin, the amount of foam may be controlled so that only a portion of the. . . target location within the nose. For example, the foam may be delivered and fill only a posterior portion of the nasal cavity, or only an anterior portion of the cavity may be filled with foam. In still other embodiments, the foam. . .

DETD The nasal volume of the first 5.2 cm of the nasal passage has been estimated by Kjoergaard to be about 5.43 cm.sup.3±1.31 cm.sup.3 per side based on acoustic rhinometry. Topical application of toxins to the nasal cavity have been reported by Rohrbach to use a sponge filled with 40 U (per side) with a concentration of 25 U/ml of toxin. Delivering the same 40 U dose to the nasal cavity with foam having a

10× expansion factor would require approximately 0.5 ml of an 80 U/ml liquid drug solution.

DETD Volunteers evaluated the sensation of various 3:1 mixtures of foam after the foam was delivered to their nasal cavities. In some instances, the pump dispenser was used to deliver the foam directly to the nostril, while in other. . . pump was used to generate the foam and then the foam was transferred to a syringe for delivery to the nasal passage. The test subjects reported that soap and SDS had a mild stinging sensation in their nose, while Tween did. . . by pinching the nostril. Use of simethicone as an anti-foaming agent did result in sneezing and a sensation of post nasal drip. The 3:1 solution of saline and Tween appears to be a promising mixture for producing foam that remains self. . .

DETD In addition to using foam to deliver a therapeutic agent to the nasal cavity, slurries may also be used. A slurry is a thick suspension of solids in a liquid. The solids take. . . the nose. Because viscosity of the slurry can be controlled to have a desired thickness, the slurry will fill the nasal cavity space and not run to undesired locations. The solid particles in the slurry may be porous if desired, but. . .

DETD . . . from the hydrogel particles. After remaining in place for a period of time, the particles can be flushed from the nasal cavity via a canula. In a more specific embodiment, hydrogel particles contain an active ingredient at less than the equilibrium. . .

DETD . . . particles, along with thrombin powder and sterile saline. This product swells during use, which may be a benefit in the nasal cavity. Spongostan (Ethicon) is an absorbable porcine gelatin sponge which liquefies in 2-5 days when applied to bleeding mucosal surfaces,. . .

DETD . . . collapsed configuration is adapted to allow the elongate shaft and expandable member to be inserted and correctly positioned into a nasal cavity or other body cavity. The expanded configuration may be adapted to substantially fill most of the cavity while leaving. . .

AB A system for delivering a therapeutic agent to a nasopharyngeal mucosa target comprises a foam generating mechanism, a gas, a therapeutic agent in liquid form that inhibits mucus production, and a delivery device. Actuation of the foam generating mechanism entraps gaseous bubbles from the gas in the liquid thereby forming a foam. The therapeutic agent is dispersed in the foam which has an expanded configuration adapted to fill a nasopharyngeal space and deliver the therapeutic agent to the mucosa targets. The delivery device is for delivering the foam to the nasopharyngeal space. The foam may also have a collapsed configuration for removal from the nasopharyngeal space or for concentration of the therapeutic agent onto the mucosa.

L11 ANSWER 9 OF 39 USPATFULL on STN

ACCESSION NUMBER: 2018:153972 USPATFULL

TITLE: NASOLACRIMAL DRAINAGE SYSTEM IMPLANTS FOR DRUG THERAPY

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	NUMBER	KIND	DATE
PATENT INFORMATION:	US 20180133150	A1	20180517
	US 10383817	B2	20190820
APPLICATION INFO.:	US 2017-15852619	A1	20171222 (15)

RELATED APPLN. INFO.: Continuation of Ser. No. US 2017-15405991, filed on 13 Jan 2017, Pat. No. US 9849082 Continuation of Ser. No. US 2015-14858555, filed on 18 Sep 2015, Pat. No. US 9549852 Continuation of Ser. No. US 2014-14265071, filed on 29 Apr 2014, Pat. No. US 9168222 Continuation of Ser. No. US 2011-13184690, filed on 18 Jul 2011, Pat. No. US 8747884 Continuation of Ser. No. US 2007-695545, filed on 2 Apr 2007, Pat. No. US 7998497

	NUMBER	DATE
PRIORITY INFORMATION:	US 2006-60871864	20061226 (60)

	US 2006-60787775 20060331 (60)
DOCUMENT TYPE:	Utility
FILE SEGMENT:	APPLICATION
NUMBER OF CLAIMS:	47
EXEMPLARY CLAIM:	1
NUMBER OF DRAWINGS:	30 Drawing Page(s)
LINE COUNT:	1976

CAS INDEXING IS AVAILABLE FOR THIS PATENT. Full-text

IN Gifford, Hanson S., Woodside, CA, UNITED STATES

DETD . . . extend through the drug core 112 to permit tear flow through the lumen for the delivery of therapeutic agent for nasal and systemic applications of the therapeutic agent. In addition or in combination with channel 112C, retention structure 132 and core. . .

AB An implant for insertion through a punctum and into a canalicular lumen of a patient. The implant includes a matrix of material, a therapeutic agent dispersed in the matrix of material, a sheath disposed over a portion of the matrix of material and configured to inhibit the therapeutic agent from being released from the matrix of material into the canalicular lumen and to allow the therapeutic agent to be released from a surface of the matrix of material to a tear film, and a retention structure configured to retain the implant within the canalicular lumen.

L11 ANSWER 10 OF 39 USPATFULL on STN

ACCESSION NUMBER:	2018:25606 USPATFULL
TITLE:	DELIVERY DEVICES FOR NASOPHARYNGEAL MUCOSA TARGETS
INVENTOR(S):	MORRISS, John, Emerald Hills, CA, UNITED STATES GIFFORD, Hanson, Woodside, CA, UNITED STATES
APPLICANT(S):	The Foundry, LLC, Menlo Park, CA, UNITED STATES

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 20180021555	A1	20180125
APPLICATION INFO.:	US 2017-15679243	A1	20170817 (15)

RELATED APPLN. INFO.: Continuation of Ser. No. US 2014-14151588, filed on 9 Jan 2014, PENDING Continuation of Ser. No. WO 2012-US46258, filed on 11 Jul 2012, PENDING

	NUMBER	DATE
PRIORITY INFORMATION:	US 2011-61507422	20110713 (61)

DOCUMENT TYPE:	Utility
FILE SEGMENT:	APPLICATION
NUMBER OF CLAIMS:	32
EXEMPLARY CLAIM:	1
NUMBER OF DRAWINGS:	20 Drawing Page(s)
LINE COUNT:	1232

CAS INDEXING IS AVAILABLE FOR THIS PATENT. Full-text

IN GIFFORD, Hanson, Woodside, CA, UNITED STATES

AB . . . configuration to an expanded configuration. The expanded configuration is adapted to engage and conform to the mucosa tissue in a nasal cavity, and the contracted configuration has a size suitable for introduction into the nasal cavity. The drug reservoir holds a therapeutic agent and is at least partially covered by the porous pad. The drug. . .

SUMM Rhinitis is commonly referred to as "stuffy nose," and results from inflammation and swelling of the mucus membranes lining the nasal cavity. Rhinitis falls into two major categories--allergic and non-allergic (or vasomotor). Chronic rhinitis can result in chronic inflammation of the nasal passages resulting in sinusitis, an infection or inflammation of the paranasal sinuses. Rhinitis includes the symptoms of rhinorrhea which is commonly referred to as "runny nose." Rhinorrhea describes 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,. . .

SUMM Allergic rhinitis is an immunologic response modulated by immunoglobulin E (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.. . .

SUMM . . . be caused by anatomic pathologies such as blockages, as seen in the case of sinusitis. Symptoms may include sneezing, itching, nasal congestion, and a runny nose. Non-allergic rhinitis is a diagnosis of

rhinitis without any IgE mediation, as documented by allergen. . .

SUMM . . . 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 toxin 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. It has been published in the scientific literature that introduction of botulinum toxin into the nasal passages of canines can reduce mucus secretion by a significant amount.

SUMM . . . 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. . . a needle being inserted into their nostril. Moreover, the use of a needle to inject a toxin deep within the nasal cavity can be very difficult. Topical application of toxins also may have short comings, particularly in terms of the accuracy of delivery of the toxin. For example, the use of botulinum-soaked gauze pads for delivering the toxin to the nasal cavities, as reported in the scientific literature, have limited ability to uniformly and selectively deliver the botulinum to the regions. . .

SUMM . . . treatment site. Such improved methods and systems are preferably used to deliver a toxin, such as botulinum toxin to the nasal membrane of a patient, particularly in a patient suffering from rhinitis or other conditions associated with nasal inflammation and conditions, such as sinus headaches and migraine headaches. Other therapeutic agents including non-toxins may also be delivered. Such. . . initial shape for insertion and may be easily deployed or activated to expand and fill the desired area of the nasal cavity. The methods and systems should be capable of providing for selective and repeatable delivery of an appropriate dose of the toxins to a 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, accurate and effective delivery of a proper dose 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.

SUMM Patents and publications related to delivery of a toxin to the nasal cavity include U.S. Pat. Nos. 5,766,605 and 6,974,578; and U.S. Patent Publication No. 2005/0281751. Related scientific literature includes Sharri et. . .

SUMM Briefly and in general terms, the present invention provides methods and systems for delivery of a therapeutic agent to the nasal cavity. The therapeutic agent may be a toxin or a non-toxin. The present disclosure focuses on preferred embodiments where 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. One of skill in the art will appreciate that this is not. . .

SUMM 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. . .

SUMM . . . and the toxin 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. . .

SUMM . . . invention further provides systems for delivering toxins to epithelial or goblet and other target cells as defined above in a nasal membrane.

SUMM . . . configuration to an expanded configuration. The expanded configuration is adapted to engage and conform to the mucosa tissue in a nasal cavity, and the contracted configuration has a size suitable for introduction into the nasal cavity. The drug reservoir holds a therapeutic agent, and is at least partially covered by the porous pad. The drug. . .

SUMM . . . The tissue penetrating needle is shielded by the outer syringe barrel or the elongate flexible sheath during insertion through the nasal cavity, and distal advancement of the inner syringe barrel relative to the outer syringe barrel slidaby advances the tissue penetrating. . .

SUMM . . . the patch is adhesively engaged therewith. The patch may be flexible and configured to conform to the anatomy of the nasal cavity.

SUMM . . . delivering a therapeutic agent to a nasopharyngeal mucosa tissue comprises inserting a porous pad in a collapsed configuration into a nasal cavity, and with the pad of material inserted in the nasal cavity, wetting the porous pad with a therapeutic agent disposed in a drug reservoir thereby expanding the porous pad into. . .

SUMM . . . invention, a method for delivering a therapeutic agent to nasopharyngeal mucosa tissue comprises advancing an elongate flexible sheath into a nasal cavity with a tissue penetrating needle thereon enclosed within the elongate sheath, and slidably advancing the tissue penetrating needle distally. . .

SUMM . . . distally from an outer syringe barrel. Advancing the elongate flexible sheath may comprise moving the outer syringe barrel toward the nasal cavity. The tissue penetrating needle may be coupled to and extend distally from an inner syringe barrel. Slidably advancing the. . .

SUMM . . . method for delivering a therapeutic agent to nasopharyngeal

mucosa tissue comprises inserting a patch carrying a therapeutic agent into a nasal cavity, and attaching the patch to the nasopharyngeal mucosa tissue. The method also comprises delivering the therapeutic agent from the. . .

SUMM . . . patch from the collapsed configuration into an expanded configuration so that the patch may conform to the anatomy of the nasal cavity. Attaching the patch may comprise adhesively bonding the patch to the nasopharyngeal mucosa tissue. The patch may comprise a. . .

SUMM . . . holds a therapeutic agent, and advancing a soft wicking tip disposed on a distal portion of the applicator into a nasal cavity. The method also includes painting the nasopharyngeal mucosa tissue with the soft wicking tip wherein the therapeutic agent is. . .

SUMM . . . The inner expandable member is disposed near the distal end and has a contracted configuration sized for introduction into the nasal cavity and an expanded volume configuration adapted to engage and conform to the mucosa tissue in a nasal cavity. The outer expandable member is disposed over the inner expandable member and has a contracted configuration sized for introduction into the nasal cavity and an expanded volume configuration adapted to fill the nasal cavity. The system also has a therapeutic agent carried by the outer expandable member and that is adapted to inhibit. . .

SUMM . . . have a collapsed configuration and an expanded configuration. The first expandable member is inserted in the collapsed configuration into a nasal cavity and the expanded from the collapsed configuration to the expanded configuration thereby filling up the nasal cavity. The second expandable member is expanded from the collapsed configuration to the expanded configuration so as to engage the mucosa tissue in the nasal cavity. The therapeutic agent is then delivered from the expandable member to the mucosa tissue.

DRWD FIG. 1 illustrates basic anatomy of the nasal cavity.

DRWD FIGS. 7A-7B illustrate an exemplary method of delivering a therapeutic agent to a nasal cavity.

DRWD FIGS. 8A-8B illustrate another exemplary method of delivering a therapeutic agent to a nasal cavity.

DRWD FIGS. 9A-9B illustrate still another exemplary method of delivering a therapeutic agent to a nasal cavity.

DRWD FIG. 10 illustrates an exemplary embodiment of a device for delivering a therapeutic agent to a nasal cavity.

DRWD FIGS. 12A-12B illustrate an exemplary method of delivering a therapeutic agent to the nasal cavity.

DRWD FIGS. 13A-13C illustrate a porous balloon for delivery of a therapeutic agent to the nasal cavity.

DRWD FIGS. 15A-15B illustrate use of the device in FIGS. 14A-14C to deliver a therapeutic agent to the nasal cavity.

DRWD FIGS. 16A-16C illustrate use of a nasal patch to deliver a therapeutic agent to the nasal cavity.

DETD . . . methods and systems for delivering one or more therapeutic

agents including toxins or non-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,. . .

DETD 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 in accordance with the principles of the present invention. The. . . energy to permeablize or porate the cell membranes of the epithelial or goblet cells or other mucus-secreting cells of the nasal lining, may facilitate botulinum and other toxins to be preferentially delivered to the targeted epithelial or goblet and other mucus-producing. . . 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. . .

DETD FIG. 1 illustrates the basic anatomy of the nasal cavity. The entrance to the nasal cavity is via the external naris. The anterior-most portion of the nasal cavity is referred to as the nasal vestibule and is enclosed by cartilage and lined by epithelium. Small hairs in the vestibule help filter dust and other contaminants in the air that is breathed in. Long, narrow, and curled bone shelves line a portion of the nasal cavity. These bones are referred to as nasal concha or turbinates. An upper or superior turbinate, a middle turbinate, and an inferior turbinate divide the nasal airway into four channel-like air passages which direct inhaled air to flow in a steady, regular pattern around the largest. . . and climate controlling tissue. Various sinus cavities are also disposed within the bones of the face and skull adjacent the nasal cavity. These sinuses, such as the frontal sinus and the sphenoid sinus are mucosa lined airspaces that produce mucus. The nasal cavity communicates with the throat via the nasopharynx.

DETD . . . extends through the lumen 25 of elongate shaft 24 and provides stiffness to the shaft to facilitate advancement into the nasal cavity, and prevent kinking or unwanted bending. Other support members including wires, plastic members, nitinol components, sutures, foam elements, etc.. . .

DETD . . . that it may have a collapsed low profile configuration suitable for delivery through the confined space of the nostrils and nasal cavity, and also have an expanded larger profile for maximum tissue contact. The foam contact element may be constrained in. . .

DETD . . . extending therefrom. The wings 42 may be sized and shaped in order to accommodate various sizes and anatomies in the nasal cavity. The wings 42 may be fabricated from any of the materials previously discussed with reference to device 22 in. . .

DETD . . . skill in the art will appreciate that the length, thickness, and number of fingers may be adjusted to fit the nasal cavity being treated. A porous reservoir 34b similar to the reservoirs previously described may be disposed in each finger 34b. . .

DETD . . . sheath (not shown) may be passed over the loop to compress it into the collapsed configuration for delivery into the nasal cavity. Upon reaching a desired target treatment site, the sheath may be retracted, or the loop 46 may be advanced. . .

DETD . . . into lumen 84 where it is stored in reservoir 89. The device may be advanced through a nostril into the nasal cavity, and the drug flows 90 through ports 88 into foam contact element 86. The drug wets the foam contact. . .

DETD . . . diameters based on the surrounding anatomy. This configuration may be useful for accommodating and treating various anatomical areas of the nasal cavity.

DETD . . . thereby increasing or decreasing its profile. This may be advantageous since it allows the device to be delivered into the nasal cavity in a low profile configuration, and then it may be easily expanded to engage the nasopharyngeal mucosa tissue.

DETD FIGS. 7A-7B illustrate an exemplary method of delivering a therapeutic agent to the nasal cavity with a foam contact element. The delivery device 230 includes an elongate shaft 240 having a foam contact element. . . the foam contact element 234 to constrain the foam contact element into a collapsed configuration that facilitates insertion into the nasal cavity via a nostril. In FIG. 7B, the delivery device 230 has been advanced into the nasal cavity via a nostril, and sheath 232 has been proximally retracted, thereby allowing the foam contact element to expand into. . . shape of the foam contact element may be varied as

discussed above in order to engage specific regions of the nasal cavity. Possible targets include any of the turbinates as well as the nasal septum, uncinate process, inferior, superior, and lateral extents of the nasopharynx. The therapeutic agent, such as botulinum toxin may then. . . even larger surface area. The size of the foam contact element may be selected depending on the size of the nasal cavity, or the size of the target area to treat. In alternative embodiments, multiple delivery devices may be used to. . .

DETD FIGS. 8A-8B illustrate another exemplary embodiment of delivering a therapeutic agent to the nasal cavity. The delivery device includes a plurality of flexible shafts 254, each having a foam contact element 256 disposed on. . . elements 256. Thus sheath 252 helps constrain the shafts 254 into a lower profile for ease of insertion into the nasal cavity. In FIG. 8B, the delivery device has been advanced into the nasal cavity via a nostril. The sheath 252 has been retracted relative to the plurality of flexible shafts 254 allowing the. . . Use of multiple flexible shafts and contact elements allow the device to reach smaller, harder to reach areas within the nasal cavity, as well as to more easily navigate around obstructions or through narrow gaps. A

delivery device may be used. . .

DETD FIGS. 9A-9B illustrate still another exemplary embodiment of a method for delivering a therapeutic agent to the nasal cavity. A porous reservoir (not illustrated, but similar to that previously described above) may include a small diameter flexible tube. . . The foam covered flexible tube 280 may be loaded into a syringe 276 for advancement through a nostril into the nasal cavity as seen in FIG. 9A. Once the syringe is advanced into the nasal cavity, the syringe plunger may be actuated and the foam covered flexible tube 280 is pushed out of the syringe into the nasal cavity as seen in FIG. 9B. Once unconstrained by the syringe, the foam expands to fill the nasal cavity. A string 278 is coupled to the foam covered flexible tube, and a free end of the string 278. . . be pulled in order to remove the foam covered flexible tube. Multiple foam covered tubes may be inserted into the nasal cavity in order to deliver the therapeutic agent to a larger surface area.

DETD FIGS. 12A-12B illustrate an exemplary method of advancing a drug delivery device having looped elements into the nasal cavity. The drug delivery device in FIGS. 12A-12B only has a single looped element, but one of skill in the. . . porous drug reservoir is retracted into and constrained by sheath 342 for minimum profile that can be advanced into the nasal cavity via a nostril. Once the device has been introduced into the nasal cavity, the sheath may be retracted (or the loop may be advanced) so that the loop becomes unconstrained and it. . .

DETD FIGS. 13A-13C illustrate use of a porous balloon to deliver a therapeutic agent to the nasal cavity. A catheter 372 includes an elongate flexible shaft 374 having a porous balloon 376 disposed at the distal end. . . component to be fluidly coupled to the catheter 372. In FIG. 13B, the catheter 372 is advanced toward the patient's nasal cavity, and the distal tip is inserted into the nostril. An optional valve member 380 may be coupled to connector. . . prevent backflow of the therapeutic agent. In FIG. 13C, the balloon 376 is advanced into a desired portion of the nasal cavity, and a syringe or other reservoir device (not illustrated) is coupled to valve 380, and the therapeutic agent is. . . drug is delivered to different areas of the anatomy. Also, in some embodiments, multiple balloons may be inserted into the nasal cavity for simultaneous delivery of a larger quantity of drug to a larger surface area. A final filling of the. . .

DETD . . . fluid such as a gas (e.g. air or nitrogen) or saline in order to reduce the remaining volume of the nasal cavity. Thus, the small remaining volume of the nasal cavity can easily be filled with the inflated outer balloon or spongy layer 388. Therefore the expanded volume of the. . . balloon is preferably greater than the expanded volume of the outer balloon or spongy layer. Because the volume of the nasal cavity has been reduced, the therapeutic agent may be delivered in a higher concentration and lower volume and it will. . .

DETD . . . of a drug delivery device having a tissue penetrating needle that may be used to deliver a therapeutic agent to nasal cavity. The delivery device includes an outer syringe barrel 404 and an inner syringe barrel 408. In preferred embodiments, the. . .

DETD . . . may help reduce patient anxiety associated with seeing a needle. Also, the sleeve is flexible, and therefore can navigate the

nasal anatomy easier than a more rigid needle. And once the device has been positioned in a desired area of the nasal cavity, the sleeve will act as a guide to help the needle smoothly advance through the anatomy to the target.. . .

DETD . . . 15A-15B illustrate exemplary usage of the device in FIGS. 14A-14C. The sleeve 402 is advanced through a nostril into the nasal cavity as seen in FIG. 15A. Advancement of the sleeve is performed while the needle is retracted into the outer. . .

DETD FIGS. 16A-16C illustrate the use of a patch to delivery a therapeutic agent to a nasal cavity. The patch 422 may be similar to transdermal drug delivery patches, and it may include a porous reservoir for. . . 428, and that is joined to a flexible adhesive structure for temporary attachment to the target tissue, such as a nasal turbinate 420. The adhesive areas 424 of the patch 422 may be arranged to ensure that the patch will stick. . . 430 may be folded in the opposite direction to be placed in the meatus between a turbinate 420 and the nasal septum or another turbinate as seen in FIG. 16C.

DETD . . . the patient exhales. Exhalation produces a strong airflow out of the lungs and closes the soft palate to seal the nasal cavity from the mouth and inferior pharynx. This prevents toxins from entering the lungs. Additionally, multiple smaller doses may be. . .

DETD . . . the device of FIG. 17. Cilial transport 464 causes the drug to flow thereby further spreading the drug in the nasal cavity.

CLM What is claimed is:

. . . configuration to an expanded configuration, the expanded configuration being adapted to engage and conform to the mucosa tissue in a nasal cavity, and the contracted configuration having a size suitable for introduction into the nasal cavity; and a drug reservoir holding a therapeutic agent, the drug reservoir being at least partially covered by the porous. . .

AB A system for delivering a therapeutic agent to nasopharyngeal mucosa tissue has a shaft, a porous pad of compliant material coupled to the shaft near the distal end, and a drug reservoir. The porous pad is configured to expand from a contracted configuration to an expanded configuration. The expanded configuration is adapted to engage and conform to the mucosa tissue in a nasal cavity, and the contracted configuration has a size suitable for introduction into the nasal cavity. The drug reservoir holds a therapeutic agent and is at least partially covered by the porous pad. The drug reservoir is configured to release a fixed volume of the therapeutic agent into the porous pad within a period of less than about 120 minutes, and has a wall with a plurality of channels fluidly coupled with the porous pad.

L11 ANSWER 11 OF 39 USPATFULL on STN

ACCESSION NUMBER: 2018:1883 USPATFULL

TITLE: CORNEAL DENERVATION FOR TREATMENT OF OCULAR PAIN

INVENTOR(S): ALSTER, YAIR, TEL-AVIV, ISRAEL
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SCHOLL, JOHN A., SAN RAMON, CA, UNITED STATES
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SUTTON, DOUGLAS, PACIFICA, CA, UNITED STATES
RAFAELI, OMER, TEL-AVIV, ISRAEL

APPLICANT(S): NEXISVISION, INC., Menlo Park, CA, UNITED STATES

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 20180000639	A1	20180104
	US 10596038	B2	20200324
APPLICATION INFO.:	US 2017-15684010	A1	20170823 (15)

RELATED APPLN. INFO.: Continuation of Ser. No. US 2012-13503841, filed on 20 Aug 2012, ABANDONED A 371 of International Ser. No. WO 2010-US53854, filed on 22 Oct 2010

	NUMBER	DATE
PRIORITY INFORMATION:	US 2009-61279612	20091023 (61)

DOCUMENT TYPE: Utility

FILE SEGMENT: APPLICATION

NUMBER OF CLAIMS: 20

EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 33 Drawing Page(s)
LINE COUNT: 1236 Full-text
IN GIFFORD, HANSON S., WOODSIDE, CA, UNITED STATES
DRWD . . . applicator as in FIG. 5A comprising at least two electrodes to deliver electrical energy to the cornea with a first nasal portion of the applicator and a second temporal portion of the applicator.
DETD . . . portion of tissue and as second outer portion of tissue. Many of the nerves extending into the cornea extend substantially nasal to temporal and temporal to nasal, such that a first outer portion 110A located on a first nasally disposed portion of the cornea and a second. . .
DETD . . . as in FIG. 5A comprising at least two electrodes 556 to deliver electrical energy to the cornea with a first nasal portion 550A of the applicator and a second temporal portion 550B of the applicator. When the first portion and second portion are substantially symmetrical, the applicator can be used on either eye, such that the nasal portion 550A can be used on the temporal portion of the opposite eye and the temporal portion 550B can be used on the nasal portion of the eye.
AB Methods and apparatus for the treatment of the eye to reduce pain can treat at least an outer region of the tissue so as to denervate nerves extending into the inner region and reduce the pain. For example, the cornea of the eye may comprise an inner region having an epithelial defect, and an outer portion of the cornea can be treated to reduce pain of the epithelial defect. The outer portion of the cornea can be treated to denervate nerves extending from the outer portion to the inner portion. The outer portion can be treated in many ways to denervate the nerve, for example with one or more of heat, cold or a denervating noxious substance such as capsaicin. The denervation of the nerve can be reversible, such that corneal innervation can return following treatment.

L11 ANSWER 12 OF 39 BIOSIS COPYRIGHT (c) 2020 Clarivate Analytics on STN
ACCESSION NUMBER: 2017:585488 BIOSIS
DOCUMENT NUMBER: PREV201700585488
TITLE: Methods and systems for toxin delivery to the nasal cavity.
AUTHOR(S): Deem, Mark E. [Inventor]; Anonymous; Gifford, Hanson [Inventor]
CORPORATE SOURCE: Mountain View, CA USA
ASSIGNEE: The Foundry LLC
PATENT INFORMATION: US 09700707 20170711
SOURCE: Official Gazette of the United States Patent and Trademark Office Patents, (JUL 11 2017)
CODEN: OGUPE7. ISSN: 0098-1133.
DOCUMENT TYPE: Patent
LANGUAGE: English
ENTRY DATE: Entered STN: 2 Aug 2017
Last Updated on STN: 2 Aug 2017 Full-text
TI Methods and systems for toxin delivery to the nasal cavity.
AU Deem, Mark E. [Inventor]; Anonymous; Gifford, Hanson [Inventor]
AB 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. . .
AB 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.

