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I hereby revoke all previous powers of attorney given in the application identified in the attached statement under 37 CFR 3.73(b).

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☒ Practitioners associated with the Customer Number:

021971

OR

☐ Practitioner(s) named below (If more than ten patent practitioners are to be named, then a customer number must be used):

Name	Registration Number	Name	Registration Number

as attorney(s) or agent(s) to represent the undersigned before the United States Patent and Trademark Office (USPTO) in connection with any and all patent applications assigned only to the undersigned according to the USPTO assignment records or assignment documents attached to this form in accordance with 37 CFR 3.73(b). I further authorize any of the above-identified practitioners to execute a Statement Under 37 CFR 3.73(b) on the undersigned's behalf to certify the chain of title and establish the undersigned's ownership in any and all patent applications in which rights have been assigned to the undersigned.

Please change the correspondence address for the application identified in the attached statement under 37 CFR 3.73(b) to:

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021971

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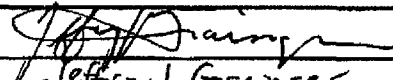
Assignee Name and Address:

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A copy of this form, together with a statement under 37 CFR 3.73(b) (Form PTO/SB/96 or equivalent) is required to be filed in each application in which this form is used. The statement under 37 CFR 3.73(b) may be completed by one of the practitioners appointed in this form if the appointed practitioner is authorized to act on behalf of the assignee, and must identify the application in which this Power of Attorney is to be filed.

SIGNATURE of Assignee of Record

The individual whose signature and title is supplied below is authorized to act on behalf of the assignee

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Title	Managing Partner		

Application Data Sheet

Application Information

Application Type::	Continuation
Subject Matter::	Utility
Title::	METHODS AND SYSTEMS FOR TOXIN DELIVERY TO THE NASAL CAVITY
Attorney Docket Number::	38077-714.301
Request for Early Publication::	No
Request for Non-Publication::	No
Suggested Drawing Figure::	5
Total Drawing Sheets::	24
Petition included?::	No
Secrecy Order in Parent Appl.::	No

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Country of mailing address::	US
Postal or Zip Code of mailing address::	94041

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Postal or Zip Code of mailing address:: 94062

Correspondence Information

Correspondence Customer Number:: 21971

Representative Information

Representative Customer Number:: 21971

Domestic Priority Information

Application::	Continuity Type::	Parent Application::	Parent Filing Date::
This application	Continuation	12/636,477	12/11/2009
12/636,477	Divisional	11/750,963	05/18/2007
11/750,963	Continuation-in-part	11/459,090	07/21/2006
11/459,090	Claims the benefit of	60/702,077	07/22/2005
		60/747,771	05/19/2006

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Country of mailing address::	US
Postal or Zip Code of mailing address::	94025

Electronic Patent Application Fee Transmittal

Application Number:				
Filing Date:				
Title of Invention:	METHODS AND SYSTEMS FOR TOXIN DELIVERY TO THE NASAL CAVITY			
First Named Inventor/Applicant Name:	Mark E. Deem			
Filer:	James Mitchell Heslin/Joy Roeder			
Attorney Docket Number:	38077-714.301			
Filed as Small Entity				
Utility under 35 USC 111(a) Filing Fees				
Description	Fee Code	Quantity	Amount	Sub-Total in USD(\$)
Basic Filing:				
Utility filing Fee (Electronic filing)	4011	1	95	95
Utility Search Fee	2111	1	310	310
Utility Examination Fee	2311	1	125	125
Pages:				
Claims:				
Miscellaneous-Filing:				
Petition:				
Patent-Appeals-and-Interference:				

Description	Fee Code	Quantity	Amount	Sub-Total in USD(\$)
Post-Allowance-and-Post-Issuance:				
Extension-of-Time:				
Miscellaneous:				
Total in USD (\$)				530

Electronic Acknowledgement Receipt

EFS ID:	11638889
Application Number:	13328203
International Application Number:	
Confirmation Number:	9512
Title of Invention:	METHODS AND SYSTEMS FOR TOXIN DELIVERY TO THE NASAL CAVITY
First Named Inventor/Applicant Name:	Mark E. Deem
Customer Number:	21971
Filer:	James Mitchell Heslin/Joy Roeder
Filer Authorized By:	James Mitchell Heslin
Attorney Docket Number:	38077-714.301
Receipt Date:	16-DEC-2011
Filing Date:	
Time Stamp:	13:55:53
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	yes
Payment Type	Deposit Account
Payment was successfully received in RAM	\$530
RAM confirmation Number	180
Deposit Account	232415
Authorized User	

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
Page 7 of 295					

1		2011_12_16_CONAPPLN_38077_714_301.pdf	264529 af1f50a0c386ad5826a48885fbce19a107e151a1	yes	26
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	Claims		25	25	
	Abstract		26	26	
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2	Drawings-only black and white line drawings	2011_12_16_DRWGS_38077_714_301.pdf	897621 18f8d9a5194d4d41e5cea00a5239626c7a68182c	no	24
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Information:					
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	Document Description		Start	End	
	Oath or Declaration filed		1	1	
	Assignee showing of ownership per 37 CFR 3.73(b).		2	2	
	Power of Attorney		3	3	
Warnings:					
Information:					
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Information:					
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Warnings:					
Information:					
Page 8 of 295			Total Files Size (in bytes): 1474881		

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New Applications Under 35 U.S.C. 111

If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

National Stage of an International Application under 35 U.S.C. 371

If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office

If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

Electronic Acknowledgement Receipt	
EFS ID:	11638889
Application Number:	13328203
International Application Number:	
Confirmation Number:	9512
Title of Invention:	METHODS AND SYSTEMS FOR TOXIN DELIVERY TO THE NASAL CAVITY
First Named Inventor/Applicant Name:	Mark E. Deem
Customer Number:	21971
Filer:	James Mitchell Heslin/Joy Roeder
Filer Authorized By:	James Mitchell Heslin
Attorney Docket Number:	38077-714.301
Receipt Date:	16-DEC-2011
Filing Date:	
Time Stamp:	13:55:53
Application Type:	Utility under 35 USC 111(a)

Payment information:				
Submitted with Payment		yes		
Payment Type		Deposit Account		
Payment was successfully received in RAM		\$530		
RAM confirmation Number		180		
Deposit Account		232415		
Authorized User				
File Listing:				
Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip Pages (if appl.)
Page 10 of 299				

1		2011_12_16_CONAPPLN_38077_714_301.pdf	264529 af1f50a0c386ad5826a48885fbce19a107e151a1	yes	26
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	Document Description		Start	End	
	Specification		1	24	
	Claims		25	25	
	Abstract		26	26	
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2	Drawings-only black and white line drawings	2011_12_16_DRWGS_38077_714_301.pdf	897621 18f8d9a5194d4d41e5cea00a5239626c7a68182c	no	24
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3		2011_12_16_DEC_373_POA_38077_714_301.pdf	200325 47ff7bdfc709f6d1d379524c3ba81bdb5f58fcf5	yes	3
	Multipart Description/PDF files in .zip description				
	Document Description		Start	End	
	Oath or Declaration filed		1	1	
	Assignee showing of ownership per 37 CFR 3.73(b).		2	2	
	Power of Attorney		3	3	
Warnings:					
Information:					
4	Application Data Sheet	2011_12_16_ADS_38077_714_301.pdf	79531 b38b8a79185a9d7d139d56eaa796572af1f19dee	no	3
Warnings:					
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This is not an USPTO supplied ADS fillable form					
5	Fee Worksheet (SB06)	fee-info.pdf	32875 a426d4b0d16d08bc98f05944478ee5e35342dd0e	no	2
Warnings:					
Information:					
Page 11 of 295			Total Files Size (in bytes): 1474881		

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PATENT APPLICATION

**METHODS AND SYSTEMS FOR TOXIN DELIVERY
TO THE NASAL CAVITY**

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METHODS AND SYSTEMS FOR TOXIN DELIVERY TO THE NASAL CAVITY

CROSS-REFERENCES TO RELATED APPLICATIONS

[0001] The present application is a continuation of Application No. 12/636,477 (Attorney Docket No. 38077-714.401), filed on December 11, 2009, which is a divisional of Application No. 11/750,963 (Attorney Docket No.: 020979-003710US), filed on May 18, 2007, which is a continuation-in-part of Application No. 11/459,090 (Attorney Docket No.: 020979-003410US), filed on July 21, 2006, which claimed the benefit of provisional application no. 60/702,077 (Attorney Docket No.: 020979-003400US), filed on July 22, 2005, and of provisional application no. 60/747,771 (Attorney Docket No.: 020979-003700US), filed on May 19, 2006, the full disclosures of which are incorporated herein by reference.

BACKGROUND OF THE INVENTION

[0002] 1. Field of the Invention. The present invention relates generally to medical methods and systems. More particularly, the present invention relates to methods and systems for delivering toxins, such as botulinum toxin light chain fragments, to target cells in a nasal cavity.

[0003] 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 rhinorrhea 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.

[0004] 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.

[0005] 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.

[0006] 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.

[0007] 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.

[0008] 2. Description of the Background Art. U.S. Patent No. 5,766,605, to Sanders et al. has been described above. Sharri et al. (1995) *Otolaryngol. Head Neck Surg.* 112: 566-571 also reports the work of Dr. Sanders described in the '605 patent. Ünal et al. (2002) *Acta Otolaryngol* 123: 1060-1063 describes the injection of botulinum toxin A into the turbinates of patients suffering from allergic rhinitis. See also, U.S. 6,974,578. The purification and possible therapeutic uses of botulinum light chain are described in US2004/0151741, US2005/0019346, and Chaddock et al. (2002) *Protein Expression and Purification* 25: 219-228. Energy-mediated transdermal delivery of intact botulinum toxin is suggested in US2005/007441 and 2004/0009180. The use of catheters and other devices for the energy-mediated delivery of botulinum light chain is described in commonly owned co-pending provisional application 60/702,077 (Attorney Docket No. 020979-003400US, filed July 22, 2005, the full disclosure of which has previously been incorporated herein by reference.

BRIEF SUMMARY OF THE INVENTION

[0009] The present invention provides treatments for any disease or condition for which rhinorrhea is a result or symptom.

[0010] 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.

[0011] 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.

[0012] 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.

[0013] According to the present invention, botulinum toxin, ricin, exotoxin A, diphtheria toxin, cholera toxin, tetanus toxin, other neurotoxins, and active fragments thereof are delivered to a patient's nasal membrane while applying energy to target cells within the membrane under conditions which cause a reversible (or in some instances non-reversible) poration of the cell membranes to enhance delivery of the toxin into the cells. The region where the toxin is introduced may comprise any portion of the nasal cavity, such as a single paranasal sinus or portion thereof, a main nasal passage, two or more paranasal sinuses, or in some cases may comprise substantially the entire nasal cavity of the patient. A particular target region for the toxin may comprise the nasopharynx which is at the back of the nasal passage. The nasopharynx comprises a cluster of epithelial or goblet cells which are responsible for mucus secretion and which are susceptible to the disabling mechanism of the botulinum toxin and other neurotoxins.

[0014] 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.

[0015] 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.

[0016] 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.

[0017] 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.

[0018] 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.

[0019] In addition to the methods described above, the present invention further provides systems for delivering toxins to epithelial or goblet and other target cells as defined above in a nasal membrane. The

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

[0020] 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

[0021] Figure 1 — depicts a schematic of the creation of neurotoxin Botulinum Toxin Type A (BoNT/A), including the light chain (LC) fragment or portion.

[0022] Figure 2A — depicts a schematic of a target cell, including the cell membrane, and inner cellular matrices.

[0023] Figure 2B — depicts a schematic of the target cell wherein LC molecule has been introduced.

[0024] Figures 3A-3B — depicts a the target cell of Figure 2 showing application of an energy field (EF) to produce permeabilization or pores (P) in the cell membrane, and introduction of the LC fragment therethrough.

[0025] Figure 4 — depicts a schematic of a cell wherein the energy field has been discontinued, and neurotransmission of the cell has been effectively blocked.

[0026] Figures 5, 5A-5B — depicts various embodiments of a delivery device of the present invention utilizing multiple energy transmission elements and an energy transmission system.

[0027] Figures 6A-6D, 6AA and 6CC — depict various electrode catheter configurations adapted to deliver energy or energy and therapeutic agents to target tissue.

[0028] Figure 7 - depicts an embodiment of the present invention utilizing an ultrasound element on a catheter device.

[0029] Figure 8 — depicts an embodiment of the present invention utilizing an aerosolizing element.

[0030] Figure 9 - depicts use on an external hand held transducer for enhancing cellular uptake of toxin delivered from a separate nasal aerosolizer.

[0031] Figures 10 and 11- depicts depict use of balloon catheters for delivering toxin to the nasopharynx.

[0032] Figures 12A-12C - depict use of a self-expanding toxin delivery structure on a catheter.

[0033] Figures 13 and 14 - depict a protocol for limiting toxin introduction by partial filling of a porous delivery balloon.

[0034] Figure 15 - depicts sizing of a delivery balloon to control distribution of toxin released into the nasal cavity.

[0035] Figure 16 - depicts placement of a delivery balloon to protect the olfactory bulb.

[0036] Figure 17 - depicts the use of multiple small balloons for selective toxin delivery into the nasal cavity.

[0037] Figure 18 - depicts sonoporation using an external mask placed over the sinuses and nose.

[0038] Figure 19 - depicts a front view of an external sonoporation mask showing placement of ultrasound transducers.

[0039] Figures 20 and 21 — depict an orally-introduced occlusion catheter and energy applicator system.

[0040] Figures 22 and 23 - depict nose plugs for occluding and optionally delivery poration energy to the nasal cavity.

[0041] Figures 24 and 25 - depict an alternate occlusion catheter system for targeted toxin delivery to the nasopharynx.

[0042] Figures 26 and 27 - depict use of a toxin delivery catheter having side holes and a distal occlusion balloon for isolating and protecting the olefactory bulb.

[0043] Figures 28 and 30- depict use of a simple catheter having a shaped distal end for aerosolizing a toxin into a target nasal sinus though an ostium open to the sinus.

[0044] Figure 29 - depicts toxin delivery using a nasal spray and energy delivery using a face mask.

[0045] Figures 31 and 32, depict use of a catheter having a shaped distal end for positioning separate infusion structures with a target sinus cavity.

[0046] Figure 33 — depicts an applicator device for delivering toxin to the nasal cavity having a handle and two applicator tips for placement within the nasal passageway.

[0047] Figure 34 — depicts a top view of the applicator device illustrated in Figure 33.

[0048] Figure 35 — depicts the applicator device illustrated in Figure 33 when placed within the nasal passageway.

[0049] Figure 36 — depicts an applicator device configured with an infusion channel and access port for infusing solution to the applicator tip.

[0050] Figures 37A-37C — depict the handle of an applicator device in an isometric view, a top view in an expanded state and a top view in a compressed state, respectively.

[0051] Figure 38 — depicts an applicator device comprising a spring element.

[0052] Figures 39A-39B — depict a sponge applicator tip for an applicator device in a dry low volume configuration and a wet expanded configuration, respectively.

[0053] Figures 40A-40B — depict an applicator tip comprising a spring element in an expanded configuration and a compressed configuration, respectively.

[0054] Figure 41 — depicts an applicator device comprising loop spring element.

[0055] Figure 42 - depicts a spring-loaded applicator tip held in a compressed state by an engaged actuator.

[0056] Figure 43 — depicts an applicator device with the actuators of both applicator tips engaged by an engagement element.

DETAILED DESCRIPTION OF THE INVENTION

[0057] 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.

[0058] 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.

[0059] 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.

[0060] Generally, the botulinum toxin molecule (BoNT) is synthesized as a single polypeptide chain of 150kD molecular weight. The neurotoxin is then exposed to enzymes, either during cultivation of the *Clostridium botulinum* organism or subsequent to purification of the toxin, wherein specific peptide bonds are cleaved or “nicked” resulting in the formation of a dichain molecule referred to as BoNT. As shown in Figure

1, dichain neurotoxin is composed of a light chain region 50kD molecular weight linked by disulfide bonds to a heavy chain 100kD molecular weight (Kistner, A., Habermann, E. (1992) *Naunyn Schmiedeberg's 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.

[0061] Over the past several years, the separation and purification of the light chain and heavy chain of BoNT has seen significant development activity. In the case of the heavy chain (HC), researchers are interested in its ability to bond with a target cell and deliver certain molecules into that cell. For example, various drug delivery applications have been suggested, for example, using the HC to bind to tPA so that a patient could inhale the HC-bound tPA allowing it to cross the membrane of the lungs and be transported into the bloodstream for anticoagulation. Of particular interest to the present invention are the efforts to isolate and purify the light chain (LC) of the botulinum molecule. In its isolated and purified form, all HC elements are removed, rendering the LC incapable of crossing the cell membrane without assistance. This renders the LC a non-toxic protein to the cell environment, while still maintaining its encoded toxicity by, once it is effectively delivered to its appropriate catalytic environment; the cell cytosol.

[0062] Various groups have been active in the area of isolation and purification. For example, companies such as Metabionics, 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.

[0063] For purposes of this specification, the terms “poration” and/or “permeabilization” include various forms of electrically-mediated poration, such as the use of pulsed electric fields (PEFs), nanosecond pulsed electric fields (nsPEFs), ionophoresis, electrophoresis, electroporation, as well as other energy mediated permeabilization, including sonoporation (mediated by ultrasonic or other acoustic energy), and/or combinations thereof, to create temporary pores in a targeted cell membrane. Similarly, the term “electrode” or “energy source” used herein, encompasses the use of various types of energy producing devices, including x-ray, radiofrequency (RF), DC current, AC current, microwave, ultrasound, adapted and applied in ranges to produce membrane permeabilization in the targeted cell.

[0064] Reversible electroporation, first observed in the early 1970's, has been used extensively in medicine and biology to transfer chemicals, drugs, genes and other molecules into targeted cells for a variety of purposes such as electrochemotherapy, gene transfer, transdermal drug delivery, vaccines, and the like.

[0065] In general, electroporation may be achieved utilizing a device adapted to activate an electrode set or series of electrodes to produce an electric field. Such a field can be generated in a bipolar or monopolar electrode configuration. When applied to cells, depending on the duration and strength of the applied pulses, this field operates to increase the permeabilization of the cell membrane and reversibly open the cell membrane for a short period of time by causing pores to form in the cell lipid bilayer allowing entry of various therapeutic elements or molecules, after which, when energy application ceases, the pores spontaneously close without killing the cell after a certain time delay. As characterized by Weaver, *Electroporation: A General Phenomenon for Manipulating Cells and Tissues* Journal of Cellular Biochemistry, 51:426-435 (1993), short(1-100 μ 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).

[0066] In addition, it is known in the art that macromolecules can be made to cross reversibly created pores at voltages of 120V or less applied to cells for durations of 20 microseconds to many milliseconds. For applications of electroporation to cell volumes, ranges of 10 V/cm to 10,000 V/cm and pulse durations ranging from 1 nanosecond to 0.1 seconds can be applied. In one example, a relatively narrow (μ sec) high voltage (200V)pulse can be followed by a longer (>msec) lower voltage pulse (<100V). The first pulse or pulses open the pores and the second pulse or series of pulses assist in the movement of the BoNT-LC across the cell membrane and into the cell.

[0067] Certain factors affect how a delivered electric field will affect a targeted cell, including cell size, cell shape, cell orientation with respect to the applied electric field, cell temperature, distance between cells (cell-cell separation), cell type, tissue heterogeneity, properties of the cellular membrane and the like.

[0068] Various waveforms or shapes of pulses may be applied to achieve electroporation, including sinusoidal AC pulses, DC pulses, square wave pulses, exponentially decaying waveforms or other pulse shapes such as combined AC/DC pulses, or DC shifted RF signals such as those described by Chang in *Cell Poration and Cell Fusion using an Oscillating Electric Field*, Biophysical Journal October 1989, Volume 56 pgs 641-652, depending on the pulse generator used or the effect desired. The parameters of applied energy may be varied, including all or some of the following: waveform shape, amplitude, pulse duration, interval between pulses, number of pulses, combination of waveforms and the like.

[0069] 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.

[0070] 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.

[0071] 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.

[0072] 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.

[0073] Yet another way in which ultrasound waves can be characterized is by the amplitude of their peak negative pressure. High acoustic pressure or HIFU applications employ waves with peak amplitudes in excess of 10MPa. Low acoustic pressure ultrasound will generally have peak negative pressures in the range of 0.01 to 5.0 MPa. Diagnostic ultrasound equipment, for example, will generally have a peak amplitude less than 3.0MPa.

[0074] Both high and low acoustic pressure ultrasound systems generally operate within the frequency range of 20KHz - 10.0 MHz. Interventional applications (such as in blood vessels) operate clinically up to about 50 MHz. Also ophthalmologic applications up to about 15 MHz. Diagnostic imaging typically uses frequencies of about 3 to about 10 MHz. Physical therapy ultrasound systems generally operate at frequencies of either 1.0MHz or 3.3MHz.

[0075] 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.

[0076] 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.

[0077] It should also be appreciated that any embodiment employing ultrasonic energy and ultrasound transducers can alternatively be configured as a microwave energy system using microwave antennas. For

example, the embodiments disclosed herein relating to delivering energy from an external mask equipped with ultrasound transducers can also be configured to deliver microwave energy using one or more microwave antennas.

[0078] A schematic example of the methods of the present invention are shown in Figures 2A, 2B, 3A, 3B and 4 in a simplified single cell model. A targeted cell, e.g., an epithelial or goblet cell of the type which line the nasal cavity membrane, is shown in Figure 2A. Fragmented neurotoxin such as BoNT-LC (LC) is introduced into the vicinity of the targeted cell as depicted in Figure 2B. An energy field (EF) is applied in accordance with the present invention resulting in the transfer of the BoNT-LC to the intracellular matrix (cytosol or cytoplasm) as shown in Figures 3A and 3B. Once this transfer has occurred, the release of acetylcholine from the presynaptic neurons at the neuromuscular junctions of the epithelial or goblet or other target cells is then blocked or disrupted. Once energy application is discontinued, the pores in the cell membrane recover or close as depicted in Figure 4.

[0079] The terms “poration” and “permeabilization” will also cover forms of cellular sonoporation. Just as pulses of high voltage electricity can open transient pores in the cell membrane, ultrasonic energy can do the same. See for example Guzman et al. “Equilibrium Loading of Cells with Macromolecules by Ultrasound: Effects of Molecular Sizing and Acoustic Energy”, *Journal of Pharmaceutical Sciences*, 91:7, 1693-1701, which examines the viability of ultrasound to deliver molecules of a variety of sizes into target cells. In addition, techniques for nebulizing fluids and aqueous drugs are well known in the art, and as such, devices of the present invention may be adapted to introduce a BoNT-LC solution to a target region, such as the nasal passages and then effect selective membrane transport of the BoNT-LC into the cell using sonoporation.

[0080] To achieve the goals of the present invention, it may be desirable to employ methods and apparatus for achieving cell membrane permeabilization via the application of an energy source, either from a catheter located directly in the vicinity of the targeted cells, or an externally focused energy system. For purposes of this specification, the term “catheter” may be used to refer to an elongate element, hollow or solid, flexible or rigid and capable of percutaneous introduction to a body (either by itself, or through a separately created incision or puncture), such as a sheath, a trocar, a needle, a lead. Further descriptions of certain electroporation catheters are described in United States Provisional Patent Application No. 60/701,747 (Attorney Docket No. 020979-003500US) and Non-provisional Patent Application No. 11/459,582 (Attorney Docket No. 020979-003510US), the full disclosures of which are expressly incorporated herein by reference.

[0081] Figures 5 and 5A-5B depict a system utilizing an electroporation catheter for selective electroporation of targeted cells. In certain configurations of the present invention, voltages may be applied via the electroporation catheter to induce reversible electroporation at the same time as the catheter delivers the fragmented neurotoxin to the targeted region.

[0082] Referring to Figure 5, electroporation catheter system 20 comprises a pulse generator 24 such as those generators available from Cytropulse Sciences, Inc. (Columbia, MD) or the Gene Pulser Xcell (Bio-Rad, Inc.), or IGEA (Carpi, Italy), electrically connected to a catheter 22 having a proximal end and a distal region 26

adapted for minimally invasive insertion into the desired region of the body as described herein. The catheter further comprises an electroporation element 28 at the distal region thereof. The electroporation element consists for example of a first electrode 30 and a second electrode 32 operatively connected to the pulse generator for delivering the desired number, duration, amplitude and frequency of pulses to affect the targeted cells. These parameters can be modified either by the system or the user, depending on the location of the catheter within the body (intervening tissues or structures), and the timing and duration of reversible cell poration desired.

[0083] Figure 5A depicts an arrangement of electrodes 30 and 32 that produces an electric field concentrated in a lateral direction from the catheter body whereas, Figure 5B shows a device with electrodes 30 and 32 configured to create a more uniform electric field about the shaft of the catheter body. Further catheter device and electrode configurations are shown in Figures 6A-6D. Figure 6A depicts an elongate catheter 40 having a first and second electrode (42 and 44) near the distal tip thereof, and including a monitoring or stimulation electrode 46 in the vicinity of the active porating electrodes for localizing the treatment area. In some embodiments, the monitoring or stimulating function may be performed by one or more of the treatment electrodes. The catheter device may have an optional sharp tip 48 to facilitate percutaneous introduction. Figure 6B is a similar catheter device, but is further adapted to be steerable, or articulate at a region 53 near the distal end of the device. Such steering ability enables the operator to introduce the device into tight or tortuous spaces (such as the bronchial passages, or cardiovascular vessels) so that optimal placement of electrodes 52, 54 and 56 of the device at the target location may be achieved.

[0084] Figure 6C depicts a further embodiment of the catheter device described above, that includes an injection element such as needle 62 to allow for the injection of a therapeutic agent such as a fragmented neurotoxin before, during or after the application of the pulsed energy or electroporation. The injection element may be a needle as shown in Figure 6C, an infusion port, or other infusion means. Electrodes 64, 66 and 68 are provided as discussed with respect to Figs. 6A and 6B.

[0085] Figure 6D depicts an alternative embodiment of the present invention, showing a catheter device 70 having electrode elements (72 and 74) that are adapted to extend laterally from the main catheter body, and in some cases, penetrate the surrounding tissue prior to application of energy. In doing so the depth and direction of the energy field created by the electroporative process, may be further controlled. A reference electrode 76 may also be provided.

[0086] Figure 7 depicts an embodiment of the present invention utilizing an ultrasonic element that may be particularly useful in delivery of the BoNT-LC to nasal tissue that provides a broad but targeted transport of the LC across the epithelial and goblet cell walls. In this device, ultrasound energy is delivered to the distal end 92 of the catheter device 90 via an ultrasonic waveguide that is operatively connected to an ultrasound energy source (U/SES) connected by cable 94. The LC fragment would be delivered from source 96 via the same lumen as the waveguide, or via a separate lumen that exits the distal tip of the device. In operation, the ultrasonic energy would cause the LC solution to be nebulized, forming mist clouds 98 within the lung, as

shown in Figure 8. The mist itself, in the appropriate concentrations, may act as an ultrasound coupler, conveying the ultrasonic energy to the wall of the lung or other targeted cellular structures, causing sonoporation of the targeted cells whereby the LC fragment is transmitted across the cell membranes to become an effective neurotransmitter blocker. In an alternative embodiment, an ultrasonic transducer may be located directly at the tip of the delivery device, eliminating the need for a wave guide. Various catheters useful for delivering vibrational energy to tissue are described in United States Patent 6,361,554 and 6,464,680 to Briskin, 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.

[0087] Any of the catheter devices described herein, or described in the contemporaneously filed United States Provisional Patent Application No. 60/701,747 (Attorney Docket No. 020979-003500US) and Non-provisional Patent Application No. 11/459,582 (Attorney Docket No. 020979-003510US), previously incorporated by reference in their entirety, may be adapted to include an energy delivery element such as those described herein for purposes of providing a membrane transport system for delivery of a toxin fragment of neurotoxin. In addition, certain catheter devices and methods such as those set forth in United States Patents 5,964,223 and 6,526,976 to Baran may be adapted to include energy transmission elements capable of producing a porative effect at the cellular level, including electrodes, ultrasonic elements and the like, for treatment in the nasal passages.

[0088] 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.

[0089] It is within the scope of the present invention to deliver the toxin, the energy, or both, non-invasively. For example, as illustrated in Figure 9, the patient may draw the toxin into the nasal cavity from a hand-held dispersion device DD. After a sufficient amount of the toxin has been infused into the nasal cavity, a separate hand-held transducer TD connected to an appropriate power supply PS will be energized and applied to the nasal cavities by passing the transducer over the appropriate regions of the forehead and nose. Optionally, the transducer can have a focused output so that the acoustic energy is focused in an appropriate depth beneath the skin surface. Typically, from about 0.1 cm to 2 cm.

[0090] While the toxins and porating energy of the present invention may be delivered to the nasal cavity in a variety of ways, the following provides a number of specific examples of catheters and other structures for delivering toxins to preselected portions of the nasal cavity. For example, as shown in Figure 10, a balloon catheter 100 may be provided with a porous balloon 102 at its distal end. The balloon would be porous over at least a portion of its body so that solution delivered to inflate the balloon, which would contain desired levels of the toxin or toxin fragment, would release the solution through the balloon at a controlled rate. By

further providing one or more ultrasonic transducers 104 within the balloon, optionally mounted on the catheter body, ultrasonic poration energy can be delivered to the adjacent nasal membranes which are receiving the toxin solution. As illustrated in Figure 10, the toxin is being delivered to a lower surface of the inferior meatus IM to localize and enhance cellular delivery at the balloon tissue interface. Alternatively, the balloon could carry the toxin in a releasable form over its exterior surface in order to deliver to any adjacent tissue structure. In some instances, the toxin could be carried or encapsulated in delivery vesicles which are preferentially fractured by the same acoustic energy which permeabilizes 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.

[0091] In all the above cases, the ultrasonic transducers can be configured in order to selectively deliver the energy to desired portions of the adjacent tissues. For example, in the embodiment of Figure 10, the internal transducers 104 can be configured to focus the ultrasonic energy generally upwardly (as viewed in Figure 10) in order to preferentially deliver the toxins into the inferior meatus IM while minimizing delivery elsewhere.

[0092] 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.

[0093] 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, MM or ultrasound imaging.

[0094] Referring now to Figure 11, a front view of particular balloons placed as generally shown in Figure 10, is shown in more detail. A single balloon 102 can be around the structures H in the inferior meatus. Alternatively, a pair of balloon structures 103 may be placed in the same space, as shown in the right hand portion of Figure 11. Optionally, the balloons could be formed from an elastic material, such as a silicone, urethane, latex, thermoplastic elastomers, or other materials where the material is treated to be appropriately porous, for example by laser drilling. Alternatively, the balloons could be formed from non-distensible materials which are 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.

[0095] Referring now to Figures 12A, 12B, and 12C, as an alternative to inflatable balloons, toxin delivery structures may be made to be various shapes, for example a generally “flattened” balloons 102, whose profile

is narrower in one axis than the other, for example by placement of an internal nitinol or other elastic frame or scaffold, or a stainless steel wire 103 that is fed into the balloon outer structure to form such shape, within a suitable porous cover or membrane. Thus, the structure 120 may be expanded by the scaffold 122 after release from a delivery tube 124. The structures can be used to deliver energy and/or toxin in any of the ways described previously with respect to balloons, including by carrying a transducer or electrode on or within the structure and delivering a toxin solution from the interior of the self-expanding structure through a porous portion of the structure wall.

[0096] In some instances, it will be desirable to protect the olfactory bulb of the sinuses from treatment with the toxin solutions of the present invention. Referring now to Figures 13 and 14, the porous portion of a delivery balloon 102 can be positioned so that the remaining non-porous segment is in contact with the olfactory bulb (Figure 13). Thus, when the balloon is inflated and the toxin solution delivered, it will not be directed at the tissues of the olfactory bulb (OB).

[0097] As shown in Figure 14, which is a cross-sectional view of Figure 13, instead of rendering the top portion of the delivery balloon non-porous, it would be possible to simply refrain from filling the top portion with the toxin solution and/or a coupling solution. This can be achieved by filling the balloon with a known volume of air 111 in addition to the toxin solution. With the patient positioned appropriately, the air will fill the portion of the balloon in proximity to the olfactory bulb, excluding this tissue from toxin contact. Additionally, the air bubble may act as an ultrasound insulator to inhibit energy delivery to the non-targeted or protected tissue. Thus, delivery of the toxin to the region around the olfactory bulb and/or delivery of the energy to the region around the olfactory bulb can be partially or wholly prevented.

[0098] Referring now to Figures 15 and 16, the balloon may be sized and positioned to target an area of high epithelial or goblet cell (G) concentration, for example in the back of the nasal passages in the area of the nasopharynx. By targeting this area of the nasal membrane, a high percentage of mucus-secreting epithelial or goblet cells can be treated with a device which is relatively small and which may carry a relatively low infusion volume and require less energy. Moreover, the olfactory bulb is inherently protected with this technique since the balloon is positioned well away from that area. If desired, of course, additional shielding, shaping or other protective balloons could be positioned between the olfactory bulb and the toxin and energy delivering components of the present invention.

[0099] As shown in Figure 17, direct infusion and treatment of particular sinuses may be effected using relatively small occlusion balloons 102 which occlude and isolate natural openings into those sinuses. Once the balloon is in place and the occlusion balloon employed, the toxic solution can be delivered by infusion, dispersion, or other conventional techniques. Once the toxin solution is present in the sinus, all or a portion of the membrane of the sinus can then be treated with an external or other ultrasonic source.

[00100] For example, as shown in Figures 18 and 19, the external transducer may comprise a mask which conforms to the nose and optionally over the sinuses, where the mask carries one or more ultrasonic or other acoustic transducers (TD) adapted to deliver energy transcutaneously into the sinuses. The mask may

comprise a plurality of individual transducers (TD), which may be made from one, two, or several generally continuous piezoelectric films which are formed over or laminated within the mask. Alternatively, multiple individual piezoelectric crystal transducers can be built into the mask.

[00101] 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.

[00102] Referring now to Figures 20 and 21, a catheter 40 is placed at the posterior outlet of the nasal passages in the region of the nasopharynx. The catheters configured to occlude outflow from these sinuses and passages into the throat. As shown in Figure 20, a balloon catheter 102 or other occlusion device could be configured to block such passage. As shown in Figure 20, the catheter is delivered in through the mouth and guided into the posterior portion of the nasal cavities, typically using a guidewire. Once the nasopharynx of the posterior portion of the nasal cavity is occluded, toxin solution (BoNT) can be infused through the occluding catheter lumen, or through a separate infusion catheter or tube, in order to treat substantially the entire sinus and/or nasal cavity membrane at once (Figure 21). When the toxin solution is introduced through the catheter at the posterior region of the cavities, it will frequently be desirable to occlude the nostrils, for example using a nasal clip 105.

[00103] As shown in Figures 22 and 23, specially designed nose plugs 105 can be provided with air bleed valves 106 which are used to occlude the nostrils in order to evacuate or bleed air from the nasal passages while filling the passages with the toxin solution. The nose plugs 105 could optionally include ultrasonic transducers in order to deliver ultrasonic or other acoustic energy into the solutions entrapped within the nasal cavities using the nostril plugs. Alternatively, of course, the ultrasound or other acoustic energy could be delivered from an external transducer as described previously.

[00104] Referring now to Figures 24 and 25, an alternate occlusion catheter system for nasopharynx occlusion is illustrated. An occlusion catheter 40 is introduced through a nostril, where the tip includes an ultrasonic transducer to provide sonoporation. A nostril plug 105 is provided proximally on the shaft of the catheter, while the cavity is blocked with a separate occlusion balloon 102 introduced through the mouth and into the posterior nasopharynx region. The toxin solution can be introduced into the cavity through either the catheters which pass through or reside in the nostrils or the catheter which occludes the posterior nasopharynx.

[00105] Figures 26 and 27 illustrate how a catheter 40 with side holes 108 can be configured to deliver toxin away from the olfactory bulb, even when used alone without separate nasopharynx occlusion catheters. The

catheters preferably carry an occlusion balloon or other structure near their distal ends 107 to prevent or inhibit toxin from reaching the olfactory bulb

[00106] 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.

[00107] Referring to Figure 29, the toxin may be delivered as a conventional nasal spray (BoNT), as mentioned hereinbefore, and the poration energy can be delivered through a face mask. The poration energy might alternatively be delivered as ultrasound energy delivered through a mist, without direct contact to the tissues. This mist might be the same mist which contains the toxin, or it might be a different, possibly denser mist delivered at some time after the toxin has been delivered. The delivery devices for these mists might be introduced a relatively short distance into the nose. Thus the entire therapy might comprise the specialized delivery of two mists.

[00108] Referring now to Figures 28 and 30, an infusion catheter 40 can be engaged against the ostium of a sinus cavity (Figure 28). A guidewire 110 may then be advanced through the infusion catheter and into the sinus cavity (Figure 30). The guidewire can be formed as a wave guide to deliver ultrasonic energy, as an electrode to deliver electroporation energy, or as an infusion wire to deliver the toxin solution itself. The wire could further be configured to perform two or more of these functions. The catheter could be configured to act as a counter electrode when the guidewire is acting as an electroporation electrode in bipolar energy delivery.

[00109] Referring now to Figure 31, the catheter advanced to the os of a sinus cavity, as illustrated, can also be used to deliver a helical or randomly shaped delivery tube 112 which is deployed within the sinus. Preferably, the tube will expand to engage a major portion of the wall of the sinus cavity. Alternatively, the geometry could be selected to selectively engage only a particular portion of the wall of the sinus cavity. The wire can further be adapted to deliver energy, either electrical or acoustic, and/or may be configured to deliver and distribute the toxin solution within the cavity. In still other configurations, the wire could be coated to deliver the agent to the wall, and still further the wire could deliver ultrasound gels, saline, degassed water, or the like, to enhance coupling of a separate ultrasonic energy source.

[00110] Referring now to Figure 32, two or more deployment catheters can be used to advance any of the guidewires or other wire structures discussed above. As illustrated in Figure 32, an electrode basket 113 may be deployed through the delivery catheter. Alternatively, a multiply tined catheter 114 structure may be delivered through the delivery catheter.

[00111] Figures 33 and 34 illustrate a device for applying BoNT to the treatment area within the nasal cavity. This device comprises a handle 115 having a proximal section, a body and a distal section. The body of the handle comprises a first member 116 and a second member 117. The first member and second member merge at the proximal section and terminate at the distal section, wherein the distal section comprises a first end and second end corresponding to the first member and second member. The device further comprises applicator tips 118 connected to each of the first end and second, wherein the applicator tips are configured for insertion into the nasal passageway, as shown in Figure 35.

[00112] Once within the nasal cavity, the applicator tips 117 and 118 can apply BoNT to the nasal passageway and, specifically, the turbinates along the nasal wall. The BoNT can be applied or affixed to the applicator tips as a liquid solution, gel, foam, cream, lotion and/or a lyophilized compound prior to being positioned within the nasal passageway. Alternatively, as illustrated in Figure 36, the handle can be configured with an infusion channel 119 for delivering the BoNT to the applicator tips following placement in the nasal passageway. In this configuration, the handle may further comprise an access port at its proximal section that is in fluid communication with a BoNT source.

[00113] As shown in Figure 33, the loop member may be configured to provide an outward lateral force such that the applicator tips 118 are firmly contacted against the nasal turbinates when placed in the nasal passageway. With reference to Figure 37A, the operator would apply inward pressure in the direction of the arrows to the handle to achieve a compressed configuration, as shown in Figure 37C, prior to inserting the applicator tips into the nose. Once the applicator tips of the device are properly inserted into the nasal passageway, this pressure would be released such that the outward bias in the handle transitions the handle from a compressed configuration to an expanded configuration, as shown in Figure 37B, wherein the applicator tips are pressed against the nasal turbinates. The applicator tips can be held against the turbinates by the outward bias for sufficient time to allow a therapeutically effective amount of BoNT to be absorbed by the nasal cavity wall.

[00114] This outward bias may be achieved by spring loading the device 120. Specifically, the handle itself may comprise a spring element, wherein the handle is dimensioned and configured with a residual spring force that exhibits this outward bias. Additionally or alternatively, the handle may comprise a material with mechanical properties to facilitate the spring action with little to no inelastic deformation resulting from the inward pressure applied by the operator. For example, at least a portion of the proximal section of the handle may comprise spring steel, stainless steel, nitinol, or MP35N alloy. Alternatively, as illustrated in Figure 38, a spring element 120 that is separate from the handle may be used to apply outward lateral pressure to the first and second members of the handle body.

[00115] To facilitate the insertion of the tip applicator through the nostril and into the nasal passageway, it may be desirable for the applicator tip to initially have a low volume configuration. Once properly positioned in the nasal passageway, it would be desirable for the applicator to have an expanded volume configuration for maximizing contact with the nasal turbinates. In one exemplary embodiment, the tip applicator may

comprise a sponge such that the sponge 121 is in a low volume configuration when dry (Figure 39A) and an expanded configuration when wet (Figure 39B), wherein the sponge 121 is configured to fit securely within the nasal passageway.

[00116] In the embodiment illustrated in Figures 39A and 39B, the dry sponge applicator could be preloaded with lyophilized BoNT and wetted with a liquid (e.g., saline) following placement of the applicator in the nasal passageway. The liquid can be introduced into the nasal passageway using a spray or a catheter, or the BoNT may simply be rewetted by the nasal secretions themselves. Alternatively, as described with respect to Figure 36, the liquid can be infused into the applicator tip through a channel 119 in the device handle. Still alternatively, the liquid infused through the channel can be a solution comprising BoNT, thereby eliminating the need for the dry sponge applicator to be preloaded with BoNT.

[00117] To facilitate the expansion of the applicator tip, thereby maximizing the surface contact between the nasal cavity wall and applicator tip, it may be desirable to incorporate a spring element 122 within the applicator tip 118. The embodiment in Figures 40A and 40B shows an applicator tip comprising a sponge 121 and a spring element 122 in an expanded and compressed configuration. This configuration can be used instead of or in addition to the wet/dry sponge embodiment discussed above.

[00118] The spring element may comprise any type of compressible spring and any number of elastically deformable polymers or metals, including, spring steel, stainless steel, nitinol, and MP35N alloy. As shown in many of the above embodiments, the spring element may comprise a v-shape spring. Alternatively, the spring element may comprise a closed-loop spring 123, as illustrated in Figure 41.

[00119] For embodiments utilizing a spring-loaded applicator tip, it will be necessary to hold the spring 122 in its compressed state until it is properly positioned within the nasal cavity, at which time the spring can be released to allow the applicator to expand into the nasal cavity. In the wet/dry sponge 121 embodiment described with respect to Figures 39A and 39B, a sponge and spring can be selected and matched such that the stiffness of the dry sponge is sufficient to overcome the spring stiffness and hold the spring in a compressed configuration until it becomes wet.