L11 ANSWER 13 OF 39 USPATFULL on STN
ACCESSION NUMBER: 2017:349935 USPATFULL
TITLE: DRUG CORES FOR SUSTAINED RELEASE OF THERAPEUTIC AGENTS
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Boyd, Stephen, Murrieta, CA, UNITED STATES
Gifford, Hanson S, Woodside, CA, UNITED STATES

De Juan, Eugene, San Francisco, CA, UNITED STATES
Reich, Cary, Los Gatos, CA, UNITED STATES
APPLICANT(S): Mati Therapeutics Inc., Austin, TX, UNITED STATES

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 20170304194	A1	20171026
APPLICATION INFO.:	US 2017-15598035	A1	20170517 (15)

RELATED APPLN. INFO.: Continuation of Ser. No. US 2008-231986, filed on 5 Sep 2008, ABANDONED

	NUMBER	DATE
PRIORITY INFORMATION:	US 2007-60970699	20070907 (60)
	US 2007-60970709	20070907 (60)
	US 2007-60970820	20070907 (60)
	US 2008-61049317	20080430 (61)

DOCUMENT TYPE: Utility
FILE SEGMENT: APPLICATION
NUMBER OF CLAIMS: 28
EXEMPLARY CLAIM: 1-41
NUMBER OF DRAWINGS: 50 Drawing Page(s)
LINE COUNT: 7222
CAS INDEXING IS AVAILABLE FOR THIS PATENT. Full-text
IN Gifford, Hanson S, Woodside, CA, UNITED STATES
DETD . . . therapeutic target, e.g., the eye, while blocking release to non-target tissue, such as the interior of the canaliculus, or the nasal sinus.
DETD . . . various embodiments, the drug cores can be used for sustained release of therapeutic agents into the ears and/or Eustachian tubes, nasal and/or sinus cavities, urethra, skin, gastrointestinal tract (including colon, bowel duct, and the like), and in or near joints such. . .
DETD . . . extend through the drug core 112 to permit tear flow through the lumen for the delivery of therapeutic agent for nasal and systemic applications of the therapeutic agent. In addition or in combination with channel 112C, retention structure 132 and core. . .
DETD . . . other therapeutic agent to an eye (e.g., to treat an infection, inflammation, glaucoma or other ocular disease or disorder), a nasal passage (e.g., to treat a sinus or allergy disorder) or an inner ear system (e.g., to treat dizziness or a. . .
DETD . . . insert can be disposed in the second cavity to provide a sustained drug or other therapeutic agent release to a nasal passage or inner ear system, for example. An implant body septum can be positioned between the first cavity and the. . .
DETD . . . having structures derived from the punctual implants described above may allow elution of one or more therapeutic agent into a nasal cavity. Modifications or differences between such nasal implants and the punctual implants described above may include providing a passage for controlled release of medicated tear fluid through the canilicular lumen. Alternative nasal tissue structures may be quite different in overall form, optionally including any of a variety of known nasal cavity drug release shapes, but optionally taking advantage of one or more aspects of the drug cores or other drug. . .
AB A solid drug core insert can be manufactured by injecting a liquid mixture comprising a therapeutic agent and a matrix precursor into a sheath body. The injection can be conducted at subambient temperatures. The mixture is cured to form a solid drug-matrix core. The therapeutic agent can be a liquid at about room temperature that forms a dispersion of droplets in the matrix material. A surface of the solid drug core is exposed, for example by cutting the tube, and the exposed surface of the solid drug core releases therapeutic quantities of the therapeutic agent when implanted into the patient. In some embodiments, the insert body inhibits release of the therapeutic agent, for example with a material substantially impermeable to the therapeutic agent, such that the therapeutic quantities are released through the exposed surface, thereby avoiding release of the therapeutic agent to non-target tissues.

L11 ANSWER 14 OF 39 USPATFULL on STN
ACCESSION NUMBER: 2017:306785 USPATFULL
TITLE: METHODS AND SYSTEMS FOR TOXIN DELIVERY TO THE NASAL

CAVITY

INVENTOR(S): Deem, Mark E., Mountain View, CA, UNITED STATES
Gifford, Hanson, Woodside, CA, UNITED STATES

APPLICANT(S): The Foundry, LLC, Menlo Park, CA, UNITED STATES

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 20170266422	A1	20170921
	US 10052465	B2	20180821
APPLICATION INFO.:	US 2017-15615344	A1	20170606 (15)

RELATED APPLN. INFO.: Continuation of Ser. No. US 2015-14841514, filed on 31 Aug 2015, Pat. No. US 9700707 Continuation of Ser. No. US 2013-14139710, filed on 23 Dec 2013, ABANDONED Continuation of Ser. No. US 2011-13328203, filed on 16 Dec 2011, Pat. No. US 8636684 Continuation of Ser. No. US 2009-636477, filed on 11 Dec 2009, Pat. No. US 8105817 Division of Ser. No. US 2007-750963, filed on 18 May 2007, Pat. No. US 7655243 Continuation-in-part of Ser. No. US 2006-459090, filed on 21 Jul 2006, Pat. No. US 7608275

	NUMBER	DATE
PRIORITY INFORMATION:	US 2006-60747771	20060519 (60)
	US 2005-60702077	20050722 (60)

DOCUMENT TYPE: Utility
FILE SEGMENT: APPLICATION
NUMBER OF CLAIMS: 35
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 24 Drawing Page(s)
LINE COUNT: 1394
CAS INDEXING IS AVAILABLE FOR THIS PATENT. Full-text

TI METHODS AND SYSTEMS FOR TOXIN DELIVERY TO THE NASAL CAVITY

IN Gifford, Hanson, Woodside, CA, UNITED STATES

AB 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. . .

SUMM . . . relates to methods and systems for delivering toxins, such as botulinum toxin light chain fragments, to target cells in a nasal cavity.

SUMM . . . 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. . . 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.

SUMM . . . 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.

SUMM . . . 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. . .

SUMM . . . 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.

SUMM 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,. . . 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.

SUMM 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.. . .

SUMM . . . 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. . . 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. . .

SUMM . . . 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. . . 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. . .

SUMM . . . 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. . . 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. . .

SUMM . . . external ultrasonic transducers and/or ultrasound wave guides capable of delivering focused or unfocused ultrasound into the target tissues of the nasal cavity.

SUMM . . . 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. . . 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. . .

SUMM . . . 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.. . .

SUMM . . . 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. . .

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

DRWD FIG. 15 depicts sizing of a delivery balloon to control distribution of

toxin released into the nasal cavity.

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

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

DRWD . . . 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.

DRWD FIG. 29 depicts toxin delivery using a nasal spray and energy delivery using a face mask.

DRWD FIG. 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.

DRWD FIG. 35 depicts the applicator device illustrated in FIG. 33 when placed within the nasal passageway.

DETD 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,. . .

DETD 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. . . 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. . . 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. . .

DETD . . . 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 FIG. 2A. Fragmented neurotoxin such as BoNT-LC (LC) is introduced into the vicinity of the. . .

DETD . . . 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.

DETD . . . 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. . .

DETD . . . of producing a porative effect at the cellular level, including electrodes, ultrasonic elements and the like, for treatment in the nasal passages.

DETD . . . the energy, or both, non-invasively. For example, as illustrated in FIG. 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. . .

DETD 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. 10, a balloon catheter 100 may be provided with a porous balloon 102. . . 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 FIG. 10, the toxin is being delivered to a lower. . .

DETD . . . 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. . .

DETD . . . 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,. . .

DETD Referring now to FIGS. 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. . . shown in FIG. 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 (FIG. 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.

DETD . . . 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. . .

DETD . . . 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. . .

DETD Referring to FIG. 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. . .

DETD FIGS. 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. . . 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 FIG. 35.

DETD 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 FIG. 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. . .

DETD . . . 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 FIG. 37A, the operator would apply inward pressure in the direction of the arrows to the. . . 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 FIG. 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.

DETD 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. . . 39A) and an expanded configuration when wet (FIG. 39B), wherein the sponge 121 is configured to fit securely within the nasal

passageway.

DETD . . . 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 FIG. 36, the liquid can be infused into the applicator tip through. . .

DETD 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.. . .

DETD . . . 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 FIGS. 39A and 39B, a sponge and spring can. . .

DETD . . . 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.

DETD . . . 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.

DETD . . . 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. . . 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.

DETD . . . 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.

DETD 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,. . . open-faced chambers. The outer member may also comprise an array of microneedles to facilitate the passage of BoNT across the nasal membrane. 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. . . 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.

DETD . . . 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. . .

DETD 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.

DETD . . . 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.

DETD . . . this application, the device described with respect to FIGS. 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. . .

DETD 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. . .

DETD 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. . .

CLM What is claimed is:

1. A system for treating a nasal condition in a patient, said system comprising: an apparatus comprising an applicator tip and insertable into a nasal cavity of the patient, the applicator tip comprising an outer expandable member and an inner expandable member disposed within the outer expandable member and configured to expand within the nasal cavity, wherein expansion of the inner expandable member causes expansion of the outer expandable member such that the outer expandable member is placed in contact with a wall of the nasal cavity; and a toxin either: (i) carried by the outer expandable member or (ii) disposed in a space between the. . . and wherein the outer expandable member is configured to deliver the toxin to target cells in the wall of the nasal cavity.

CLM What is claimed is:

. . . system of claim 1, wherein the inner expandable member comprises a low volume configuration adapted to facilitate insertion into the nasal cavity and an expanded volume configuration adapted to place the outer expandable member in contact with the wall of the nasal cavity.

CLM What is claimed is:

. . . expandable member is configured to deliver the toxin from the porous portion to target cells in the wall of the nasal cavity.

CLM What is claimed is:

21. An apparatus for treating a nasal condition in a patient, said apparatus comprising: an applicator tip comprising an outer expandable member and an inner expandable member, wherein the applicator tip is configured to be inserted into a nasal cavity of the patient, wherein the inner expandable member is disposed within the outer expandable member and configured to expand within the nasal cavity, wherein expansion of the inner expandable member causes expansion of the outer expandable member such that the outer expandable member is placed in contact with a wall of the nasal cavity, wherein (i) the outer expandable member is configured to carry a toxin or (ii) the applicator tip comprises a. . . and wherein the outer expandable member in configured to deliver the toxin to target cells in the wall of the nasal cavity.

CLM What is claimed is:

. . . apparatus of claim 21, wherein the inner expandable member comprises a low volume configuration adapted to facilitate insertion into the nasal cavity and an expanded volume configuration adapted to place the outer expandable member in contact with the wall of the nasal cavity.

CLM What is claimed is:

. . . expandable member is configured to deliver the toxin from the porous portion to target cells in the wall of the nasal cavity.

AB 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.

L11 ANSWER 15 OF 39 USPATFULL on STN
ACCESSION NUMBER: 2017:148318 USPATFULL
TITLE: NASOLACRIMAL DRAINAGE SYSTEM IMPLANTS FOR DRUG THERAPY
INVENTOR(S): de Juan, Jr., Eugene, San Francisco, CA, UNITED STATES
Boyd, Stephen, Murrieta, CA, UNITED STATES
Reich, Cary, Los Gatos, CA, UNITED STATES
Rapacki, Alan, Redwood, CA, UNITED STATES
Gifford, Hanson S, Woodside, CA, UNITED STATES
Deem, Mark, Mountain View, CA, UNITED STATES
APPLICANT(S): Mati Therapeutics Inc., Austin, TX, UNITED STATES

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 20170128361	A1	20170511
	US 9849082	B2	20171226
APPLICATION INFO.:	US 2017-15405991	A1	20170113 (15)

RELATED APPLN. INFO.: Continuation of Ser. No. US 2015-14858555, filed on 18 Sep 2015, Pat. No. US 9549852 Continuation of Ser. No. US 2014-14265071, filed on 29 Apr 2014, Pat. No. US 9168222 Continuation of Ser. No. US 2011-13184690, filed on 18 Jul 2011, Pat. No. US 8747884 Continuation of Ser. No. US 2007-695545, filed on 2 Apr 2007, Pat. No. US 7998497

	NUMBER	DATE
PRIORITY INFORMATION:	US 2006-60787775	20060331 (60)
	US 2006-60871864	20061226 (60)

DOCUMENT TYPE: Utility
FILE SEGMENT: APPLICATION
NUMBER OF CLAIMS: 25
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 30 Drawing Page(s)
LINE COUNT: 1862
CAS INDEXING IS AVAILABLE FOR THIS PATENT. Full-text
IN Gifford, Hanson S, Woodside, CA, UNITED STATES
DETD . . . extend through the drug core 112 to permit tear flow through the lumen for the delivery of therapeutic agent for nasal and systemic applications of the therapeutic agent. In addition or in combination with channel 112C, retention structure 132 and core. . .
AB An implant for insertion through a punctum and into a canalicular lumen of a patient. The implant includes a matrix of material, a therapeutic agent dispersed in the matrix of material, a sheath disposed over a portion of the matrix of material and configured to inhibit the therapeutic agent from being released from the matrix of material into the canalicular lumen and to allow the therapeutic agent to be released from a surface of the matrix of material to a tear film, and a retention structure configured to retain the implant within the canalicular lumen.

L11 ANSWER 16 OF 39 BIOSIS COPYRIGHT (c) 2020 Clarivate Analytics on STN
DUPLICATE 1
ACCESSION NUMBER: 2017:53857 BIOSIS
DOCUMENT NUMBER: PREV201700053857
TITLE: Apparatus for toxin delivery to the nasal cavity.
AUTHOR(S): Deem, Mark E. [Inventor]; Anonymous; Gifford, Hanson [Inventor]; Kim, Steven [Inventor]; Salamini, Alexey [Inventor]
CORPORATE SOURCE: Mountain View, CA USA
ASSIGNEE: THE FOUNDRY LLC
PATENT INFORMATION: US 09511210 20161206
SOURCE: Official Gazette of the United States Patent and Trademark Office Patents, (DEC 6 2016)
CODEN: OGUPE7. ISSN: 0098-1133.

DOCUMENT TYPE: Patent
LANGUAGE: English
ENTRY DATE: Entered STN: 28 Dec 2016
Last Updated on STN: 1 Mar 2017 Full-text
TI Apparatus for toxin delivery to the nasal cavity.
AU Deem, Mark E. [Inventor]; Anonymous; Gifford, Hanson [Inventor]; Kim, Steven [Inventor]; Salamini, Alexey [Inventor]
AB Apparatus 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. . .
AB Apparatus 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.

L11 ANSWER 17 OF 39 USPATFULL on STN
ACCESSION NUMBER: 2016:242484 USPATFULL
TITLE: METHODS AND APPARATUS FOR DELIVERING A THERAPEUTIC AGENT TO NASPHARYNGEAL MUCOSA TARGETS
INVENTOR(S): MORRISS, John, San Francisco, CA, UNITED STATES
REICH, Cary, Los Gatos, CA, UNITED STATES
GIFFORD, Hanson, Woodside, CA, UNITED STATES
APPLICANT(S): The Foundry, LLC, Menlo Park, CA, UNITED STATES

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 20160213758	A1	20160728
	US 10004789	B2	20180626
APPLICATION INFO.:	US 2016-15089007	A1	20160401 (15)

RELATED APPLN. INFO.: Division of Ser. No. US 2014-14151767, filed on 9 Jan 2014, Pat. No. US 9327104 Continuation of Ser. No. WO 2012-US46089, filed on 10 Jul 2012, PENDING

	NUMBER	DATE
PRIORITY INFORMATION:	US 2011-61507417	20110713 (61)

DOCUMENT TYPE: Utility
FILE SEGMENT: APPLICATION
NUMBER OF CLAIMS: 23
EXEMPLARY CLAIM: 1-57
NUMBER OF DRAWINGS: 7 Drawing Page(s)
LINE COUNT: 820
CAS INDEXING IS AVAILABLE FOR THIS PATENT. Full-text
IN GIFFORD, Hanson, Woodside, CA, UNITED STATES
SUMM Rhinitis is commonly referred to as "stuffy nose," and results from inflammation and swelling of the mucus membranes lining the nasal cavity Rhinitis falls into two major categories--allergic and non-allergic (or vasomotor). Chronic rhinitis can result in chronic inflammation of the nasal passages resulting in sinusitis, an infection or inflammation of the paranasal sinuses. Rhinitis includes the symptoms of rhinorrhea which is commonly referred to as "runny nose." Rhinorrhea describes 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,. . .
SUMM Allergic rhinitis is an immunologic response modulated by immunoglobulin E (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.. . .
SUMM . . . be caused by anatomic pathologies such as blockages, as seen in the case of sinusitis. Symptoms may include sneezing, itching, nasal congestion, and a runny nose. Non-allergic rhinitis is a diagnosis of rhinitis without any IgE mediation, as documented by allergen. . .
SUMM . . . 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 toxin 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. It has been published in the scientific literature that introduction of botulinum toxin into the nasal passages of canines can reduce mucus secretion by a significant amount.

This work is further discussed in scientific and patent. . .

SUMM . . . 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 reported in the scientific literature, will have limited ability to uniformly and selectively deliver the botulinum to the. . .

SUMM . . . treatment site. Such improved methods and systems are preferably used to deliver a toxin, such as botulinum toxin to the nasal membrane of a patient, particularly in 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 an appropriate dose of the toxins to a 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, accurate and effective delivery of a proper dose 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.

SUMM Patents and publications related to delivery of a toxin to the nasal cavity include U.S. Pat. Nos. 5,766,605 and 6,974,578; and U.S. Patent Publication No. 2005/0281751. Related scientific literature includes Sharri et. . .

SUMM . . . therapeutic agent. The therapeutic agent may be a toxin or a non-toxin and in preferred embodiments is delivered to the nasal cavity. When toxins are used, the invention provides for the delivery of the 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.

SUMM The region where the toxin is introduced may comprise any portion of the nasal cavity, such as the turbinates, 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. . .

SUMM . . . and the toxin 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. . .

SUMM . . . invention further provides systems for delivering toxins to epithelial or goblet and other target cells as defined above in a nasal membrane.

DRWD FIG. 1 illustrates basic anatomy of the nasal cavity.

DRWD FIGS. 5A-5H illustrate an exemplary method of using foam to deliver a toxin to the nasal cavity.

DETD . . . directed to methods and systems for delivering therapeutic agents such as toxins or non-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,. . .

DETD 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 in accordance with the principles of the present invention. The. . . energy to permeablize or porate the cell membranes of the epithelial or goblet cells or other mucus-secreting cells of the nasal lining, may facilitate botulinum and other toxins to be preferentially delivered to the targeted epithelial or goblet and other mucus-producing. . . 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. . .

DETD FIG. 1 illustrates the basic anatomy of the nasal cavity. The entrance to the nasal cavity is via the external naris. Long, narrow, and curled bone shelves line a portion of the nasal cavity. These bones

are referred to as nasal concha or turbinates. An upper or superior turbinate, a middle turbinate, and an inferior turbinate divide the nasal airway into four channel-like air passages which direct inhaled air to flow in a steady, regular pattern around the largest. . . and climate controlling tissue. Various sinus cavities are also disposed within the bones of the face and skull adjacent the nasal cavity. These sinuses, such as the frontal sinus and the sphenoid sinus are mucosa lined airspaces that produce mucus. The nasal cavity communicates with the throat via the nasopharynx.

DETD FIGS. 5A-5H illustrate an exemplary method of using foam to deliver a toxin to the nasal cavity. A toxin such as botulinum toxin is contained in the pump dispenser 22 along with a liquid such as. . . shaft extending laterally outward from the pump dispenser. The nozzle may be used to help direct the foam into the nasal cavity or other target area. The surfactant reduces surface tension of the liquid facilitating formation of foam, and actuation of. . . the foam.

Additionally, any of the foam delivery devices disclosed herein may be used to deliver the foam into the nasal cavity.

DETD FIG. 5A is a cross-sectional model of the nasal cavity NC with a translucent top surface to allow the interior of the nose to be seen. The model includes the mouth M, nose N, nasal cavity NC, turbinates, and throat T. The three turbinates include the superior turbinate ST, middle turbinate MT, and inferior turbinate. . .

DETD . . . of the nose N. A first actuation of the pump dispenser 22 forces foam F containing the toxin into the nasal cavity NC. A second actuation of the pump dispenser 22 forces additional foam F into the nasal cavity NC as seen in FIG. 5C. A third, fourth, and fifth actuation of the pump dispenser 22 continue to deliver foam F into the nasal cavity as seen in FIGS. 5D-5F, until the nasal cavity is substantially filled with foam as seen in FIG. 5F. Continued introduction of foam into the nasal cavity can also direct foam into the sinuses via various ducts and apertures in the nasal wall. While the nasal cavity NC is substantially filled with foam, it is not overfilled with foam F so as to avoid the passage. . . therein is not delivered to an undesired location such as the lungs. The foam is permitted to reside in the nasal cavity for a predetermined time in order to allow the therapeutic agent that is dispersed therein to be delivered into. . .

DETD . . . also plug the nostril, to prevent the inadvertent inhalation of the foam. The plug will keep the foam in the nasal passage for the desired time, at which point the plug can be removed.

DETD After the foam F has resided in the nasal cavity for a sufficient time to allow an effective amount of the therapeutic agent to be delivered to the mucosa, the foam is removed from the nasal cavity, preferably by aspiration. Optionally, an anti-foaming agent such as simethicone may be delivered via a syringe 24 placed in. . . polyethylene glycol, polypropylene glycol copolymers, and dishwasher detergents. After a sufficient amount of the anti-foaming agent is delivered to the nasal cavity NC, the syringe 24 is removed from the nose, and the foam F continues to collapse, as seen in. . .

DETD While the exemplary embodiment above describes substantially filling the nasal cavity with the foam and toxin, the amount of foam may be controlled so that only a portion of the. . . target location within the nose. For example, the foam may be delivered and fill only a posterior portion of the nasal cavity, or only an anterior portion of the cavity may be filled with foam. In still other embodiments, the foam. . .

DETD The nasal volume of the first 5.2 cm of the nasal passage has been estimated by Kjoergaard to be about 5.43 cm.sup.3±1.31 cm.sup.3 per side based on acoustic rhinometry. Topical application of toxins to the nasal cavity have been reported by Rohrbach to use a sponge filled with 40 U (per side) with a concentration of 25 U/ml of toxin. Delivering the same 40 U dose to the nasal cavity with foam having a 10× expansion factor would require approximately 0.5 ml of an 80 U/ml liquid drug solution.

DETD Experiment 3. Volunteers evaluated the sensation of various 3:1 mixtures of foam after the foam was delivered to their nasal cavities. In some instances, the pump dispenser was used to deliver the foam directly to the nostril, while in other. . . pump was used to generate the foam and then the foam was transferred to a syringe for delivery to the nasal passage. The test subjects reported that soap and SDS had a mild

stinging sensation in their nose, while Tween did. . . by pinching the nostril. Use of simethicone as an anti-foaming agent did result in sneezing and a sensation of post nasal drip. The 3:1 solution of saline and Tween appears to be a promising mixture for producing foam that remains self. . .

DETD In addition to using foam to deliver a therapeutic agent to the nasal cavity, slurries may also be used. A slurry is a thick suspension of solids in a liquid. The solids take. . . the nose. Because viscosity of the slurry can be controlled to have a desired thickness, the slurry will fill the nasal cavity space and not run to undesired locations. The solid particles in the slurry may be porous if desired, but. . .

DETD . . . from the hydrogel particles. After remaining in place for a period of time, the particles can be flushed from the nasal cavity via a canula. In a more specific embodiment, hydrogel particles contain an active ingredient at less than the equilibrium. . .

DETD . . . particles, along with thrombin powder and sterile saline. This product swells during use, which may be a benefit in the nasal cavity. Spongostan (Ethicon) is an absorbable porcine gelatin sponge which liquefies in 2-5 days when applied to bleeding mucosal surfaces,. . .

DETD . . . collapsed configuration is adapted to allow the elongate shaft and expandable member to be inserted and correctly positioned into a nasal cavity or other body cavity. The expanded configuration may be adapted to substantially fill most of the cavity while leaving. . .

AB A system for delivering a therapeutic agent to a nasopharyngeal mucosa target comprises a foam generating mechanism, a gas, a therapeutic agent in liquid form that inhibits mucus production, and a delivery device. Actuation of the foam generating mechanism entraps gaseous bubbles from the gas in the liquid thereby forming a foam. The therapeutic agent is dispersed in the foam which has an expanded configuration adapted to fill a nasopharyngeal space and deliver the therapeutic agent to the mucosa targets. The delivery device is for delivering the foam to the nasopharyngeal space. The foam may also have a collapsed configuration for removal from the nasopharyngeal space or for concentration of the therapeutic agent onto the mucosa.

L11 ANSWER 18 OF 39 USPATFULL on STN

ACCESSION NUMBER:	2016:10112 USPATFULL
TITLE:	NASOLACRIMAL DRAINAGE SYSTEM IMPLANTS FOR DRUG THERAPY
INVENTOR(S):	de Juan, JR., Eugene, San Francisco, CA, UNITED STATES Boyd, Stephen, Murrieta, CA, UNITED STATES Reich, Cary, Los Gatos, CA, UNITED STATES Rapacki, Alan, Redwood, CA, UNITED STATES Gifford, Hanson S., Woodside, CA, UNITED STATES Deem, Mark, Mountain View, CA, UNITED STATES
APPLICANT(S):	Mati Therapeutics Inc, Austin, TX, UNITED STATES

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 20160008171	A1	20160114
	US 9549852	B2	20170124
APPLICATION INFO.:	US 2015-14858555	A1	20150918 (14)

RELATED APPLN. INFO.: Continuation of Ser. No. US 2014-14265071, filed on 29 Apr 2014, Pat. No. US 9168222 Continuation of Ser. No. US 2011-13184690, filed on 18 Jul 2011, Pat. No. US 8747884 Continuation of Ser. No. US 2007-695545, filed on 2 Apr 2007, Pat. No. US 7998497

	NUMBER	DATE
PRIORITY INFORMATION:	US 2006-60871864	20061226 (60)
	US 2006-60787775	20060331 (60)
	US 2006-60871864	20061226 (60)

DOCUMENT TYPE:	Utility
FILE SEGMENT:	APPLICATION
NUMBER OF CLAIMS:	14
EXEMPLARY CLAIM:	1
NUMBER OF DRAWINGS:	30 Drawing Page(s)
LINE COUNT:	1850

CAS INDEXING IS AVAILABLE FOR THIS PATENT. Full-text

IN Gifford, Hanson S., Woodside, CA, UNITED STATES

DETD . . . extend through the drug core 112 to permit tear flow through

the lumen for the delivery of therapeutic agent for nasal and systemic applications of the therapeutic agent. In addition or in combination with channel 112C, retention structure 132 and core. . .

AB An implant for insertion through a punctum and into a canalicular lumen of a patient. The implant includes a matrix of material, a therapeutic agent dispersed in the matrix of material, a sheath disposed over a portion of the matrix of material and configured to inhibit the therapeutic agent from being released from the matrix of material into the canalicular lumen and to allow the therapeutic agent to be released from a surface of the matrix of material to a tear film, and a retention structure configured to retain the implant within the canalicular lumen.

L11 ANSWER 19 OF 39 USPATFULL on STN

ACCESSION NUMBER:	2015:413714 USPATFULL
TITLE:	METHODS AND SYSTEMS FOR TOXIN DELIVERY TO THE NASAL CAVITY
INVENTOR(S):	Deem, Mark E., Mountain View, CA, UNITED STATES Gifford, Hanson, Woodside, CA, UNITED STATES
APPLICANT(S):	The Foundry LLC, Menlo Park, CA, UNITED STATES

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 20150367115	A1	20151224
	US 20170021148	A9	20170126
	US 9700707	B2	20170711
APPLICATION INFO.:	US 2015-14841514	A1	20150831 (14)

RELATED APPLN. INFO.: Continuation of Ser. No. US 2013-14139710, filed on 23 Dec 2013, ABANDONED Continuation of Ser. No. US 2011-13328203, filed on 16 Dec 2011, Pat. No. US 8636684 Continuation of Ser. No. US 2009-636477, filed on 11 Dec 2009, Pat. No. US 8105817 Division of Ser. No. US 2007-750963, filed on 18 May 2007, Pat. No. US 7655243 Continuation-in-part of Ser. No. US 2006-459090, filed on 21 Jul 2006, Pat. No. US 7608275

	NUMBER	DATE
PRIORITY INFORMATION:	US 2005-60702077	20050722 (60)

DOCUMENT TYPE:	Utility
FILE SEGMENT:	APPLICATION
NUMBER OF CLAIMS:	24
EXEMPLARY CLAIM:	1
NUMBER OF DRAWINGS:	24 Drawing Page(s)
LINE COUNT:	1360

CAS INDEXING IS AVAILABLE FOR THIS PATENT. Full-text

TI METHODS AND SYSTEMS FOR TOXIN DELIVERY TO THE NASAL CAVITY

IN Gifford, Hanson, Woodside, CA, UNITED STATES

AB 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. . .