[00120] In another embodiment employing a spring-loaded applicator tip, an actuator can be used to hold the spring in a compressed state. Figure 42 illustrates a spring-loaded applicator tip 124 that is restrained in a compressed state by a slidably-engaged actuator 125. The slidably-engaged actuator may comprise a retractable sheath or collar 126 for holding the spring in its compressed configuration. Once the applicator is positioned within the nasal cavity, the actuator can be retracted to release the spring, thereby expanding the applicator.

[00121] The device may optionally comprise an engagement element 127 for engaging and retracting the actuators on both applicators. Figure 43 shows a device comprising a handle 115, two actuator-equipped applicator tips 124 and an engagement element 127 in contact with each applicator tip actuator 124. The engagement element is configured for movement along the longitudinal axis of the handle, wherein such

movement may engage or retract the actuator resulting in compression or expansion of the spring-loaded applicator tip, respectively.

[00122] It may be desirable for the spring-assisted expansion of the applicator tip to be directionally biased to maximize contact with the wall of the nasal cavity and optimize contact pressure with the nasal turbinates. For example, the spring element can be dimensioned and configured such that the applicator expands laterally towards the turbinates of the nasal cavity. Alternatively or additionally, portions of the applicator tip may comprise an impermeable lining such that delivery of BoNT to certain portions of the nasal cavity is optimized and undesirable migration of BoNT solution is minimized.

[00123] Although toxins can be administered to the body to achieve a therapeutic benefit, the same toxins can cause local and systematic damage to non-targeted body tissues. Accordingly, it would also be desirable for the apparatus to be configured such that only the amount of toxin necessary to treat the nasal cavity is loaded on the applicator tip and applied to the nasal wall. In this embodiment, it would be desirable for the applicator to carry a predetermined quantity of toxin, wherein the predetermined quantity is the amount necessary to provide a therapeutic effect. It would also be desirable for the applicator to be configured such that most, if not all, of the toxin carried on the applicator is delivered to the nasal wall, wherein little to no toxin runs, escapes or migrates to non-target portions of body tissue.

[00124] Additionally, it would be desirable for the applicator to be configured to provide a controlled delivery of toxin to facilitate absorption of the toxin into the walls of the nasal cavity. An applicator providing a controlled delivery of toxin can be configured such that the rate of toxin delivery is proportionate with the rate of BoNT absorption across the nasal membrane. Such a controlled delivery will ensure that the toxin is absorbed into the nasal tissue and not dispersed elsewhere in the body.

[00125] An apparatus for treating a nasal cavity of a patient via a controlled and uniform delivery of BoNT may comprise an applicator having an inner member, an outer member and an impermeable lining, wherein the impermeable lining separates the inner member and outer member. In this embodiment, the outer member serves as a carrier for a toxin (e.g., BoNT). The outer member may comprise any material or structure for carrying BoNT such as an open cell foam (e.g., sponge), mesh pad, porous or perforated balloon, polymeric sheet having microchannels, bioresorbable coating or muco-adhesive surface having wells or open-faced chambers. The outer member may also comprise an array of microneedles to facilitate the passage of BoNT across the nasal membrane. The inner member is configured for occupying space when the applicator is positioned within the nasal cavity such that the outer member is placed in contact with the wall of the nasal cavity. The inner member may be any compliant material such as a sponge, balloon or foam rubber. The impermeable lining (e.g., tetrafluoroethylene) prevents the BoNT from retreating from the outer member to inner member and, accordingly, facilitates the transfer of BoNT from the applicator to the tissue of the nasal wall. As with applicator embodiments that have been previously discussed herein, the outer member can be pre soaked or filled with BoNT solution, infused with BoNT following placement in the nasal passageway, or pre-loaded with freeze-dried BoNT that can be reconstituted with infused saline.

[00126] In one embodiment, both the inner and outer members may comprise balloons, wherein the BoNT is carried in the space between the inner and outer balloons. The outer balloon can be a perforated polymer (e.g., polyethylene terephthalate or expanded polytetrafluoroethylene) for releasing BoNT in a controlled and uniform manner. The inner member can be a compliant balloon, wherein the volume occupied by the inner balloon can be adjusted by injecting a fluid (e.g., air or saline) into the inner balloon. In this configuration, the impermeable lining is comprised of the wall of the inner balloon and the applicator's BoNT carrying capacity is based on the volume of the outer balloon relative to that of the inner balloon. For example, an applicator could be configured to carry less BoNT by increasing the inner balloon's volume relative to the outer balloon's volume.

[00127] In a preferred embodiment, the inner member comprises (1) a low volume configuration to facilitate the applicator's insertion into and placement within the nasal passageway and (2) an expanded volume configuration for pressing the outer member against the walls of the nasal cavity. The expansion of the inner member relative to the outer member can also facilitate the controlled release of BoNT from the outer member. Once the applicator is in its expanded volume configuration, additional fluid can be infused into the inner member to reduce the volume of the outer member relative to the inner member, thereby forcing the BoNT from the outer member. In fact, the expansion of the inner member may be configured such that the resulting stretching and compression of the outer member causes a controlled release of BoNT from the outer member, wherein the rate of BoNT release is proportional to the inner member's rate of expansion. In the embodiment comprising an inner balloon and outer balloon, the expansion of the inner member can be facilitated by the introduction of fluid into the inner member. In other embodiments, the expansion of the inner member can be facilitated by a spring member.

[00128] 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.

[00129] To achieve a more focal treatment, the applicator tip can be equipped with a muco-adhesive pad that is pre-loaded with BoNT solution rather than a sponge. This pad can be configured to optimize the delivery of BoNT to the mucosa. Alternatively, the applicator tip may further comprise a bioabsorbable coating or film carrying BoNT. In this embodiment, the applicator tip may comprise a BoNT-loaded bioresorbable polymer that can be absorbed into the nasal cavity tissue. The tip can be configured such that the BoNT can be delivered to the nasal wall both immediately and as the coating is absorbed into the tissue.

[00130] Similar to the other devices discussed in this application, the device described with respect to Figure 33 and 34 can be used to deliver BoNT-LC to the nasal cavity instead of the BoNT intact molecule. In cases where this device is used to deliver BoNT-LC to the nasal cavity, any of the previously-described, energy-based delivery systems can be used to cause poration in the nasal tissue to facilitate delivery of the

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

[00131] 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.

[00132] For instance, commercially available botulinum toxins (such as Botoxtm - 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.

[00133] The lyophilized powder could also be formed into sheets, ribbons, pellets microspheres, or any other desirable form, and introduced to the target tissues.

[00134] 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.

[00135] 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.

[00136] 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).

[00137] 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.

[00138] 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.

[00139] 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.

[00140] While the above is a complete description of the preferred embodiments of the invention, various alternatives, modifications, and equivalents may be used. Therefore, the above description should not be taken as limiting the scope of the invention which is defined by the appended claims.

CLAIMS

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 applicator configured for applying energy to the target cells under conditions which cause poration of the cell membranes to enhance delivery of the toxin; and
a source of toxin suitable for introduction from the catheter.

ABSTRACT OF THE DISCLOSURE

[00141] Methods and systems for delivering toxin and toxin fragments to a patient's nasal cavity provide for both release of the toxin and delivery of energy which selectively porates target cells to enhance uptake of the toxin. The use of energy-mediated delivery is particularly advantageous with light chain fragment toxins which lack cell binding capacity.

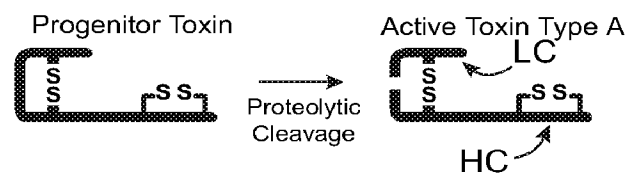


FIG. 1

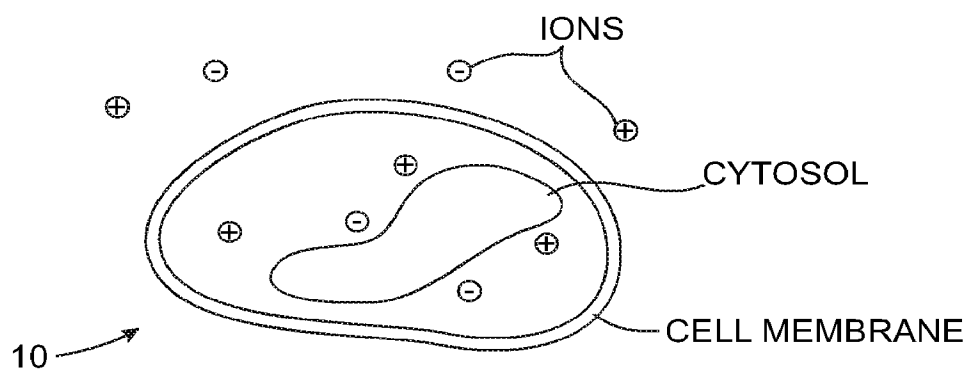


FIG. 2A

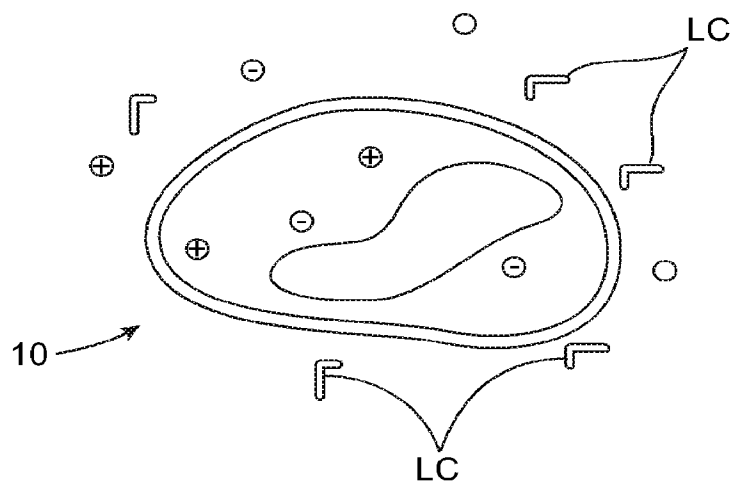
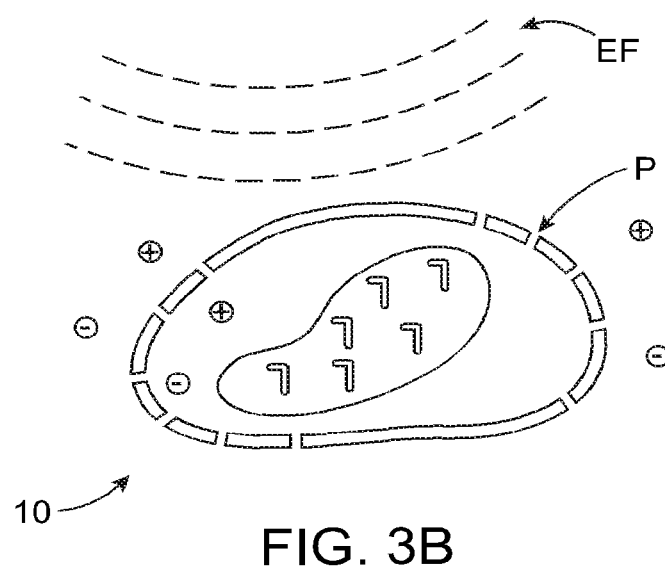
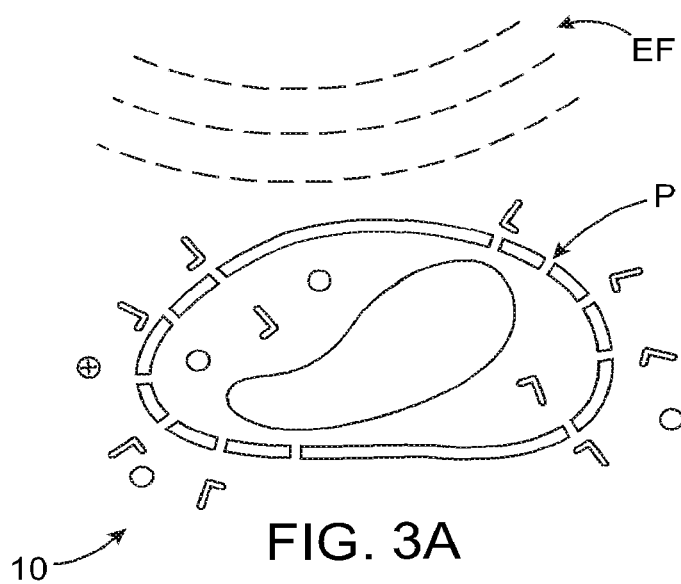


FIG. 2B



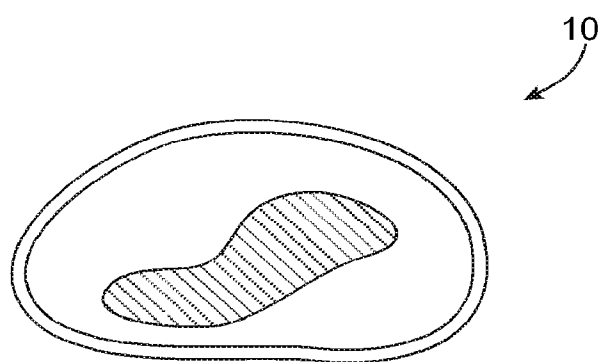
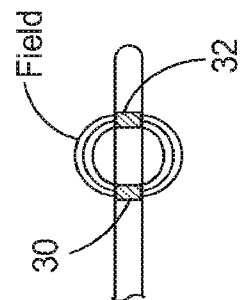
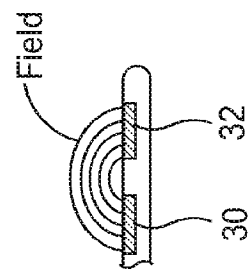
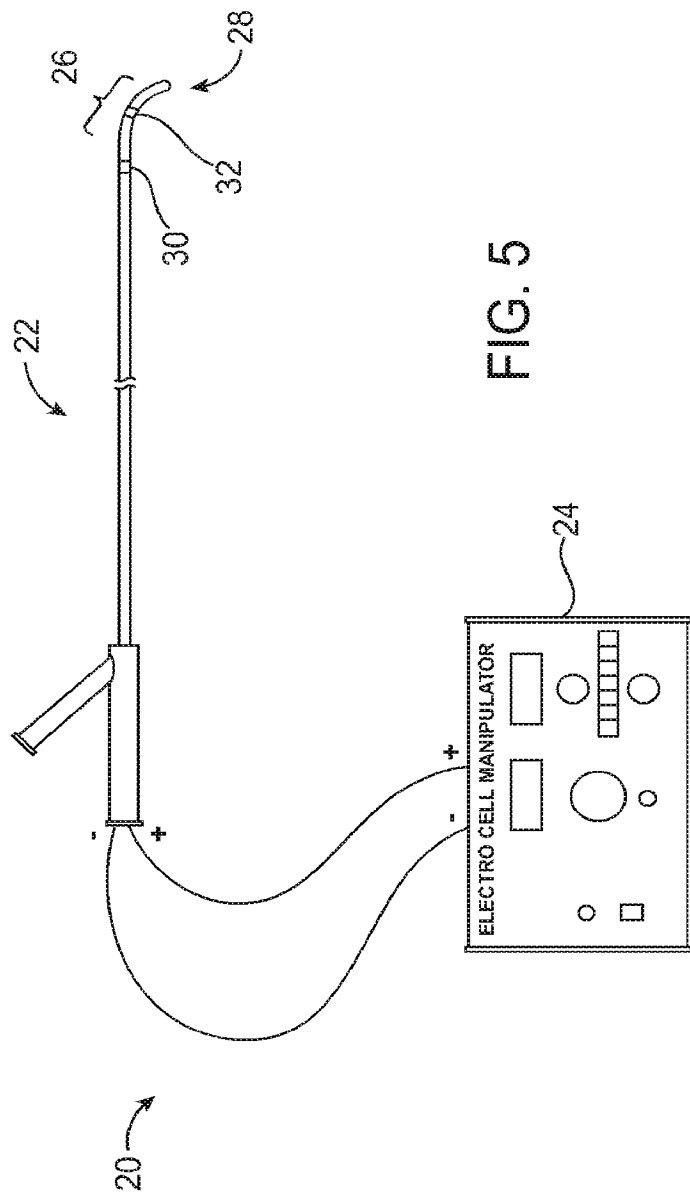