SUMM . . . relates to methods and systems for delivering toxins, such as botulinum toxin light chain fragments, to target cells in a nasal cavity.

SUMM . . . 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. . . 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.

SUMM . . . 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.

SUMM . . . 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. . .

SUMM . . . 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.

SUMM 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,. . . 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.

SUMM 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.. . .

SUMM . . . 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. . . 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. . .

SUMM . . . 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. . . 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. . .

SUMM . . . 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. . . 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. . .

SUMM . . . external ultrasonic transducers and/or ultrasound wave guides capable of delivering focused or unfocused ultrasound into the target tissues of the nasal cavity.

SUMM . . . 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. . . 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. . .

SUMM . . . 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.. . .

SUMM . . . 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. . .

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

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

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

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

DRWD . . . 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.

DRWD FIG. 29 depicts toxin delivery using a nasal spray and energy delivery using a face mask.

DRWD FIG. 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.

DRWD FIG. 35 depicts the applicator device illustrated in FIG. 33 when placed within the nasal passageway.

DETD 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,. . .

DETD 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. . . 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. . . 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. . .

DETD . . . 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 FIG. 2A. Fragmented neurotoxin such as BoNT-LC (LC) is introduced into the vicinity of the. . .

DETD . . . 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.

DETD . . . 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. . .

DETD . . . of producing a porative effect at the cellular level, including electrodes, ultrasonic elements and the like, for treatment in the nasal passages.

DETD . . . the energy, or both, non-invasively. For example, as illustrated in FIG. 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. . .

DETD 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. 10, a balloon catheter 100 may be provided with a porous balloon 102. . . 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 FIG. 10, the toxin is being delivered to a lower. . .

DETD . . . 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. . .

DETD . . . 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,. . .

DETD Referring now to FIGS. 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. . . shown in FIG. 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 (FIG. 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.

DETD . . . 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. . .

DETD . . . 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. . .

DETD Referring to FIG. 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. . .

DETD FIGS. 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. . . 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 FIG. 35.

DETD 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 FIG. 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. . .

DETD . . . 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 FIG. 37A, the operator would apply inward pressure in the direction of the arrows to the. . . 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 FIG. 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.

DETD 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.

. . 39A) and an expanded configuration when wet (FIG. 39B), wherein the sponge 121 is configured to fit securely within the nasal passageway.

DETD . . . 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 FIG. 36, the liquid can be infused into the applicator tip through. . .

DETD 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.. . .

DETD . . . 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 FIGS. 39A and 39B, a sponge and spring can. . .

DETD . . . 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.

DETD . . . 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.

DETD . . . 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. . . 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.

DETD . . . 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.

DETD 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,. . . open-faced chambers. The outer member may also comprise an array of microneedles to facilitate the passage of BoNT across the nasal membrane. 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. . . 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.

DETD . . . 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. . .

DETD 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.

DETD . . . 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.

DETD . . . this application, the device described with respect to FIGS. 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. . .

DETD 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. . .

DETD 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. . .

CLM What is claimed is:

1. A method for treating a nasal condition in a patient, said method comprising: inserting an applicator tip of an apparatus through a nostril of the patient and into a nasal cavity of the patient, wherein the applicator tip comprises an inner expandable member and an outer expandable member extending around the inner expandable member, wherein the inner expandable member is expanded in the nasal cavity thereby causing the outer expandable member to expand and contact a wall of the nasal cavity, and wherein a toxin is delivered from the expanded outer expandable member to target cells in the wall of the nasal cavity.

CLM What is claimed is:

12. The method of claim 1, wherein the inner expandable member substantially fills the nasal cavity when expanded, thereby inhibiting release of the toxin into portions of the nasal cavity other than the wall.

CLM What is claimed is:

. . . The method of claim 12, wherein the toxin is delivered by delivering a therapeutic dose to the wall of the nasal cavity while inhibiting release of the toxin into other portions of the nasal cavity.

CLM What is claimed is:

15. The method of claim 14, wherein the applicator tip is inserted into the nasal cavity with the handle in the compressed configuration.

CLM What is claimed is:

. . . the handle is biased to be in the expanded configuration such that when the applicator tip is inserted into the nasal cavity, the applicator tip is pressed against a nasal turbinate of the nasal cavity.

CLM What is claimed is:

. . . of claim 1, wherein the toxin is delivered at a rate proportionate with a rate of toxin absorption across a nasal membrane of the patient.

CLM What is claimed is:

. . . wherein the outer expandable member when expanded is configured to match a shape of at least a portion of the nasal cavity.

CLM What is claimed is:
24. A method for treating a nasal condition in a patient, said method comprising: inserting a first applicator tip and a second applicator tip of an apparatus respectively through a first nostril and a second nostril of the patient and into a nasal cavity of the patient with a handle of the apparatus, wherein the first applicator tip and the second applicator tip. . . and an outer expandable member extending around the inner expandable member, wherein the inner expandable members are expanded in the nasal cavity thereby causing the outer expandable member to expand and contact a wall of the nasal cavity, and wherein a toxin is delivered from the expanded outer expandable members to target cells in the wall of the nasal cavity.

AB 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.

L11 ANSWER 20 OF 39 CA COPYRIGHT 2020 ACS on STN DUPLICATE 2
ACCESSION NUMBER: 161:396131 CA
TITLE: Delivery devices for nasopharyngeal mucosa targets
INVENTOR(S): Morriss, John; Gifford, Hanson
PATENT ASSIGNEE(S): The Foundry, LLC, USA
SOURCE: U.S. Pat. Appl. Publ., 32pp., Cont. of Appl. No. PCT/US2012/046258.
CODEN: USXXCO
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.		DATE
US 20140243793	A1	20140828	US 2014-14151588		20140109
US 9867972	B2	20180116			
CN 107510872	A	20171226	CN 2017-10703190		20120711
EP 2731654	B1	20181226	EP 2012-811642		20120711
US 20180021555	A1	20180125	US 2017-15679243		20170817
PRIORITY APPLN. INFO.:			US 2011-61507422	P	20110713
			WO 2012-US46258	A1	20120711
			CN 2012-80044685	A3	20120711
			US 2014-14151588	A1	20140109

ASSIGNMENT HISTORY FOR US PATENT AVAILABLE IN LSUS DISPLAY FORMAT Full-text
IN Morriss, John; Gifford, Hanson
AB . . . configuration to an expanded configuration. The expanded configuration is adapted to engage and conform to the mucosa tissue in a nasal cavity, and the contracted configuration has a size suitable for introduction into the nasal cavity. The drug reservoir holds a therapeutic agent and is at least partially covered by the porous pad. The drug. . .
IT Dissolution
Medical adhesives
Mucus
Needles (tools)
Pharmaceutical nasal sprays
Pressure
Rhinitis
Syringes
Targeted drug delivery systems
Valves
Wetting
(delivery devices for nasopharyngeal mucosa targets)
IT Mucosal drug delivery systems
Nasal drug delivery systems
Nasal mucosa

(nasopharyngeal; delivery devices for nasopharyngeal mucosa targets)
AB A system for delivering a therapeutic agent to nasopharyngeal mucosa tissue has a shaft, a porous pad of compliant material coupled to the shaft near the distal end, and a drug reservoir. The porous pad is configured to expand from a contracted configuration to an expanded configuration. The expanded configuration is adapted to engage and conform to the mucosa tissue in a nasal cavity, and the contracted configuration has a size suitable for introduction into the nasal cavity. The drug reservoir holds a therapeutic agent and is at least partially covered by the porous pad. The drug reservoir is configured to release a fixed vol. of the therapeutic agent into the porous pad within a period of less than about 120 min, and has a wall with a plurality of channels fluidly coupled with the porous pad. Detailed scheme of the device design is provided.
OS.CITING REF COUNT: 1 THERE ARE 1 CAPLUS RECORDS THAT CITE THIS RECORD (1 CITINGS)

L11 ANSWER 21 OF 39 BIOSIS COPYRIGHT (c) 2020 Clarivate Analytics on STN
ACCESSION NUMBER: 2014:257758 BIOSIS
DOCUMENT NUMBER: PREV201400257758
TITLE: Methods and systems for toxin delivery to the nasal cavity.
AUTHOR(S): Deem, Mark E. [Inventor]; Anonymous; Gifford, Hanson [Inventor]
CORPORATE SOURCE: Mountain View, CA USA
ASSIGNEE: The Foundry LLC
PATENT INFORMATION: US 08636684 20140128
SOURCE: Official Gazette of the United States Patent and Trademark Office Patents, (JAN 28 2014)
CODEN: OGUPE7. ISSN: 0098-1133.
DOCUMENT TYPE: Patent
LANGUAGE: English
ENTRY DATE: Entered STN: 19 Mar 2014
Last Updated on STN: 19 Mar 2014 Full-text
TI Methods and systems for toxin delivery to the nasal cavity.
AU Deem, Mark E. [Inventor]; Anonymous; Gifford, Hanson [Inventor]
AB 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. . .
IT Methods & Equipment
nasal cavity providing toxin delivery system: medical equipment;
nasal cavity providing toxin delivery method: clinical techniques
AB 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.

L11 ANSWER 22 OF 39 USPATFULL on STN
ACCESSION NUMBER: 2014:368120 USPATFULL
TITLE: DRUG DELIVERY METHODS, STRUCTURES, AND COMPOSITIONS FOR NASOLACRIMAL SYSTEM
INVENTOR(S): de Juan, JR., Eugene, San Francisco, CA, UNITED STATES
Reich, Cary, Los Gatos, CA, UNITED STATES
Boyd, Stephen, Murrieta, CA, UNITED STATES
Gifford, Hanson S., Woodside, CA, UNITED STATES
Deem, Mark, Mountain View, CA, UNITED STATES
APPLICANT(S): Mati Therapeutics, Austin, TX, UNITED STATES

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 20140328894	A1	20141106
APPLICATION INFO.:	US 2014-14333349	A1	20140716 (14)

RELATED APPLN. INFO.: Continuation of Ser. No. US 2007-695537, filed on 2 Apr 2007, Pat. No. US 8795711

NUMBER	DATE

PRIORITY INFORMATION: US 2006-60787775 20060331 (60)
US 2006-60871864 20061226 (60)
DOCUMENT TYPE: Utility
FILE SEGMENT: APPLICATION
NUMBER OF CLAIMS: 53
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 25 Drawing Page(s)
LINE COUNT: 1908
CAS INDEXING IS AVAILABLE FOR THIS PATENT. Full-text
IN Gifford, Hanson S., Woodside, CA, UNITED STATES
DETD . . . extend through the drug core 112 to permit tear flow through the lumen for the delivery of therapeutic agent for nasal and systemic applications of the therapeutic agent. In addition or in combination with channel 112C, retention structure 132 and core. . .
AB An implant for insertion into a punctum of a patient comprises a body. The body has a distal end, a proximal end, and an axis therebetween. The distal end of the body is insertable distally through the punctum into the canalicular lumen. The body comprises a therapeutic agent included within an agent matrix drug core. Exposure of the agent matrix to the tear fluid effects an effective therapeutic agent release into the tear fluid over a sustained period. The body has a sheath disposed over the agent matrix to inhibit release of the agent away from the proximal end. The body also has an outer surface configured to engage luminal wall tissues so as to inhibit expulsion when disposed therein. In specific embodiments, the agent matrix comprises a non-bioabsorbable polymer, for example silicone in a non-homogenous mixture with the agent.

L11 ANSWER 23 OF 39 USPATFULL on STN
ACCESSION NUMBER: 2014:272055 USPATFULL
TITLE: METHODS AND APPARATUS FOR DELIVERING A THERAPEUTIC AGENT TO NASOPHARYNGEAL MUCOSA TARGETS
INVENTOR(S): Morriss, John, San Francisco, CA, UNITED STATES
Reich, Cary, Los Gatos, CA, UNITED STATES
Gifford, Hanson, Woodside, CA, UNITED STATES
PATENT ASSIGNEE(S): The Foundry, LLC, Menlo Park, CA, UNITED STATES (U.S. corporation)

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 20140242064	A1	20140828
	US 9327104	B2	20160503
APPLICATION INFO.:	US 2014-14151767	A1	20140109 (14)

RELATED APPLN. INFO.: Continuation of Ser. No. WO 2012-US46089, filed on 10 Jul 2012, PENDING

	NUMBER	DATE
PRIORITY INFORMATION:	US 2011-61507417	20110713 (61)

DOCUMENT TYPE: Utility
FILE SEGMENT: APPLICATION
NUMBER OF CLAIMS: 46
EXEMPLARY CLAIM: 1-33
NUMBER OF DRAWINGS: 7 Drawing Page(s)
LINE COUNT: 887
CAS INDEXING IS AVAILABLE FOR THIS PATENT. Full-text
IN Gifford, Hanson, Woodside, CA, UNITED STATES
SUMM Rhinitis is commonly referred to as "stuffy nose," and results from inflammation and swelling of the mucus membranes lining the nasal cavity Rhinitis falls into two major categories--allergic and non-allergic (or vasomotor). Chronic rhinitis can result in chronic inflammation of the nasal passages resulting in sinusitis, an infection or inflammation of the paranasal sinuses. Rhinitis includes the symptoms of rhinorrhea which is commonly referred to as "runny nose." Rhinorrhea describes 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,. . .
SUMM Allergic rhinitis is an immunologic response modulated by immunoglobulin E (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.. . .
SUMM . . . be caused by anatomic pathologies such as blockages, as seen in

the case of sinusitis. Symptoms may include sneezing, itching, nasal congestion, and a runny nose. Non-allergic rhinitis is a diagnosis of rhinitis without any IgE mediation, as documented by allergen. . .

SUMM . . . 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 toxin 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. It has been published in the scientific literature that introduction of botulinum toxin into the nasal passages of canines can reduce mucus secretion by a significant amount. This work is further discussed in scientific and patent. . .

SUMM . . . 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 reported in the scientific literature, will have limited ability to uniformly and selectively deliver the botulinum to the. . .

SUMM . . . treatment site. Such improved methods and systems are preferably used to deliver a toxin, such as botulinum toxin to the nasal membrane of a patient, particularly in 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 an appropriate dose of the toxins to a 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, accurate and effective delivery of a proper dose 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.

SUMM Patents and publications related to delivery of a toxin to the nasal cavity include U.S. Pat. Nos. 5,766,605 and 6,974,578; and U.S. Patent Publication No. 2005/0281751. Related scientific literature includes Sharri et. . .

SUMM . . . therapeutic agent. The therapeutic agent may be a toxin or a non-toxin and in preferred embodiments is delivered to the nasal cavity. When toxins are used, the invention provides for the delivery of the 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.

SUMM The region where the toxin is introduced may comprise any portion of the nasal cavity, such as the turbinates, 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. . .

SUMM . . . and the toxin 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. . .

SUMM . . . invention further provides systems for delivering toxins to epithelial or goblet and other target cells as defined above in a nasal membrane.

DRWD FIG. 1 illustrates basic anatomy of the nasal cavity.

DRWD FIGS. 5A-5H illustrate an exemplary method of using foam to deliver a toxin to the nasal cavity.

DETD . . . directed to methods and systems for delivering therapeutic agents such as toxins or non-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,. . .

DETD 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 in accordance with the principles of the present invention. The. . . energy to permeablize

or porate the cell membranes of the epithelial or goblet cells or other mucus-secreting cells of the nasal lining, may facilitate botulinum and other toxins to be preferentially delivered to the targeted epithelial or goblet and other mucus-producing. . . 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. . .

DETD FIG. 1 illustrates the basic anatomy of the nasal cavity. The entrance to the nasal cavity is via the external naris. Long, narrow, and curled bone shelves line a portion of the nasal cavity. These bones are referred to as nasal concha or turbinates. An upper or superior turbinate, a middle turbinate, and an inferior turbinate divide the nasal airway into four channel-like air passages which direct inhaled air to flow in a steady, regular pattern around the largest. . . and climate controlling tissue. Various sinus cavities are also disposed within the bones of the face and skull adjacent the nasal cavity. These sinuses, such as the frontal sinus and the sphenoid sinus are mucosa lined airspaces that produce mucus. The nasal cavity communicates with the throat via the nasopharynx.

DETD FIGS. 5A-5H illustrate an exemplary method of using foam to deliver a toxin to the nasal cavity. A toxin such as botulinum toxin is contained in the pump dispenser 22 along with a liquid such as. . . shaft extending laterally outward from the pump dispenser. The nozzle may be used to help direct the foam into the nasal cavity or other target area. The surfactant reduces surface tension of the liquid facilitating formation of foam, and actuation of. . . the foam. Additionally, any of the foam delivery devices disclosed herein may be

used to deliver the foam into the nasal cavity.

DETD FIG. 5A is a cross-sectional model of the nasal cavity NC with a translucent top surface to allow the interior of the nose to be seen. The model includes the mouth M, nose N, nasal cavity NC, turbinates, and throat T. The three turbinates include the superior turbinate ST, middle turbinate MT, and inferior turbinate. . .

DETD . . . of the nose N. A first actuation of the pump dispenser 22 forces foam F containing the toxin into the nasal cavity NC. A second actuation of the pump dispenser 22 forces additional foam F into the nasal cavity NC as seen in FIG. 5C. A third, fourth, and fifth actuation of the pump dispenser 22 continue to deliver foam F into the nasal cavity as seen in FIGS. 5D-5F, until the nasal cavity is substantially filled with foam as seen in FIG. 5F. Continued introduction of foam into the nasal cavity can also direct foam into the sinuses via various ducts and apertures in the nasal wall. While the nasal cavity NC is substantially filled with foam, it is not overfilled with foam F so as to avoid the passage. . . therein is not delivered to an undesired location such as the lungs. The foam is permitted to reside in the nasal cavity for a predetermined time in order to allow the therapeutic agent that is dispersed therein to be delivered into. . .

DETD . . . also plug the nostril, to prevent the inadvertent inhalation of the foam. The plug will keep the foam in the nasal passage for the desired time, at which point the plug can be removed.

DETD After the foam F has resided in the nasal cavity for a sufficient time to allow an effective amount of the therapeutic agent to be delivered to the mucosa, the foam is removed from the nasal cavity, preferably by aspiration. Optionally, an anti-foaming agent such as simethicone may be delivered via a syringe 24 placed in. . . polyethylene glycol, polypropylene glycol copolymers, and dishwasher detergents. After a sufficient amount of the anti-foaming agent is delivered to the nasal cavity NC, the syringe 24 is removed from the nose, and the foam F continues to collapse, as seen in. . .

DETD While the exemplary embodiment above describes substantially filling the nasal cavity with the foam and toxin, the amount of foam may be controlled so that only a portion of the. . . target location within the nose. For example, the foam may be delivered and fill only a posterior portion of the nasal cavity, or only an anterior portion of the cavity may be filled with foam. In still other embodiments, the foam. . .

DETD The nasal volume of the first 5.2 cm of the nasal passage has been estimated by Kjoergaard to be about 5.43 cm.sup.3±1.31 cm.sup.3 per side based on acoustic rhinometry. Topical application of toxins to the

nasal cavity have been reported by Rohrbach to use a sponge filled with 40 U (per side) with a concentration of 25 U/ml of toxin. Delivering the same 40 U dose to the nasal cavity with foam having a 10× expansion factor would require approximately 0.5 ml of an 80 U/ml liquid drug solution.

DETD Experiment 3. Volunteers evaluated the sensation of various 3:1 mixtures of foam after the foam was delivered to their nasal cavities. In some instances, the pump dispenser was used to deliver the foam directly to the nostril, while in other. . . pump was used to generate the foam and then the foam was transferred to a syringe for delivery to the nasal passage. The test subjects reported that soap and SDS had a mild stinging sensation in their nose, while Tween did. . . by pinching the nostril. Use of simethicone as an anti-foaming agent did result in sneezing and a sensation of post nasal drip.

DETD In addition to using foam to deliver a therapeutic agent to the nasal cavity, slurries may also be used. A slurry is a thick suspension of solids in a liquid. The solids take. . . the nose. Because viscosity of the slurry can be controlled to have a desired thickness, the slurry will fill the nasal cavity space and not run to undesired locations. The solid particles in the slurry may be porous if desired, but. . .

DETD . . . from the hydrogel particles. After remaining in place for a period of time, the particles can be flushed from the nasal cavity via a canula. In a more specific embodiment, hydrogel particles contain an active ingredient at less than the equilibrium. . .

DETD . . . particles, along with thrombin powder and sterile saline. This product swells during use, which may be a benefit in the nasal cavity. Spongostan (Ethicon) is an absorbable porcine gelatin sponge which liquefies in 2-5 days when applied to bleeding mucosal surfaces,. . .

DETD . . . collapsed configuration is adapted to allow the elongate shaft and expandable member to be inserted and correctly positioned into a nasal cavity or other body cavity. The expanded configuration may be adapted to substantially fill most of the cavity while leaving. . .

AB A system for delivering a therapeutic agent to a nasopharyngeal mucosa target comprises a foam generating mechanism, a gas, a therapeutic agent in liquid form that inhibits mucus production, and a delivery device. Actuation of the foam generating mechanism entraps gaseous bubbles from the gas in the liquid thereby forming a foam. The therapeutic agent is dispersed in the foam which has an expanded configuration adapted to fill a nasopharyngeal space and deliver the therapeutic agent to the mucosa targets. The delivery device is for delivering the foam to the nasopharyngeal space. The foam may also have a collapsed configuration for removal from the nasopharyngeal space or for concentration of the therapeutic agent onto the mucosa.

L11 ANSWER 24 OF 39 USPATFULL on STN

ACCESSION NUMBER: 2014:265257 USPATFULL

TITLE: NASOLACRIMAL DRAINAGE SYSTEM IMPLANTS FOR DRUG THERAPY

INVENTOR(S): De Juan, JR., Eugene, San Francisco, CA, UNITED STATES
Boyd, Stephen, Murrieta, CA, UNITED STATES
Reich, Cary, Los Gatos, CA, UNITED STATES
Rapacki, Alan, Redwood, CA, UNITED STATES
Gifford, Hanson S., Woodside, CA, UNITED STATES
Deem, Mark, Mountain View, CA, UNITED STATES

PATENT ASSIGNEE(S): Mati Therapeutics Inc., Austin, TX, UNITED STATES (U.S. corporation)

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 20140236293	A1	20140821
	US 9168222	B2	20151027
APPLICATION INFO.:	US 2014-14265071	A1	20140429 (14)

RELATED APPLN. INFO.: Continuation of Ser. No. US 2011-13184690, filed on 18 Jul 2011, Pat. No. US 8747884 Continuation of Ser. No. US 2007-695545, filed on 2 Apr 2007, Pat. No. US 7998497

	NUMBER	DATE
PRIORITY INFORMATION:	US 2006-60871864	20061226 (60)
	US 2006-60787775	20060331 (60)

DOCUMENT TYPE: Utility

FILE SEGMENT: APPLICATION
NUMBER OF CLAIMS: 21
EXEMPLARY CLAIM: 1-20
NUMBER OF DRAWINGS: 30 Drawing Page(s)
LINE COUNT: 1848
CAS INDEXING IS AVAILABLE FOR THIS PATENT. Full-text
IN Gifford, Hanson S., Woodside, CA, UNITED STATES
DETD . . . extend through the drug core 112 to permit tear flow through the lumen for the delivery of therapeutic agent for nasal and systemic applications of the therapeutic agent. In addition or in combination with channel 112C, retention structure 132 and core. . .
AB An implant for insertion through a punctum and into a canalicular lumen of a patient. The implant includes a matrix of material, a therapeutic agent dispersed in the matrix of material, a sheath disposed over a portion of the matrix of material and configured to inhibit the therapeutic agent from being released from the matrix of material into the canalicular lumen and to allow the therapeutic agent to be released from a surface of the matrix of material to a tear film, and a retention structure configured to retain the implant within the canalicular lumen.

L11 ANSWER 25 OF 39 USPATFULL on STN
ACCESSION NUMBER: 2014:208960 USPATFULL
TITLE: DRUG CORES FOR SUSTAINED RELEASE OF THERAPEUTIC AGENTS
INVENTOR(S): Utkhede, Deepank, Surrey, CANADA
Shimizu, Robert W., Laguna Niguel, CA, UNITED STATES
Jain, Rachna, Milpitas, CA, UNITED STATES
Boyd, Stephen, Murrieta, CA, UNITED STATES
Gifford, Hanson S., Woodside, CA, UNITED STATES
De Juan, JR., Eugene, San Francisco, CA, UNITED STATES
Reich, Cary J., Los Gatos, CA, UNITED STATES
PATENT ASSIGNEE(S): Mati Therapeutics, Inc., Austin, TX, UNITED STATES (non-U.S. corporation)

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 20140186420	A1	20140703
APPLICATION INFO.:	US 2013-14098317	A1	20131205 (14)

RELATED APPLN. INFO.: Continuation of Ser. No. US 2012-13367823, filed on 7 Feb 2012, Pat. No. US 8628792 Division of Ser. No. US 2008-231986, filed on 5 Sep 2008, PENDING

	NUMBER	DATE
PRIORITY INFORMATION:	US 2007-60970699	20070907 (60)
	US 2007-60970709	20070907 (60)
	US 2007-60970820	20070907 (60)
	US 2008-61049317	20080430 (61)

DOCUMENT TYPE: Utility
FILE SEGMENT: APPLICATION
NUMBER OF CLAIMS: 19
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 50 Drawing Page(s)
LINE COUNT: 7171
CAS INDEXING IS AVAILABLE FOR THIS PATENT. Full-text
IN Gifford, Hanson S., Woodside, CA, UNITED STATES
DETD . . . therapeutic target, e.g., the eye, while blocking release to non-target tissue, such as the interior of the canaliculus, or the nasal sinus.
DETD . . . various embodiments, the drug cores can be used for sustained release of therapeutic agents into the ears and/or Eustachian tubes, nasal and/or sinus cavities, urethra, skin, gastrointestinal tract (including colon, bowel duct, and the like), and in or near joints such. . .
DETD . . . extend through the drug core 112 to permit tear flow through the lumen for the delivery of therapeutic agent for nasal and systemic applications of the therapeutic agent. In addition or in combination with channel 112C, retention structure 132 and core. . .
DETD . . . other therapeutic agent to an eye (e.g., to treat an infection, inflammation, glaucoma or other ocular disease or disorder), a nasal passage (e.g., to treat a sinus or allergy disorder) or an inner ear system (e.g., to treat dizziness or a. . .

DETD . . . insert can be disposed in the second cavity to provide a sustained drug or other therapeutic agent release to a nasal passage or inner ear system, for example. An implant body septum can be positioned between the first cavity and the. . .

DETD . . . having structures derived from the punctual implants described above may allow elution of one or more therapeutic agent into a nasal cavity. Modifications or differences between such nasal implants and the punctual implants described above may include providing a passage for controlled release of medicated tear fluid through the canilicular lumen. Alternative nasal tissue structures may be quite different in overall form, optionally including any of a variety of known nasal cavity drug release shapes, but optionally taking advantage of one or more aspects of the drug cores or other drug. . .

AB A solid drug core insert can be manufactured by injecting a liquid mixture comprising a therapeutic agent and a matrix precursor into a sheath body. The injection can be conducted at subambient temperatures. The mixture is cured to form a solid drug-matrix core. The therapeutic agent can be a liquid at about room temperature that forms a dispersion of droplets in the matrix material. A surface of the solid drug core is exposed, for example by cutting the tube, and the exposed surface of the solid drug core releases therapeutic quantities of the therapeutic agent when implanted into the patient. In some embodiments, the insert body inhibits release of the therapeutic agent, for example with a material substantially impermeable to the therapeutic agent, such that the therapeutic quantities are released through the exposed surface, thereby avoiding release of the therapeutic agent to non-target tissues.