FIG. 4



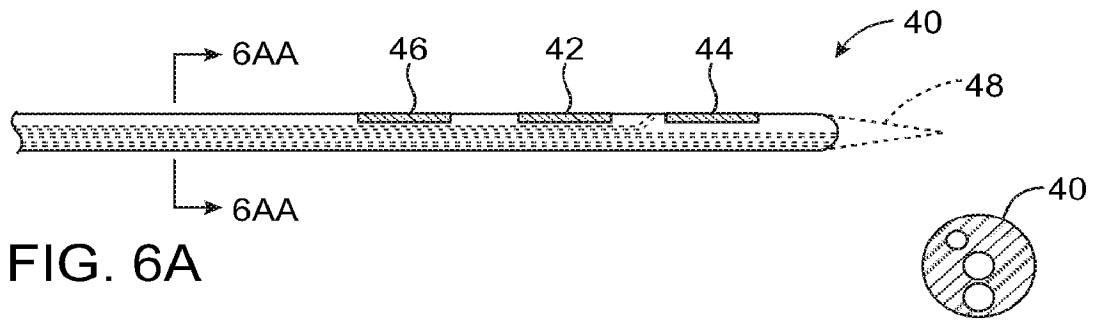


FIG. 6A

FIG. 6AA

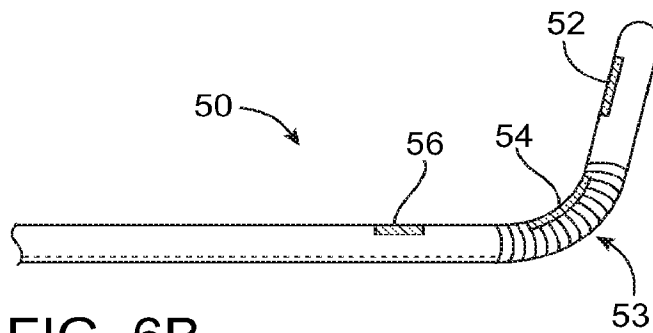


FIG. 6B

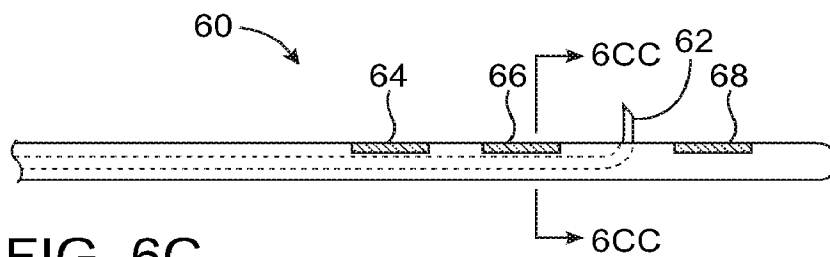


FIG. 6C

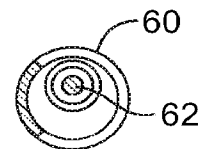


FIG. 6CC

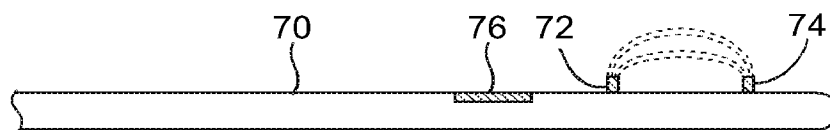


FIG. 6D

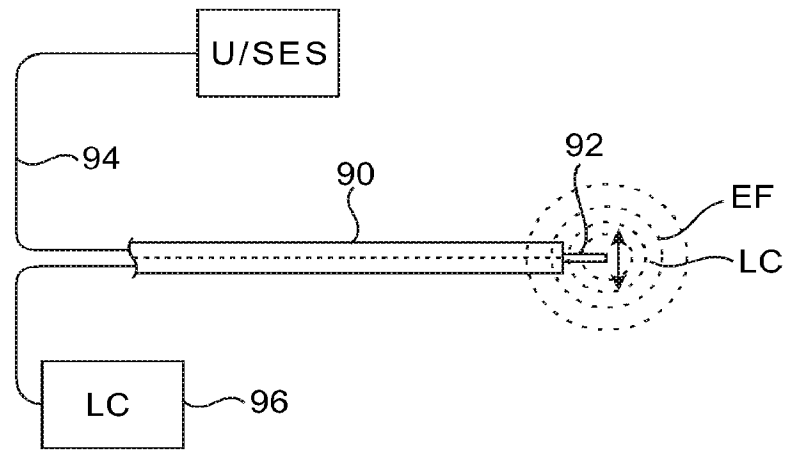


FIG. 7

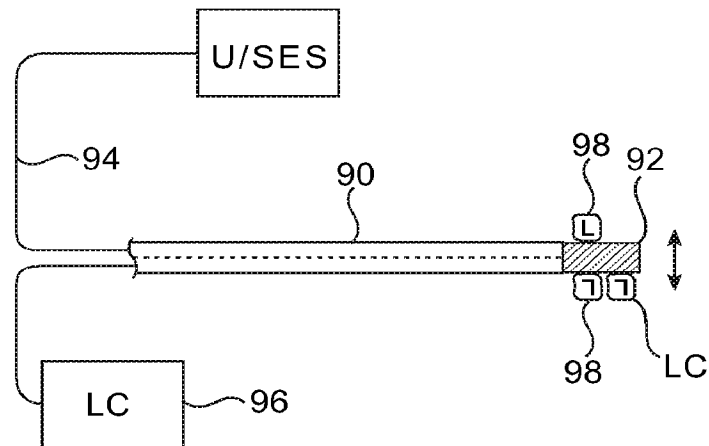


FIG. 8

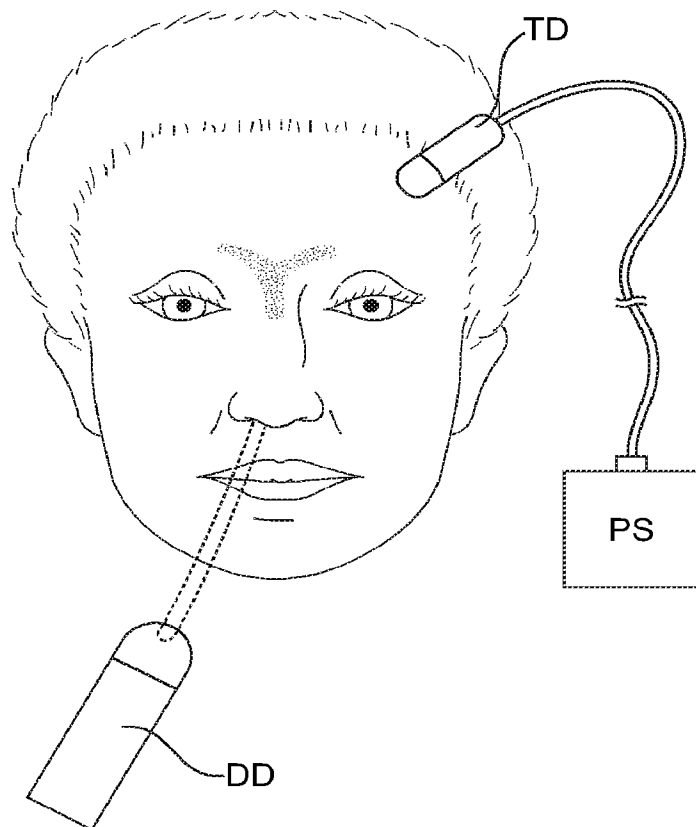


FIG. 9

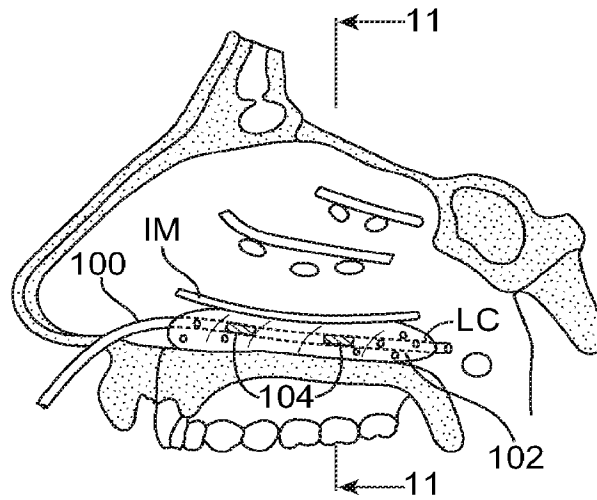


FIG. 10

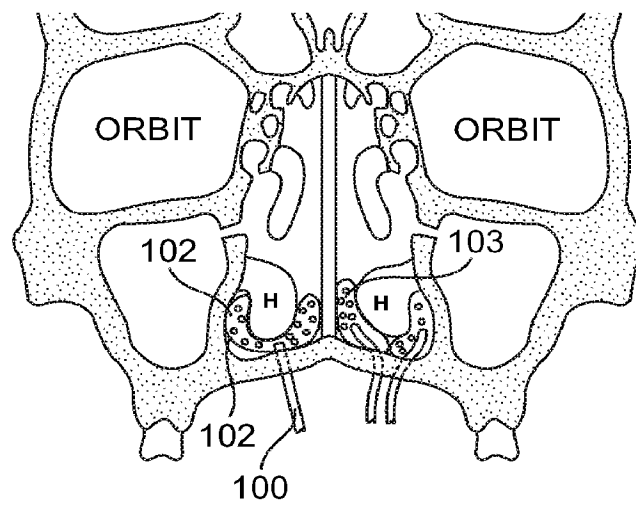


FIG. 11

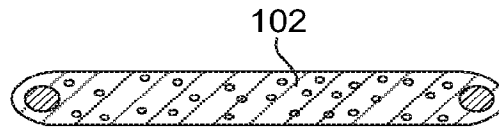


FIG. 12A

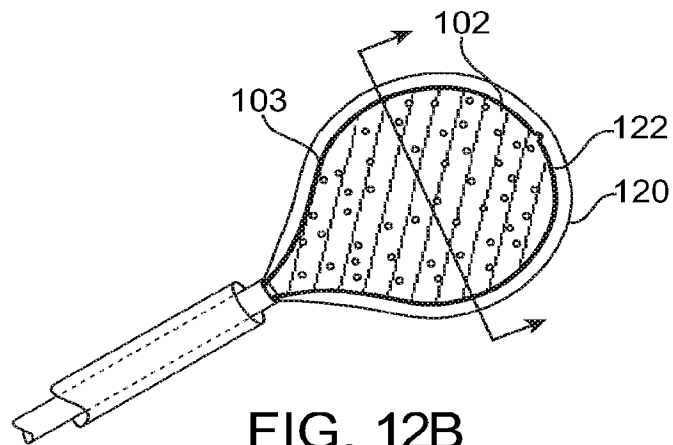


FIG. 12B

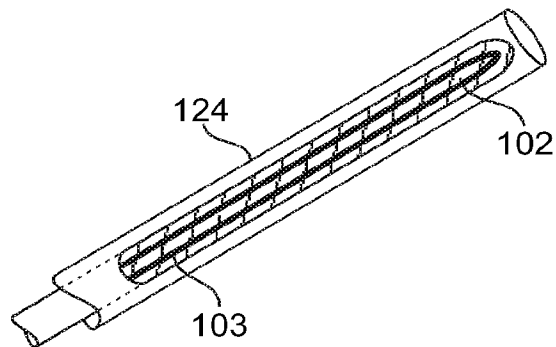


FIG. 12C

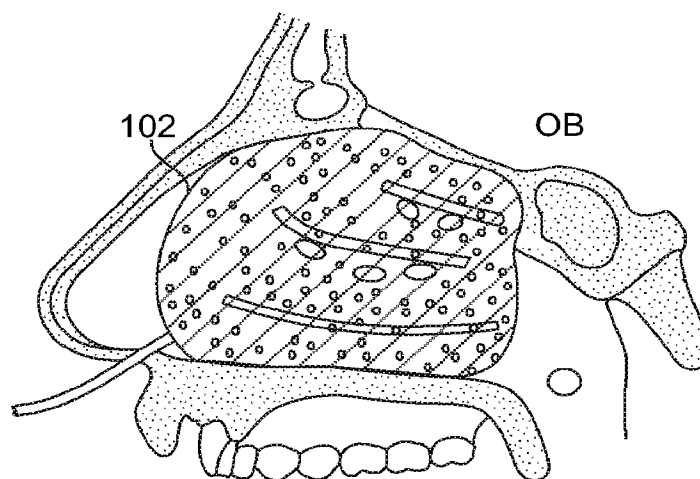


FIG. 13

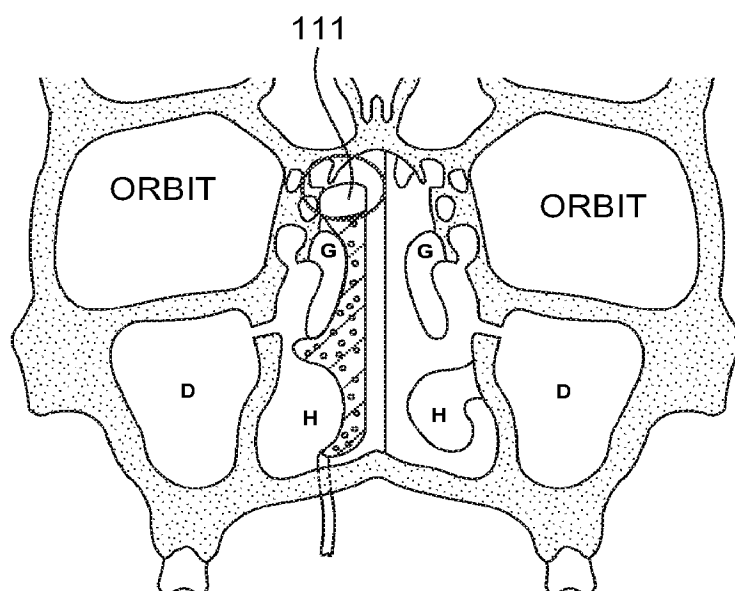


FIG. 14

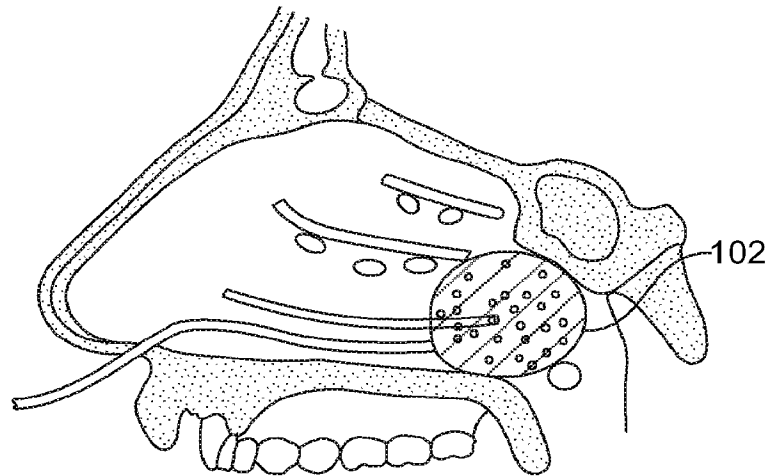


FIG. 15

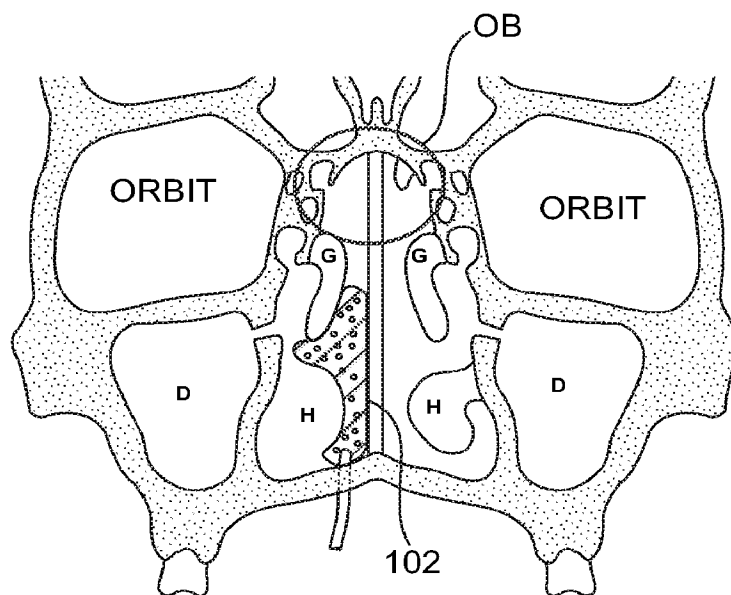


FIG. 16

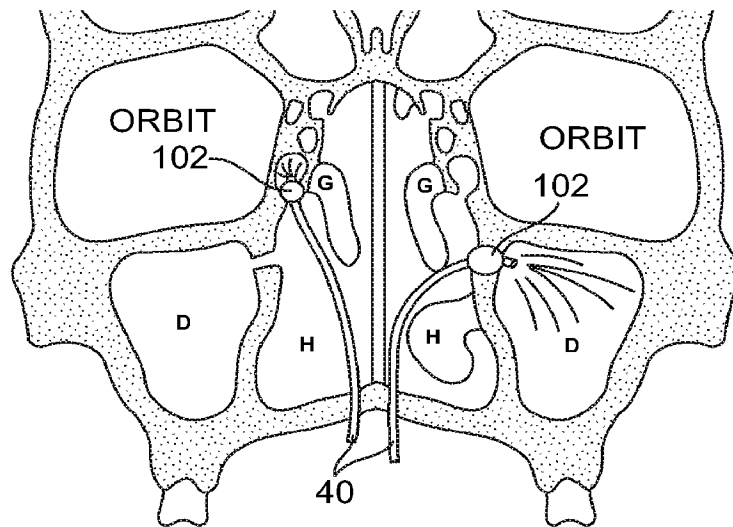


FIG. 17

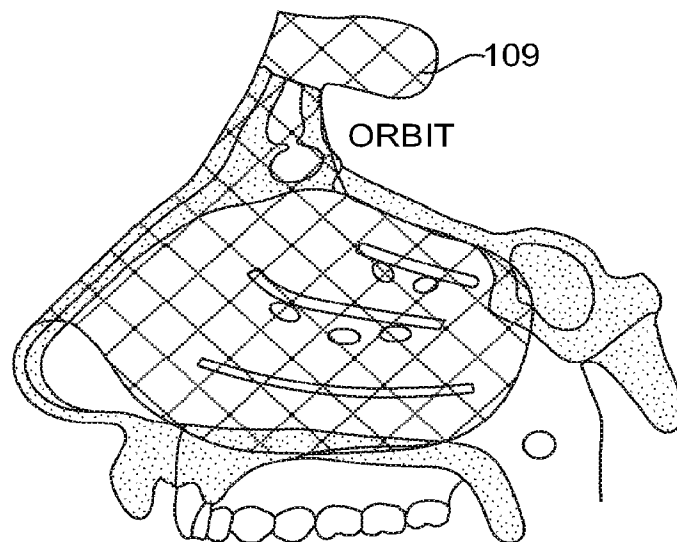


FIG. 18

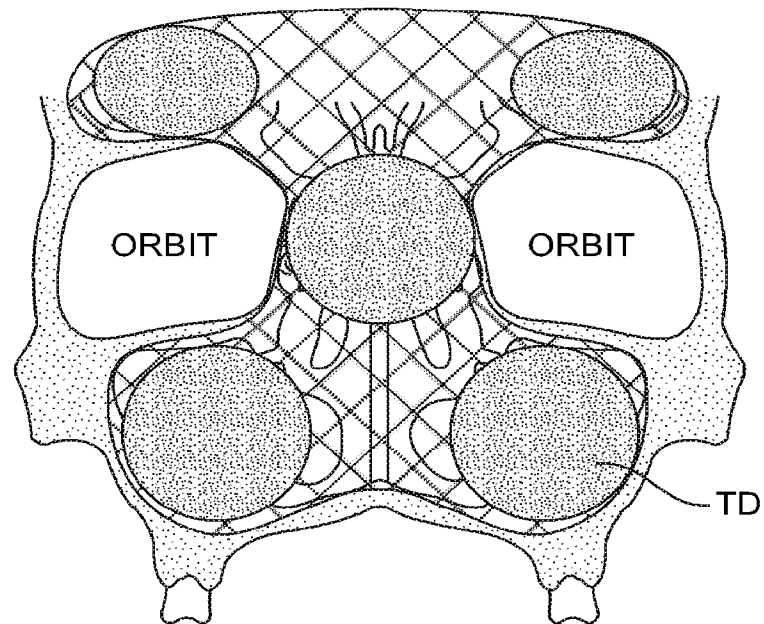


FIG. 19

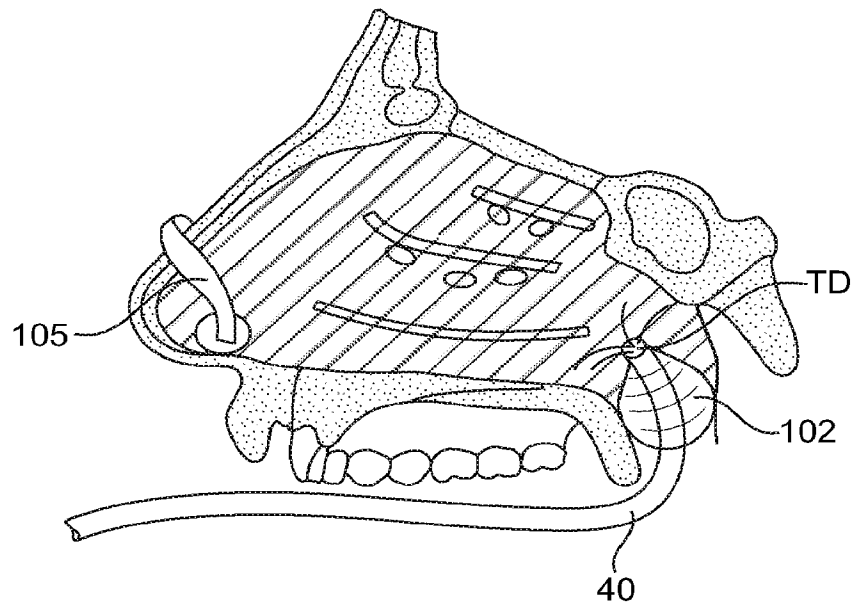


FIG. 20

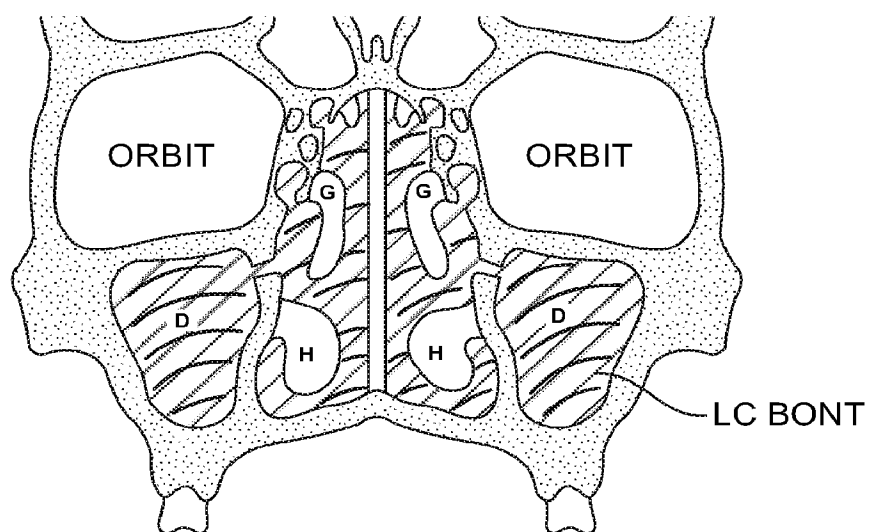


FIG. 21

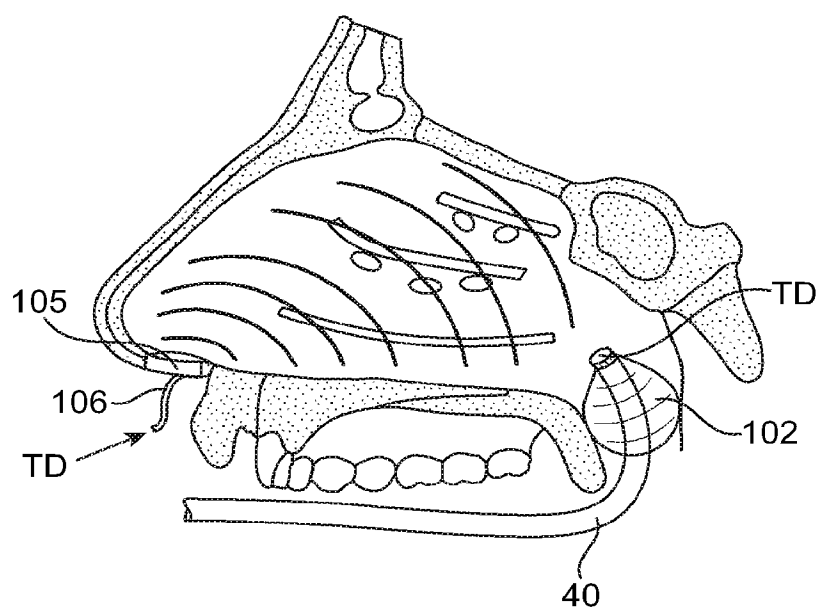


FIG. 22

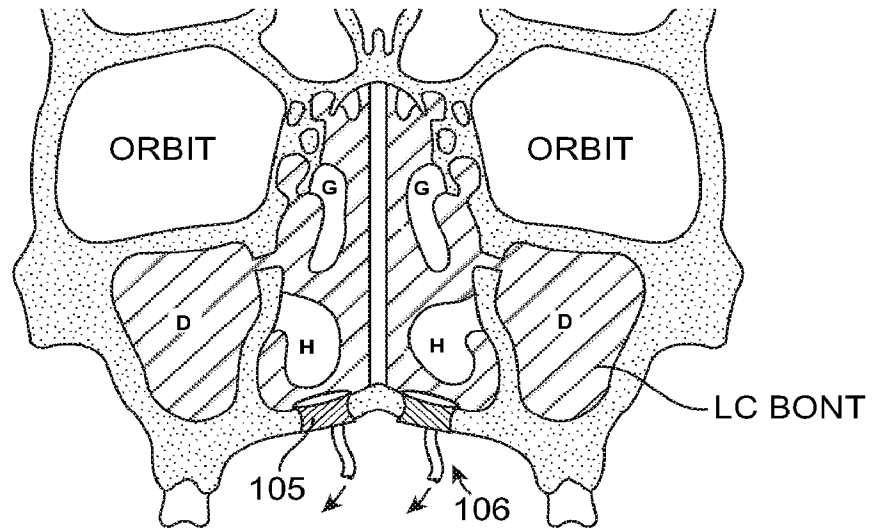


FIG. 23

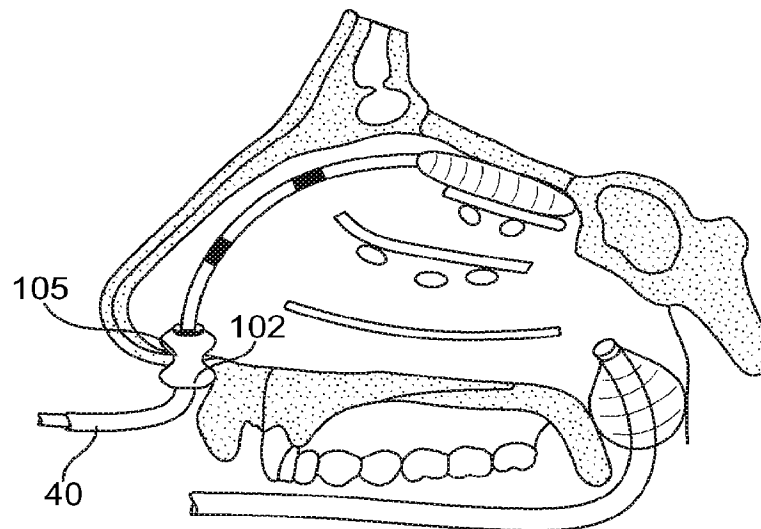


FIG. 24

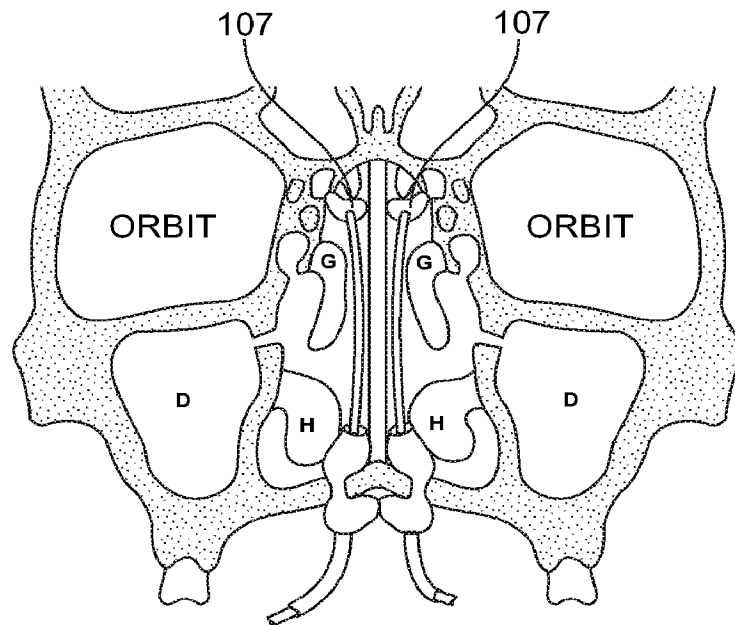