L11 ANSWER 26 OF 39 USPATFULL on STN

ACCESSION NUMBER:	2014:127127 USPATFULL
TITLE:	METHODS AND SYSTEMS FOR TOXIN DELIVERY TO THE NASAL CAVITY
INVENTOR(S):	Deem, Mark E., Mountain View, CA, UNITED STATES Gifford, Hanson, Woodside, CA, UNITED STATES
PATENT ASSIGNEE(S):	The Foundry, LLC, Menlo Park, CA, UNITED STATES (U.S. corporation)

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 20140114233	A1	20140424
APPLICATION INFO.:	US 2013-14139710	A1	20131223 (14)

RELATED APPLN. INFO.: Continuation of Ser. No. US 2011-13328203, filed on 16 Dec 2011, Pat. No. US 8636684 Continuation of Ser. No. US 2009-636477, filed on 11 Dec 2009, Pat. No. US 8105817 Division of Ser. No. US 2007-750963, filed on 18 May 2007, Pat. No. US 7655243 Continuation-in-part of Ser. No. US 2006-459090, filed on 21 Jul 2006, Pat. No. US 7608275

	NUMBER	DATE
PRIORITY INFORMATION:	US 2005-60702077	20050722 (60)
	US 2006-60747771	20060519 (60)

DOCUMENT TYPE:	Utility
FILE SEGMENT:	APPLICATION
NUMBER OF CLAIMS:	31
EXEMPLARY CLAIM:	1
NUMBER OF DRAWINGS:	24 Drawing Page(s)
LINE COUNT:	1374

CAS INDEXING IS AVAILABLE FOR THIS PATENT. Full-text

TI METHODS AND SYSTEMS FOR TOXIN DELIVERY TO THE NASAL CAVITY

IN Gifford, Hanson, Woodside, CA, UNITED STATES

AB 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. . .

SUMM . . . relates to methods and systems for delivering toxins, such as botulinum toxin light chain fragments, to target cells in a nasal cavity.

SUMM . . . 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. . . 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.

SUMM . . . 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.

SUMM . . . 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. . .

SUMM . . . 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.

SUMM 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,. . . 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.

SUMM 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.. . .

SUMM . . . 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. . . 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. . .

SUMM . . . 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. . . 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. . .

SUMM . . . 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. . . 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. . .

SUMM . . . external ultrasonic transducers and/or ultrasound wave guides capable of delivering focused or unfocused ultrasound into the target tissues of the nasal cavity.

SUMM . . . 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. . . 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. . .

SUMM . . . 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.. . .

SUMM . . . 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. . .

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

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

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

DRWD FIGS. 22 and 23--depict nose plugs for occluding and optionally delivery

poration energy to the nasal cavity.

DRWD . . . 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.

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

DRWD FIG. 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.

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

DETD 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,. . .

DETD 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. . . 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. . . 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. . .

DETD . . . 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 FIG. 2A. Fragmented neurotoxin such as BoNT-LC (LC) is introduced into the vicinity of the. . .

DETD . . . 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.

DETD . . . 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. . .

DETD . . . of producing a porative effect at the cellular level, including

electrodes, ultrasonic elements and the like, for treatment in the nasal passages.

DETD . . . the energy, or both, non-invasively. For example, as illustrated in FIG. 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. . .

DETD 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. 10, a balloon catheter 100 may be provided with a porous balloon 102. . . 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 FIG. 10, the toxin is being delivered to a lower. . .

DETD . . . 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. . .

DETD . . . 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,. . .

DETD Referring now to FIGS. 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. . . shown in FIG. 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 (FIG. 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.

DETD . . . 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. . .

DETD . . . 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. . .

DETD Referring to FIG. 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. . .

DETD FIGS. 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. . . 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 FIG. 35.

DETD 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 FIG. 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. . .

DETD . . . 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 FIG. 37A, the operator would apply inward pressure in the direction of the arrows to the. . . 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 FIG. 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.

DETD 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. . . 39A) and an expanded configuration when wet (FIG. 39B), wherein

the sponge 121 is configured to fit securely within the nasal passageway.

DETD . . . 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 FIG. 36, the liquid can be infused into the applicator tip through. . .

DETD 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.. . .

DETD . . . 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 FIGS. 39A and 39B, a sponge and spring can. . .

DETD . . . 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.

DETD . . . 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.

DETD . . . 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. . . 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.

DETD . . . 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.

DETD 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,. . . open-faced chambers. The outer member may also comprise an array of microneedles to facilitate the passage of BoNT across the nasal membrane. 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. . . 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.

DETD . . . 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. . .

DETD 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.

DETD . . . 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.

DETD . . . this application, the device described with respect to FIGS. 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. . .

DETD 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. . .

DETD 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. . .

CLM What is claimed is:

1. A system for treating a nasal condition in a patient, said system comprising: an apparatus insertable into a nasal cavity of the patient, the apparatus comprising an outer expandable member and an inner expandable member disposed within the outer expandable member and configured to expand within the nasal cavity, wherein expansion of the inner expandable member causes expansion of the outer expandable member such that the outer expandable member is placed in contact with a wall of the nasal cavity; and a toxin either: (i) carried by the outer expandable member or (ii) disposed in a space between the. . . members, wherein the outer expandable member is configured to deliver the toxin to target cells in the wall of the nasal cavity.

CLM What is claimed is:

. . . system of claim 1, wherein the inner expandable member comprises a low volume configuration adapted to facilitate insertion into the nasal cavity and an expanded volume configuration adapted to place the outer expandable member in contact with the wall of the nasal cavity.

CLM What is claimed is:

19. A method for treating a nasal condition in a patient, said method comprising: inserting an apparatus into a nasal cavity of the patient,

wherein the apparatus comprises an inner and an outer expandable member; expanding the inner expandable member thereby causing the outer expandable member to expand and contact a wall of the nasal cavity; and delivering a toxin from the outer expandable member to target cells in the wall of the nasal cavity.

CLM What is claimed is:
30. The method of claim 19, wherein expanding the inner balloon substantially fills the nasal cavity, thereby inhibiting release of the toxin into portions of the nasal cavity other than the wall.

CLM What is claimed is:
. . . 31. The method of claim 30, wherein delivering the toxin comprises delivering a therapeutic dose to the wall of the nasal cavity while inhibiting release of the toxin into other portions of the nasal cavity.

AB 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.

L11 ANSWER 27 OF 39 CA COPYRIGHT 2020 ACS on STN DUPLICATE 3
ACCESSION NUMBER: 158:197331 CA
TITLE: Methods and apparatus for delivering a therapeutic agent to nasopharyngeal mucosa targets
INVENTOR(S): Moriss, John; Reich, Cary; Gifford, Hanson
PATENT ASSIGNEE(S): The Foundry, LLC, USA
SOURCE: PCT Int. Appl., 40pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2013009761	A1	20130117	WO 2012-US46089	20120710
EP 2731590	A1	20140521	EP 2012-811983	20120710
EP 2731590	B1	20180523		
CN 103874481	A	20140618	CN 2012-80044533	20120710
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US 9327104	B2	20160503		
US 20160213758	A1	20160728	US 2016-15089007	20160401
US 10004789	B2	20180626		
US 20180264092	A1	20180920	US 2018-15988801	20180524

PRIORITY APPLN. INFO.:
US 2011-61507417 P 20110713
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US 2014-14151767 A3 20140109
US 2016-15089007 A3 20160401

ASSIGNMENT HISTORY FOR US PATENT AVAILABLE IN LSUS DISPLAY FORMAT
OTHER SOURCE(S): CASFORMULTNS 2013:87239 Full-text
IN Moriss, John; Reich, Cary; Gifford, Hanson
IT Nasal drug delivery systems
(nasopharyngeal mucosa; methods and app. for delivering therapeutic agent to nasopharyngeal mucosa targets)
AB A system for delivering a therapeutic agent to a nasopharyngeal mucosa target comprises a foam generating mechanism, a gas, a therapeutic agent in liq. form that inhibits mucus prodn., and a delivery device. Actuation of the foam generating mechanism entraps gaseous bubbles from the gas in the liq. thereby forming a foam. The therapeutic agent is dispersed in the foam which has an expanded configuration adapted to fill a nasopharyngeal space and deliver the therapeutic agent to the mucosa targets. The delivery device is for delivering the foam to the nasopharyngeal space. The foam may also have a collapsed configuration for removal from the nasopharyngeal space or for concn. of the therapeutic agent onto the mucosa. Thus, 0.9 % sodium chloride aq. soln. was combined with a surfactant; surfactants included liq. soaps, sodium dodecyl sulfate (SDS) or Polysorbate 20; the liq. soaps contained water, vegetable oils (such as coconut, castor, soybean, apricot kernel, sunflower seed, meadow

flower seed, and shea butter), and potassium hydroxide; various ratios of saline to surfactant were used; a 3:1 ratio of saline to surfactant easily generated foam when passed through a foam generating mechanism; the foam generating mechanism included a pump dispenser similar to a hand soap pump or a whipped cream canister with nitrous oxide cartridges; a 6:1 ratio also produced foam, but the foam had shorter longevity than the foam formed with a 3:1 ratio of saline to surfactant; using the 3:1 ratio with a pump bottle contg. saline, and either soap, SDS, or Tween produced foams of similar appearance; the foams were white, with a distribution of small uniform bubbles and remained self supporting for at least 15 min.

OS.CITING REF COUNT: 1 THERE ARE 1 CAPLUS RECORDS THAT CITE THIS RECORD (1 CITINGS)

REFERENCE COUNT: 11 THERE ARE 11 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L11 ANSWER 28 OF 39 USPATFULL on STN

ACCESSION NUMBER: 2013:74774 USPATFULL

TITLE: Corneal Denervation for Treatment of Ocular Pain

INVENTOR(S): Alster, Yair, Palo Alto, CA, UNITED STATES
Gifford, Hanson S., Woodside, CA, UNITED STATES
Reich, Cary J., Los Gatos, CA, UNITED STATES
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Scholl, John A., San Ramon, CA, UNITED STATES
Alejandro, Jose D., Sunnyvale, CA, UNITED STATES
Sutton, Douglas, Pacifica, CA, UNITED STATES
Rafaeli, Omer, Tel Aviv, ISRAEL

PATENT ASSIGNEE(S): NexisVision, Inc., Menlo Park, CA, UNITED STATES (U.S. corporation)

	NUMBER	KIND	DATE	
PATENT INFORMATION:	US 20130066283	A1	20130314	
APPLICATION INFO.:	US 2012-13503841	A1	20101022	(13)
	WO 2010-US53854		20101022	
			20120820	PCT 371 date

	NUMBER	DATE
PRIORITY INFORMATION:	US 2009-61279612	20091023 (61)

DOCUMENT TYPE: Utility

FILE SEGMENT: APPLICATION

NUMBER OF CLAIMS: 14

EXEMPLARY CLAIM: 1-148

NUMBER OF DRAWINGS: 33 Drawing Page(s)

LINE COUNT: 1252 Full-text

IN Gifford, Hanson S., Woodside, CA, UNITED STATES

DRWD . . . applicator as in FIG. 5A comprising at least two electrodes to deliver electrical energy to the cornea with a first nasal portion of the applicator and a second temporal portion of the applicator.

DETD . . . portion of tissue and as second outer portion of tissue. Many of the nerves extending into the cornea extend substantially nasal to temporal and temporal to nasal, such that a first outer portion 110A located on a first nasally disposed portion of the cornea and a second. . .

DETD . . . as in FIG. 5A comprising at least two electrodes 556 to deliver electrical energy to the cornea with a first nasal portion 550A of the applicator and a second temporal portion 550B of the applicator. When the first portion and second portion are substantially symmetrical, the applicator can be used on either eye, such that the nasal portion 550A can be used on the temporal portion of the opposite eye and the temporal portion 550B can be used on the nasal portion of the eye.

AB Methods and apparatus for the treatment of the eye to reduce pain can treat at least an outer region of the tissue so as to denervate nerves extending into the inner region and reduce the pain. For example, the cornea of the eye may comprise an inner region having an epithelial defect, and an outer portion of the cornea can be treated to reduce pain of the epithelial defect. The outer portion of the cornea can be treated to denervate nerves extending from the outer portion to the inner portion. The outer portion can be treated in many ways to denervate the nerve, for example with one or more of heat, cold or a denervating noxious substance such as capsaicin. The denervation of the nerve can be

reversible, such that corneal innervation can return following treatment.

L11 ANSWER 29 OF 39 BIOSIS COPYRIGHT (c) 2020 Clarivate Analytics on STN
ACCESSION NUMBER: 2012:369512 BIOSIS
DOCUMENT NUMBER: PREV201200369512
TITLE: Methods and systems for toxin delivery to the nasal cavity.
AUTHOR(S): Deem, Mark E. [Inventor]; Anonymous; Gifford, Hanson [Inventor]
CORPORATE SOURCE: Mountain View, CA USA
ASSIGNEE: The Foundry LLC
PATENT INFORMATION: US 08105817 20120131
SOURCE: Official Gazette of the United States Patent and Trademark Office Patents, (JAN 31 2012)
CODEN: OGUPE7. ISSN: 0098-1133.
DOCUMENT TYPE: Patent
LANGUAGE: English
ENTRY DATE: Entered STN: 9 May 2012
Last Updated on STN: 9 May 2012 Full-text
TI Methods and systems for toxin delivery to the nasal cavity.
AU Deem, Mark E. [Inventor]; Anonymous; Gifford, Hanson [Inventor]
AB 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. . .
IT Methods & Equipment
nasal cavity targeted toxin/toxin fragment delivery method: therapeutic and prophylactic techniques, clinical techniques; nasal cavity targeted toxin/toxin fragment delivery system: drug delivery device
AB 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.

L11 ANSWER 30 OF 39 USPATFULL on STN
ACCESSION NUMBER: 2012:210534 USPATFULL
TITLE: DRUG CORES FOR SUSTAINED RELEASE OF THERAPEUTIC AGENTS
INVENTOR(S): Utkhede, Deepank, Surrey, CANADA
Shimizu, Robert W., Laguna Niguel, CA, UNITED STATES
Jain, Rachna, Milpitas, CA, UNITED STATES
Boyd, Stephen, Murrieta, CA, UNITED STATES
Gifford, Hanson S., Woodside, CA, UNITED STATES
de Juan, Eugene, San Francisco, CA, UNITED STATES
Reich, Cary J., Los Gatos, CA, UNITED STATES
PATENT ASSIGNEE(S): QLT INC., Vancouver, CANADA (non-U.S. corporation)

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 20120187594	A1	20120726
	US 8628792	B2	20140114
APPLICATION INFO.:	US 2012-13367823	A1	20120207 (13)

RELATED APPLN. INFO.: Continuation of Ser. No. US 2008-231986, filed on 5 Sep 2008, PENDING

	NUMBER	DATE
PRIORITY INFORMATION:	US 2008-61049317	20080430 (61)
	US 2007-60970820	20070907 (60)
	US 2007-60970699	20070907 (60)
	US 2007-60970709	20070907 (60)

DOCUMENT TYPE: Utility
FILE SEGMENT: APPLICATION
NUMBER OF CLAIMS: 41
EXEMPLARY CLAIM: 1-29
NUMBER OF DRAWINGS: 50 Drawing Page(s)
LINE COUNT: 7250

CAS INDEXING IS AVAILABLE FOR THIS PATENT. Full-text
IN Gifford, Hanson S., Woodside, CA, UNITED STATES
DETD . . . therapeutic target, e.g., the eye, while blocking release to non-target tissue, such as the interior of the canaliculus, or the nasal sinus.
DETD . . . various embodiments, the drug cores can be used for sustained release of therapeutic agents into the ears and/or Eustachian tubes, nasal and/or sinus cavities, urethra, skin, gastrointestinal tract (including colon, bowel duct, and the like), and in or near joints such. . .
DETD . . . extend through the drug core 112 to permit tear flow through the lumen for the delivery of therapeutic agent for nasal and systemic applications of the therapeutic agent. In addition or in combination with channel 112C, retention structure 132 and core. . .
DETD . . . other therapeutic agent to an eye (e.g., to treat an infection, inflammation, glaucoma or other ocular disease or disorder), a nasal passage (e.g., to treat a sinus or allergy disorder) or an inner ear system (e.g., to treat dizziness or a. . .
DETD . . . insert can be disposed in the second cavity to provide a sustained drug or other therapeutic agent release to a nasal passage or inner ear system, for example. An implant body septum can be positioned between the first cavity and the. . .
DETD . . . having structures derived from the punctual implants described above may allow elution of one or more therapeutic agent into a nasal cavity. Modifications or differences between such nasal implants and the punctual implants described above may include providing a passage for controlled release of medicated tear fluid through the canilicular lumen. Alternative nasal tissue structures may be quite different in overall form, optionally including any of a variety of known nasal cavity drug release shapes, but optionally taking advantage of one or more aspects of the drug cores or other drug. . .
AB A solid drug core insert can be manufactured by injecting a liquid mixture comprising a therapeutic agent and a matrix precursor into a sheath body. The injection can be conducted at subambient temperatures. The mixture is cured to form a solid drug-matrix core. The therapeutic agent can be a liquid at about room temperature that forms a dispersion of droplets in the matrix material. A surface of the solid drug core is exposed, for example by cutting the tube, and the exposed surface of the solid drug core releases therapeutic quantities of the therapeutic agent when implanted into the patient. In some embodiments, the insert body inhibits release of the therapeutic agent, for example with a material substantially impermeable to the therapeutic agent, such that the therapeutic quantities are released through the exposed surface, thereby avoiding release of the therapeutic agent to non-target tissues.

L11 ANSWER 31 OF 39 USPATFULL on STN

ACCESSION NUMBER:	2012:99920 USPATFULL
TITLE:	METHODS AND SYSTEMS FOR TOXIN DELIVERY TO THE NASAL CAVITY
INVENTOR(S):	Deem, Mark E., Mountain View, CA, UNITED STATES Gifford, Hanson, Woodside, CA, UNITED STATES
PATENT ASSIGNEE(S):	The Foundry, LLC, Menlo Park, CA, UNITED STATES (U.S. corporation)

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 20120089078	A1	20120412
	US 8636684	B2	20140128
APPLICATION INFO.:	US 2011-13328203	A1	20111216 (13)

RELATED APPLN. INFO.: Continuation of Ser. No. US 2009-636477, filed on 11 Dec 2009, Pat. No. US 8105817 Division of Ser. No. US 2007-750963, filed on 18 May 2007, Pat. No. US 7655243 Continuation-in-part of Ser. No. US 2006-459090, filed on 21 Jul 2006, Pat. No. US 7608275

	NUMBER	DATE
PRIORITY INFORMATION:	US 2005-60702077	20050722 (60)
	US 2006-60747771	20060519 (60)

DOCUMENT TYPE:	Utility
FILE SEGMENT:	APPLICATION

NUMBER OF CLAIMS: 68
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 24 Drawing Page(s)
LINE COUNT: 1435
CAS INDEXING IS AVAILABLE FOR THIS PATENT. Full-text
TI METHODS AND SYSTEMS FOR TOXIN DELIVERY TO THE NASAL CAVITY
IN Gifford, Hanson, Woodside, CA, UNITED STATES
AB 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. . .
SUMM . . . relates to methods and systems for delivering toxins, such as botulinum toxin light chain fragments, to target cells in a nasal cavity.
SUMM . . . 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. . . 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.
SUMM . . . 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.
SUMM . . . 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. . .
SUMM . . . 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.
SUMM 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,. . . 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
SUMM 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.. . .
SUMM . . . 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. . . 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. . .

SUMM . . . 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. . . 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. . .

SUMM . . . 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. . . 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. . .

SUMM . . . external ultrasonic transducers and/or ultrasound wave guides capable of delivering focused or unfocused ultrasound into the target tissues of the nasal cavity.

SUMM . . . 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. . . 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. . .

SUMM . . . 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.. . .

SUMM . . . 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. . .

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

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

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

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

DRWD . . . 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.

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

DRWD FIG. 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.

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

DETD 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,. . .

DETD 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. . . 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. . . 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. . .

DETD . . . 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 FIG. 2A. Fragmented neurotoxin such as BoNT-LC (LC) is introduced into the vicinity of the. . .

DETD . . . 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.

DETD . . . 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. . .

DETD . . . of producing a porative effect at the cellular level, including electrodes, ultrasonic elements and the like, for treatment in the nasal passages.

DETD . . . the energy, or both, non-invasively. For example, as illustrated in FIG. 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. . .

DETD 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. 10, a balloon catheter 100 may be provided with a porous balloon 102. . . 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 FIG. 10, the toxin is being delivered to a lower. . .

DETD . . . 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. . .

DETD . . . 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,. . .

DETD Referring now to FIGS. 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. . . shown in FIG. 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 (FIG. 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.

DETD . . . 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. . .

DETD . . . 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. . .

DETD Referring to FIG. 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. . .

DETD FIGS. 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. . . 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 FIG. 35.

DETD 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 FIG. 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. . .

DETD . . . 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 FIG. 37A, the operator would apply inward pressure in the direction of the arrows to the. . . 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 FIG. 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.

DETD 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. . . 39A) and an expanded configuration when wet (FIG. 39B), wherein the sponge 121 is configured to fit securely within the nasal

passageway.

DETD . . . 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 FIG. 36, the liquid can be infused into the applicator tip through. . .

DETD 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.. . .

DETD . . . 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 FIGS. 39A and 39B, a sponge and spring can. . .

DETD . . . 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.

DETD . . . 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

DETD . . . 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. . . 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.

DETD . . . 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.

DETD 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,. . . open-faced chambers. The outer member may also comprise an array of microneedles to facilitate the passage of BoNT across the nasal membrane. 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. . . 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.

DETD . . . 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. . .

DETD 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

DETD . . . 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.

DETD . . . this application, the device described with respect to FIGS. 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. . .

DETD 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. . .

DETD 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. . .

CLM What is claimed is:

2. A method of treating a nasal condition comprising: positioning one or more occlusion devices in a nasal cavity to fluidly isolate a treatment region therein from a remaining portion of the nasal cavity, the treatment region containing target cells; and introducing a toxin to

the treatment region while the one or more occlusion devices block the toxin from entering the remaining portion of the nasal cavity, wherein the toxin inhibits mucous secretion in the target.

CLM What is claimed is:
. . . method of claim 2, wherein the one or more occlusion devices comprise one or more plugs positioned to block a nasal passage of the patient.

CLM What is claimed is:
27. The method of claim 2, wherein the treatment region comprises at least one paranasal sinus, a main nasal passage, or a nasal turbinate.

CLM What is claimed is:
28. The method of claim 2, wherein the treatment region comprises substantially the entire nasal cavity.

CLM What is claimed is:
34. A method of treating a nasal condition in a patient, said method comprising: introducing a gel or foam carrier comprising a toxin to a treatment region in a nasal cavity containing target cells, wherein the toxin is delivered from the gel or foam carrier to the target cells so. . .

CLM What is claimed is:
39. The method of claim 34, further comprising filling a targeted airway of the nasal cavity of the patient with the gel or foam carrier.

CLM What is claimed is:
40. The method of claim 39, further comprising fluidly isolating a treatment region of the nasal cavity, wherein the toxin is introduced into the treatment region.

CLM What is claimed is:
41. The method of claim 34, wherein the gel or foam carrier remains in place in the nasal cavity following introduction while the toxin is delivered to the target cells.

CLM What is claimed is:
62. The method of claim 34, wherein the treatment region comprises at least one paranasal sinus, a main nasal passage, or a nasal turbinate.

CLM What is claimed is:
63. The method of claim 34, wherein the treatment region comprises substantially the entire nasal cavity.

AB 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.

L11 ANSWER 32 OF 39 BIOSIS COPYRIGHT (c) 2020 Clarivate Analytics on STN
ACCESSION NUMBER: 2010:122525 BIOSIS
DOCUMENT NUMBER: PREV201000122525
TITLE: Methods and systems for toxin delivery to the nasal cavity.
AUTHOR(S): Deem, Mark E. [Inventor]; Anonymous; Gifford, Hanson [Inventor]
CORPORATE SOURCE: Mountain View, CA USA
ASSIGNEE: The Foundry LLC
PATENT INFORMATION: US 07655243 20100202
SOURCE: Official Gazette of the United States Patent and Trademark Office Patents, (FEB 2 2010)
CODEN: OGUPE7. ISSN: 0098-1133.
DOCUMENT TYPE: Patent
LANGUAGE: English
ENTRY DATE: Entered STN: 24 Feb 2010
Last Updated on STN: 24 Feb 2010 Full-text
TI Methods and systems for toxin delivery to the nasal cavity.
AU Deem, Mark E. [Inventor]; Anonymous; Gifford, Hanson [Inventor]
AB 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. . .

IT Methods & Equipment
nasal cavity based toxin delivery system: drug delivery device

AB 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.

L11 ANSWER 33 OF 39 USPATFULL on STN

ACCESSION NUMBER:	2010:98403 USPATFULL		
TITLE:	METHODS AND SYSTEMS FOR TOXIN DELIVERY TO THE NASAL CAVITY		
INVENTOR(S):	DEEM, MARK E., MOUNTAIN VIEW, CA, UNITED STATES GIFFORD, HANSON, WOODSIDE, CA, UNITED STATES		
PATENT ASSIGNEE(S):	THE FOUNDY, LLC, MENLO PARK, CA, UNITED STATES (U.S. corporation)		
	NUMBER	KIND	DATE
PATENT INFORMATION:	US 20100087775	A1	20100408
	US 8105817	B2	20120131
APPLICATION INFO.:	US 2009-636477	A1	20091211 (12)
RELATED APPLN. INFO.:	Division of Ser. No. US 2007-750963, filed on 18 May 2007, Pat. No. US 7655243 Continuation-in-part of Ser. No. US 2006-459090, filed on 21 Jul 2006, Pat. No. US 7608275		
	NUMBER		DATE
PRIORITY INFORMATION:	US 2006-60747771		20060519 (60)
	US 2005-60702077		20050722 (60)
DOCUMENT TYPE:	Utility		
FILE SEGMENT:	APPLICATION		
LEGAL REPRESENTATIVE:	TOWNSEND AND TOWNSEND AND CREW, LLP, TWO EMBARCADERO CENTER, EIGHTH FLOOR, SAN FRANCISCO, CA, 94111-3834, US		
NUMBER OF CLAIMS:	31		
EXEMPLARY CLAIM:	1		
NUMBER OF DRAWINGS:	24 Drawing Page(s)		
LINE COUNT:	1356		

CAS INDEXING IS AVAILABLE FOR THIS PATENT. Full-text

TI METHODS AND SYSTEMS FOR TOXIN DELIVERY TO THE NASAL CAVITY

IN GIFFORD, HANSON, WOODSIDE, CA, UNITED STATES

AB 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. . .

SUMM . . . relates to methods and systems for delivering toxins, such as botulinum toxin light chain fragments, to target cells in a nasal cavity.

SUMM . . . 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. . . 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.

SUMM . . . 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.

SUMM . . . 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. . .

SUMM . . . 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.

SUMM 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,. . . 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.

SUMM 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.. . .

SUMM . . . 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. . . 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. . .

SUMM . . . 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. . . 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. . .

SUMM . . . 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. . . 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. . .

SUMM . . . external ultrasonic transducers and/or ultrasound wave guides capable of delivering focused or unfocused ultrasound into the target tissues of the nasal cavity.

SUMM . . . 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. . . 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. . .

SUMM . . . 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.. . .

SUMM . . . 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. . .

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

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

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

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

DRWD . . . 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.

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

DRWD FIG. 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.

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

DETD 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,. . .

DETD 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. . . 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. . . 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. . .

DETD . . . 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 FIG. 2A. Fragmented neurotoxin such as BoNT-LC (LC)is introduced into the vicinity of the targeted. . .

DETD . . . 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.

DETD . . . 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. . .

DETD . . . of producing a porative effect at the cellular level, including electrodes, ultrasonic elements and the like, for treatment in the nasal passages.

DETD . . . the energy, or both, non-invasively. For example, as illustrated in FIG. 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. . .

DETD 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. 10, a balloon catheter 100 may be provided

with a porous balloon 102. . . 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 FIG. 10, the toxin is being delivered to a lower. . .

DETD . . . 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. . .

DETD . . . 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,. . .

DETD Referring now to FIGS. 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. . . shown in FIG. 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 (FIG. 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.

DETD . . . 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. . .

DETD . . . 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. . .

DETD Referring to FIG. 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. . .

DETD FIGS. 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. . . 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 FIG. 35.

DETD 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 FIG. 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. . .