FIG. 25

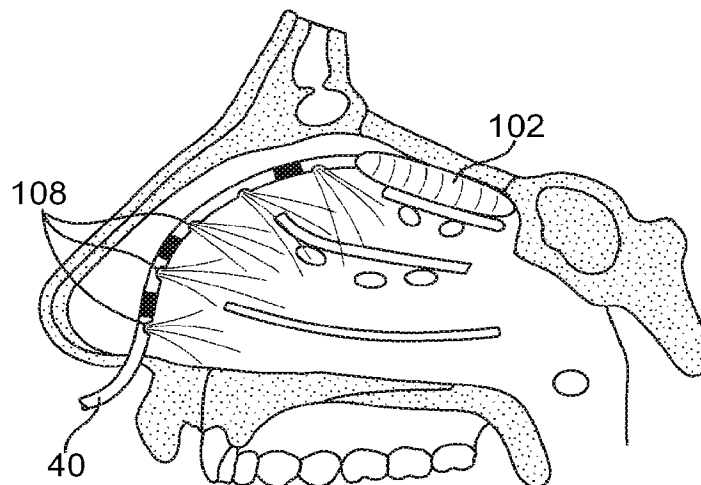


FIG. 26

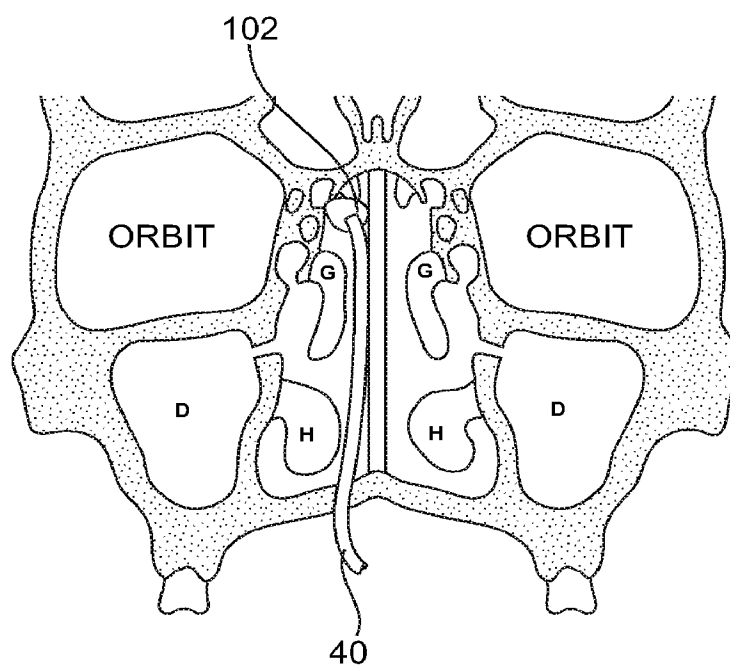


FIG. 27

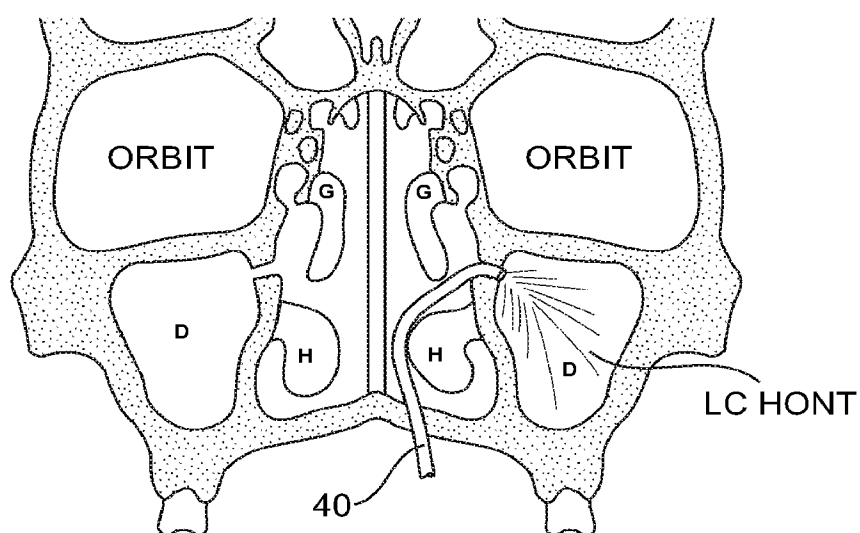


FIG. 28

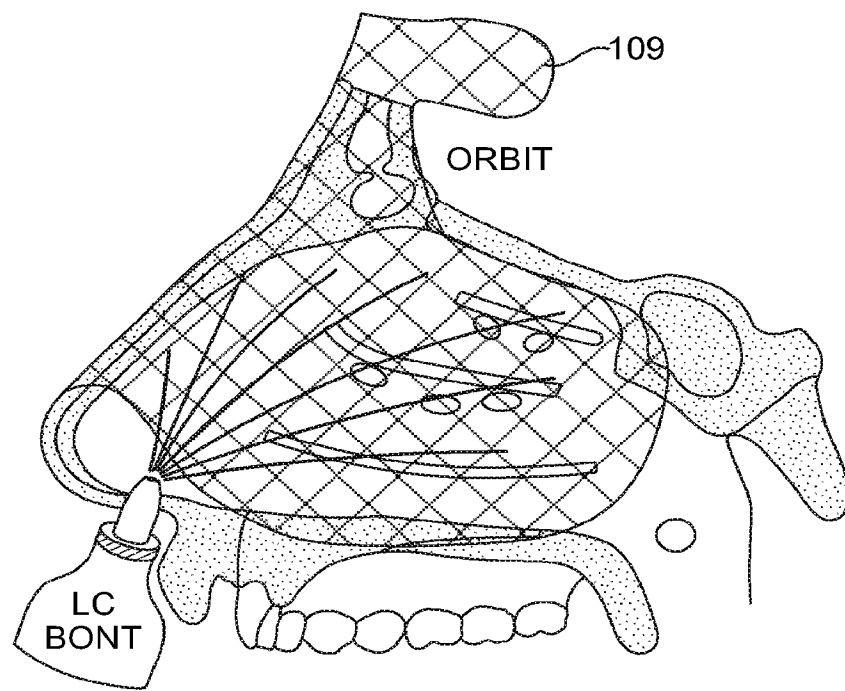


FIG. 29

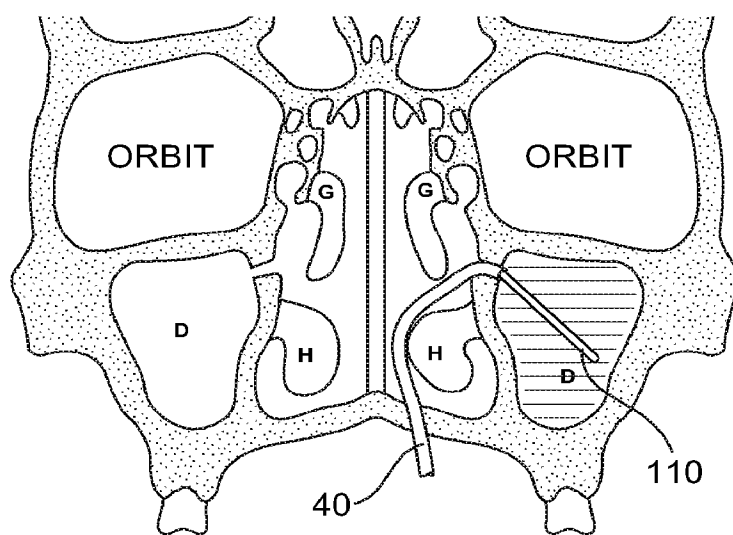


FIG. 30

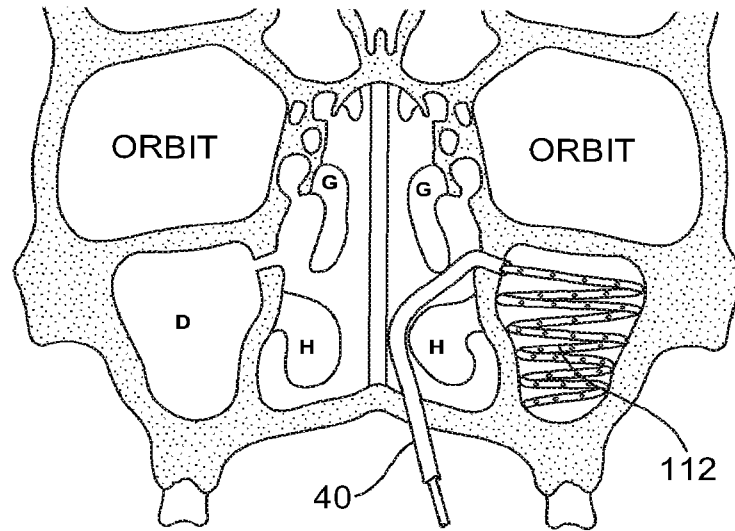


FIG. 31

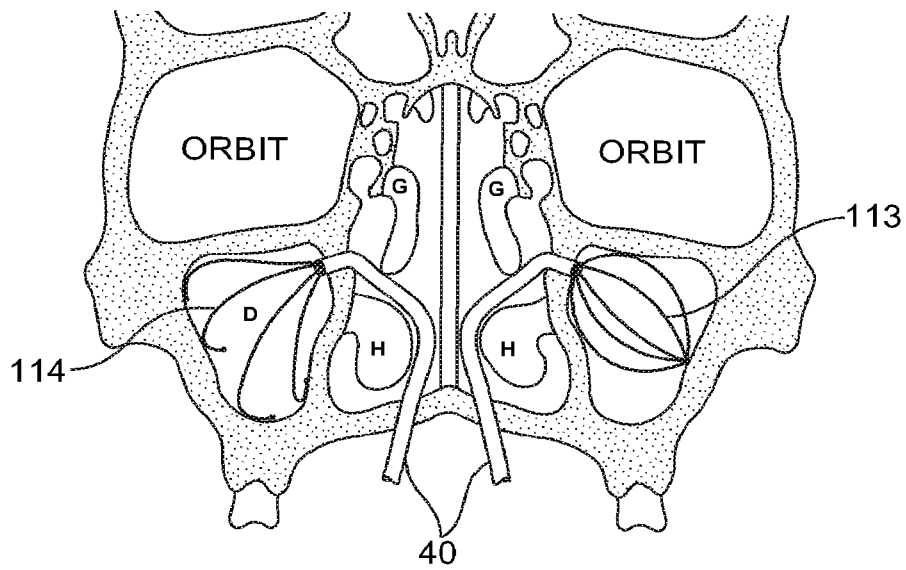


FIG. 32

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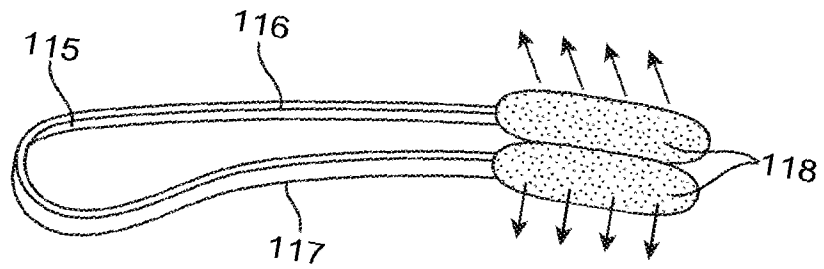


FIG. 33

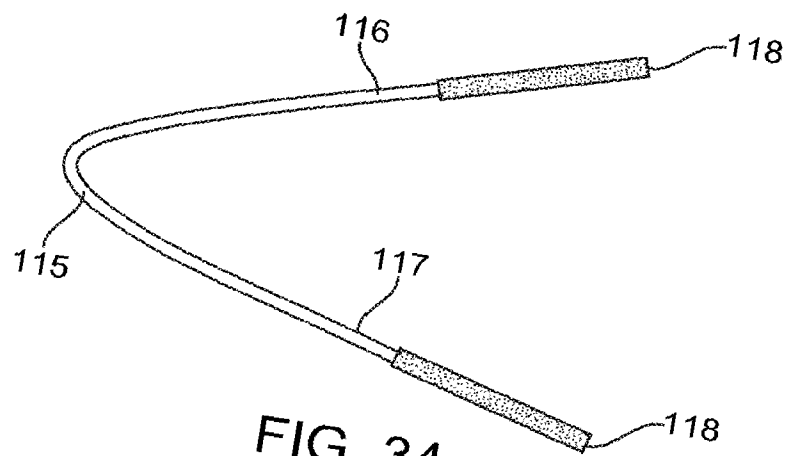


FIG. 34

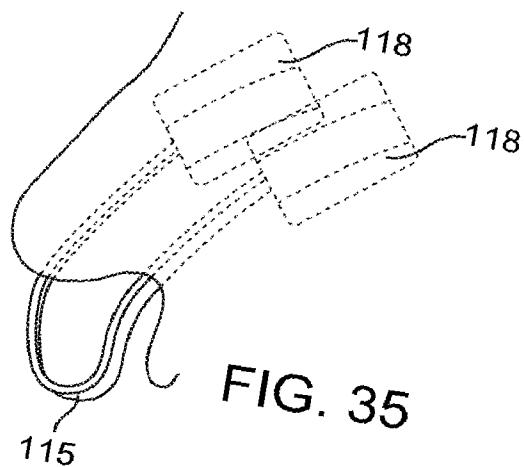


FIG. 35

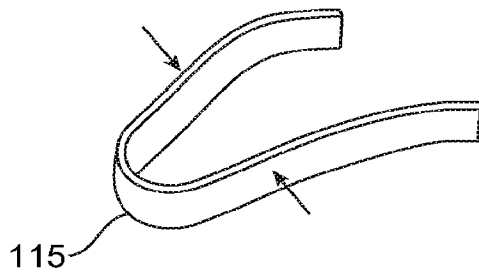
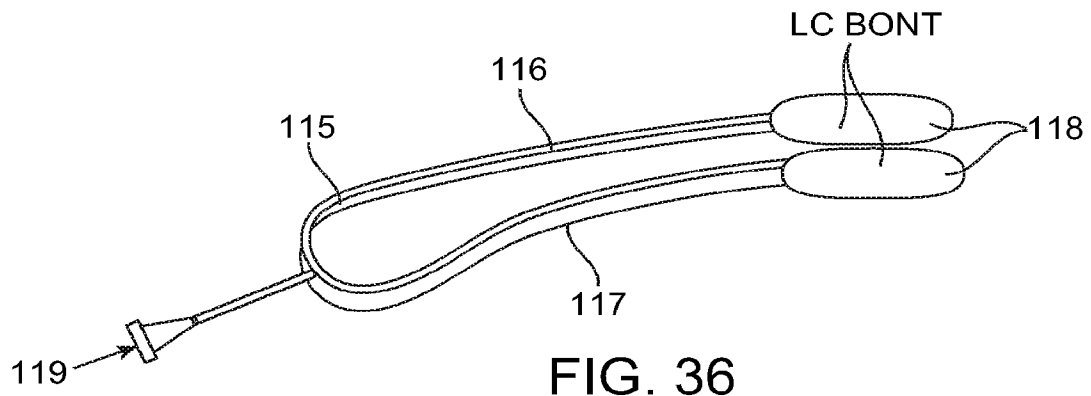


FIG. 37A

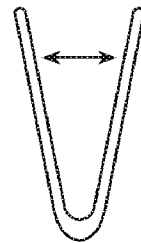


FIG. 37B

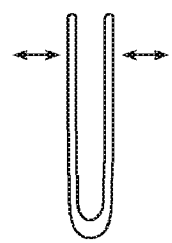


FIG. 37C

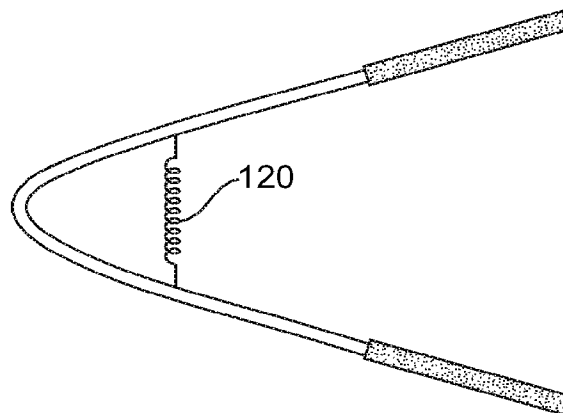


FIG. 38

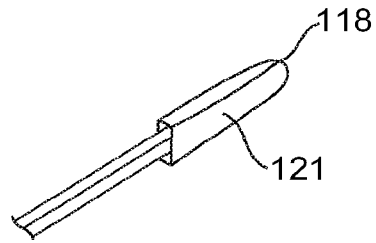


FIG. 39A

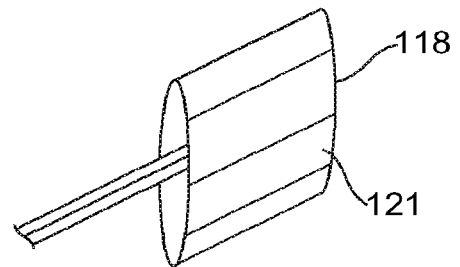


FIG. 39B

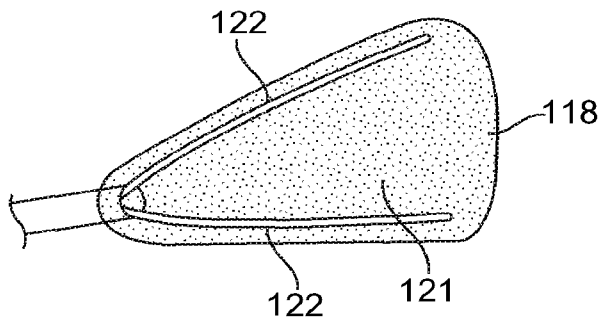


FIG. 40A

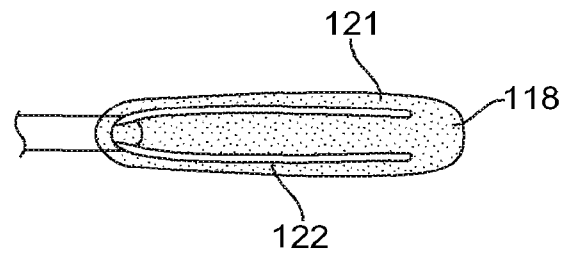


FIG. 40B

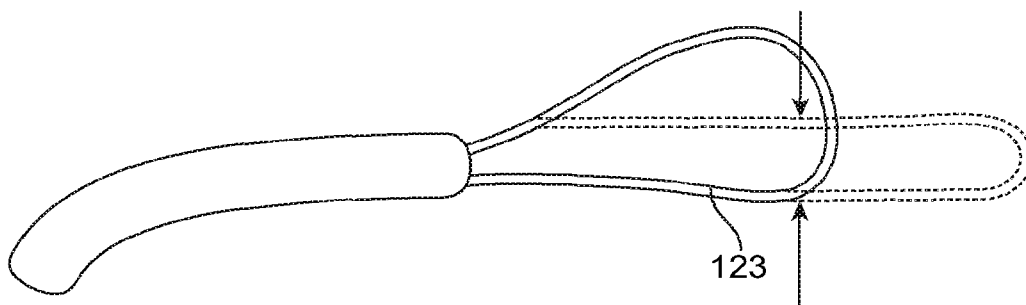


FIG. 41

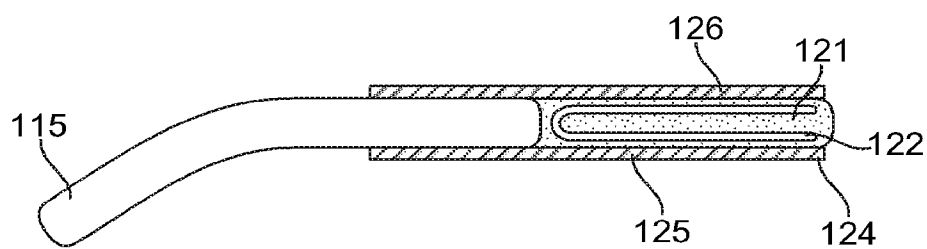


FIG. 42

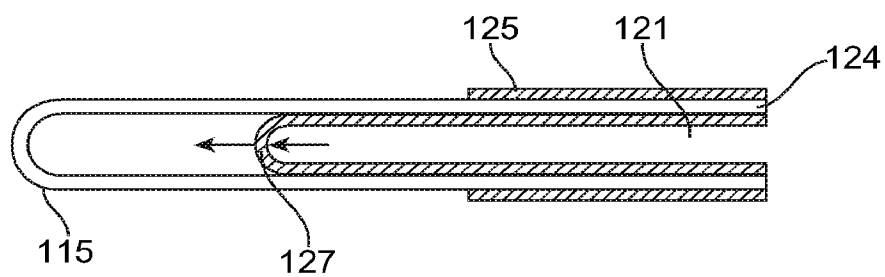


FIG. 43

DECLARATION (37 CFR 1.63) FOR UTILITY OR DESIGN APPLICATION USING AN APPLICATION DATA SHEET (37 CFR 1.76)**Title of
Invention**

METHODS AND SYSTEMS FOR TOXIN DELIVERY TO THE NASAL CAVITY

As the below named inventor(s), I/we declare that:

This declaration is directed to:

- ☐ The attached application, or
- ☒ Application No. 11/750,963, filed on May 18, 2007,
- ☐ as amended on _____ (if applicable);

I/we believe that I/we am/are the original and first inventor(s) of the subject matter which is claimed and for which a patent is sought;

I/we have reviewed and understand the contents of the above-identified application, including the claims, as amended by any amendment specifically referred to above;

I/we acknowledge the duty to disclose to the United States Patent and Trademark Office all information known to me/us to be material to patentability as defined in 37 CFR 1.56, including for continuation-in-part applications, material information which became available between the filing date of the prior application and the national or PCT International filing date of the continuation-in-part application.

WARNING:

Petitioner/applicant is cautioned to avoid submitting personal information in documents filed in a patent application that may contribute to identity theft. Personal information such as social security numbers, bank account numbers, or credit card numbers (other than a check or credit card authorization form PTO-2038 submitted for payment purposes) is never required by the USPTO to support a petition or an application. If this type of personal information is included in documents submitted to the USPTO, petitioners/applicants should consider redacting such personal information from the documents before submitting them to the USPTO. Petitioner/applicant is advised that the record of a patent application is available to the public after publication of the application (unless a non-publication request in compliance with 37 CFR 1.213(a) is made in the application) or issuance of a patent. Furthermore, the record from an abandoned application may also be available to the public if the application is referenced in a published application or an issued patent (see 37 CFR 1.14). Checks and credit card authorization forms PTO-2038 submitted for payment purposes are not retained in the application file and therefore are not publicly available.

All statements made herein of my/our own knowledge are true, all statements made herein 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 are punishable by fine or imprisonment, or both, under 18 U.S.C. 1001, and may jeopardize the validity of the application or any patent issuing thereon.

FULL NAME OF INVENTOR(S)Inventor one: MARK E. DEEMCitizen of: United StatesSignature: [Signature]Date: 9/21/07Inventor two: HANSON GIFFORDCitizen of: United StatesSignature: [Signature]Date: 9/21/07

☐ Additional inventors or a legal representative are being named on _____ additional form(s) attached hereto.

STATEMENT UNDER 37 CFR 3.73(b)Applicant/Patent Owner: Mark E. DeemApplication No./Patent No.: Unassigned Filed/Issue Date: HerewithEntitled: METHODS AND SYSTEMS FOR TOXIN DELIVERY TO THE NASAL CAVITYThe Foundry, LLC, a Corporation

(Name of Assignee)

(Type of Assignee, e.g., corporation, partnership, university, government agency, etc.)

states that it is:

1. ☒ the assignee of the entire right, title, and interest in;
2. ☐ an assignee of less than the entire right, title and interest in
(The extent (by percentage) of its ownership interest is _____ %); or
3. ☐ the assignee of an undivided interest in the entirety of (a complete assignment from one of the joint inventors was made)

in the patent application/patent identified above by virtue of either:

- A. ☐ An assignment from the inventor(s) of the patent application/patent identified above. The assignment was recorded in the United States Patent and Trademark Office at Reel __, Frame __, or for which a copy thereof is attached.

OR

- B. ☒ A chain of title from the inventor(s), of the patent application/patent identified above, to the current assignee as follows:

1. From: Inventors To: The Foundry, Inc.The document was recorded in the United States Patent and Trademark Office at
Reel 019926, Frame 0861, or for which a copy thereof is attached.2. From: The Foundry, Inc. To: The Foundry, LLCThe document was recorded in the United States Patent and Trademark Office at
Reel 022520, Frame 0499, or for which a copy thereof is attached.

3. From: _____ To: _____

The document was recorded in the United States Patent and Trademark Office at
Reel __, Frame __, or for which a copy thereof is attached.☐ Additional documents in the chain of title are listed on a supplemental sheet(s).

- ☒ As required by 37 CFR 3.73(b)(1)(i), the documentary evidence of the chain of title from the original owner to the assignee was, or concurrently is being, submitted for recordation pursuant to 37 CFR 3.11.

[NOTE: A separate copy (i.e., a true copy of the original assignment document(s)) must be submitted to Assignment Division in accordance with 37 CFR Part 3, to record the assignment in the records of the USPTO. See MPEP 302.08]

The undersigned (whose title is supplied below) is authorized to act on behalf of the assignee.

Signature

December 16, 2011

Date

Douglas Portnow

Attorney of Record

Printed or Typed Name

Title

This collection of information is required by 37 CFR 3.73(b). 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 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 FEE DETERMINATION RECORD Substitute for Form PTO-875						Application or Docket Number 13/328,203				
APPLICATION AS FILED - PART I										
(Column 1)		(Column 2)		SMALL ENTITY		OR OTHER THAN SMALL ENTITY				
FOR	NUMBER FILED	NUMBER EXTRA	RATE(\$)	FEE(\$)		RATE(\$)	FEE(\$)			
BASIC FEE (37 CFR 1.16(a), (b), or (c))	N/A	N/A	N/A	95		N/A				
SEARCH FEE (37 CFR 1.16(k), (l), or (m))	N/A	N/A	N/A	310		N/A				
EXAMINATION FEE (37 CFR 1.16(o), (p), or (q))	N/A	N/A	N/A	125		N/A				
TOTAL CLAIMS (37 CFR 1.16(j))	1	minus 20 = *	x 30 =	0.00	OR					
INDEPENDENT CLAIMS (37 CFR 1.16(h))	1	minus 3 = *	x 125 =	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						
			TOTAL	530		TOTAL				
* If the difference in column 1 is less than zero, enter "0" in column 2.										
APPLICATION AS AMENDED - PART II										
(Column 1)		(Column 2)		(Column 3)		SMALL ENTITY		OR OTHER THAN SMALL ENTITY		
AMENDMENT A		CLAIMS REMAINING AFTER AMENDMENT		HIGHEST NUMBER PREVIOUSLY PAID FOR	PRESENT EXTRA	RATE(\$)	ADDITIONAL FEE(\$)		RATE(\$)	ADDITIONAL FEE(\$)
	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))							OR		
	FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))							OR		
						TOTAL ADD'L FEE		OR	TOTAL ADD'L FEE	
AMENDMENT B		CLAIMS REMAINING AFTER AMENDMENT		HIGHEST NUMBER PREVIOUSLY PAID FOR	PRESENT EXTRA	RATE(\$)	ADDITIONAL FEE(\$)		RATE(\$)	ADDITIONAL FEE(\$)
	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))							OR		
	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
13/328,203	12/16/2011	1645	530	38077-714.301	1	1

CONFIRMATION NO. 9512

21971
WILSON, SONSINI, GOODRICH & ROSATI
650 PAGE MILL ROAD
PALO ALTO, CA 94304-1050

FILING RECEIPT



Date Mailed: 01/03/2012

Receipt is acknowledged of this non-provisional 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 APPLICANT, 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 Filing Receipt Correction. Please provide a copy of this Filing Receipt with the changes noted thereon. If you received a "Notice to File Missing Parts" for this application, please submit any corrections 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**

Applicant(s)

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

Assignment For Published Patent Application

The Foundry, LLC, Menlo Park, CA

Power of Attorney: The patent practitioners associated with Customer Number 021971

Domestic Priority data as claimed by applicant

This application is a CON of 12/636,477 12/11/2009
which is a DIV of 11/750,963 05/18/2007 PAT 7655243
which is a CIP of 11/459,090 07/21/2006 PAT 7608275
which claims benefit of 60/702,077 07/22/2005
and claims benefit of 60/747,771 05/19/2006

Foreign Applications (You may be eligible to benefit from the **Patent Prosecution Highway** program at the USPTO. Please see <http://www.uspto.gov> for more information.)

If Required, Foreign Filing License Granted: 12/29/2011

The country code and number of your priority application, to be used for filing abroad under the Paris Convention, is **US 13/328,203**

Projected Publication Date: Perfected

Non-Publication Request: No

Early Publication Request: No

**** SMALL ENTITY ****

Title

METHODS AND SYSTEMS FOR TOXIN DELIVERY TO THE NASAL CAVITY

Preliminary Class

424

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 (1-866-999-4158).

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APPLICATION NUMBER	FILING OR 371(C) DATE	FIRST NAMED APPLICANT	ATTY. DOCKET NO./TITLE
13/328,203	12/16/2011	Mark E. Deem	38077-714.301

21971
WILSON, SONSINI, GOODRICH & ROSATI
650 PAGE MILL ROAD
PALO ALTO, CA 94304-1050

CONFIRMATION NO. 9512
POA ACCEPTANCE LETTER



Date Mailed: 01/03/2012

NOTICE OF ACCEPTANCE OF POWER OF ATTORNEY

This is in response to the Power of Attorney filed 12/16/2011.

The Power of Attorney in this application is accepted. Correspondence in this application will be mailed to the above address as provided by 37 CFR 1.33.

/kthai/

Office of Data Management, Application Assistance Unit (571) 272-4000, or (571) 272-4200, or 1-888-786-0101

PATENT APPLICATION FEE DETERMINATION RECORD Substitute for Form PTO-875						Application or Docket Number 13/328,203	
APPLICATION AS FILED - PART I							
(Column 1)		(Column 2)		SMALL ENTITY		OTHER THAN SMALL ENTITY	
FOR	NUMBER FILED	NUMBER EXTRA	RATE(\$)	FEE(\$)		RATE(\$)	FEE(\$)
BASIC FEE (37 CFR 1.16(a), (b), or (c))	N/A	N/A	N/A	95		N/A	
SEARCH FEE (37 CFR 1.16(k), (l), or (m))	N/A	N/A	N/A	310		N/A	
EXAMINATION FEE (37 CFR 1.16(o), (p), or (q))	N/A	N/A	N/A	125		N/A	
TOTAL CLAIMS (37 CFR 1.16(j))	1	minus 20 = *	x 30 =	0.00	OR		
INDEPENDENT CLAIMS (37 CFR 1.16(h))	1	minus 3 = *	x 125 =	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			
			TOTAL	530		TOTAL	
* If the difference in column 1 is less than zero, enter "0" in column 2.							
APPLICATION AS AMENDED - PART II							
(Column 1)		(Column 2)		(Column 3)		SMALL ENTITY	
AMENDMENT A	CLAIMS REMAINING AFTER AMENDMENT	HIGHEST NUMBER PREVIOUSLY PAID FOR	PRESENT EXTRA	RATE(\$)	ADDITIONAL FEE(\$)		RATE(\$)
	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))					OR	
	FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))					OR	
				TOTAL ADD'L FEE		OR	TOTAL ADD'L FEE
(Column 1)		(Column 2)		(Column 3)		SMALL ENTITY	
AMENDMENT B	CLAIMS REMAINING AFTER AMENDMENT	HIGHEST NUMBER PREVIOUSLY PAID FOR	PRESENT EXTRA	RATE(\$)	ADDITIONAL FEE(\$)		RATE(\$)
	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))					OR	
	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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www.uspto.gov

APPLICATION NUMBER	FILING or 371(c) DATE	GRP ART UNIT	FIL FEE REC'D	ATTY. DOCKET NO	TOT CLAIMS	IND CLAIMS
13/328,203	12/16/2011	1645	530	38077-714.301	1	1

CONFIRMATION NO. 9512

21971
WILSON, SONSINI, GOODRICH & ROSATI
650 PAGE MILL ROAD
PALO ALTO, CA 94304-1050

FILING RECEIPT



Date Mailed: 01/04/2012

Receipt is acknowledged of this non-provisional 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 APPLICANT, 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 Filing Receipt Correction. Please provide a copy of this Filing Receipt with the changes noted thereon. If you received a "Notice to File Missing Parts" for this application, please submit any corrections 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**

Applicant(s)

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

Assignment For Published Patent Application

The Foundry, LLC, Menlo Park, CA

Power of Attorney: The patent practitioners associated with Customer Number 021971

Domestic Priority data as claimed by applicant

This application is a CON of 12/636,477 12/11/2009
which is a DIV of 11/750,963 05/18/2007 PAT 7655243
which is a CIP of 11/459,090 07/21/2006 PAT 7608275
which claims benefit of 60/702,077 07/22/2005
and claims benefit of 60/747,771 05/19/2006

Foreign Applications (You may be eligible to benefit from the **Patent Prosecution Highway** program at the USPTO. Please see <http://www.uspto.gov> for more information.)

If Required, Foreign Filing License Granted: 12/29/2011

The country code and number of your priority application, to be used for filing abroad under the Paris Convention, is **US 13/328,203**

Projected Publication Date: 04/12/2012

Non-Publication Request: No

Early Publication Request: No

**** SMALL ENTITY ****

Title

METHODS AND SYSTEMS FOR TOXIN DELIVERY TO THE NASAL CAVITY

Preliminary Class

435

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.

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PATENT
Attorney Docket No.: 38077-714.301

WILSON SONSINI GOODRICH & ROSATI

By: /Joy A. Roeder/
Joy A. Roeder

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of:

Mark E. Deem et al.

Application No.: 13/328,203

Filed: December 16, 2011

For: METHODS AND SYSTEMS FOR
TOXIN DELIVERY TO THE NASAL
CANAL

Customer No.: 21971

Confirmation No. 9512

Examiner: Not Yet Assigned

Technology Center/Art Unit: 1645

PRELIMINARY AMENDMENT

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

Commissioner:

Prior to examination of the above-referenced application, please enter the
following amendments and remarks:

Amendments to the Claims are reflected in the listing of claims which begins on page 2 of this
paper.

Remarks begin on page 10 of this paper.

Amendments to the Claims:

This listing of claims will replace all prior versions, and listings of claims in the application:

Listing of Claims:

1. (Canceled)
2. (New) 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.
3. (New) The method of claim 2, wherein the toxin comprises a light chain fragment of a neurotoxin substantially free of heavy chain fragments of the neurotoxin.
4. (New) The method of claim 3, wherein the neurotoxin consists of botulinum toxin.
5. (New) The method of claim 4, wherein the light chain fragment is derived from at least one of botulinum toxins A, B, C, D, E, F, and G.
6. (New) The method of claim 2, wherein the one or more occlusion devices comprise one or more balloons.
7. (New) The method of claim 6, further comprising inflating the one or more balloons to isolate the treatment region.

8. (New) The 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.

9. (New) The method of claim 2, wherein the toxin is introduced by a catheter.

10. (New) The method of claim 9, wherein the toxin is introduced by a balloon on the catheter.

11. (New) The method of claim 10, wherein the balloon comprises one or more pores and the toxin is introduced through the pores of the balloon.

12. (New) The method of claim 9, wherein the toxin is introduced through a needle on the catheter.

13. (New) The method of claim 9, wherein the toxin is aerosolized from the catheter.

14. (New) The method of claim 2, further comprising applying energy to the target cells under conditions which cause poration of the cell membranes to enhance delivery of the toxin.

15. (New) The method of claim 14, wherein applying energy to the target cells comprises applying an electric pulse of between 1 V and 500 V to the target cells.

16. (New) The method of claim 15, wherein the electric pulse comprises an RF signal.

17. (New) The method of claim 15, wherein the electric pulse is applied for durations between 5 microseconds to 100 milliseconds.

18. (New) The method of claim 15, wherein the electric pulse is produced by a DC power source.

19. (New) The method of claim 15, wherein the electric pulse is produced by an AC power source.

20. (New) The method of claim 14, wherein applying energy to the target cells comprises applying acoustic energy to the target cells.

21. (New) The method of claim 20, wherein the acoustic energy comprises ultrasonic energy.

22. (New) The method of claim 14, wherein applying energy to the target cells comprises applying electromagnetic energy to the target cells.

23. (New) The method of claim 22, wherein the electromagnetic energy comprises microwaves.

24. (New) The method of claim 22, wherein the electromagnetic energy comprises X-rays.

25. (New) The method of claim 14, wherein energy is selectively applied to the target cells.

26. (New) The method of claim 14, wherein energy is non-selectively applied to the target cells.

27. (New) The method of claim 2, wherein the treatment region comprises at least one paranasal sinus, a main nasal passage, or a nasal turbinate.

28. (New) The method of claim 2, wherein the treatment region comprises substantially the entire nasal cavity.

29. (New) The method of claim 2, wherein the treatment region comprises substantially the nasopharynx.

30. (New) The method of claim 2, wherein the target cells comprises epithelial or goblet cells.

31. (New) The method of claim 2, wherein the patient suffers from or is at risk of suffering from rhinorrhea.

32. (New) The method of claim 2, wherein the patient suffers from or is at risk of suffering from sinus headaches.

33. (New) The method of claim 2, wherein the patient suffers from or is at risk of suffering from migraine headaches.

34. (New) 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 as to inhibit mucous secretion in the target cells.

35. (New) The method of claim 34, wherein the toxin comprises a light chain fragment of a neurotoxin substantially free of heavy chain fragments of the neurotoxin.

36. (New) The method of claim 35, wherein the neurotoxin consists of botulinum toxin.

37. (New) The method of claim 36, wherein the light chain fragment is derived from at least one of botulinum toxins A, B, C, D, E, F, and G.

38. (New) The method of claim 34, wherein the gel or foam carrier further comprises hyaluronic acid.

39. (New) The method of claim 34, further comprising filling a targeted airway of the nasal cavity of the patient with the gel or foam carrier.

40. (New) 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.

41. (New) 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.

42. (New) The method of claim 34, further comprising applying energy to the gel or foam carrier to enhance delivery of the toxin to the cells.

43. (New) The method of claim 42, wherein ultrasonic energy is applied to the gel or foam carrier to enhance delivery of the toxin to the cells.

44. (New) The method of claim 34, wherein the gel or foam carrier is introduced by a catheter.

45. (New) The method of claim 44, wherein the gel or foam carrier is introduced by a balloon on the catheter.

46. (New) The method of claim 45, wherein the balloon comprises one or more pores and the gel or foam carrier is introduced through the pores of the balloon.

47. (New) The method of claim 44, wherein the gel or foam carrier is introduced through a needle on the catheter.

48. (New) The method of claim 34, further comprising applying energy to the target cells to enhance delivery of the toxin to the cells.

49. (New) The method of claim 48, wherein the energy is applied to the target cells under conditions which cause poration of the cell membranes to enhance delivery of the toxin.

50. (New) The method of claim 48, wherein applying energy to the target cells comprises applying an electric pulse of between 1 V and 500 V to the target cells.

51. (New) The method of claim 50, wherein the electric pulse comprises an RF signal.

52. (New) The method of claim 48, wherein the electric pulse is applied for durations between 5 microseconds to 100 milliseconds.

53. (New) The method of claim 48, wherein the electric pulse is produced by a DC power source.

54. (New) The method of claim 48, wherein the electric pulse is produced by an AC power source.

55. (New) The method of claim 48, wherein applying energy to the target cells comprises applying acoustic energy to the target cells.

56. (New) The method of claim 55, wherein the acoustic energy comprises ultrasonic energy.