DETD . . . 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 FIG. 37A, the operator would apply inward pressure in the direction of the arrows to the. . . 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 FIG. 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.

DETD 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. . . 39A) and an expanded configuration when wet (FIG. 39B), wherein

the sponge 121 is configured to fit securely within the nasal passageway.

DETD . . . 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 FIG. 36, the liquid can be infused into the applicator tip through. . .

DETD 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.. . .

DETD . . . 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 FIGS. 39A and 39B, a sponge and spring can. . .

DETD . . . 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.

DETD . . . 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.

DETD . . . 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. . . 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.

DETD . . . 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.

DETD 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,. . . open-faced chambers. The outer member may also comprise an array of microneedles to facilitate the passage of BoNT across the nasal membrane. 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. . . 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.

DETD . . . 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. . .

DETD 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.

DETD . . . 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.

DETD . . . this application, the device described with respect to FIGS. 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. . .

DETD 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. . .

DETD 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. . .

CLM What is claimed is:
1. 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. . .

CLM What is claimed is:
. . . A system as in claim 1, wherein the energy applicator comprises a wave guide configured to be positioned within a nasal passageway.

CLM What is claimed is:
30. A system as in claim 17, wherein the balloon is configured to be positioned within a nasal passageway.

AB 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.

L11 ANSWER 34 OF 39 USPATFULL on STN

ACCESSION NUMBER:	2009:115740 USPATFULL
TITLE:	Drug cores for sustained release of therapeutic agents
INVENTOR(S):	Utkhede, Deepank, Surrey, CANADA Shimizu, Robert W., Laguna Niguel, CA, UNITED STATES Jain, Rachna, Milpitas, CA, UNITED STATES Boyd, Stephen, Murrieta, CA, UNITED STATES Gifford, Hanson S., Woodside, CA, UNITED STATES de Juan, JR., Eugene, San Francisco, CA, UNITED STATES Reich, Cary J., Los Gatos, CA, UNITED STATES
PATENT ASSIGNEE(S):	QLT Plug Delivery, Inc. - QPDI, Menlo Park, CA, UNITED STATES (U.S. corporation)

	NUMBER	KIND	DATE	
PATENT INFORMATION:	US 20090104243	A1	20090423	
APPLICATION INFO.:	US 2008-231986	A1	20080905	(12)

	NUMBER	DATE
PRIORITY INFORMATION:	US 2007-60970699	20070907 (60)
	US 2007-60970709	20070907 (60)
	US 2007-60970820	20070907 (60)
	US 2008-61049317	20080430 (61)

DOCUMENT TYPE: Utility
FILE SEGMENT: APPLICATION
LEGAL REPRESENTATIVE: SCHWEGMAN, LUNDBERG & WOESSNER, P.A., P.O. BOX 2938, MINNEAPOLIS, MN, 55402, US
NUMBER OF CLAIMS: 32
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 50 Drawing Page(s)
LINE COUNT: 7264
CAS INDEXING IS AVAILABLE FOR THIS PATENT. Full-text
IN Gifford, Hanson S., Woodside, CA, UNITED STATES
DETD . . . therapeutic target, e.g., the eye, while blocking release to non-target tissue, such as the interior of the canaliculus, or the nasal sinus.
DETD . . . various embodiments, the drug cores can be used for sustained release of therapeutic agents into the ears and/or Eustachian tubes, nasal and/or sinus cavities, urethra, skin, gastrointestinal tract (including colon, bowel duct, and the like), and in or near joints such. . .
DETD . . . extend through the drug core 112 to permit tear flow through the lumen for the delivery of therapeutic agent for nasal and systemic applications of the therapeutic agent. In addition or in combination with channel 112C, retention structure 132 and core. . .
DETD . . . other therapeutic agent to an eye (e.g., to treat an infection, inflammation, glaucoma or other ocular disease or disorder), a nasal passage (e.g., to treat a sinus or allergy disorder) or an inner ear system (e.g., to treat dizziness or a. . .
DETD . . . insert can be disposed in the second cavity to provide a sustained drug or other therapeutic agent release to a nasal passage or inner ear system, for example. An implant body septum can be positioned between the first cavity and the. . .
DETD . . . having structures derived from the punctual implants described above may allow elution of one or more therapeutic agent into a nasal cavity. Modifications or differences between such nasal implants and the punctual implants described above may include providing a passage for controlled release of medicated tear fluid through the canilicular lumen. Alternative nasal tissue structures may be quite different in overall form, optionally including any of a variety of known nasal cavity drug release shapes, but optionally taking advantage of one or more aspects of the drug cores or other drug. . .
AB A solid drug core insert can be manufactured by injecting a liquid mixture comprising a therapeutic agent and a matrix precursor into a sheath body. The injection can be conducted at subambient temperatures. The mixture is cured to form a solid drug-matrix core. The therapeutic agent can be a liquid at about room temperature that forms a dispersion of droplets in the matrix material. A surface of the solid drug core is exposed, for example by cutting the tube, and the exposed surface of the solid drug core releases therapeutic quantities of the therapeutic agent when implanted into the patient. In some embodiments, the insert body inhibits release of the therapeutic agent, for example with a material substantially impermeable to the therapeutic agent, such that the therapeutic quantities are released through the exposed surface, thereby avoiding release of the therapeutic agent to non-target tissues.

L11 ANSWER 35 OF 39 CA COPYRIGHT 2020 ACS on STN DUPLICATE 4
ACCESSION NUMBER: 148:175883 CA
TITLE: Methods and systems for toxin delivery to the nasal cavity
INVENTOR(S): Deem, Mark E.; Gifford, Hanson
PATENT ASSIGNEE(S): The Foundry Inc., USA
SOURCE: U.S. Pat. Appl. Publ., 38pp., Cont.-in-part of U. S. Ser. No. 459,090.
CODEN: USXXCO
DOCUMENT TYPE: Patent
LANGUAGE: English

FAMILY ACC. NUM. COUNT: 4
PATENT INFORMATION:

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JP 2017038963	A	20170223	JP 2016-227703	20161124
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US 10052465	B2	20180821		
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US 10610675	B2	20200407		

PRIORITY APPLN. INFO.:	US 2005-60702077	P	20050722
	US 2006-60747771	P	20060519
	US 2006-459090	A2	20060721
	JP 2008-522980	A3	20060721
	US 2007-750963	A	20070518
	US 2007-750967	A	20070518
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	US 2012-13660629	A1	20121025
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	JP 2015-120827	A3	20150616
	US 2015-14841514	A1	20150831
	US 2016-15358187	A1	20161122
	US 2018-16036381	A1	20180716

ASSIGNMENT HISTORY FOR US PATENT AVAILABLE IN LSUS DISPLAY FORMAT Full-text
TI Methods and systems for toxin delivery to the nasal cavity
IN Deem, Mark E.; Gifford, Hanson
AB 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. . .
ST system toxin delivery nasal cavity
IT Catheters
Epithelium
Headache
Human

Microwave
Migraine
Nasopharynx
Nose
Sound and Ultrasound
(methods and systems for toxin delivery to nasal cavity)

IT Toxins
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(methods and systems for toxin delivery to nasal cavity)

IT 93384-43-1, Botulin A 93384-44-2, Botulin B 93384-45-3, Botulin C 93384-46-4, Botulin D 93384-47-5, Botulin E 107231-12-9, Botulinum toxin 107231-15-2, Botulin F 107231-16-3, Botulin G
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(methods and systems for toxin delivery to nasal cavity)

AB 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. The use of balloon catheters for delivering toxins to the nasopharynx is depicted (no data).

OS.CITING REF COUNT: 16 THERE ARE 16 CAPLUS RECORDS THAT CITE THIS RECORD (26 CITINGS)
REFERENCE COUNT: 75 THERE ARE 75 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L11 ANSWER 36 OF 39 CA COPYRIGHT 2020 ACS on STN DUPLICATE 5
ACCESSION NUMBER: 147:548133 CA
TITLE: Apparatus, methods and systems for toxin delivery to the nasal cavity
INVENTOR(S): Deem, Mark E.; Gifford, Hanson; Kim, Steven; Salamini, Alexey
PATENT ASSIGNEE(S): The Foundry Inc., USA
SOURCE: PCT Int. Appl., 68 pp., Chemical Indexing Equivalent to 166:33837 (US)
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 4
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2007137235	A2	20071129	WO 2007-US69391	20070521
WO 2007137235	A3	20080522		
US 20080021369	A1	20080124	US 2007-750963	20070518
US 7655243	B2	20100202		
US 9511210	B2	20161206	US 2007-750967	20070518
US 20070267011	A1	20071122		
EP 2021022	A2	20090211	EP 2007-784000	20070521
EP 2021022	B1	20170412		
JP 2009538641	T	20091112	JP 2009-511262	20070521
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US 20150150625	A1	20150604	US 2015-14601529	20150121
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JP 2015186597	A	20151029	JP 2015-120827	20150616
JP 6290139	B2	20180307		
JP 2017038963	A	20170223	JP 2016-227703	20161124

PRIORITY APPLN. INFO.:

US 2006-60747771	P	20060519
US 2007-750963	A	20070518
US 2007-750967	A	20070518
US 2005-60702077	P	20050722
JP 2008-522980	A3	20060721
US 2006-459090	A2	20060721
WO 2007-US69391	W	20070521
US 2009-559278	A1	20090914
US 2011-13253595	A1	20111005
US 2012-13660629	A1	20121025

ASSIGNMENT HISTORY FOR US PATENT AVAILABLE IN LSUS DISPLAY FORMAT
OTHER SOURCE(S): CASFORMULTNS 2007:1363693 Full-text
TI Apparatus, methods and systems for toxin delivery to the nasal cavity
IN Deem, Mark E.; Gifford, Hanson; Kim, Steven; Salamini, Alexey
AB App., 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. . .
ST toxin delivery nasal cavity inflammation
IT Medical goods
(balloons; toxin delivery to the nasal cavity)
IT Coating materials
(bioresorbable; toxin delivery to the nasal cavity)
IT Medical goods
(springs; toxin delivery to the nasal cavity)
IT Anti-inflammatory agents
Inflammation
Medical sponges
Microwave
Nasal drug delivery systems
Nasal mucosa
Nose
Pulsed electric current
Sound and Ultrasound
Springs (mechanical)
X-ray
(toxin delivery to the nasal cavity)
IT Toxins
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(toxin delivery to the nasal cavity)
IT 93384-43-1, Botulin A 93384-44-2, Botulin B 93384-45-3, Botulin C 93384-46-4, Botulin D 93384-47-5, Botulin E 107231-15-2, Botulin F 107231-16-3, Botulin G
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(toxin delivery to the nasal cavity)
AB App., 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.

L11 ANSWER 37 OF 39 USPATFULL on STN
ACCESSION NUMBER: 2007:308397 USPATFULL
TITLE: Drug Delivery Methods, Structures, and Compositions for Nasolacrimal System
INVENTOR(S): de Juan, Eugene JR., San Francisco, CA, UNITED STATES
Reich, Cary, Los Gatos, CA, UNITED STATES
Boyd, Stephen, Murrieta, CA, UNITED STATES
Gifford, Hanson G. III, Woodside, CA, UNITED STATES
Deem, Mark, Mountain View, CA, UNITED STATES
PATENT ASSIGNEE(S): FORSIGHT LABS, LLC, Menlo Park, CA, UNITED STATES, 94025 (U.S. corporation)

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 20070269487	A1	20071122
	US 8795711	B2	20140805
APPLICATION INFO.:	US 2007-695537	A1	20070402 (11)

	NUMBER	DATE
PRIORITY INFORMATION:	US 2006-60787775	20060331 (60)
	US 2006-60871864	20061226 (60)

DOCUMENT TYPE: Utility
FILE SEGMENT: APPLICATION
LEGAL REPRESENTATIVE: TOWNSEND AND TOWNSEND AND CREW, LLP, TWO EMBARCADERO CENTER, EIGHTH FLOOR, SAN FRANCISCO, CA, 94111-3834, US
NUMBER OF CLAIMS: 53
EXEMPLARY CLAIM: 1

NUMBER OF DRAWINGS: 25 Drawing Page(s)
LINE COUNT: 1911
CAS INDEXING IS AVAILABLE FOR THIS PATENT. Full-text
IN Gifford, Hanson G. III, Woodside, CA, UNITED STATES
DETD . . . extend through the drug core 112 to permit tear flow through the lumen for the delivery of therapeutic agent for nasal and systemic applications of the therapeutic agent. In addition or in combination with channel 112C, retention structure 132 and core. . .
AB An implant for insertion into a punctum of a patient comprises a body. The body has a distal end, a proximal end, and an axis therebetween. The distal end of the body is insertable distally through the punctum into the canalicular lumen. The body comprises a therapeutic agent included within an agent matrix drug core. Exposure of the agent matrix to the tear fluid effects an effective therapeutic agent release into the tear fluid over a sustained period. The body has a sheath disposed over the agent matrix to inhibit release of the agent away from the proximal end. The body also has an outer surface configured to engage luminal wall tissues so as to inhibit expulsion when disposed therein. In specific embodiments, the agent matrix comprises a non-bioabsorbable polymer, for example silicone in a non-homogenous mixture with the agent.

L11 ANSWER 38 OF 39 USPATFULL on STN
ACCESSION NUMBER: 2007:305933 USPATFULL
TITLE: APPARATUS FOR TOXIN DELIVERY TO THE NASAL CAVITY
INVENTOR(S): Deem, Mark E., Mountain View, CA, UNITED STATES
Gifford, Hanson, Woodside, CA, UNITED STATES
Kim, Steven, Los Altos, CA, UNITED STATES
Salamini, Alexey, San Francisco, CA, UNITED STATES
PATENT ASSIGNEE(S): The Foundry Inc., Menlo Park, CA, UNITED STATES (U.S. corporation)

	NUMBER	KIND	DATE	
PATENT INFORMATION:	US 20070267011	A1	20071122	
	US 9511210	B2	20161206	
APPLICATION INFO.:	US 2007-750967	A1	20070518	(11)

	NUMBER	DATE
PRIORITY INFORMATION:	US 2006-60747771	20060519 (60)

DOCUMENT TYPE: Utility
FILE SEGMENT: APPLICATION
LEGAL REPRESENTATIVE: TOWNSEND AND TOWNSEND AND CREW, LLP, TWO EMBARCADERO CENTER, EIGHTH FLOOR, SAN FRANCISCO, CA, 94111-3834, US
NUMBER OF CLAIMS: 43
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 24 Drawing Page(s)
LINE COUNT: 1513
CAS INDEXING IS AVAILABLE FOR THIS PATENT. Full-text
TI APPARATUS FOR TOXIN DELIVERY TO THE NASAL CAVITY
IN Gifford, Hanson, Woodside, CA, UNITED STATES
AB Apparatus 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. . .
DRWD FIG. 9--depicts use on an external hand held transducer for enhancing cellular uptake of toxin delivered from a separate nasal aerosolizer.
DRWD FIG. 15--depicts sizing of a delivery balloon to control distribution of toxin released into the nasal cavity.
DRWD FIG. 17--depicts the use of multiple small balloons for selective toxin delivery into the nasal cavity.
DRWD FIGS. 22 and 23--depict nose plugs for occluding and optionally delivery poration energy to the nasal cavity.
DRWD . . . 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.
DRWD FIG. 29--depicts toxin delivery using a nasal spray and energy delivery using a face mask.
DRWD FIG. 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.
DRWD FIG. 35--depicts the applicator device illustrated in FIG. 33 when

placed within the nasal passageway.

DETD . . . relates to methods and systems for delivering toxins, such as botulinum toxin light chain fragments, to target cells in a nasal cavity.

DETD . . . 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. . . 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.

DETD . . . 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.

DETD . . . 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. . .

DETD . . . 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.

DETD 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.

DETD 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,. . . 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.

DETD 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.. . .

DETD 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.

DETD . . . 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. The outward bias from this spring element can result in an expanded treatment configuration for delivering toxin to the nasal tissue.

DETD . . . 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. . .

DETD 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. . .

DETD . . . 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. . .

DETD . . . 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.

DETD . . . 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. . .

DETD 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,. . .

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.

DETD 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.. . .

DETD . . . 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. . . 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. . .

DETD . . . 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. . . 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. . .

DETD . . . 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. . . 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. . .

DETD . . . external ultrasonic transducers and/or ultrasound wave guides capable of delivering focused or unfocused ultrasound into the target tissues of the nasal cavity.

DETD . . . 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. . . 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. . .

DETD . . . 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.. . .

DETD . . . 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. . .

DETD 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,. . .

DETD 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. . . 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. . . 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. . .

DETD . . . 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 FIG. 2A. Fragmented neurotoxin such as BoNT-LC (LC) is introduced into the vicinity of the. . .

DETD . . . 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.

DETD . . . 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. . .

DETD . . . of producing a porative effect at the cellular level, including electrodes, ultrasonic elements and the like, for treatment in the nasal passages.

DETD . . . the energy, or both, non-invasively. For example, as illustrated in FIG. 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. . .

DETD 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. 10, a balloon catheter 100 may be provided with a porous balloon 102. . . 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 FIG. 10, the toxin is being delivered to a lower. . .

DETD . . . 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. . .

DETD . . . 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,. . .

DETD Referring now to FIGS. 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. . . shown in FIG. 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 (FIG. 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.

DETD . . . 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. . .

DETD . . . 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. . .

DETD Referring to FIG. 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. . .

DETD FIGS. 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. . . 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 FIG. 35.

DETD 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 FIG. 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. . .

DETD . . . 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 FIG. 37A, the operator would apply inward pressure in the direction of the arrows to the. . . 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 FIG. 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.

DETD 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. . . 39A) and an expanded configuration when wet (FIG. 39B), wherein the sponge 121 is configured to fit securely within the nasal passageway.

DETD . . . 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 FIG. 36, the liquid can be infused into the applicator tip through. . .

DETD 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.. . .

DETD . . . 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 FIGS. 39A and 39B, a sponge and spring can. . .

DETD . . . 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.

DETD . . . 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.

DETD . . . 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. . . 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.

DETD . . . 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.

DETD 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,. . . 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. . . 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. . . 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.

DETD . . . 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. . .

DETD 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.

DETD . . . 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.

DETD . . . this application, the device described with respect to FIGS. 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. . .

DETD 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. . .

DETD 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. . .

CLM What is claimed is:
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. . . 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.

CLM What is claimed is:
4. 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 toxin to the region of nasal tissue.

CLM What is claimed is:
. . . 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.

CLM What is claimed is:
. . . 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.

CLM What is claimed is:
. . . 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.

CLM What is claimed is:
. . . apparatus of claim 17, wherein the applicator tips are configured to receive the toxin prior to being positioned in the nasal passageway.

CLM What is claimed is:
. . . The apparatus of claim 17, wherein the applicator tips are configured to receive the toxin after being positioned in the nasal passageway.

CLM What is claimed is:
. . . 26. The apparatus of claim 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.

CLM What is claimed is:
. . . applicator is adapted to deliver energy under conditions which cause

poration of at least one cell in the region of nasal tissue.

CLM What is claimed is:
31. 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: 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.

CLM What is claimed is:
. . . 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.

CLM What is claimed is:
40. The apparatus of claim 39, wherein expansion of the inner member facilitates delivery of the toxin to the nasal tissue.

CLM What is claimed is:
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:. . . 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.

CLM What is claimed is:
. . . element is configured to provide the applicator tips with an outward bias when the applicator tips are placed within the nasal passageway.

CLM What is claimed is:
43. The apparatus of claim 42, wherein the outward bias presses each applicator tip against a turbinate in the nasal cavity.

AB Apparatus 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.

L11 ANSWER 39 OF 39 USPATFULL on STN

ACCESSION NUMBER:	2007:277801 USPATFULL
TITLE:	Nasolacrimal Drainage System Implants for Drug Therapy
INVENTOR(S):	de Juan, Eugene JR., San Francisco, CA, UNITED STATES Boyd, Stephen, Murrieta, CA, UNITED STATES Reich, Cary, Los Gatos, CA, UNITED STATES Rapacki, Alan, Redwood City, CA, UNITED STATES Gifford, Hanson S. III, Woodside, CA, UNITED STATES Deem, Mark, Mountain View, CA, UNITED STATES
PATENT ASSIGNEE(S):	ForSight Labs, LLC, Menlo Park, CA, UNITED STATES (U.S. corporation)

	NUMBER	KIND	DATE	
PATENT INFORMATION:	US 20070243230	A1	20071018	
	US 7998497	B2	20110816	
APPLICATION INFO.:	US 2007-695545	A1	20070402	(11)

	NUMBER	DATE	
PRIORITY INFORMATION:	US 2006-60787775	20060331	(60)
	US 2006-60871864	20061226	(60)

DOCUMENT TYPE:	Utility
FILE SEGMENT:	APPLICATION

LEGAL REPRESENTATIVE: TOWNSEND AND TOWNSEND AND CREW, LLP, TWO EMBARCADERO CENTER, EIGHTH FLOOR, SAN FRANCISCO, CA, 94111-3834, US
NUMBER OF CLAIMS: 47
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 30 Drawing Page(s)
LINE COUNT: 1982
CAS INDEXING IS AVAILABLE FOR THIS PATENT. Full-text
IN Gifford, Hanson S. III, Woodside, CA, UNITED STATES
DETD . . . extend through the drug core 112 to permit tear flow through the lumen for the delivery of therapeutic agent for nasal and systemic applications of the therapeutic agent. In addition or in combination with channel 112C, retention structure 132 and core. . .
AB Implant devices, systems and methods for insertion into a punctum of a patient optionally comprises a drug core and a sheath body disposed over the drug core. The drug core includes a therapeutic agent deliverable into the eye, and the sheath defines at least one exposed surface of the drug core. The exposed surface(s) of the drug core may contact a tear or tear film fluid and release the therapeutic agent at therapeutic levels over a sustained period when the implant is implanted for use. The implant may include a retention element to retain the drug core and sheath body near the punctum, optionally comprising a shape memory alloy that can resiliently expand. An occlusive element may be attached to the retention element to at least partially occlude tear flow through the canalicular lumen.

=>

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
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APPLICATION NUMBER	FILING OR 371(C) DATE	FIRST NAMED APPLICANT	ATTY. DOCKET NO./TITLE
16/842,209	04/07/2020	Mark E. Deem	5187.01US02AP

CONFIRMATION NO. 2844

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

PUBLICATION NOTICE

OC000000118842262

Title:SYSTEMS AND METHODS FOR DELIVERY OF A THERAPEUTIC AGENT

Publication No.US-2020-0238064-A1
Publication Date:07/30/2020

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.

In addition, information on the status of the application, including the mailing date of Office actions and the dates of receipt of correspondence filed in the Office, may also be accessed via the Internet through the Patent Electronic Business Center at www.uspto.gov using the public side of the Patent Application Information and Retrieval (PAIR) system. The direct link to access this status information is currently https://portal.uspto.gov/pair/PublicPair. Prior to publication, such status information is confidential and may only be obtained by applicant using the private side of PAIR.

Further assistance in electronically accessing the publication, or about PAIR, is available by calling the Patent Electronic Business Center at 1-866-217-9197.

Office of Data Managment, Application Assistance Unit (571) 272-4000, or (571) 272-4200, or 1-888-786-0101

PTO/SB/06 (09-11)
Approved for use through 1/31/2014. OMB 0651-0032
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
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PATENT APPLICATION FEE DETERMINATION RECORD Substitute for Form PTO-875	Application or Docket Number 16/842,209	Filing Date 04/07/2020	☑ To be Mailed

ENTITY: ☐ LARGE ☑ SMALL ☐ MICRO

APPLICATION AS FILED - PART I

FOR	(Column 1) NUMBER FILED	(Column 2) NUMBER EXTRA		RATE ($)	FEE ($)
☐ BASIC FEE (37 CFR 1.16(a), (b), or (c))	N/A	N/A		N/A	
☐ SEARCH FEE (37 CFR 1.16(k), (i), or (m))	N/A	N/A		N/A	
☐ EXAMINATION FEE (37 CFR 1.16(o), (p), or (q))	N/A	N/A		N/A	
TOTAL CLAIMS (37 CFR 1.16(i))	minus 20 =	*		x $50 =	
INDEPENDENT CLAIMS (37 CFR 1.16(h))	minus 3 =	*		x $230 =	
☐ 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).				
☐ MULTIPLE DEPENDENT CLAIM PRESENT (37 CFR 1.16(j))					
* If the difference in column 1 is less than zero, enter "0" in column 2.				TOTAL	

APPLICATION AS AMENDED - PART II

		(Column 1)		(Column 2)	(Column 3)			
AMENDMENT	09/08/2020	CLAIMS REMAINING AFTER AMENDMENT		HIGHEST NUMBER PREVIOUSLY PAID FOR	PRESENT EXTRA		RATE ($)	ADDITIONAL FEE ($)
	Total (37 CFR 1.16(i))	* 29	Minus	** 29	= 0		x $50 =	0
	Independent (37 CFR 1.16(h))	* 2	Minus	*** 3	= 0		x $230 =	0
	☐ Application Size Fee (37 CFR 1.16(s))							
	☐ FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))							
							TOTAL ADD'L FEE	0

		(Column 1)		(Column 2)	(Column 3)			
AMENDMENT		CLAIMS REMAINING AFTER AMENDMENT		HIGHEST NUMBER PREVIOUSLY PAID FOR	PRESENT EXTRA		RATE ($)	ADDITIONAL FEE ($)
	Total (37 CFR 1.16(i))	*	Minus	**	=		x $0 =	
	Independent (37 CFR 1.16(h))	*	Minus	***	=		x $0 =	
	☐ Application Size Fee (37 CFR 1.16(s))							
	☐ FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))							
							TOTAL ADD'L FEE	

* If the entry in column 1 is less than the entry in column 2, write "0" in column 3.	LIE
** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 20, enter "20".	/ANGELA D JOHNSON/
*** 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 number found in the appropriate box in column 1.	

This collection of information is required by 37 CFR 1.16. 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 12 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

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re the application of: Attorney Docket No.: 5187.01US02AP

Deem et al. Confirmation No.: 2844

Application No.: 16/842,209 Examiner: Albert Mark Navarro

Filed: April 7, 2020 Group Art Unit: 1645

For: SYSTEMS AND METHODS FOR DELIVERY OF A THERAPEUTIC AGENT

AMENDMENT

Mail Stop Amendment
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Commissioner:

INTRODUCTORY COMMENTS

In response to the Office Action of May 8, 2020, and in accordance with the automatic extension of time for response provided by 37 CFR § 1.136(a), amendment to the above-identified patent application is requested.

The present amendment comprises the following sections:

A. Amendments to the Claims

B. Remarks

Please grant any extension of time necessary for entry; charge any fee due to Deposit Account No. 16-0631.

Electronic Patent Application Fee Transmittal

Application Number:	16842209
Filing Date:	07-Apr-2020
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:	5187.01US02AP

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:				
Extension-of-Time:				

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Extension - 1 month with $0 paid	2251	1	100	100
Miscellaneous:				
			Total in USD ($)	**100**

Electronic Acknowledgement Receipt

EFS ID:	40497975
Application Number:	16842209
International Application Number:	
Confirmation Number:	2844
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:	5187.01US02AP
Receipt Date:	08-SEP-2020
Filing Date:	07-APR-2020
Time Stamp:	18:23:31
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	yes
Payment Type	CARD
Payment was successfully received in RAM	$100
RAM confirmation Number	E202098I23582045
Deposit Account	160631
Authorized User	Valerie Mitchell

The Director of the USPTO is hereby authorized to charge indicated fees and credit any overpayment as follows:

37 CFR 1.16 (National application filing, search, and examination fees)

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	Extension of Time	5187_01US02AP_Extension.pdf	65874 d2039d91e3d318bf387be2db2455df6ac16b11c1	no	1
Warnings:					
Information:					
2		5187_01US02AP_AMEND.pdf	122191 002665f49ccd452705333ff403f501f595dee637	yes	11

Multipart Description/PDF files in .zip description

Document Description	Start	End
Applicant Arguments/Remarks Made in an Amendment	8	11
Claims	2	7
Amendment/Req. Reconsideration-After Non-Final Reject	1	1

Warnings:					
Information:					
3	Fee Worksheet (SB06)	fee-info.pdf	30873 152bb09340352acca05ab41a5d9eb3faa9615684	no	2
Warnings:					
Information:					
		Total Files Size (in bytes):	218938		

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.