57. (New) The method of claim 48, wherein applying energy to the target cells comprises applying electromagnetic energy to the target cells.

58. (New) The method of claim 57, wherein the electromagnetic energy comprises microwaves.

59. (New) The method of claim 57, wherein the electromagnetic energy comprises X-rays.

60. (New) The method of claim 48, wherein energy is selectively applied to the target cells.

61. (New) The method of claim 48, wherein energy is non-selectively applied to the target cells.

62. (New) The method of claim 34, wherein the treatment region comprises at least one paranasal sinus, a main nasal passage, or a nasal turbinate.

63. (New) The method of claim 34, wherein the treatment region comprises substantially the entire nasal cavity.

64. (New) The method of claim 34, wherein the treatment region comprises substantially the nasopharynx.

65. (New) The method of claim 34, wherein the target cells comprises epithelial or goblet cells.

66. (New) The method of claim 34, wherein the patient suffers from or is at risk of suffering from rhinorrhea.

67. (New) The method of claim 34, wherein the patient suffers from or is at risk of suffering from sinus headaches.

68. (New) The method of claim 34, wherein the patient suffers from or is at risk of suffering from migraine headaches.

REMARKS

Claim 1 has been canceled. New claims 2-68 have been added. Support for the claims is replete in the original specification as described, for example, by the table below. No new matter has been added.

Claim	Supporting Paragraphs and Figures from Original Specification
2	[0099], [00102] – [00104]; Figs. 17, 22 – 25
3	[0013], [0015], [0058] – [0061]
4	[0013], [0015], [0058] – [0061]
5	[0013], [0015], [0058] – [0061]
6	[0099], [00104]; Figs. 17, 24, 25
7	[0099], [00104]; Figs. 17, 24, 25
8	[00103]; Figs. 22, 23
9	[0017], [0099], [00104]; Figs. 24, 25
10	[0017]
11	[0017]
12	[0017]
13	[0017]
14	[0014] – [0019]
15	[0014] – [0019], [0065] – [0068]
16	[0014] – [0019], [0063]
17	[0014] – [0019], [0065] – [0068]
18	[0014] – [0019]
19	[0014] – [0019]
20	[0014] – [0019], [0069] – [0075]
21	[0014] – [0019], [0069] – [0075]
22	[0014] – [0019], [0077]
23	[0014] – [0019], [0077]

24	[0014] – [0019]
25	[0014] – [0019]
26	[0014] – [0019]
27	[0013], [0014]
28	[0013], [0014]
29	[0013], [0014]
30	[0013], [0014]
31	[0003], [0009] – [0012]
32	[0007]
33	[0007]
34	[0017], [00112], [00125], [00134], [00135]
35	[0013], [0015], [0058] – [0061]
36	[0013], [0015], [0058] – [0061]
37	[0013], [0015], [0058] – [0061]
38	[00134]
39	[00134], [00135]
40	[00103], [00104], [00134], [00135]
41	[00134], [00135]
42	[00134], [00135]
43	[00134], [00135]
44	[0017], [0099], [00104]; Figs. 24, 25
45	[0017]
46	[0017]
47	[0017]
48	[0014] – [0019]
49	[0014] – [0019]
50	[0014] – [0019], [0065] – [0068]
51	[0014] – [0019], [0063]

52	[0014] – [0019], [0065] – [0068]
53	[0014] – [0019], [0065] – [0068]
54	[0014] – [0019], [0065] – [0068]
55	[0014] – [0019], [0069] – [0075]
56	[0014] – [0019], [0069] – [0075]
57	[0014] – [0019], [0077]
58	[0014] – [0019], [0077]
59	[0014] – [0019]
60	[0014] – [0019]
61	[0013], [0014]
62	[0013], [0014]
63	[0013], [0014]
64	[0013], [0014]
65	[0013], [0014]
66	[0003], [0009] – [0012]
67	[0007]
68	[0007]

CONCLUSION

In view of the foregoing, Applicants believe all claims now pending in this Application are in condition for allowance. The issuance of a formal Notice of Allowance at an early date is respectfully requested.

Further, the Commissioner is hereby authorized to charge any additional fees or credit any overpayment in connection with this paper to Deposit Account No. 23-2415.

If the Examiner believes a telephone conference would expedite prosecution of this application, please telephone the undersigned at 650-493-9300.

Respectfully submitted,

/Darby J. Chan/

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Reg. No. 62,407

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Attachments
DJC:djc

4745401v1

Electronic Patent Application Fee Transmittal

Application Number:	13328203			
Filing Date:	16-Dec-2011			
Title of Invention:	METHODS AND SYSTEMS FOR TOXIN DELIVERY TO THE NASAL CAVITY			
First Named Inventor/Applicant Name:	Mark E. Deem			
Filer:	James Mitchell Heslin/Joy Roeder			
Attorney Docket Number:	38077-714.301			
Filed as Small Entity				
Utility under 35 USC 111(a) Filing Fees				
Description	Fee Code	Quantity	Amount	Sub-Total in USD(\$)
Basic Filing:				
Pages:				
Claims:				
Claims in excess of 20	2202	48	30	1440
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:				
Total in USD (\$)				1440

Electronic Acknowledgement Receipt

EFS ID:	11825168
Application Number:	13328203
International Application Number:	
Confirmation Number:	9512
Title of Invention:	METHODS AND SYSTEMS FOR TOXIN DELIVERY TO THE NASAL CAVITY
First Named Inventor/Applicant Name:	Mark E. Deem
Customer Number:	21971
Filer:	James Mitchell Heslin/Joy Roeder
Filer Authorized By:	James Mitchell Heslin
Attorney Docket Number:	38077-714.301
Receipt Date:	12-JAN-2012
Filing Date:	16-DEC-2011
Time Stamp:	16:59:41
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	yes
Payment Type	Deposit Account
Payment was successfully received in RAM	\$ 1440
RAM confirmation Number	4009
Deposit Account	232415
Authorized User	

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
Page 89 of 299					

1		2012_01_12_PRELIMAMDT_38 077_714_301.pdf	113582 a7d8d1f9be4b7b77f6801e10dd1d7f5d36d826ff	yes	13				
	Multipart Description/PDF files in .zip description								
	Document Description		Start	End					
	Preliminary Amendment		1	1					
	Claims		2	9					
	Applicant Arguments/Remarks Made in an Amendment		10	13					
Warnings:									
Information:									
2	Fee Worksheet (SB06)	fee-info.pdf	29834 aef9d8c71673226a9dec341c665b1baf101af03	no	2				
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Total Files Size (in bytes):			143416						
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				Application Number	13/328,203
				Filing Date	December 16, 2011
				First Named Inventor	Mark E. Deem
				Art Unit	1645
				Examiner Name	Albert Mark Navarro
Sheet	1	of	6	Attorney Docket Number	38077-714.301

U.S. PATENT DOCUMENTS					
Examiner Initials*	Cite No. ¹	Document Number	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear
		Number-Kind Code ² (if known)			
	1.	US 1,695,107	12/11/1928	Kahl	
	2.	US 2,566,806	09/04/1951	Miller	
	3.	US 2001/0044596 A1	11/22/2001	Jaafar	
	4.	US 2002/0082197 A1	06/27/2002	Aoki et al.	
	5.	US 2002/0111620 A1	08/15/2002	Cooper et al.	
	6.	US 2002/0198512 A1	12/26/2002	Seward	
	7.	US 2003/0018344 A1	01/23/2003	Kaji et al.	
	8.	US 2003/0050591 A1	03/13/2003	McHale	
	9.	US 2003/0153881 A1	08/14/2003	Roche et al.	
	10.	US 2003/0202990 A1	10/30/2003	Donovan et al.	
	11.	US 2003/0211121 A1	11/13/2003	Donovan	
	12.	US 2004/0009180 A1	01/15/2004	Donovan	
	13.	US 2004/0010290 A1	01/15/2004	Schroeppel et al.	
	14.	US 2004/0086531 A1	05/06/2004	Barron	
	15.	US 2004/0091880 A1	05/13/2004	Wiebusch et al.	
	16.	US 2004/0142005 A1	07/22/2004	Brooks et al.	
	17.	US 2004/0151741 A1	08/05/2004	Borodic	
	18.	US 2004/0175399 A1	09/09/2004	Schiffman	
	19.	US 2004/0186435 A1	09/23/2004	Seward	
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	21.	US 2004/0213814 A1	10/28/2004	Ackerman	
	22.	US 2004/0226556 A1	11/18/2004	Deem et al.	
	23.	US 2004/0253274 A1	12/16/2004	Voet	
	24.	US 2005/0019346 A1	01/27/2005	Boulis	
	25.	US 2005/0074461 A1	04/07/2005	Donovan	
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	27.	US 2005/0152924 A1	07/14/2005	Voet	
	28.	US 2005/0281751 A1	12/22/2005	Levin	
	29.	US 2006/0008462 A1	01/12/2006	Sanders	

Examiner Signature		Date Considered	
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				Application Number	13/328,203
				Filing Date	December 16, 2011
				First Named Inventor	Mark E. Deem
				Art Unit	1645
				Examiner Name	Albert Mark Navarro
Sheet	2	of	6	Attorney Docket Number	38077-714.301

U.S. PATENT DOCUMENTS					
Examiner Initials*	Cite No. ¹	Document Number	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear
		Number-Kind Code ² (if known)			
	30.	US 2006/0106361 A1	05/18/2006	Muni et al.	
	31.	US 2006/0222667 A1	10/05/2006	Deem et al.	
	32.	US 2006/0225742 A1	10/12/2006	Deem et al.	
	33.	US 2007/0021803 A1	01/25/2007	Deem et al.	
	34.	US 2007/0267011 A1	11/22/2007	Deem et al.	
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	38.	US 3,788,296	01/29/1974	Klatt et al.	
	39.	US 3,918,449	11/11/1975	Pistor	
	40.	US 4,767,402	08/30/1988	Kost et al.	
	41.	US 5,056,529	10/15/1991	de Groot	
	42.	US 5,139,029	08/18/1992	Fishman et al.	
	43.	US 5,286,254	02/15/1994	Shapland et al.	
	44.	US 5,496,304	10/06/1998	Krespi	
	45.	US 5,766,605	06/16/1998	Sanders et al.	
	46.	US 5,817,073	10/06/1998	Krespi	
	47.	US 5,820,589	10/13/1998	Torgerson et al.	
	48.	US 5,964,223	10/12/1999	Baran	
	49.	US 6,063,768	05/16/2000	First	
	50.	US 6,139,845	10/31/2000	Donovan	
	51.	US 6,265,379	07/24/2001	Donovan	
	52.	US 6,306,423	10/23/2001	Donovan et al.	
	53.	US 6,358,926	03/19/2002	Donovan	
	54.	US 6,361,554	03/26/2002	Briskin	
	55.	US 6,383,509	05/07/2002	Donovan et al.	
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	57.	US 6,432,092	08/13/2002	Miller	
	58.	US 6,447,785	09/10/2002	Donovan	

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				Filing Date	December 16, 2011
				First Named Inventor	Mark E. Deem
				Art Unit	1645
				Examiner Name	Albert Mark Navarro
Sheet	3	of	6	Attorney Docket Number	38077-714.301

U.S. PATENT DOCUMENTS					
Examiner Initials*	Cite No. ¹	Document Number	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear
		Number-Kind Code ² (if known)			
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	60.	US 6,464,680	10/15/2002	Briskin et al.	
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	66.	US 6,601,581	08/05/2003	Babaev	
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	69.	US 6,626,855	09/30/2003	Weng et al.	
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	71.	US 6,645,496	11/11/2003	Aoki et al.	
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	82.	US 6,847,849	01/25/2005	Mamo et al.	
	83.	US 6,861,058	03/01/2005	Aoki et al.	
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	86.	US 7,238,357	07/03/2007	Barron	
	87.	US 7,608,275	10/27/2009	Deem et al.	

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Sheet	4	of	6	Attorney Docket Number	38077-714.301

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		Number-Kind Code ² (if known)			
	88.	US 7,655,243	02/02/2010	Deem et al.	

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		Country Code ³ - Number ⁴ - Kind Code ⁵ (if known)				
	89.	WO 2004/048519 A2	06/10/2004	Sanders		
	90.	WO 2004/048519 A3	07/01/2004	Sanders		
	91.	WO 2004/101028 A2	11/25/2004	Deem et al.		
	92.	WO 2004/101028 A3	12/14/2006	Deem et al.		
	93.	WO 2007/014003 A2	02/01/2007	Deem et al.		
	94.	WO 2007/014003 A3	10/04/2007	Deem et al.		

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	105.	KORPELA, et al. Comparison of tissue reactions in the tracheal mucosa surrounding a bioabsorbable and silicone airway stents. Ann Thorac Surg. 1998 Nov;66(5):1772-6.	
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	114.	International search report and written opinion dated 03/03/2008 for PCT/US2007/069391.	
	115.	European search report and opinion dated 06/18/2010 for EP Application No. 07784000.7.	

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(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property
Organization
International Bureau



(43) International Publication Date
10 June 2004 (10.06.2004)

PCT

(10) International Publication Number
WO 2004/048519 A2

(51) International Patent Classification⁷: **C12N**

(21) International Application Number:
PCT/US2003/037286

(22) International Filing Date:
20 November 2003 (20.11.2003)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
60/427,749 21 November 2002 (21.11.2002) US

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(81) Designated States (national): AE, AG, AL, AM, AT, AU,
AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU,

CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH,
GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC,
LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW,
MX, MZ, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC,
SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA,
UG, UZ, VC, VN, YU, ZA, ZM, ZW.

(84) Designated States (regional): ARIPO patent (BW, GH,
GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW),
Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM),
European patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE,
ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE,
SI, SK, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA,
GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Declaration under Rule 4.17:

— of inventorship (Rule 4.17(iv)) for US only

Published:

— without international search report and to be republished
upon receipt of that report

For two-letter codes and other abbreviations, refer to the "Guid-
ance Notes on Codes and Abbreviations" appearing at the begin-
ning of each regular issue of the PCT Gazette.

(54) Title: TREATMENT OF MAMMALIAN PHYSIOLOGICAL REACTION OF IgE ANTIBODIES PRESENT IN SAID MAM-
MAL UPON CONTACT WITH THE CORRESPONDING ANTIGEN

(57) Abstract: A method is disclosed for blocking or reducing physiological reaction in a mammal to the interaction of IgE antibod-
ies present in said mammal upon contact with the corresponding antigen, by the administration to said mammal of a therapeutically
effective amount of a neurotoxin (CnT) derived from Clostridia sp.

TREATMENT OF MAMMALIAN PHYSIOLOGICAL REACTION OF IgE ANTIBODIES PRESENT IN SAID MAMMAL UPON CONTACT WITH THE CORRESPONDING ANTIGEN.

FIELD OF THE INVENTION

5 A method is disclosed for blocking or reducing physiological reaction in a mammal to the interaction of IgE antibodies present in said mammal upon contact with the corresponding antigen, by the administration to said mammal of a therapeutically effective amount of a neurotoxin (CnT) derived from Clostridia sp.

BACKGROUND OF THE INVENTION

10 Throughout this application various publications are referred to within parentheses or by footnote. The contents of these publications are hereby incorporated by reference in their entirety.

Introduction

15 The physiological reaction in a mammal to the interaction of IgE antibodies present in said mammal upon contact with the corresponding antigen is generally referred to as allergy. It is believed that the allergic response evolved to combat infections with parasites. As parasitic infections are rare in industrialized countries this mechanism becomes pathologic in certain susceptible (atopic) individuals. Characteristic of allergies is that the antigen, also called the allergen, is normally
20 innocuous, and the body's reaction is inappropriate.

 Allergic reactions can involve all body tissues but are most prominent in the boundaries with the external environment: the airway, eye, gastrointestinal tract and skin. The conditions are known as allergic rhinitis in the nose (hay fever), allergic asthma in the lungs, food allergies in the GI tract and allergic hypersensitivity (hives)
25 or dermatitis in the skin. Anaphylaxis refers to the systemic reaction that occurs when an allergen is introduced directly into the circulation, such as occurs with injection of drugs and insect stings. A massive early phase reaction occurs throughout the body. Symptoms include diffuse airway swelling and hypotension which can be life threatening.

30 Each year more than 50 million Americans suffer from allergic diseases, costing the health care system \$18 billion annually (American Academy of Allergy,

Asthma and Immunology (AAAAI). The Allergy Report: Science Based Findings on the Diagnosis & Treatment of Allergic Disorders, 1996-2001)

Alarming, the prevalence and severity of allergic disorders has rapidly increased in the United States over the past twenty years, so there is a need for new therapies for these conditions.

In 1998, an estimated 15 million Americans, or 6.4 percent of the population, had asthma, with 5 million being children. Children account for 4.8 million of Americans with asthma. Each year, 1.8 million emergency room visits are for asthma, nearly 500,000 Americans are hospitalized and more than 5,000 die from the disease. Although asthma deaths are infrequent, they have increased significantly during the last two decades. From 1975-1979, the death rate was 8.2 per 100,000 people. That rate jumped in 1993-1995 to 17.9 per 100,000. Asthma cost the U.S. economy an estimated \$10.7 billion in 1994, including a direct health care cost of \$6.1 billion and indirect costs, such as lost workdays, of \$4.6 billion.

Approximately 16.7 million office visits to health care providers each year are attributed to allergic rhinitis alone (CDC. Fast Stats A-Z, Vital and Health Statistics, Series 10, no. 13. 1999)

A related condition, chronic sinusitis, is the most commonly reported chronic disease, affecting 12.6 percent of people (approximately 38 million) in the United States in 1996. Another related condition, serous otitis media, is the most common condition in children requiring an office visit to a health care provider.

Atopic dermatitis is one of the most common skin diseases, particularly in infants and children. The estimated prevalence in the United States is 9 percent¹ Rudikoff D and Lebwohl M. "Atopic dermatitis." Lancet 351(9117): 1715-21. 1998ⁱ

Experts estimate that food allergy occurs in 8 percent of children 6 years of age or under, and in 1 to 2 percent of adults Sampson HA. In Allergy, Principles and Practice, 5th Ed., E. Middleton et al, ed. Mosby, St. Louis, p. 1162. 1998ⁱⁱ.

Pathophysiology of allergy

Allergy is an ailment that affects millions of individuals worldwide. Attempts to desensitize an individual against a material that causes an allergic response (hereafter designated as an "allergen") by injection of measured dosages of the allergen heretofore has failed to achieve complete relief of allergy symptoms reproducibly in all allergic individuals. An allergic response is a term of art and has a well-defined meaning. Within the context of the present invention, an allergic or reagenic response includes, in particular, at least one of the features of 1.) production of an abnormally high level of IgE in an individual's serum, 2.) immunologic interaction between an allergen, an individual's IgE and leukocytes resulting in release of histamines, 3.) production of hives, rashes, wheal and flare and similar dermatological manifestation of hypersensitivity, and 4.) anaphylaxis.

An allergic response is a state of hypersensitivity in which an exaggerated immune response is induced by the exposure to a particular antigen or allergen. Hypersensitivity reactions can be classified as immediate or delayed. Immediate or type I hypersensitivity (or anaphylactic response) is an allergic reaction which develops very quickly, i.e., within seconds or minutes of exposure of the patient to the causative allergen, and it is mediated by IgE antibodies produced by B lymphocytes. In non-allergic patients, there is no IgE antibody of clinical relevance. However, in a person suffering with allergic diseases, IgE antibody mediates immediate hypersensitivity by sensitizing mast cells which are abundant in the skin, membranes of the eye, nose and mouth, and in the respiratory tract and intestines.

IgE secreted from activated B cells can attach to Fc receptors located on the surface of mast cells and basophil granulocytes, which contain numerous cytoplasmic granules packed with chemical mediators e.g. histamine (J. Klein, "Immunology", Blackwell Sci. Pub., London, 1990; E. Benjamini & S. Leskowitz, "Immunology", Wiley-Liss, N.Y. 1991). This receptor binds circulating IgE with very high affinity and retains it at the mast cell surface for extended periods of time. Activation is accomplished through the binding of an allergen simultaneously to more than one polyvalent molecule of Fc receptor-bound IgE. This "cross linking" of at least two surface-bound IgE molecules brings Fc receptor proteins into close association with one another in the plane of the mast cell plasma membrane. When the bound IgE is contacted by the appropriate allergen, the mast cell becomes

activated. Kinases associated with these receptors become activated as a result of this proximity. They initiate the second messenger cascade, which results in the fusion of the granules with the cell surface membrane, leading to the exocytosis of the granule contents, such as histamine, cytokines, and leukotrienes into the surrounding tissue, and the concomitant induction of allergic symptoms. It is the activity of these substances which is responsible for the clinical symptoms typical of immediate hypersensitivity. These include contraction of smooth muscle in the airways or the intestine, the dilation of small blood vessels and the increase in their permeability to water and plasma proteins, the secretion of thick sticky mucus, and in the skin, , swelling and the stimulation of nerve endings that results in itching.

Delayed type hypersensitivity (DTH) reactions are mediated by T-cells and macrophages and become evident only after 1 to 2 days and persist from several days to a few weeks. DTH is also referred to as cell-mediated hypersensitivity (i.e., T-cell mediated) and is part of a larger group of reactions called cell-mediated immunity.

Anaphylaxis, or anaphylactic shock, is an acute systemic (whole body) type of allergic reaction. It occurs when a person has become sensitized to a certain substance or allergen (that is, the immune system has been abnormally triggered to recognize that allergen as a threat to the body). On the second or subsequent exposure to the substance, an allergic reaction occurs. This reaction is sudden, severe, and involves the whole body. Anaphylaxis is life-threatening and can occur at any time.