PATENT APPLICATION

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re the application of:	Attorney Docket No.: 5187.01US02AP
Deem et al.	Confirmation No.: 2844
Application No.: 16/842,209	Examiner: Albert Mark Navarro
Filed: April 7, 2020	Group Art Unit: 1645

For: SYSTEMS AND METHODS FOR DELIVERY OF A THERAPEUTIC AGENT

PETITION FOR EXTENSION OF PERIOD FOR RESPONSE
UNDER 37 CFR 1.136(a)

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Commissioner:

Pursuant to 37 CFR § 1.136(a), an extension of time of one (1) month (from August 8, 2020 to September 8, 2020) within which to respond to the Office Action dated May 8, 2020 is requested. Electronic payment is submitted by credit card to cover the extension fee. Applicant is entitled to small entity status in accordance with 37 CFR 1.27. The Commissioner is authorized to charge to Deposit Account No. 16-0631 any underpayments, overpayments or additionally required fees.

Respectfully submitted,

/Daidre L. Burgess/

Daidre L. Burgess
Registration No. 60389

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4800 IDS Center
80 South 8th Street
Minneapolis, Minnesota 55402-2100
Telephone: 612.252.1558

Please grant any extension of time necessary for entry; charge any fee due to Deposit Account No. 16-0631.

REMARKS

Claims 1-29 are pending. By this Amendment, claims 1 and 23 are amended, and no claims are added or cancelled.

Response to Double Patenting Rejections

Claims 1-29 stand provisionally rejected under non-statutory double patenting over claims 21-40 of Application No. 16/036,381, recently issued as U.S. Pat. No. 10,729,897. In particular, the Office Action asserts that

> [a]lthough the claims at issue are not identical, they are not patentably distinct from each other because the instantly filed claims directed to an apparatus for treatment comprising a hand held elongate body having proximal and distal portions, the distal portion being configured for positioning in a nasopharyngeal passage, an energy transmission element, and an energy source are anticipated by the claims of 16/036,381, directed to devices for altering functions of a bronchial airway comprising a main catheter body configured to extend and at least one energy applicator which delivers energy in a lateral direction.

(Office Action, p. 3-4.) Applicant respectfully traverses the rejection.

A nonstatutory double patenting rejection is appropriate where a claim in an application under examination claims subject matter that is different, but not patentably distinct, from the subject matter claimed in a prior patent or a copending application. Per MPEP § 804, "[t]he doctrine of double patenting seeks to prevent the unjustified extension of patent exclusivity beyond the term of a patent. The public policy behind this doctrine is that...[t]he public should...be able to act on the assumption that upon the expiration of the patent it will be free to use not only the invention claimed in the patent but also modifications or variants which would have been obvious to those of ordinary skill in the art at the time the invention was made, taking

into account the skill in the art and prior art other than the invention claimed in the issued patent." (*Citing* In re Zickendraht, 319 F.2d 225, 232, (CCPA 1963)). "Double patenting results when the right to exclude granted by a first patent is unjustly extended by the grant of a later issued patent or patents." (MPEP § 804, *citing* In re Van Ornum, 686 F.2d 937 (CCPA 1982)).

In its application, a claim under examination is not patentably distinct from the reference claim(s) if the claim under examination is anticipated by the reference claim(s). See, e.g., *In re Berg,* 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman,* 11 F.3d 1046, 1052, 29 USPQ2d 2010, 2015-16 (Fed. Cir. 1993). As such, a double patenting rejection must rely on a comparison with the claims in an issued patent or pending application. (MPEP § 804)

In the instant case, Applicant respectfully submits that the claims of the instant application are not anticipated by and are patentably distinct from and the subject matter claimed in Application No. 16/036,381. Fundamentally, and referring to claim 1 as an example, the instant claim is directed to so-called "above the neck" treatment technology, i.e. application of energy to the *nasopharyngeal passage* of a patient, which includes he posterior part of the nasal cavity from the posterior limits of the conchae to the choanae, and does not include the trachea or bronchial airway. Claim 1 of Application No. 16/036,381, on the other hand, is directed to "below the neck" treatment technology, i.e. altering the function of the bronchial airway by application of energy to the wall of the bronchial airway of a patient. The two technologies are necessarily distinct, as is evident in comparing the two claims, and as one of ordinary skill in the art would recognize.

For example, claim 1 requires, in combination with the other limitations of the claim, an "[a]pparatus for treatment of a nasal condition comprising: a hand-held elongate body having

proximal and distal portions, *the distal portion being configured for positioning in a nasopharyngeal passage* of a patient with *the proximal portion positioned outside the nasopharyngeal passage*" (emphasis added). In contrast, claim 1 of Application No. 16/036,381 discloses "[a] device for altering function of a bronchial airway of a patient by controlling mucus secretion, the device comprising: *a main catheter body configured to extend through a trachea into the bronchial airway*[.]" (emphasis added). A main catheter body configured to extend through a trachea and into the bronchial airway, i.e. beyond the nasopharayngeal passage, is not evidence of an elongate body with a distal portion positioned in a nasopharyngeal passage and a proximal portion positioned outside the nasopharyngeal passage. In fact, one of ordinary skill in the art would recognize that the trachea and bronchial airway can be accessed via the oral cavity, thereby completely bypassing the nasopharayngeal passage, and that the two bodies have relatively distinct structures; more particularly, instant claim 1 requires specific distal and proximal portions of the device not disclosed in claim 1 of Application No. 16/036,381.

Claim 1 further requires, in combination with the other limitations of the claim, "an energy source operatively coupled to the energy transmission element for supplying energy thereto according to one or more parameters selected *so as to alter nasopharyngeal cells in the target tissue* such that nasal congestion is reduced." In contrast, claim 1 of Application No. 16/036,381 discloses "wherein the device is adapted to deliver energy from the at least one energy emitter to produce an energy field concentrated in a target region in a wall of the bronchial airway in a first lateral direction from the catheter body to alter cells within the target region." Moreover, the "below the neck" altering of function of a bronchial airway by

controlling mucus secretion is not evidence of the claimed "above the neck" altering of nasopharyngeal cells in the target tissue to reduce nasal congestion.

As such, claim 1 of Application No. 16/036,381 quite simply does not describe each and every element, in as complete detail, as set forth in claim 1 of the instant claim, in an anticipation analysis comparison with the claims, as required by *In re Berg, In re Goodman,* and MPEP § 804. Furthermore, one of ordinary skill in the art would appreciate the right to exclude granted by Application No. 16/036,381 would not be unjustly extended by the grant of the instant application. Applicant therefore respectfully requests withdrawal of the non-statutory double patenting rejections.

Conclusion

In view of the foregoing, it is submitted that this application is in condition for allowance. Favorable consideration and prompt allowance of the application are respectfully requested.

The Examiner is invited to telephone the undersigned if the Examiner believes it would be useful to advance prosecution.

Respectfully submitted,

/Daidre L. Burgess/

Daidre L. Burgess
Registration No. 60389

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Patterson Thuente Pedersen, P.A.
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Minneapolis, Minnesota 55402-2100
Telephone: 612.252.1558

AMENDMENTS TO THE CLAIMS

A detailed listing of all claims that are, or were, in the present application, irrespective of whether the claim(s) remain(s) under examination in the application is presented below. The claims are presented in ascending order and each includes one status identifier. Those claims not cancelled or withdrawn but amended by the current amendment utilize the following notations for amendment: 1. deleted matter is shown by strikethrough for six or more characters and double brackets for five or fewer characters; and 2. added matter is shown by underlining.

1. (Currently Amended) Apparatus for treatment of a nasal condition by altering function of a nasopharyngeal passage of a patient, the apparatus comprising:

a hand-held elongate body having proximal and distal portions, the distal portion being configured for positioning in a nasopharyngeal passage of a patient with the proximal portion positioned outside the nasopharyngeal passage;

an energy transmission element in the distal portion configured to deliver energy to target tissue in the nasopharyngeal passage; and

an energy source operatively coupled to the energy transmission element for supplying energy thereto according to one or more parameters selected so as to alter nasopharyngeal cells in the target tissue such that nasal congestion is reduced.

2. (Original) The apparatus of claim 1, wherein the energy transmission element comprises at least one electrode.

3. (Original) The apparatus of claim 1, wherein the energy transmission element comprises an ultrasound transducer.

4. (Original) The apparatus of claim 1, wherein the energy transmission element comprises a microwave antenna.

5. (Original) The apparatus of claim 1, wherein the energy supplying means comprises an RF generator.

6. (Original) The apparatus of claim 1, wherein the energy supplying means comprises an ultrasound generator.

7. (Original) The apparatus of claim 1, wherein the energy supplying means comprises an AC or DC current source.

8. (Original) The apparatus of claim 1, wherein the energy transmission element is movable relative to the distal portion of the body.

9. (Original) The apparatus of claim 8, wherein the energy transmission element is configured to deliver energy laterally relative to the distal portion of the body.

10. (Original) The apparatus of clam 9, wherein the energy transmission element is configured to extend laterally from the distal portion of the body.

11. (Original) The apparatus of claim 8, wherein the energy transmission element is configured to penetrate the nasal tissue.

12. (Original) The apparatus of claim 1, further comprising: a sensing element on the distal portion of the body.

13. (Original) The apparatus of claim 12, wherein the sensing element comprises a temperature sensor.

14. (Original) The apparatus of claim 12, further comprising: a monitoring system operatively coupled to the sensing element for indicating a degree of treatment of the target tissue.

15. (Original) The apparatus of claim 1, further comprising: an agent delivery element in the distal portion of the body configured to deliver a therapeutic agent to the target tissue.

16. (Original) The apparatus of claim 15, wherein the agent delivery element comprises a porous member through which the agent may be delivered.

17. (Original) The apparatus of claim 16, wherein the agent delivery element comprises an inflatable member.

18. (Original) The apparatus of claim 16, wherein the agent delivery element comprises an injection element configured to penetrate the target tissue.

19. (Original) The apparatus of claim 15, further comprising: a source of therapeutic agent coupled to the proximal portion of the body.

20. (Original) The apparatus of claim 19, wherein the therapeutic agent comprises a neurotoxin.

21. (Original) The apparatus of claim 1, wherein the energy source and the energy transmission element are configured to deliver the energy so as to disable adrenergic cells in the target tissue.

22. (Original) The apparatus of claim 21, wherein the energy is delivered so as to block or disrupt acetycholine release in the adrenergic cells.

23. (Currently Amended) Apparatus for treatment of a nasal condition by altering function of a nasopharyngeal passage of a patient, the apparatus comprising:

a hand-held elongate body having proximal and distal portions, the distal portion being configured for positioning in a nasopharyngeal passage of a patient with the proximal portion positioned outside the nasopharyngeal passage; and

a transmission element in the distal portion configured to change the temperature of target tissue in the nasopharyngeal passage so as to disrupt neural activity in the target tissue such that nasal congestion is reduced.

24. (Original) The apparatus of claim 23, wherein the transmission element is configured to transfer thermal energy between the transmission element and the target tissue.

25. (Original) The apparatus of claim 23, wherein the transmission element is configured to change the temperature of the target tissue so as to disable adrenergic cells therein.

26. (Original) The apparatus of claim 23, wherein the transmission element is configured to change the temperature of the target tissue so as to block or disrupt acetycholine production in nasopharyngeal cells.

27. (Original) The apparatus of claim 23, wherein the transmission element is configured to contain a fluid to change the temperature of the target tissue.

28. (Original) The apparatus of claim 27, wherein the transmission element comprises an injection device configured to direct the fluid to the target tissue.

29. (Original) The apparatus of claim 28, wherein the fluid is heated.

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INFORMATION DISCLOSURE STATEMENT BY APPLICANT

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Sheet 1 of 17

Complete if Known	
Application Number	16/842,209
Filing Date	April 7, 2020
First Named Inventor	MARK; E. Deem
Art Unit	1645
Examiner Name	Albert Mark Navarro
Attorney Docket Number	5187.01US02AP

Examiner Initials*	Cite No.[1]	Document Number Number-Kind Code[2] (if known)	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document
		US-1695107	12-11-1928	KAHL; Franz
		US-2566806	09-04-1951	MILLER; Hugh A.
		US-3463149	08-26-1969	ALBU; Theodor
		US-3469139	09-23-1969	COLVIN; Alex D.
		US-3788296	01-29-1974	KLATT; Peter et al.
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		US-4658836	04-21-1987	TURNER; Paul F.
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		US-5056529	10-15-1991	DE GROOT; William J.
		US-5139029	08-18-1992	FISHMAN; Henry et al.
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		US-5192290	03-09-1993	HILAL; ;Said
		US-5286254	02-15-1994	SHAPLAND; James E. et al.
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		US-5432092	07-11-1995	BAILEY; Jerome M. et al.
		US-5496304	03-05-1996	CHASAN; Paul E.
		US-5562608	10-08-1996	SEKINS; K. Michael et al.
		US-5766605	06-16-1998	SANDERS; Ira et al.
		US-5807306	09-15-1998	SHAPLAND; J. Edward et al.

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Sheet 2 of 17

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Attorney Docket Number	5187.01US02AP

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		US-5817073	10-06-1998	KRESPI; Yosef P.
		US-5820589	10-13-1998	TORGERSON; Nathan A. et al.
		US-5843088	12-01-1998	BARRA; Jean-Aubert et al.
		US-5860974	01-19-1999	ABELE; John E.
		US-5902268	05-11-1999	SAAB; Mark A.
		US-5957961	09-28-1999	MAGUIRE; Mark A. et al.
		US-5964223	10-12-1999	BARAN; George
		US-5972026	10-26-1999	LAUFER; Michael D. et al.
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		US-6056744	05-02-2000	EDWARDS; Stuart D.
		US-6063768	05-16-2000	FIRST; Eric R.
		US-6139845	10-31-2000	DONOVAN; Stephen
		US-6200333	03-13-2001	LAUFER; Michael D.
		US-6216704	04-17-2001	INGLE; Frank et al.
		US-6265379	07-24-2001	DONOVAN; Stephen
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		US-6322559	11-27-2001	DAULTON; Jay S. et al.
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		US-6361554	03-26-2002	BRISKEN; Axel F.
		US-6383509	05-07-2002	DONOVAN; Stephen et al.

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Sheet 3 of 17

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First Named Inventor	MARK; E. Deem
Art Unit	1645
Examiner Name	Albert Mark Navarro
Attorney Docket Number	5187.01US02AP

Examiner Initials*	Cite No.[1]	Document Number Number-Kind Code[2] (if known)	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document
		US-6411852	06-25-2002	DANEK; Christopher J. et al.
		US-6425887	07-30-2002	MCGUCKIN; James Frederick et al.
		US-6432092	08-13-2002	MILLER; Eric C.
		US-6447785	09-10-2002	DONOVAN; Stephen
		US-6448231	09-10-2002	GRAHAM; Herbert Kerr
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		US-6475160	11-05-2002	SHER; Nathan
		US-6488673	12-03-2002	LAUFER; Michael D. et al.
		US-6506399	01-14-2003	DONOVAN; Stephen
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		US-6620415	09-16-2003	DONOVAN; Stephen
		US-6623742	09-23-2003	VOET; Martin A.
		US-6626855	09-30-2003	WENG; Lee et al.
		US-6632440	10-14-2003	QUINN; Conrad Padraig et al.
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		US-6649161	11-18-2003	DONOVAN; Stephen
		US-6658279	12-02-2003	SWANSON; David K. et al.
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		US-6740321	05-25-2004	DONOVAN; Stephen

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Art Unit	1645
Examiner Name	Albert Mark Navarro
Attorney Docket Number	5187.01US02AP

Examiner Initials*	Cite No.[1]	Document Number Number-Kind Code[2] (if known)	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document
		US-6767544	07-27-2004	BROOKS; Gregory F. et al.
		US-6770070	08-03-2004	BALBIERZ; Daniel J.
		US-6773711	08-10-2004	VOET; Martin A. et al.
		US-6776991	08-17-2004	NAUMANN; Markus K.
		US-6827931	12-07-2004	DONOVAN; Stephen
		US-6838434	01-04-2005	VOET; Martin A.
		US-6841156	01-11-2005	AOKI; K. Roger et al.
		US-6843998	01-18-2005	STEWARD; Lance E. et al.
		US-6846312	01-25-2005	EDWARDS; Stuart D. et al.
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		US-6861058	03-01-2005	AOKI; K. Roger et al.
		US-6872397	03-29-2005	AOKI; K. Roger et al.
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		US-7628789	12-08-2009	SOLTESZ; Peter P. et al.
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		US-7747324	06-29-2010	ERRICO; Joseph P. et al.
		US-7853331	12-14-2010	KAPLAN; Gary S. et al.

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Sheet 5 of 17

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Filing Date	April 7, 2020
First Named Inventor	MARK; E. Deem
Art Unit	1645
Examiner Name	Albert Mark Navarro
Attorney Docket Number	5187.01US02AP

Examiner Initials*	Cite No.[1]	Document Number Number-Kind Code[2] (if known)	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document
		US-8007495	08-30-2011	MCDANIEL; Benjamin D. et al.
		US-8088127	01-03-2012	MAYSE; Martin L. et al.
		US-8105817	01-31-2012	DEEM; Mark E. et al.
		US-8133497	03-13-2012	DEEM; Mark E. et al.
		US-8172827	05-08-2012	DEEM; Mark E. et al.
		US-8226638	07-24-2012	MAYSE; Martin L. et al.
		US-8338164	12-25-2012	DEEM; Mark E. et al.
		US-8483831	07-09-2013	HLAVKA; Edwin J. et al.
		US-8489192	07-16-2013	HLAVKA; Edwin J. et al.
		US-8636684	01-28-2014	DEEM; Mark E. et al.
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		US-8777943	07-15-2014	MAYSE; Martin L. et al.
		US-8808280	08-19-2014	MAYSE; Martin L. et al.
		US-8821489	09-02-2014	MAYSE; Martin L. et al.
		US-8911439	12-16-2014	MAYSE; Martin L. et al.
		US-8932289	01-13-2015	MAYSE; Martin L. et al.
		US-8961391	02-24-2015	DEEM; Mark E. et al.
		US-8961507	02-24-2015	MAYSE; Martin L. et al.
		US-8961508	02-24-2015	MAYSE; Martin L. et al.
		US-9005195	04-14-2015	MAYSE; Martin L. et al.
		US-9017324	04-28-2015	MAYSE; Martin L. et al.
		US-9125643	09-08-2015	HLAVKA; Edwin J. et al.

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Sheet 6 of 17

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Art Unit	1645
Examiner Name	Albert Mark Navarro
Attorney Docket Number	5187.01US02AP

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		US-9149328	10-06-2015	DIMMER; Steven C. et al.
		US-9339618	05-17-2016	DEEM; Mark E. et al.
		US-9511210	12-06-2016	DEEM; Mark E. et al.
		US-9498283	11-22-2016	DEEM; Mark E. et al.
		US-9700707	07-11-2017	DEEM; Mark E. et al.
		US-10022529	07-17-2018	DEEM; Mark E. et al.
		US-10052465	08-21-2018	DEEM; Mark E. et al.
		US-10610675	04-07-2020	DEEM; Mark E. et al.
		US-10729897	08-04-2020	DEEM; Mark E. et al.
		US-20010044596	11-22-2001	JAAFAR; Ali
		US-20020013581	01-31-2002	EDWARDS; Stuart et al.
		US-20020082197	06-27-2002	AOKI; Kei Roger et al.
		US-20020087208	07-04-2002	KOBLISH; Josef V. et al.
		US-20020111620	08-15-2002	COOPER; Joel D. et al.
		US-20020143302	10-03-2002	HINCHLIFFE; Peter W.J. et al.
		US-20020198512	12-26-2002	SEWARD; Kirk Patrick
		US-20030018344	01-23-2003	KAJI; Hinako et al.
		US-20030023287	01-30-2003	EDWARDS; Stuart D. et al.
		US-20030036755	02-20-2003	GINN; Richard S.
		US-20030050591	03-13-2003	PATRICK; Mchale Anthony
		US-20030113349	06-19-2003	COLEMAN; William P.
		US-20030153881	08-14-2003	ROCHE; Bruno et al.
		US-20030118327	06-26-2003	UM; Soung Hyun et al.

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INFORMATION DISCLOSURE STATEMENT BY APPLICANT

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Sheet 7 of 17

Complete if Known	
Application Number	16/842,209
Filing Date	April 7, 2020
First Named Inventor	MARK; E. Deem
Art Unit	1645
Examiner Name	Albert Mark Navarro
Attorney Docket Number	5187.01US02AP

Examiner Initials*	Cite No.[1]	Document Number Number-Kind Code[2] (if known)	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document
		US-20030159700	08-28-2003	LAUFER; Michael D. et al.
		US-20030202990	10-30-2003	DONOVAN; Stephen et al.
		US-20030211121	11-13-2003	DONOVAN; Stephen
		US-20030233099	12-18-2003	DANAEK; Christopher James et al.
		US-20040009180	01-15-2004	DONOVAN; Stephen
		US-20040010290	01-15-2004	SCHROEPPEL; Edward A. et al.
		US-20040028676	02-12-2004	KLEIN; Dean A. et al.
		US-20040086531	05-06-2004	BARRON; Richard L.
		US-20040091880	05-13-2004	WIEBUSCH; Heiko et al.
		US-20040142005	07-22-2004	BROOKS; Gregory F. et al.
		US-20040151741	08-05-2004	BORODIC; Gary
		US-20040175399	09-09-2004	SCHIFFMAN; Rhett M.
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		US-20040213813	10-28-2004	ACKERMAN; Alan H.
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		US-20040220562	11-04-2004	GARABEDIAN; Robert J. et al.
		US-20040226556	11-18-2004	DEEM; Mark E. et al.
		US-20040248188	12-09-2004	SANDERS; Ira
		US-20040253274	12-16-2004	VOET; Martin A.
		US-20050007441	01-13-2005	HYUGA; Hiroaki
		US-20050019346	01-27-2005	BOULIS; Nicholas M.
		US-20050065575	03-24-2005	DOBAK; John D.
		US-20050074461	04-07-2005	DONOVAN; Stephen

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Sheet 8 of 17

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Examiner Name	Albert Mark Navarro
Attorney Docket Number	5187.01US02AP

Examiner Initials*	Cite No.[1]	Document Number Number-Kind Code[2] (if known)	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document
		US-20050107853	05-19-2005	KRESPI; Yosef et al.
		US-20050152924	07-14-2005	VOET; Martin A.
		US-20050182393	08-18-2005	ABBOUD; Marwan et al.
		US-20050183732	08-25-2005	EDWARDS; Stuart D.
		US-20050240147	10-27-2005	MAKOWER; Joshua et al.
		US-20050245926	11-03-2005	EDWARDS; Stuart D. et al.
		US-20050281751	12-22-2005	LEVIN; Bruce H.
		US-2006/0004323	01-05-2006	CHANG; John Y. et al.
		US-2006/0008462	01-12-2006	SANDERS; Ira
		US-20060084966	04-20-2006	MAGUIRE; Mark A. et al.
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		US-20060222667	10-05-2006	DEEM; Mark E. et al.
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		US-20060254600	11-16-2006	DANEK; Christopher J. et al.
		US-20070021803	01-25-2007	DEEM; Mark E. et al.
		US-20070025919	02-01-2007	DEEM; Mark E. et al.
		US-20070043350	02-22-2007	SOLTESZ; Peter P. et al.
		US-20070083194	04-12-2007	KUNIS; Christopher G. et al.
		US-20070100390	05-03-2007	DANAEK; Christopher J. et al.
		US-20070106292	05-10-2007	KAPLAN; Gary S. et al.
		US-20070118184	05-24-2007	DANEK; Christopher J. et al.
		US-20070129720	06-07-2007	DEMARAIS; Denise et al.

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Sheet 9 of 17

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Filing Date	April 7, 2020
First Named Inventor	MARK; E. Deem
Art Unit	1645
Examiner Name	Albert Mark Navarro
Attorney Docket Number	5187.01US02AP

Examiner Initials*	Cite No.[1]	Document Number Number-Kind Code[2] (if known)	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document
		US-20070156185	07-05-2007	SWANSON; David K. et al.
		US-20070250050	10-25-2007	LAFONTAINE; Daniel M.
		US-20070267011	11-22-2007	DEEM; Mark E. et al.
		US-20070270794	11-22-2007	ANDERSON; Neil L. et al.
		US-20080021369	01-24-2008	DEEM; Mark E. et al.
		US-20080051839	02-28-2008	LIBBUS; Imad et al.
		US-20080091379	04-17-2008	LYNCH; John J. et al.
		US-20080161890	07-03-2008	LAFONTAINE; Daniel M.
		US-20080255642	10-16-2008	ZARINS; Denise et al.
		US-20080312725	12-18-2008	PENNER; Abraham
		US-20090018538	01-15-2009	WEBSTER; Noah et al.
		US-20090043301	02-12-2009	JARRARD; Jerry et al.
		US-20090177192	07-09-2009	RIOUX; Robert F. et al.
		US-20090221997	09-03-2009	ARNOLD; Jeffrey M. et al.
		US-20100003282	01-07-2010	DEEM; Mark E. et al.
		US-20100087775	04-08-2010	DEEM; Mark E. et al.
		US-20110118725	05-19-2011	MAYSE; Martin L. et al.
		US-20110152855	06-23-2011	MAYSE; Martin L. et al.
		US-20110257647	10-20-2011	MAYSE; Martin L. et al.
		US-20110301587	12-08-2011	DEEM; Mark et al.
		US-20120016363	01-19-2012	MAYSE; Martin L. et al.
		US-20120016364	01-19-2012	MAYSE; Martin L. et al.
		US-20120029261	02-02-2012	DEEM; Mark E. et al.

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Sheet 10 of 17

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Application Number	16/842,209
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First Named Inventor	MARK; E. Deem
Art Unit	1645
Examiner Name	Albert Mark Navarro
Attorney Docket Number	5187.01US02AP

Examiner Initials*	Cite No.[1]	Document Number Number-Kind Code[2] (if known)	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document
		US-20120158101	06-21-2012	STONE; Corbett W. et al.
		US-20120203216	08-09-2012	MAYSE; Martin L. et al.
		US-20120203222	08-09-2012	MAYSE; Martin L. et al.
		US-20120209261	08-16-2012	MAYSE; Martin L. et al.
		US-20120209296	08-16-2012	MAYSE; Martin L. et al.
		US-20120302909	11-29-2012	MAYSE; Martin L. et al.
		US-20120310233	12-06-2012	DIMMER; Steven C. et al.
		US-20120316552	12-13-2012	MAYSE; Martin L. et al.
		US-20120316559	12-13-2012	MAYSE; Martin L. et al.
		US-20130123751	05-16-2013	DEEM; Mark E. et al.
		US-20130289555	10-31-2013	MAYSE; Martin L. et al.
		US-20130289556	10-31-2013	MAYSE; Martin L. et al.
		US-20130303948	11-14-2013	DEEM; Mark E. et al.
		US-20130310822	11-21-2013	MAYSE; Martin L. et al.
		US-20140186341	07-03-2014	MAYSE; Martin L.
		US-20140257271	09-11-2014	MAYSE; Martin L. et al.
		US-20140276792	09-18-2014	KAVECKIS; Ryan et al.
		US-20150051597	02-19-2015	MAYSE; Martin L. et al.
		US-20150141985	05-21-2015	MAYSE; Martin L. et al.
		US-20150190193	07-09-2015	MAYSE; Martin L. et al.
		US-20150366603	12-24-2015	HLAVKA; Edwin J. et al.
		US-20160022351	01-28-2016	KAVECKIS; Ryan et al.
		US-20160038725	02-11-2016	MAYSE; Martin L. et al.

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Sheet 11 of 17

Complete if Known	
Application Number	16/842,209
Filing Date	April 7, 2020
First Named Inventor	MARK; E. Deem
Art Unit	1645
Examiner Name	Albert Mark Navarro
Attorney Docket Number	5187.01US02AP

Examiner Initials*	Cite No.[1]	Document Number Number-Kind Code[2] (if known)	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document
		US-20190083768	03-21-2019	DEEM; Mark E. et al.

Examiner Initials*	Cite No.[1]	Foreign Patent Document 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]
		CA-2152002-A1	12-18-1995	TRUDELL MEDICAL LTD [CA]	☐
		EP-3248612-A1	2017-11-29	THE FOUNDRY, LLC [US]	☐
		JP-2002145784-A	05-22-2002	MORISHITA RYUICHI.	☒
		WO-9119529-A1	12-26-1991	CORTRAK MEDICAL, INC. [US]	☐
		WO-0062699-A2	10-26-2000	BRONCUS TECH INC [US], et al.	☐
		WO-2004006954-A2	01-22-2004	ALLERGAN INC [US], et al.	☐
		WO-2004048519-A2	06-10-2004	IRA SANDERS	☐
		WO-2004077987-A1	09-16-2004	LALINE INTERNATIONAL SARL [TN]	☐

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INFORMATION DISCLOSURE STATEMENT BY APPLICANT

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Sheet 12 of 17

Complete if Known	
Application Number	16/842,209
Filing Date	April 7, 2020
First Named Inventor	MARK; E. Deem
Art Unit	1645
Examiner Name	Albert Mark Navarro
Attorney Docket Number	5187.01US02AP

Examiner Initials*	Cite No.[1]	Foreign Patent Document 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]
		WO-2004101028-A2	11-25-2004	THE FOUNDRY INC [US], et al.	☐
		WO-2004101028-A3	12-14-2006	THE FOUNDRY INC [US], et al.	☐
		WO-2007014003-A2	02-01-2007	THE FOUNDRY INC. [US]	☐
		WO-2005032646-A2	04-14-2005	EASTERN VIRGINIA MED SCHOOL [US], et al.	☐
		WO-2005048988-A1	06-02-2005	SCOTT NEAL [US], et al.	☐
		WO-9519805-A1	07-27-1995	GENETRONICS INC [US], et al.	☐
		WO-9934831-A1	07-15-1999	UNIV WASHINGTON [US], et al.	☐

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First Named Inventor	MARK; E. Deem
Art Unit	1645
Examiner Name	Albert Mark Navarro
Attorney Docket Number	5187.01US02AP

NON-PATENT LITERATURE DOCUMENTS			
Examiner Initials*	Cite No.[1]	Include name of the author(in CAPITAL LETTERS),title of the article(when appropriate), title of the item (book,magazine,journal,serial,symposium,catalog,etc.),date,page(s),volume-issue number(s),publisher, city and/or country where published.	T[2]
		"Anonymous: Neurotoxin (from Wikipedia)," Retrieved from http://en.wikipedia.org/w/index.php?title=Neurotoxin&printable=yes, 2 April 2015, 23 pages.	☐
		AHNERT-HILGER., et al., "Introduction of Macromolecules into Bovine Adrenal-Medullary Chromaffin Cells and Rat Pheochromocytoma Cells (PC12) by Permeabilization with Streptolysin O: Inhibitory Effect of Teanus Toxin on Catecholamine Secretion," J. Neurochem, June 1989, Vol. 52 (6), pp. 1751-1758.	☐
		Application and File History for U.S. Patent Application No. 16/659,893, filed 22 October 2019, Inventors: Deem et al.	☐
		Application and File History for U.S. Patent Application No. 11/459,090, filed 21 July 2006, Inventors: Deem et al.	☐
		Application and File History for U.S. Patent Application No. 12/559,278, filed 14 September 2009, Inventors: Deem et al., as available on PAIR at www.uspto.gov.	☐
		Application and File History for U.S. Patent Application No. 13/253,595, filed 5 October 2011, Inventors: Deem et al., as available on PAIR at www.uspto.gov.	☐
		Application and File History for U.S. Patent Application No. 13/660,629, filed 25 October 2012, Inventors: Deem et al., as available on PAIR at www.uspto.gov.	☐
		Application and File history for U.S. Patent Application No. 14/601,529, filed January 21, 2015, Inventors: Deem et al., as available on PAIR at www.uspto.gov.	☐
		Application and File History for U.S. Patent Application No. 15/358,187, filed November 22, 2016, Inventors: Deem et al, as available on PAIR at www.uspto.gov.	☐

Examiner Signature		Date Considered	

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INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(Use as many sheets as necessary)

Sheet 14 of 17

Complete if Known	
Application Number	16/842,209
Filing Date	April 7, 2020
First Named Inventor	MARK; E. Deem
Art Unit	1645
Examiner Name	Albert Mark Navarro
Attorney Docket Number	5187.01US02AP

NON-PATENT LITERATURE DOCUMENTS

Examiner Initials*	Cite No.[1]	Include name of the author(in CAPITAL LETTERS),title of the article(when appropriate), title of the item (book,magazine,journal,serial,symposium,catalog,etc.),date,page(s),volume-issue number(s),publisher, city and/or country where published.	T[2]
		Application and File History for U.S. Patent Application No. 16/036,381, filed July 16, 2018, Inventors: Deem et al, as available on PAIR at www.uspto.gov.	☐
		Application and File History for U.S. Patent Application No. 11/757,963, filed May 18, 2007, Inventors: Deem et al, as available on PAIR at www.uspto.gov.	☐
		Application and File History for U.S. Patent Application No. 11/750,967, filed May 18,2007, Inventors: Deem et al, as available on PAIR at www.uspto.gov.	☐
		Application and File History for U.S. Patent Application No. 12/636,477, filed December 11, 2009, Inventors: Deem et al, as available on PAIR at www.uspto.gov.	☐
		Application and File History for U.S. Patent Application No. 13/328,203, filed December 16, 2011, Inventors: Deem et al, as available on PAIR at www.uspto.gov.	☐
		Application and File History for U.S. Patent Application No. 14/841,514, filed August 31, 2015, Inventors: Deem et al, as available on PAIR at www.uspto.gov.	☐
		Application and File History for U.S. Patent Application No. 15/615,344, filed June 6, 2017, Inventors: Deem et al, as available on PAIR at www.uspto.gov.	☐
		File History for EP Application No. 17165407.2, filed May 29, 2018, Inventors: Deem et al.	☐
		BIGALKE., et al., "Clostridial Neurotoxins," Handbook of Experimental Pharmacology (Aktories, K., and Just, I., eds), 2000, Vol. 145, pp. 407-443.	☐
		BITTNER., et al., "Isolated Light Chains of Botulinum Neurotoxins Inhibit Exocytosis," The Journal of Biological Chemistry, 1989, Vol. 264(18), pp. 10354-10360.	☐

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Sheet 15 of 17

Complete if Known	
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Filing Date	April 7, 2020
First Named Inventor	MARK; E. Deem
Art Unit	1645
Examiner Name	Albert Mark Navarro
Attorney Docket Number	5187.01US02AP

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		BLINDT., et al., "Development of a New Biodegradable Intravascular Polymer Stent with Simultaneous Incorporation of Bioactive Substances," The International Journal of Artificial Organs, 1999, Vol. 22 (12), pp. 843-853.	☐
		BUZZI., "Diphtheria Toxin Treatment of Human Advanced Cancer," Cancer Research, 1982, Vol. 42, pp. 2054-2058.	☐
		CHADDOCK., et al., "Expression and Purification of Catalytically Active, Non-Toxic Endopeptidase Derivatives of Clostridium Botulinum Toxin Type A," Protein Expression and Purification, July 2002, Vol. 25 (2), pp. 219-228.	☐
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		Co-pending US provisional application No. 60/701,747, filed on 22 July 2005.	☐
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		European Search Report for Application No. EP06788062, mailed on 07 January 2014, 9 pages.	☐
		GUZMAN H.R, et al., "Equilibrium Loading of Cells with Macromolecules by Ultrasound: Effects of Molecular Size and Acoustic Energy," J Pharm Sci., July 2002, Vol. 91 (7), pp. 1693-1701.	☐
		GUZMAN., et al., "Bioeffects Caused by Changes in Acoustic Cavitation Bubble Density and Cell Concentration: A Unified Explanation Based on Cell-to-Bubble Ratio and Blast Radius," Ultrasound in medicine & biology, 2003, Vol. 29 (8), pp. 1211-1222.	☐

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INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(Use as many sheets as necessary)

Sheet 16 of 17

Complete if Known	
Application Number	16/842,209
Filing Date	April 7, 2020
First Named Inventor	MARK; E. Deem
Art Unit	1645
Examiner Name	Albert Mark Navarro
Attorney Docket Number	5187.01US02AP

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		International Preliminary Report on Patentability for Application No. PCT/US2006/028310, mailed on 22 January 2008, 7 pages.	☐
		International Search Report and Written Opinion for Application No. PCT/US2006/028310, mailed on 8 August 2007, 7 pages.	☐
		KISTNER., et al., "Reductive Cleavage of Tetanus Toxin and Botulinum Neurotoxin A by the Thioredoxin System from Brain," Naunyn-Schmiedebergs Arch Pharmacal, February, 1992, Vol. 345 (2), pp. 227-234.	☐
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		KREITMAN., "Taming Ricin Toxin," Nature Biotechnology, 2003, Vol. 21, pp. 372-374.	☐
		Office Action mailed 24 May 2016 for Japanese Application No. JP2015-120827 filed 16 June 2015, 7 pages.	☐
		Office Action mailed 21 August 2017 for Japanese Application No. 2016- 227703 filed 24 November 2016, 4 pages.	☒
		RAJ., "Editorial," Pain Practice, 2004, Vol. 4 (1S), pp. S1-S3.	☐
		SCHMITT G.S., et al., "Indwelling Transbronchial Catheter Drainage of Pulmonary Abscess," Ann Thorac Surg, January 1988, Vol. 45 (1), pp. 43-47.	☐
		SHAARI., et al., "Rhinorrhea is Decreased in Dogs After Nasal Application of Botulinum Toxin," Otolaryngol Head Neck Surgery, April 1995, Vol. 112 (4), pp. 566-571.	☐

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INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(Use as many sheets as necessary)

Sheet 17 of 17

Complete if Known	
Application Number	16/842,209
Filing Date	April 7, 2020
First Named Inventor	MARK; E. Deem
Art Unit	1645
Examiner Name	Albert Mark Navarro
Attorney Docket Number	5187.01US02AP

NON-PATENT LITERATURE DOCUMENTS

Examiner Initials*	Cite No.[1]	Include name of the author(in CAPITAL LETTERS),title of the article(when appropriate), title of the item (book,magazine,journal,serial,symposium,catalog,etc.),date,page(s),volume-issue number(s),publisher, city and/or country where published.	T[2]
		SIMPSON L.L., "The Origin, Structure, and Pharmacological Activity of Botulinum Toxin," Pharmacol Reviews, September 1981, Vol. 33 (3), pp. 155-188.	☐
		SIMPSON., et al., "Isolation and Characterization of the botulinum Neurotoxins," Methods Enzymol, 1988, Vol. 165, pp. 76-85.	☐
		SUNDARAM, et al., "An Experimental and Theoretical Analysis of Ultrasound-Induced Permeabilization of Cell Membranes," Biophysical Journal, May 2003, Vol. 84 (5), pp. 3087-3101.	☐
		TSUJI., et al., "Biodegradable Stents as a Platform to Drug Loading," International Journal of Cardiovascular Interventions, 2003, Vol. 5(1), pp. 13-16.	☐
		UNAL., et al., "Effect of Botulinum Toxin Type A on Nasal Symptoms in Patients with Allergic Rhinitis: A Double-blind, Placebo-controlled Clinical Trial," Acta Oto-Laryngologica, December 2003, Vol. 123 (9), pp. 1060-1063.	☐
		WEAVER, "Electroporation: A General Phenomenon for Manipulating Cells and Tissues," Journal of Cellular Biochemistry, Apr. 1993, Vol. 51(4), pp.426-435.	☐

Examiner Signature		Date Considered	

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PATENT APPLICATION

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re the application of:	Attorney Docket No.: 5187.01US02AP
Deem et al.	Confirmation No.: 2844
Application No.: 16/842,209	Examiner: Albert Mark Navarro
Filed: April 7, 2020	Group Art Unit: 1645

For: SYSTEMS AND METHODS FOR DELIVERY OF A THERAPEUTIC AGENT

INFORMATION DISCLOSURE STATEMENT

Mail Stop Amendment
Commissioner for Patents
P.O. Box 1450
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 more than three months after the U.S. filing date and after the mailing date of the first Office Action on the merits, but before the mailing of a Final Action or Notice of Allowance. This Information Disclosure Statement is being filed with a fee pursuant to 37 CFR § 1.97(c)(2). Electronic payment is submitted by credit card to cover the fee. Please credit or debit Deposit Account No. 16-0631 as needed to ensure consideration of the disclosed information.

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,

/Daidre L. Burgess/

Daidre L. Burgess
Registration No. 60389

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4800 IDS Center
80 South 8th Street
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Please grant any extension of time necessary for entry; charge any fee due to Deposit Account No. 16-0631.

Electronic Patent Application Fee Transmittal

Application Number:	16842209
Filing Date:	07-Apr-2020
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:	5187.01US02AP

Filed as Large 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:				
Extension-of-Time:				

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Miscellaneous:				
SUBMISSION- INFORMATION DISCLOSURE STMT	1806	1	240	240
		Total in USD ($)		**240**

Electronic Acknowledgement Receipt

EFS ID:	40536914
Application Number:	16842209
International Application Number:	
Confirmation Number:	2844
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:	5187.01US02AP
Receipt Date:	11-SEP-2020
Filing Date:	07-APR-2020
Time Stamp:	16:54:13
Application Type:	Utility under 35 USC 111(a)

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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-2326 (04-2019)
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REQUEST FOR REFUND

Reference # *(Patent #, Application #, Trademark Serial #, Registration #, etc.)*	**Title of Invention or Mark Information**	
16/842,209	SYSTEMS AND METHODS FOR DELIVERY OF A THERAPEUTIC AGENT	
Attorney Docket # *(if applicable)*	**Payment Date** *(mm/dd/yyyy)*	**Refund Request Amount**
5187.01US02AP	09/11/2020	$ 120.00

Refund Option *(Select one)*

- (●) If approved, issue the refund to the account associated with the original payment.
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- [ ] Small Entity Later Established* (*must be filed within 3 months of payment date, 37 CFR 1.28)
- [x] Other Applicant entitled to small entity status

Rationale *(Supporting documentation may be submitted with this form)*

Large entity IDS filing fee submitted with IDS filed 09/11/2020. Applicant is entitled to small entity status.

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Company or Firm Name *(if applicable)*		
Patterson Thuente Pedersen, P.A		
Address Line 1	**City**	**State/Region**
80 South 8th Street	Minneapolis	MN
Address Line 2 *(if applicable)*	**Country**	**Zip/Postal Code**
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mitchell@ptslaw.com	612-252-1558	
Requester's Name	**Registration Number** *(if applicable)*	
Daidre L. Burgess	60389	
Signature	**Date** *(mm/dd/yyyy)*	
/Daidre L. Burgess/	09/11/2020	

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Application Number:	16842209
International Application Number:	
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First Named Inventor/Applicant Name:	Mark E. Deem
Customer Number:	24113
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Filer Authorized By:	Daidre L. Burgess
Attorney Docket Number:	5187.01US02AP
Receipt Date:	11-SEP-2020
Filing Date:	07-APR-2020
Time Stamp:	17:49:36
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	Refund Request	5187_01US02AP_Refund_Request.pdf	749449 3214bcb7d35a1bd12461f7ee0fb8af1bebc7e712	no	1

Warnings:

Information:	
Total Files Size (in bytes):	749449

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.



United States Patent and Trademark Office

Office of the Chief Financial Officer

Document Code:WFEE

User :72376

Sale Accounting Date:09/28/2020

Sale Item Reference Number	Effective Date
16842209	09/11/2020

Document Number	Fee Code	Fee Code Description	Amount Paid	Payment Method
I20209R923115517	2806	SUBMISSION- INFORMATION DISCLOSURE STMT	$120.00	Salea

UNITED STATES PATENT AND TRADEMARK OFFICE

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

NOTICE OF ALLOWANCE AND FEE(S) DUE

24113 7590 10/15/2020

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: 10/15/2020

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
16/842,209	04/07/2020	Mark E. Deem	5187.01US02AP	2844

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	$600	$0.00	$0.00	$600	01/15/2021

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 10/15/2020
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.
16/842,209	04/07/2020	Mark E. Deem	5187.01US02AP	2844

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	$600	$0.00	$0.00	$600	01/15/2021

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. _____

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UNITED STATES DEPARTMENT OF COMMERCE
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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
16/842,209	04/07/2020	Mark E. Deem	5187.01US02AP	2844

24113 7590 10/15/2020

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MINNEAPOLIS, MN 55402-2100

EXAMINER	
NAVARRO, ALBERT MARK	
ART UNIT	PAPER NUMBER
1645	

DATE MAILED: 10/15/2020

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. 16/842,209	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 the amendment filed September 8, 2020.
   ☐ 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 1-29 . 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

Issue Classification	Application/Control No.	Applicant(s)/Patent Under Reexamination
	16/842,209	Deem et al.
	Examiner	**Art Unit**
	Mark NAVARRO	1645

CPC								
Symbol							**Type**	**Version**
A61K	/	9	/	0021			F	2013-01-01
A61K	/	38	/	164			I	2013-01-01
A61K	/	38	/	168			I	2013-01-01
A61K	/	38	/	4893			I	2013-01-01
A61K	/	41	/	00			I	2013-01-01
A61K	/	41	/	0028			I	2013-01-01
A61N	/	1	/	327			I	2013-01-01
A61K	/	9	/	0078			I	2013-01-01
A61N	/	1	/	08			I	2013-01-01
A61N	/	1	/	303			I	2013-01-01
A61N	/	7	/	00			I	2013-01-01
A61B	/	18	/	1492			I	2013-01-01
A61B	/	18	/	1815			I	2013-01-01
A61N	/	5	/	10			I	2013-01-01
A61K	/	41	/	0047			I	2013-01-01
A61M	/	37	/	00			I	2013-01-01
A61M	/	37	/	0092			I	2013-01-01
C12Y	/	304	/	24069			I	2013-01-01
Y02A	/	50	/	30			A	2018-01-01
A61B	/	2018	/	0016			A	2013-01-01
A61B	/	2018	/	00214			A	2013-01-01
A61B	/	2018	/	00434			A	2013-01-01
A61B	/	2018	/	1861			A	2013-01-01
A61N	/	2007	/	003			A	2013-01-01
A61M	/	2210	/	1035			A	2013-01-01

CPC Combination Sets								
Symbol					**Type**	**Set**	**Ranking**	**Version**
A61K	/	38	/	4893	I	1	1	2013-01-01
A61K	/	2300	/	00	I	1	2	2013-01-01

NONE		**Total Claims Allowed:**	
(Assistant Examiner)	(Date)	29	
/ALBERT M NAVARRO/ Primary Examiner, Art Unit 1645	17 September 2020	O.G. Print Claim(s)	O.G. Print Figure
(Primary Examiner)	(Date)	1	NONE

U.S. Patent and Trademark Office

Part of Paper No.: 20200917

Issue Classification	Application/Control No.	Applicant(s)/Patent Under Reexamination
	16/842,209	Deem et al.
	Examiner	**Art Unit**
	Mark NAVARRO	1645

INTERNATIONAL CLASSIFICATION					
CLAIMED					
C12M	/	1	/	00	
NON-CLAIMED					
	/		/		

US ORIGINAL CLASSIFICATION	
CLASS	**SUBCLASS**
435	283.1

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

NONE (Assistant Examiner)	(Date)	**Total Claims Allowed:** 29	
/ALBERT M NAVARRO/ Primary Examiner, Art Unit 1645 (Primary Examiner)	17 September 2020 (Date)	O.G. Print Claim(s) 1	O.G. Print Figure NONE

U.S. Patent and Trademark Office

Part of Paper No.: 20200917

Issue Classification	Application/Control No.	Applicant(s)/Patent Under Reexamination
	16/842,209	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

NONE		**Total Claims Allowed:**	
(Assistant Examiner)	(Date)	29	
/ALBERT M NAVARRO/ Primary Examiner, Art Unit 1645	17 September 2020	O.G. Print Claim(s)	O.G. Print Figure
(Primary Examiner)	(Date)	1	NONE

U.S. Patent and Trademark Office Part of Paper No.: 20200917

Search Notes	Application/Control No.	Applicant(s)/Patent Under Reexamination
	16/842,209	Deem et al.
	Examiner	Art Unit
	Mark NAVARRO	1645

CPC - Searched*		
Symbol	Date	Examiner
A61K 9/0021	09/17/2020	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 16/659,893, 16/036,381, 15/358,187, 14/601,529, 13/660,629, 13/253,595, 12/559,278, 11/459,090	09/17/2020	MN

Interference Search			
US Class/CPC Symbol	US Subclass/CPC Group	Date	Examiner
A61K	9/0021	09/17/2020	MN

Approved for use through 11/30/2020. OMB 0651-0031
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
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Substitute for form 1449/PTO

INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(Use as many sheets as necessary)

Sheet 1 of 17

Complete if Known	
Application Number	16/842,209
Filing Date	April 7, 2020
First Named Inventor	MARK; E. Deem
Art Unit	1645
Examiner Name	Albert Mark Navarro
Attorney Docket Number	5187.01US02AP

Examiner Initials*	Cite No.[1]	Document Number Number-Kind Code[2] (if known)	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document
		US-1695107	12-11-1928	KAHL; Franz
		US-2566806	09-04-1951	MILLER; Hugh A.
		US-3463149	08-26-1969	ALBU; Theodor
		US-3469139	09-23-1969	COLVIN; Alex D.
		US-3788296	01-29-1974	KLATT; Peter et al.
		US-3918449	11-11-1975	PISTOR; Michel Louis Paul
		US-4658836	04-21-1987	TURNER; Paul F.
		US-4767402	08-30-1988	KOST; Joseph et al.
		US-4976710	12-11-1990	MACKIN; Robert A.
		US-5056529	10-15-1991	DE GROOT; William J.
		US-5139029	08-18-1992	FISHMAN; Henry et al.
		US-5158536	10-27-1992	SEKINS; K. Michael et al.
		US-5192290	03-09-1993	HILAL; ;Said
		US-5286254	02-15-1994	SHAPLAND; James E. et al.
		US-5304120	04-19-1994	CRANDELL; Lois J. et al.
		US-5331947	07-26-1994	SHTURMAN; Leonid
		US-5336178	08-09-1994	KAPLAN; Aaron V. et al.
		US-5409483	04-25-1995	CAMPBELL; Peter et al.
		US-5432092	07-11-1995	BAILEY; Jerome M. et al.
		US-5496304	03-05-1996	CHASAN; Paul E.
		US-5562608	10-08-1996	SEKINS; K. Michael et al.
		US-5766605	06-16-1998	SANDERS; Ira et al.
		US-5807306	09-15-1998	SHAPLAND; J. Edward et al.

Examiner Signature		Date Considered	

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INFORMATION DISCLOSURE STATEMENT BY APPLICANT

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Sheet 2 of 17

Complete if Known	
Application Number	16/842,209
Filing Date	April 7, 2020
First Named Inventor	MARK; E. Deem
Art Unit	1645
Examiner Name	Albert Mark Navarro
Attorney Docket Number	5187.01US02AP

Examiner Initials*	Cite No.[1]	Document Number Number-Kind Code[2] (if known)	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document
		US-5817073	10-06-1998	KRESPI; Yosef P.
		US-5820589	10-13-1998	TORGERSON; Nathan A. et al.
		US-5843088	12-01-1998	BARRA; Jean-Aubert et al.
		US-5860974	01-19-1999	ABELE; John E.
		US-5902268	05-11-1999	SAAB; Mark A.
		US-5957961	09-28-1999	MAGUIRE; Mark A. et al.
		US-5964223	10-12-1999	BARAN; George
		US-5972026	10-26-1999	LAUFER; Michael D. et al.
		US-6033397	03-07-2000	LAUFER; Michael D. et al.
		US-6056744	05-02-2000	EDWARDS; Stuart D.
		US-6063768	05-16-2000	FIRST; Eric R.
		US-6139845	10-31-2000	DONOVAN; Stephen
		US-6200333	03-13-2001	LAUFER; Michael D.
		US-6216704	04-17-2001	INGLE; Frank et al.
		US-6265379	07-24-2001	DONOVAN; Stephen
		US-6283989	09-04-2001	LAUFER; Michael D. et al.
		US-6299633	10-09-2001	LAUFER; Michael D. et al.
		US-6302780	10-16-2001	AHN; Young Kill et al.
		US-6306423	10-23-2001	DONOVAN; Stephen et al.
		US-6322559	11-27-2001	DAULTON; Jay S. et al.
		US-6358926	03-19-2002	DONOVAN; Stephen
		US-6361554	03-26-2002	BRISKEN; Axel F.
		US-6383509	05-07-2002	DONOVAN; Stephen et al.

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Sheet 3 of 17

Complete if Known	
Application Number	16/842,209
Filing Date	April 7, 2020
First Named Inventor	MARK; E. Deem
Art Unit	1645
Examiner Name	Albert Mark Navarro
Attorney Docket Number	5187.01US02AP

Examiner Initials*	Cite No.[1]	Document Number Number-Kind Code[2] (if known)	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document
		US-6411852	06-25-2002	DANEK; Christopher J. et al.
		US-6425887	07-30-2002	MCGUCKIN; James Frederick et al.
		US-6432092	08-13-2002	MILLER; Eric C.
		US-6447785	09-10-2002	DONOVAN; Stephen
		US-6448231	09-10-2002	GRAHAM; Herbert Kerr
		US-6464680	10-15-2002	BRISKEN; Axel et al.
		US-6475160	11-05-2002	SHER; Nathan
		US-6488673	12-03-2002	LAUFER; Michael D. et al.
		US-6506399	01-14-2003	DONOVAN; Stephen
		US-6526976	03-04-2003	BARAN; George et al.
		US-6546932	04-15-2003	NAHON; Daniel et al.
		US-6562057	05-13-2003	SANTIN; Ernest
		US-6601581	08-05-2003	BABAEV; Eilaz
		US-6620415	09-16-2003	DONOVAN; Stephen
		US-6623742	09-23-2003	VOET; Martin A.
		US-6626855	09-30-2003	WENG; Lee et al.
		US-6632440	10-14-2003	QUINN; Conrad Padraig et al.
		US-6634363	10-21-2003	DANEK; Christopher James et al.
		US-6645496	11-11-2003	AOKI; K. Roger et al.
		US-6649161	11-18-2003	DONOVAN; Stephen
		US-6658279	12-02-2003	SWANSON; David K. et al.
		US-6719694	04-13-2004	WENG; Lee et al.
		US-6740321	05-25-2004	DONOVAN; Stephen

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Sheet 4 of 17

Complete if Known	
Application Number	16/842,209
Filing Date	April 7, 2020
First Named Inventor	MARK; E. Deem
Art Unit	1645
Examiner Name	Albert Mark Navarro
Attorney Docket Number	5187.01US02AP

Examiner Initials*	Cite No.[1]	Document Number Number-Kind Code[2] (if known)	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document
		US-6767544	07-27-2004	BROOKS; Gregory F. et al.
		US-6770070	08-03-2004	BALBIERZ; Daniel J.
		US-6773711	08-10-2004	VOET; Martin A. et al.
		US-6776991	08-17-2004	NAUMANN; Markus K.
		US-6827931	12-07-2004	DONOVAN; Stephen
		US-6838434	01-04-2005	VOET; Martin A.
		US-6841156	01-11-2005	AOKI; K. Roger et al.
		US-6843998	01-18-2005	STEWARD; Lance E. et al.
		US-6846312	01-25-2005	EDWARDS; Stuart D. et al.
		US-6847849	01-25-2005	MAMO; George et al.
		US-6861058	03-01-2005	AOKI; K. Roger et al.
		US-6872397	03-29-2005	AOKI; K. Roger et al.
		US-6917834	07-12-2005	KOBLISH; Josef V. et al.
		US-6974578	12-13-2005	AOKI; K. Roger et al.
		US-7027869	04-11-2006	DANEK; Christopher J. et al.
		US-7184811	02-27-2007	PHAN; Huy D. et al.
		US-7371231	05-13-2008	RIOUX; Robert J. et al.
		US-7462179	12-09-2008	EDWARDS; Stuart D. et al.
		US-7608275	10-27-2009	DEEM; Mark E. et al.
		US-7628789	12-08-2009	SOLTESZ; Peter P. et al.
		US-7655243	02-02-2010	DEEM; Mark E. et al.
		US-7747324	06-29-2010	ERRICO; Joseph P. et al.
		US-7853331	12-14-2010	KAPLAN; Gary S. et al.

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Sheet 5 of 17

Complete if Known	
Application Number	16/842,209
Filing Date	April 7, 2020
First Named Inventor	MARK; E. Deem
Art Unit	1645
Examiner Name	Albert Mark Navarro
Attorney Docket Number	5187.01US02AP

Examiner Initials*	Cite No.[1]	Document Number Number-Kind Code[2] (if known)	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document
		US-8007495	08-30-2011	MCDANIEL; Benjamin D. et al.
		US-8088127	01-03-2012	MAYSE; Martin L. et al.
		US-8105817	01-31-2012	DEEM; Mark E. et al.
		US-8133497	03-13-2012	DEEM; Mark E. et al.
		US-8172827	05-08-2012	DEEM; Mark E. et al.
		US-8226638	07-24-2012	MAYSE; Martin L. et al.
		US-8338164	12-25-2012	DEEM; Mark E. et al.
		US-8483831	07-09-2013	HLAVKA; Edwin J. et al.
		US-8489192	07-16-2013	HLAVKA; Edwin J. et al.
		US-8636684	01-28-2014	DEEM; Mark E. et al.
		US-8731672	05-20-2014	HLAVKA; Edwin J. et al.
		US-8740895	06-03-2014	MAYSE; Martin L. et al.
		US-8777943	07-15-2014	MAYSE; Martin L. et al.
		US-8808280	08-19-2014	MAYSE; Martin L. et al.
		US-8821489	09-02-2014	MAYSE; Martin L. et al.
		US-8911439	12-16-2014	MAYSE; Martin L. et al.
		US-8932289	01-13-2015	MAYSE; Martin L. et al.
		US-8961391	02-24-2015	DEEM; Mark E. et al.
		US-8961507	02-24-2015	MAYSE; Martin L. et al.
		US-8961508	02-24-2015	MAYSE; Martin L. et al.
		US-9005195	04-14-2015	MAYSE; Martin L. et al.
		US-9017324	04-28-2015	MAYSE; Martin L. et al.
		US-9125643	09-08-2015	HLAVKA; Edwin J. et al.

Examiner Signature		Date Considered	

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INFORMATION DISCLOSURE STATEMENT BY APPLICANT

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Sheet 6 of 17

Complete if Known	
Application Number	16/842,209
Filing Date	April 7, 2020
First Named Inventor	MARK; E. Deem
Art Unit	1645
Examiner Name	Albert Mark Navarro
Attorney Docket Number	5187.01US02AP

Examiner Initials*	Cite No.[1]	Document Number Number-Kind Code[2] (if known)	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document
		US-9149328	10-06-2015	DIMMER; Steven C. et al.
		US-9339618	05-17-2016	DEEM; Mark E. et al.
		US-9511210	12-06-2016	DEEM; Mark E. et al.
		US-9498283	11-22-2016	DEEM; Mark E. et al.
		US-9700707	07-11-2017	DEEM; Mark E. et al.
		US-10022529	07-17-2018	DEEM; Mark E. et al.
		US-10052465	08-21-2018	DEEM; Mark E. et al.
		US-10610675	04-07-2020	DEEM; Mark E. et al.
		US-10729897	08-04-2020	DEEM; Mark E. et al.
		US-20010044596	11-22-2001	JAAFAR; Ali
		US-20020013581	01-31-2002	EDWARDS; Stuart et al.
		US-20020082197	06-27-2002	AOKI; Kei Roger et al.
		US-20020087208	07-04-2002	KOBLISH; Josef V. et al.
		US-20020111620	08-15-2002	COOPER; Joel D. et al.
		US-20020143302	10-03-2002	HINCHLIFFE; Peter W.J. et al.
		US-20020198512	12-26-2002	SEWARD; Kirk Patrick
		US-20030018344	01-23-2003	KAJI; Hinako et al.
		US-20030023287	01-30-2003	EDWARDS; Stuart D. et al.
		US-20030036755	02-20-2003	GINN; Richard S.
		US-20030050591	03-13-2003	PATRICK; Mchale Anthony
		US-20030113349	06-19-2003	COLEMAN; William P.
		US-20030153881	08-14-2003	ROCHE; Bruno et al.
		US-20030118327	06-26-2003	UM; Soung Hyun et al.

Examiner Signature		Date Considered	

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Sheet 7 of 17

Complete if Known	
Application Number	16/842,209
Filing Date	April 7, 2020
First Named Inventor	MARK; E. Deem
Art Unit	1645
Examiner Name	Albert Mark Navarro
Attorney Docket Number	5187.01US02AP

Examiner Initials*	Cite No.[1]	Document Number Number-Kind Code[2] (if known)	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document
		US-20030159700	08-28-2003	LAUFER; Michael D. et al.
		US-20030202990	10-30-2003	DONOVAN; Stephen et al.
		US-20030211121	11-13-2003	DONOVAN; Stephen
		US-20030233099	12-18-2003	DANAEK; Christopher James et al.
		US-20040009180	01-15-2004	DONOVAN; Stephen
		US-20040010290	01-15-2004	SCHROEPPEL; Edward A. et al.
		US-20040028676	02-12-2004	KLEIN; Dean A. et al.
		US-20040086531	05-06-2004	BARRON; Richard L.
		US-20040091880	05-13-2004	WIEBUSCH; Heiko et al.
		US-20040142005	07-22-2004	BROOKS; Gregory F. et al.
		US-20040151741	08-05-2004	BORODIC; Gary
		US-20040175399	09-09-2004	SCHIFFMAN; Rhett M.
		US-20040186435	09-23-2004	SEWARD; Kirk Patrick
		US-20040213813	10-28-2004	ACKERMAN; Alan H.
		US-20040213814	10-28-2004	ACKERMAN; Alan H.
		US-20040220562	11-04-2004	GARABEDIAN; Robert J. et al.
		US-20040226556	11-18-2004	DEEM; Mark E. et al.
		US-20040248188	12-09-2004	SANDERS; Ira
		US-20040253274	12-16-2004	VOET; Martin A.
		US-20050007441	01-13-2005	HYUGA; Hiroaki
		US-20050019346	01-27-2005	BOULIS; Nicholas M.
		US-20050065575	03-24-2005	DOBAK; John D.
		US-20050074461	04-07-2005	DONOVAN; Stephen

Examiner Signature		Date Considered	

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INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(Use as many sheets as necessary)

Sheet 8 of 17

Complete if Known	
Application Number	16/842,209
Filing Date	April 7, 2020
First Named Inventor	MARK; E. Deem
Art Unit	1645
Examiner Name	Albert Mark Navarro
Attorney Docket Number	5187.01US02AP

Examiner Initials*	Cite No.[1]	Document Number Number-Kind Code[2] (if known)	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document
		US-20050107853	05-19-2005	KRESPI; Yosef et al.
		US-20050152924	07-14-2005	VOET; Martin A.
		US-20050182393	08-18-2005	ABBOUD; Marwan et al.
		US-20050183732	08-25-2005	EDWARDS; Stuart D.
		US-20050240147	10-27-2005	MAKOWER; Joshua et al.
		US-20050245926	11-03-2005	EDWARDS; Stuart D. et al.
		US-20050281751	12-22-2005	LEVIN; Bruce H.
		US-2006/0004323	01-05-2006	CHANG; John Y. et al.
		US-2006/0008462	01-12-2006	SANDERS; Ira
		US-20060084966	04-20-2006	MAGUIRE; Mark A. et al.
		US-20060106361	05-18-2006	MUNI; Ketan P. et al.
		US-20060153876	07-13-2006	SANDERS; Ira
		US-20060222667	10-05-2006	DEEM; Mark E. et al.
		US-20060225742	10-12-2006	DEEM; Mark E. et al.
		US-20060254600	11-16-2006	DANEK; Christopher J. et al.
		US-20070021803	01-25-2007	DEEM; Mark E. et al.
		US-20070025919	02-01-2007	DEEM; Mark E. et al.
		US-20070043350	02-22-2007	SOLTESZ; Peter P. et al.
		US-20070083194	04-12-2007	KUNIS; Christopher G. et al.
		US-20070100390	05-03-2007	DANAEK; Christopher J. et al.
		US-20070106292	05-10-2007	KAPLAN; Gary S. et al.
		US-20070118184	05-24-2007	DANEK; Christopher J. et al.
		US-20070129720	06-07-2007	DEMARAIS; Denise et al.

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Sheet 9 of 17

Complete if Known	
Application Number	16/842,209
Filing Date	April 7, 2020
First Named Inventor	MARK; E. Deem
Art Unit	1645
Examiner Name	Albert Mark Navarro
Attorney Docket Number	5187.01US02AP

Examiner Initials*	Cite No.[1]	Document Number Number-Kind Code[2] (if known)	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document
		US-20070156185	07-05-2007	SWANSON; David K. et al.
		US-20070250050	10-25-2007	LAFONTAINE; Daniel M.
		US-20070267011	11-22-2007	DEEM; Mark E. et al.
		US-20070270794	11-22-2007	ANDERSON; Neil L. et al.
		US-20080021369	01-24-2008	DEEM; Mark E. et al.
		US-20080051839	02-28-2008	LIBBUS; Imad et al.
		US-20080091379	04-17-2008	LYNCH; John J. et al.
		US-20080161890	07-03-2008	LAFONTAINE; Daniel M.
		US-20080255642	10-16-2008	ZARINS; Denise et al.
		US-20080312725	12-18-2008	PENNER; Abraham
		US-20090018538	01-15-2009	WEBSTER; Noah et al.
		US-20090043301	02-12-2009	JARRARD; Jerry et al.
		US-20090177192	07-09-2009	RIOUX; Robert F. et al.
		US-20090221997	09-03-2009	ARNOLD; Jeffrey M. et al.
		US-20100003282	01-07-2010	DEEM; Mark E. et al.
		US-20100087775	04-08-2010	DEEM; Mark E. et al.
		US-20110118725	05-19-2011	MAYSE; Martin L. et al.
		US-20110152855	06-23-2011	MAYSE; Martin L. et al.
		US-20110257647	10-20-2011	MAYSE; Martin L. et al.
		US-20110301587	12-08-2011	DEEM; Mark et al.
		US-20120016363	01-19-2012	MAYSE; Martin L. et al.
		US-20120016364	01-19-2012	MAYSE; Martin L. et al.
		US-20120029261	02-02-2012	DEEM; Mark E. et al.

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Sheet 10 of 17

Complete if Known	
Application Number	16/842,209
Filing Date	April 7, 2020
First Named Inventor	MARK; E. Deem
Art Unit	1645
Examiner Name	Albert Mark Navarro
Attorney Docket Number	5187.01US02AP

Examiner Initials*	Cite No.[1]	Document Number Number-Kind Code[2] (if known)	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document
		US-20120158101	06-21-2012	STONE; Corbett W. et al.
		US-20120203216	08-09-2012	MAYSE; Martin L. et al.
		US-20120203222	08-09-2012	MAYSE; Martin L. et al.
		US-20120209261	08-16-2012	MAYSE; Martin L. et al.
		US-20120209296	08-16-2012	MAYSE; Martin L. et al.
		US-20120302909	11-29-2012	MAYSE; Martin L. et al.
		US-20120310233	12-06-2012	DIMMER; Steven C. et al.
		US-20120316552	12-13-2012	MAYSE; Martin L. et al.
		US-20120316559	12-13-2012	MAYSE; Martin L. et al.
		US-20130123751	05-16-2013	DEEM; Mark E. et al.
		US-20130289555	10-31-2013	MAYSE; Martin L. et al.
		US-20130289556	10-31-2013	MAYSE; Martin L. et al.
		US-20130303948	11-14-2013	DEEM; Mark E. et al.
		US-20130310822	11-21-2013	MAYSE; Martin L. et al.
		US-20140186341	07-03-2014	MAYSE; Martin L.
		US-20140257271	09-11-2014	MAYSE; Martin L. et al.
		US-20140276792	09-18-2014	KAVECKIS; Ryan et al.
		US-20150051597	02-19-2015	MAYSE; Martin L. et al.
		US-20150141985	05-21-2015	MAYSE; Martin L. et al.
		US-20150190193	07-09-2015	MAYSE; Martin L. et al.
		US-20150366603	12-24-2015	HLAVKA; Edwin J. et al.
		US-20160022351	01-28-2016	KAVECKIS; Ryan et al.
		US-20160038725	02-11-2016	MAYSE; Martin L. et al.

Examiner Signature		Date Considered	

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Sheet 11 of 17

Complete if Known	
Application Number	16/842,209
Filing Date	April 7, 2020
First Named Inventor	MARK; E. Deem
Art Unit	1645
Examiner Name	Albert Mark Navarro
Attorney Docket Number	5187.01US02AP

Examiner Initials*	Cite No.[1]	Document Number Number-Kind Code[2] (if known)	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document
		US-20190083768	03-21-2019	DEEM; Mark E. et al.

Examiner Initials*	Cite No.[1]	Foreign Patent Document 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]
		CA-2152002-A1	12-18-1995	TRUDELL MEDICAL LTD [CA]	☐
		EP-3248612-A1	2017-11-29	THE FOUNDRY, LLC [US]	☐
		JP-2002145784-A	05-22-2002	MORISHITA RYUICHI.	☒
		WO-9119529-A1	12-26-1991	CORTRAK MEDICAL, INC. [US]	☐
		WO-0062699-A2	10-26-2000	BRONCUS TECH INC [US], et al.	☐
		WO-2004006954-A2	01-22-2004	ALLERGAN INC [US], et al.	☐
		WO-2004048519-A2	06-10-2004	IRA SANDERS	☐
		WO-2004077987-A1	09-16-2004	LALINE INTERNATIONAL SARL [TN]	☐

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INFORMATION DISCLOSURE STATEMENT BY APPLICANT

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Sheet 12 of 17

Complete if Known	
Application Number	16/842,209
Filing Date	April 7, 2020
First Named Inventor	MARK; E. Deem
Art Unit	1645
Examiner Name	Albert Mark Navarro
Attorney Docket Number	5187.01US02AP

Examiner Initials*	Cite No.[1]	Foreign Patent Document 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]
		WO-2004101028-A2	11-25-2004	THE FOUNDRY INC [US], et al.	☐
		WO-2004101028-A3	12-14-2006	THE FOUNDRY INC [US], et al.	☐
		WO-2007014003-A2	02-01-2007	THE FOUNDRY INC. [US]	☐
		WO-2005032646-A2	04-14-2005	EASTERN VIRGINIA MED SCHOOL [US], et al.	☐
		WO-2005048988-A1	06-02-2005	SCOTT NEAL [US], et al.	☐
		WO-9519805-A1	07-27-1995	GENETRONICS INC [US], et al.	☐
		WO-9934831-A1	07-15-1999	UNIV WASHINGTON [US], et al.	☐

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INFORMATION DISCLOSURE STATEMENT BY APPLICANT

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Sheet 13 of 17

Complete if Known	
Application Number	16/842,209
Filing Date	April 7, 2020
First Named Inventor	MARK; E. Deem
Art Unit	1645
Examiner Name	Albert Mark Navarro
Attorney Docket Number	5187.01US02AP

NON-PATENT LITERATURE DOCUMENTS			
Examiner Initials*	Cite No.[1]	Include name of the author(in CAPITAL LETTERS),title of the article(when appropriate), title of the item (book,magazine,journal,serial,symposium,catalog,etc.),date,page(s),volume-issue number(s),publisher, city and/or country where published.	T[2]
		"Anonymous: Neurotoxin (from Wikipedia)," Retrieved from http://en.wikipedia.org/w/index.php?title=Neurotoxin&printable=yes, 2 April 2015, 23 pages.	☐
		AHNERT-HILGER., et al., "Introduction of Macromolecules into Bovine Adrenal-Medullary Chromaffin Cells and Rat Pheochromocytoma Cells (PC12) by Permeabilization with Streptolysin O: Inhibitory Effect of Teanus Toxin on Catecholamine Secretion," J. Neurochem, June 1989, Vol. 52 (6), pp. 1751-1758.	☐
		Application and File History for U.S. Patent Application No. 16/659,893, filed 22 October 2019, Inventors: Deem et al.	☐
		Application and File History for U.S. Patent Application No. 11/459,090, filed 21 July 2006, Inventors: Deem et al.	☐
		Application and File History for U.S. Patent Application No. 12/559,278, filed 14 September 2009, Inventors: Deem et al., as available on PAIR at www.uspto.gov.	☐
		Application and File History for U.S. Patent Application No. 13/253,595, filed 5 October 2011, Inventors: Deem et al., as available on PAIR at www.uspto.gov.	☐
		Application and File History for U.S. Patent Application No. 13/660,629, filed 25 October 2012, Inventors: Deem et al., as available on PAIR at www.uspto.gov.	☐
		Application and File history for U.S. Patent Application No. 14/601,529, filed January 21, 2015, Inventors: Deem et al., as available on PAIR at www.uspto.gov.	☐
		Application and File History for U.S. Patent Application No. 15/358,187, filed November 22, 2016, Inventors: Deem et al, as available on PAIR at www.uspto.gov.	☐

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Examiner Name	Albert Mark Navarro
Attorney Docket Number	5187.01US02AP

NON-PATENT LITERATURE DOCUMENTS

Examiner Initials*	Cite No.[1]	Include name of the author(in CAPITAL LETTERS),title of the article(when appropriate), title of the item (book,magazine,journal,serial,symposium,catalog,etc.),date,page(s),volume-issue number(s),publisher, city and/or country where published.	T[2]
		Application and File History for U.S. Patent Application No. 16/036,381, filed July 16, 2018, Inventors: Deem et al, as available on PAIR at www.uspto.gov.	☐
		Application and File History for U.S. Patent Application No. 11/757,963, filed May 18, 2007, Inventors: Deem et al, as available on PAIR at www.uspto.gov.	☐
		Application and File History for U.S. Patent Application No. 11/750,967, filed May 18,2007, Inventors: Deem et al, as available on PAIR at www.uspto.gov.	☐
		Application and File History for U.S. Patent Application No. 12/636,477, filed December 11, 2009, Inventors: Deem et al, as available on PAIR at www.uspto.gov.	☐
		Application and File History for U.S. Patent Application No. 13/328,203, filed December 16, 2011, Inventors: Deem et al, as available on PAIR at www.uspto.gov.	☐
		Application and File History for U.S. Patent Application No. 14/841,514, filed August 31, 2015, Inventors: Deem et al, as available on PAIR at www.uspto.gov.	☐
		Application and File History for U.S. Patent Application No. 15/615,344, filed June 6, 2017, Inventors: Deem et al, as available on PAIR at www.uspto.gov.	☐
		File History for EP Application No. 17165407.2, filed May 29, 2018, Inventors: Deem et al.	☐
		BIGALKE., et al., "Clostridial Neurotoxins," Handbook of Experimental Pharmacology (Aktories, K., and Just, I., eds), 2000, Vol. 145, pp. 407-443.	☐
		BITTNER., et al., "Isolated Light Chains of Botulinum Neurotoxins Inhibit Exocytosis," The Journal of Biological Chemistry, 1989, Vol. 264(18), pp. 10354-10360.	☐

Examiner Signature		Date Considered	

*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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INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(Use as many sheets as necessary)

Sheet 15 of 17

Complete if Known	
Application Number	16/842,209
Filing Date	April 7, 2020
First Named Inventor	MARK; E. Deem
Art Unit	1645
Examiner Name	Albert Mark Navarro
Attorney Docket Number	5187.01US02AP

NON-PATENT LITERATURE DOCUMENTS

Examiner Initials*	Cite No.[1]	Include name of the author(in CAPITAL LETTERS),title of the article(when appropriate), title of the item (book,magazine,journal,serial,symposium,catalog,etc.),date,page(s),volume-issue number(s),publisher, city and/or country where published.	T[2]
		BLINDT., et al., "Development of a New Biodegradable Intravascular Polymer Stent with Simultaneous Incorporation of Bioactive Substances," The International Journal of Artificial Organs, 1999, Vol. 22 (12), pp. 843-853.	☐
		BUZZI., "Diphtheria Toxin Treatment of Human Advanced Cancer," Cancer Research, 1982, Vol. 42, pp. 2054-2058.	☐
		CHADDOCK., et al., "Expression and Purification of Catalytically Active, Non-Toxic Endopeptidase Derivatives of Clostridium Botulinum Toxin Type A," Protein Expression and Purification, July 2002, Vol. 25 (2), pp. 219-228.	☐
		CHANG., "Cell Poration and Cell Fusion Using an Oscillating Electric Field," Biophys. J, 1989, Vol. 56 (4), pp. 641-652.	☐
		Co-pending US provisional application No. 60/701,747, filed on 22 July 2005.	☐
		DE PAIVA., et al., "Light Chain of Botulinum Neurotoxin is Active in Mammalian Motor Nerve Terminals When Delivered Via Liposomes," FEBS Lett, December 1990, Vol. 17:277(1-2), pp. 171-174.	☐
		European Search Report for Application No. EP06788062, mailed on 07 January 2014, 9 pages.	☐
		GUZMAN H.R, et al., "Equilibrium Loading of Cells with Macromolecules by Ultrasound: Effects of Molecular Size and Acoustic Energy," J Pharm Sci., July 2002, Vol. 91 (7), pp. 1693-1701.	☐
		GUZMAN., et al., "Bioeffects Caused by Changes in Acoustic Cavitation Bubble Density and Cell Concentration: A Unified Explanation Based on Cell-to-Bubble Ratio and Blast Radius," Ultrasound in medicine & biology, 2003, Vol. 29 (8), pp. 1211-1222.	☐

Examiner Signature		Date Considered	

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INFORMATION DISCLOSURE STATEMENT BY APPLICANT

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Sheet 16 of 17

Complete if Known	
Application Number	16/842,209
Filing Date	April 7, 2020
First Named Inventor	MARK; E. Deem
Art Unit	1645
Examiner Name	Albert Mark Navarro
Attorney Docket Number	5187.01US02AP

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Examiner Initials*	Cite No.[1]	Include name of the author(in CAPITAL LETTERS),title of the article(when appropriate), title of the item (book,magazine,journal,serial,symposium,catalog,etc.),date,page(s),volume-issue number(s),publisher, city and/or country where published.	T[2]
		International Preliminary Report on Patentability for Application No. PCT/US2006/028310, mailed on 22 January 2008, 7 pages.	☐
		International Search Report and Written Opinion for Application No. PCT/US2006/028310, mailed on 8 August 2007, 7 pages.	☐
		KISTNER., et al., "Reductive Cleavage of Tetanus Toxin and Botulinum Neurotoxin A by the Thioredoxin System from Brain," Naunyn-Schmiedebergs Arch Pharmacal, February, 1992, Vol. 345 (2), pp. 227-234.	☐
		KORPELA., et al., "Comparison of Tissue Reactions in the Tracheal Mucosa Surrounding a Bioabsorbable and Silicone Airway Stents," Annals of Thoracic Surgery, 1998, Vol. 66, pp. 1772-1776.	☐
		KREITMAN., "Taming Ricin Toxin," Nature Biotechnology, 2003, Vol. 21, pp. 372-374.	☐
		Office Action mailed 24 May 2016 for Japanese Application No. JP2015-120827 filed 16 June 2015, 7 pages.	☐
		Office Action mailed 21 August 2017 for Japanese Application No. 2016- 227703 filed 24 November 2016, 4 pages.	☒
		RAJ., "Editorial," Pain Practice, 2004, Vol. 4 (1S), pp. S1-S3.	☐
		SCHMITT G.S., et al., "Indwelling Transbronchial Catheter Drainage of Pulmonary Abscess," Ann Thorac Surg, January 1988, Vol. 45 (1), pp. 43-47.	☐
		SHAARI., et al., "Rhinorrhea is Decreased in Dogs After Nasal Application of Botulinum Toxin," Otolaryngol Head Neck Surgery, April 1995, Vol. 112 (4), pp. 566-571.	☐

Examiner Signature		Date Considered	

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INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(Use as many sheets as necessary)

Sheet 17 of 17

Complete if Known	
Application Number	16/842,209
Filing Date	April 7, 2020
First Named Inventor	MARK; E. Deem
Art Unit	1645
Examiner Name	Albert Mark Navarro
Attorney Docket Number	5187.01US02AP

NON-PATENT LITERATURE DOCUMENTS

Examiner Initials*	Cite No.[1]	Include name of the author(in CAPITAL LETTERS),title of the article(when appropriate), title of the item (book,magazine,journal,serial,symposium,catalog,etc.),date,page(s),volume-issue number(s),publisher, city and/or country where published.	T[2]
		SIMPSON L.L., "The Origin, Structure, and Pharmacological Activity of Botulinum Toxin," Pharmacol Reviews, September 1981, Vol. 33 (3), pp. 155-188.	☐
		SIMPSON., et al., "Isolation and Characterization of the botulinum Neurotoxins," Methods Enzymol, 1988, Vol. 165, pp. 76-85.	☐
		SUNDARAM, et al., "An Experimental and Theoretical Analysis of Ultrasound-Induced Permeabilization of Cell Membranes," Biophysical Journal, May 2003, Vol. 84 (5), pp. 3087-3101.	☐
		TSUJI., et al., "Biodegradable Stents as a Platform to Drug Loading," International Journal of Cardiovascular Interventions, 2003, Vol. 5(1), pp. 13-16.	☐
		UNAL., et al., "Effect of Botulinum Toxin Type A on Nasal Symptoms in Patients with Allergic Rhinitis: A Double-blind, Placebo-controlled Clinical Trial," Acta Oto-Laryngologica, December 2003, Vol. 123 (9), pp. 1060-1063.	☐
		WEAVER, "Electroporation: A General Phenomenon for Manipulating Cells and Tissues," Journal of Cellular Biochemistry, Apr. 1993, Vol. 51(4), pp.426-435.	☐

Examiner Signature	/ALBERT M NAVARRO/	Date Considered	09/17/2020

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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.

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24113 7590 10/15/2020
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.

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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.

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

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
16/842,209	04/07/2020	Mark E. Deem	5187.01US02AP	2844

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	$600	$0.00	$0.00	$600	01/15/2021

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 Patterson Thuente Pedersen, P.A.
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: 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

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)*

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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 /Daidre L. Burgess/ Date 12/11/2020

Typed or printed name Daidre L. Burgess Registration No. 60389

Electronic Patent Application Fee Transmittal

Application Number:	16842209
Filing Date:	07-Apr-2020
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:	5187.01US02AP

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	600	600

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Extension-of-Time:				
Miscellaneous:				
			Total in USD ($)	**600**

Electronic Acknowledgement Receipt

EFS ID:	41367009
Application Number:	16842209
International Application Number:	
Confirmation Number:	2844
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:	5187.01US02AP
Receipt Date:	11-DEC-2020
Filing Date:	07-APR-2020
Time Stamp:	18:19:53
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	yes
Payment Type	CARD
Payment was successfully received in RAM	$600
RAM confirmation Number	E2020BAI20289341
Deposit Account	160631
Authorized User	Valerie Mitchell

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File Listing:

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1	Issue Fee Payment (PTO-85B)	5187_01US02AP_ISSUE_FEE.pdf	242719 31b95e5a1a87926a8a3d3767bbb6ad58e77687c2	no	1
Warnings:					
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2	Fee Worksheet (SB06)	fee-info.pdf	30571 44883ad50bb224ac3d8bc1137b77114fdb6ef240	no	2
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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.

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United States Patent and Trademark Office
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APPLICATION NO.	ISSUE DATE	PATENT NO.	ATTORNEY DOCKET NO.	CONFIRMATION NO.
16/842,209	01/19/2021	10894011	5187.01US02AP	2844

24113 7590 12/29/2020

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

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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