Therapeutically, many agents are used to try to prevent the release of mediators from mast cells and basophils and/or to treat the downstream events by blocking or ameliorating the effects of the mediators on target tissues. Therapeutic agents commonly employed fall under the following main groups.

Antihistamines block and mop up the released histamine, i.e. the major mediator of the allergic response.

01 02 agonists, e.g., Epinephrine, Salbutamol overcome indirectly the downstream effects on vasculature and smooth muscle.

Chromoglycate is useful for primary prevention of mast cells/basophil degranulation.

This prophylactic must be taken continuously. It does not prevent the cross-linking of IgE but it somehow interferes with subsequent events. Theophylline and other phosphodiesterase inhibitors again influence downstream biochemical events particularly associated with cyclic nucleotides. Steroids have multiple sites of activities against the allergic response. They are either administered locally and/or systematically/ systemically.

None of the above treatments are ideal for the modulation of allergic responses because each has specific problems such as side effects including drowsiness, they also lack specificity in the immune system leading to global immuno-suppression. Also many of these therapeutic agents need to be administered continuously. Therefore, new improved treatments are constantly being sought to control the allergic response prophylactically and/or therapeutically without the above-mentioned limitations.

Individuals who wish to become desensitized against an allergen often must submit himself/herself to injections of measured doses of the allergen, first administered at weekly or biweekly intervals, then gradually decreases to bimonthly or monthly intervals throughout the year. Such injections generally commence with a small dose of the allergen and then gradually increasing the dosage until a maximally-tolerated maintenance dose is achieved. The individual is then kept on a maintenance dose of the allergen for long periods of time or until the individual no longer exhibits an allergic reaction to the allergen.

Other treatment regimes have been devised to reduce or eliminate an allergic response.

Allergen injection therapy (allergen immunotherapy also known as subcutaneous immunotherapy (SCIT) is known to reduce the severity of allergic rhinitis. This treatment is theorized to involve the production of a different form of antibody, a protective antibody which is termed a "blocking antibody" (Cooke, RA et al., Serologic Evidence of Immunity with Coexisting Sensitization in a Type of Human Allergy, Exp. Med. 1935; 62:733). Chemical agents have been developed which inhibit the interactions between the IgE and its receptor (Cheng et al., U.S. Patent No. 5,965,605 and Ra et al., U.S. Patent No. 6,090,034). IgE antagonists have also been used to treat allergic disease (Presta et al., U.S. Patent No 5,965709) and compounds that exhibit immunosuppressive activity and inhibits the release of

histamine (Bycroft et al., U.S. Patent No. 5,969,158). St. Remy et al., U.S. Patent No. 4,740,371, discloses an immune complex of an allergen for treating allergies involving a combination of the specific allergen and the corresponding antibody to that allergen. The injection of the complex into a patient is said to reduce a patient's allergic reaction to that specific allergen. Others have suggested that certain human proteins can neutralize IgE by blocking it from interacting with the mast cells, but this has not been established clearly as a clinically effective therapy (Stanworth, et al., Allergy Treatment with a Peptide Vaccine, Lancet 1990; 336:1279-81). Patterson et al., U.S. Patent No. 5,314,690 disclosed a method and preparations for reducing IgE antibodies to allergens in allergic subjects wherein substance P (a neuropeptide) and an allergen or fragments of allergens or haptens acting as allergens are administered together to the allergic subjects through a non-oral route.

Cholera Toxin and B Subunit as Adjuvants Cholera toxin (CT) and the closely related heat-labile toxin (LT) from *Escherichia coli* are known as exceptionally potent immunoadjuvants when co-administered with antigens by various mucosal routes (Elson et al., J. huminol. 1984; 133:2892-2897; Hohnngren et al., Vaccine 1973; 1 1: 1 179-1184; Lycke et al, Eur. J. Immunol. 1992; 22:2277-228 1. Both CT and LT are recognized as "AB" toxins in that they are composed of two distinct structural and functional components: a single toxic-active A subunit component and a non-toxic cell-binding B subunit. The latter is a homopentamer component with strong binding affinity for GM1 ganglioside receptors (Holingren et al., Nature 19 8 1; 292:413 -417). Such receptors are known to be present on most mammalian cells, e.g., on skin and other epithelial cells, on all known antigen-presenting cells including dendritic cells (DC) and Langerhan's cells (LC), as well as on B and T lymphocytes. Recently, Gleim et al., U.S. Patent No. 5,980,898 disclosed a system for transcutaneous immunization that induces an immune response (e.g., humoral and/or cellular effectors) in an animal or human. The system provides a simple application to intact skin of both rodents and humans of a formulation comprised of antigen and an adjuvant that was whole cholera toxin.

Common to allergies is the involvement of the IgE class of antibody. Individuals are not born with allergies; rather they acquire them by exposure to allergens. The steps of the IgE allergic reaction are sensitization upon first exposure to the allergen, and then the allergic response to subsequent exposures. The allergic response consists of an immediate and delayed response referred to as the early

and late phase responses respectively. In atopic individuals, those prone to allergies, the initial exposure to an antigen results in the production of IgE antibodies that specifically recognize that allergen. This process is called sensitization.

5 The early phase response (ERP) is the immediate reaction that occurs within minutes of exposure to an allergen. IgE are bound to the surface of a neuroimmune cell called the mast cell (in the circulation these cells are called basophils). Sufficient numbers of bound IgE antibodies that react with an allergen causes the mast cell to release its content of secretory vesicles, a process known as degranulation. The secretory vesicles contain histamine and other stored substances such as nerve
10 growth factor (NGF). In addition the mast cell and T cells immediately begin manufacturing leukotrienes, cytokines, enzymes and substances that activate blood platelets and attract secondary cells such as eosinophils. Symptoms vary depending on the site, but common reactions are smooth muscle contraction, mucus secretion, vascular permeability, and sensory nerve stimulation.

15 The late phase response (LPR) develops over hours to days of exposure as eosinophils and other cells are attracted to the area. Eosinophils produce major basic protein, eosinophil cationic protein, leukotrienes and nerve growth factor. TH2 lymphocytes release cytokines that promote further IgE production and eosinophil chemo attraction, and increased numbers of mast cells.

20 **Nerve involvement in allergy**

The sensory nerve stimulation causes reflexes that are designed to aid in defending the tissue. These reflexes are often a larger problem than the local allergic response. Reflexes can range from large gross motor actions to regional afferent and efferent arcs or even local axon-axonal reflexes involving a single neuron.

25 Some reflexes recruit major motor actions that are well recognized. In the nose sneezing is a reflex attempt to expel unwanted material and coughing is the equivalent response in the lungs.

30 Regional reflex arcs involve the sensing of the stimulus by the sensory neuron, the transfer of the message to the ganglia and the central nervous system and an efferent response via autonomic neurons. Reflex excitation by the autonomic nervous system directly causes mast cell to degranulate, thereby spreading the reaction. In addition these reflexes control a variety of other functions. In the nose

these reflexes cause increased mucus production, increased cilia movement, nasal congestion and sneezing. In the lungs reflexes cause bronchospasm, increased mucosal congestion, production of airway secretions and coughing. In the GI tract reflexes cause dysmotility, mucosal congestion and secretions. In the skin the
5 reflexes cause swelling and itching.

Finally there are local axon-axonal reflexes in sensory nociceptive nerve fibers. Allergic stimulation of a single neuron causes release of mediators from other axons of the same neuron. (Barnes P et al. 1991 Neuropeptides in the respiratory tract. Am Rev Resp Dis 144:1187-1198, 1391-1399)

10 In chronic allergic stimulation the mast cells and eosinophils releases nerve growth factor which causes growth of the nerves in the region. Thereby allowing for increased neural responses and hyper reactivity. This hyper reactivity is not limited to allergic reactions but extends to non-allergic conditions such as respiratory tract infections including viral and bacterial infections. Specifically viral rhinitis, viral and
15 bacterial sinusitis, suppurative otitis media, bronchitis and pneumonia. Therefore individuals become more susceptible to these conditions and have more frequent and severe infections.

Furthermore the repeated allergic reactions cause changes in the qualitative response of the neural reflexes such that they are inappropriately activated. This
20 negatively effects non-allergic conditions, such as bronchospasm mucus production and coughing in non-allergic lung conditions such as bronchitis and emphysema.

Allergic reactions differ from inflammatory reactions

Allergic reactions differ from inflammation. Allergies represent the body's inappropriate response to what is in essence a harmless antigen. It is believed that
25 the IgE allergic reactions evolved to combat parasitic infections which are now rare in industrialized societies. In contrast, inflammation is the body's response to actual tissue damage or infection. Inflammation is clinically distinguished by the classical symptoms of calor, rubor and dolor: heat, redness and pain. Inflammation is a process that triggers a cascade of mediators with wide effects, both locally and
30 systemically. Local reactions include pain, vasodilation and migration of macrophages and neutrophils. Systemic reactions include fever. Certain conditions, such as rhinitis or asthma, can be triggered by allergies, infections, irritating

chemicals or may be entirely neurogenic, the result of nerve activity without prior inflammatory or allergic stimulation.

Specific Allergic Conditions

Rhinitis

5 Allergic rhinitis

The inner lining of the nose is a mucosa that contains serous and mucus glands and large numbers of mast cells. This mucosa extends to the openings leading to the sinuses as well as the Eustachian tube where it is continuous with the mucosa of the sinuses and middle ear, respectively. The EPR of the nasal mucosa causes mast cell degranulation. The release of histamine, heparin and neuropeptides provokes vasodilation and acute swelling of the mucosa and has some minor direct stimulatory effect on the mucus secreting glands. Reflex excitation causes reflex sneezing, congestion and neural stimulation of the seromucinous glands and further congestion. LPR attracts eosinophils and prolongs the reaction.

15 Allergic reactions can also be chronic, a condition known as perennial rhinitis. In these cases airborne allergens are constantly in the environment. Chronic low-level allergic reactions cause a thickening of the nasal mucosa due to edema and hypertrophy of glandular elements. As a result the primary symptoms of perennial rhinitis are nasal congestion, and postnasal drip. After each allergic reaction the mucosa swells; repeated allergic reactions enlarges the mucosa permanently and may form polyps. Thickening of the mucosa can cause obstruction of the small openings that allow drainage from the sinus. Obstruction of these openings allows nasal secretions to collect and become infected, thereby causing sinusitis.

25 Topical treatment of allergic rhinitis includes steroid sprays and chromalyn sodium (Nasocrom®) a chemical that blocks mast cell degranulation, and/or nasal decongestants (Neosynephrine). Systemic treatment includes oral anti-histamines and non-sedating antihistamines (Allegra®, Zyrtec®, Claritin®). Long-term therapy requires immune desensitization to the allergen by progressive intradermal injections of the allergen over months to years. rhinitis can lead

30 Allergic rhinitis can lead to pulmonary disease, including but not limited to asthma and emphysema, suitably asthma caused by hyperreactivity and/or the

symptoms of bronchoconstriction, mucosal edema, increased secretions and cough. These can be treated by the application of CnT to the nasal cavity of patients with allergic rhinitis. It is well known in the art that allergic conditions of the nose can cause reflex changes in the lung that mimic or exacerbate asthma. (McCusker C et al
5 2002, Site-specific sensitization in a murine model of allergic rhinitis: Role of the upper airway in lower airway disease, J Allergy Clin Immunol, 110:891-898)

Perennial allergic rhinitis

Perennial rhinitis is a chronic condition and certain symptoms, such as nasal congestion, are more prominent than others such as sneezing. Therefore therapy for
10 this condition needs to be over more prolonged period, if not indefinitely. Although the same treatments as disclosed for seasonal allergic rhinitis can be used repeatedly, certain method of treatment as disclosed here that are more efficient and convenient for longer term therapy.

Parasympathetic neurons do not extend from the central nervous system to
15 their target organs in the nose. Instead parasympathetic preganglionic neurons have their cell bodies in the brain stem and have an axon that extends partway and synapses on the cell body of a second neuron called the postganglionic neuron. The axons of the postganglionic neurons extend into nose and sinuses and modulate many of the biological responses seen during allergic reactions. The cell body of the
20 post ganglionic parasympathetic neuron also receives collateral afferent synapses from sensory neurons that are stimulated during allergic reactions. Therefore much of the neuronal circuit involved in the allergic reaction converges onto the cell body of the postganglionic neuron.

All of the postganglionic neuron cell bodies are concentrated in small
25 structure called the sphenopalatine ganglion. Moreover all afferent synaptic connections on these neurons is cholinergic, the neurotransmitter most sensitive to BoNT. Therefore application of CnT to the sphenopalatine ganglion is the most efficient way of blocking the allergic neural reaction.

The sphenopalatine ganglion is accessible to needle injection via the
30 sphenopalatine canal. This canal passes through the hard palate and is accessible about one centimeter medial to the second molar. Injections of anesthetic and

vasoconstrictor agents are commonly performed by clinicians skilled in the art of nasal surgery.

Infectious rhinitis

Although they share some of the same symptoms, allergic rhinitis differs from
5 infectious rhinitis. The most common cause of infectious rhinitis is a viral infection,
known as the common cold. Bacterial and fungal infections of the nose occur also
but these are comparatively rare as primary events. During viral infections the
epithelial cells release secretions that trigger an inflammatory response. The classic
10 signs of calor, rubor and dolor; heat, redness, and pain characterize inflammation.
White blood cells such as macrophages and neutrophils migrate from small blood
vessels in the area to the infected mucosa. These cells in turn release a variety of
chemical mediators that increase the inflammation. Infectious rhinitis is characterized
by a purulent or pus like postnasal drip, and nasal congestion. In many viral
15 infections there are systemic symptoms such as fever. Treatment of viral infectious is
symptomatic with topical and systemic decongestants, and antipyretic and anti-
inflammatory drugs.

Vasomotor and other causes of rhinitis

Vasomotor rhinitis is strictly a neural hyper stimulation of the serous secretory
glands of the nose. This condition is characterized by a watery nasal discharge with
20 a very small content of mucus. Vasomotor rhinitis results directly from neural
stimulation of temperature changes or while eating, and associated other symptoms
such as congestion, and sneezing are not prominent. US 5,766, 605 discloses a
method of blocking the symptom of rhinorrhea in vasomotor rhinitis using clostridia
neurotoxins.

Serous otitis media

Direct reaction of the middle ear mucosa to allergens, or indirect effects by
blockage of the Eustachian tube, leads to serous otitis media. In this condition the
middle ear fills with fluid and hearing is impaired. As this condition most often affects
young children they are risk of learning disabilities due to the decreased hearing
30 acuity.

Sinusitis, a complication of rhinitis

Sinusitis is an infection of the sinuses. The sinuses are air filled cavities surrounding and opening into the nasal cavity via small openings called ostia. The maxillary sinuses compose the mass of the cheeks and the ostia are between the inferior and middle turbinate. The frontal sinuses are above the brow underneath the skin of the forehead, they open into the nasal cavity via a duct that enters beneath the middle turbinate. The sphenoid sinuses are in the nasopharynx and have ostia on their anterior surface. The ethmoid sinuses are located between the eyes and are composed of numerous small air cells. The anterior and posterior cells drain independently. The anterior ethmoid region is especially important due to the confluence of drainage ostia. The area is called the infundibulum, and a small amount of obstruction can cause widespread sinus infections.

Sinus infections are either acute or chronic. In acute sinusitis a bacterial infection follows a viral infection of the upper respiratory tract. However, sinusitis can also occur from obstruction of the draining ostia of the sinuses by inflammation or mass lesion. Topical nasal decongestants and systemic antibiotics are used to treat acute sinusitis. Severe or complicated infections may require surgical drainage of the involved sinus. Chronic sinusitis is a low-grade ongoing or recurrent infection of the sinuses. In these cases the mucosa of the sinuses has become thickened and enlarged due to edema and increased secretory glandular elements. In these cases small abscess may persist and relatively mild inflammatory stimuli may cause obstruction of the narrowed sinus ostia. Treatment of chronic sinusitis includes topical steroid sprays, systemic anti histamines and decongestants, and/or surgical removal of diseased mucosa with enlargement of the ostia.

Asthma

Asthma is a general term given to a similar constellation of symptoms: bronchospasm, mucosal swelling and increased secretions. Allergic stimulation, infections, irritating chemicals, cold air or exercise can trigger asthma.

Allergic asthma is a specific subset of asthma that is initiated by allergens and involves the IgE mediated reaction. Local and organ reactions include bronchial smooth muscle constriction, mucosal swelling and increased secretions.

Other Allergic conditions

Other allergic conditions include food allergies, and allergic dermatitis.

Clostridia neurotoxins (CnT)

Clostridium (C.) botulinum and the closely related species C. butyricum and
5 beratti produce an extremely powerful neurotoxin that causes the paralytic condition
known as botulism. The botulinum neurotoxin (BoNT) protein consists of a light and
heavy chain that together weigh approximately 150 kD. In botulism the primary target
is the synapse of the motor neuron with the muscle fiber. Here BoNT is taken up by
the membrane of the motor neuron and is internalized. The effect of BoNT is to
10 inhibit the release of neurotransmitters and neuropeptides by neurons. In clinical use
each serotype appears to differ in its potency in blocking different classes of neurons.

BoNT works by a two-stage mechanism, uptake and molecular action.
Peripheral nerve terminals take up BoNT. After translocation across the cell
membrane BoNT interferes with the molecular mechanism of neurosecretion.
15 Specifically, BoNT cleaves the proteins involved in synaptic vesicle docking and
release called the SNARE complex. The result is to block neural signals.

C. tetani produce tetanus neurotoxin (TeNT). TeNT is similar to the BoNTs in
that it interferes with vesicle release by cleaving VAMP, one of the SNARE family of
proteins. However the in vivo biological activity of TeNT is usually quite different from
20 BoNT. The systemic disorder tetanus results from TnT produced at a wound site and
disseminated throughout the body via the blood stream. The TeNT is taken up by
peripheral motor neurons and transported to the central nervous system. The TeNT
then preferentially blocks inhibitory neurons connecting to the motor neuron, thereby
allowing unopposed excitatory input. However, at higher doses TeNT and when
25 introduced directly into the neuron also blocks all neurons in the same manner as
BoNT. In this application it is assumed that the when BoNT is discussed is includes
the TeNT when used at higher blocking doses.

At present seven immunologically distinct serotypes of the BoNT are known,
named A, B, C, D, E, F and G. The type C serotype is now known to be divided into
30 three different toxins with distinct biological effects. Only C1 is a neurotoxin, whereas
C2 and C3 are not. C2 is distinctive for blocking actin formation, which can prevent
mast cell degranulation. Although all BoNT serotypes interfere with proteins that

cause the release of synaptic vesicles from cells they each interfere with different proteins, or different parts of the same protein:

BoNT A & E cleave SNAP-25 (synapse associated protein)

BoNT C cleaves SNAP-25 and syntaxin

- 5 BoNT B, D, F & G (and TeNT) cleave VAMP (vesicle associated membrane protein)

- Most if not all cell types use the vesicle system for secretion, although the molecules within these vesicles differ for each type of cell. If experimentally introduced into any cell BoNT appears capable of blocking its vesicle release.
- 10 However, in nature BoNT appears to be internalized into neurons, particularly the efferent neurons. The vesicles within neurons contain classical neurotransmitters (acetylcholine, epinephrine, nor epinephrine, dopamine, serotonin, glutamate, GABA and others) and/or neuropeptides (substance P, neurokinin A, calcitonin gene related peptide (CGRP), neuropeptide Y, interleukins, growth factors and others). Although
- 15 the highest affinity of BoNT is for cholinergic neurons, in various preparations BoNT has been shown to block secretion of all these molecules.

The clinical effects of botulinum toxin on different classes of neurons

Voluntary motor nerves

- The first and still primary use of BoNT is to block motor nerve communication
- 20 with muscle fibers. BT is injected within the target muscle. The BoNT is then internalized into motor neurons where it decreases or stops the release of the neurotransmitter acetylcholine (AChE), thereby causing paresis or paralysis of the muscle. Scott introduced the concept of localized muscular injections of BoNT in the specific condition of strabismus (squint, crossed eyes). Later BoNT was found to be
- 25 particularly useful for movement disorders such as tics, spasms, contractures, cramps and tremors. More recently, the injection of BoNT into facial muscles has been found to ameliorate skin wrinkling and lines related to aging. Another recent application of BoNT injections is to decrease the pain accompanying muscle tension in conditions such as headache and temporo-mandibular joint syndrome.

Autonomic motor neurons

Effector neurons of the autonomic system innervate and control the contraction of smooth muscles using AChE as the neurotransmitter. Injections of BoNT have been used to decrease tone in the smooth muscles of the lower esophageal sphincter, esophagus, stomach wall, and pyloric sphincter, sphincter of Odi, anal sphincter, and urinary bladder.

Autonomic secretory neurons

Effector neurons of the autonomic system control or modulate the secretion of various water and mucoid fluids throughout the body. BoNT injections have been used to decrease sweating, salivary gland flow, gastric secretions including acid production, nasal and other respiratory secretions, and tearing.

Sensory neurons

Sensory neurons release a wide variety of neuropeptides, cytokines, growth factors and other substances that effect parenchymal cells, blood vessels and immune cells. Notable is that these substances can activate mast cells directly thereby extending the allergic reaction. Except for nitrous oxide these substances are released via the SNARE mechanism and can be blocked by CnT.

SUMMARY OF THE INVENTION

As used herein 'local administration' includes but is not limited to injection by needle and in-dwelling catheter (including pressure jet injectors), topical administration in lyophilized powder, liquid solutions, creams, ointments, aerosolized or introduced by liposomal (niosomes) vectors, or as nucleic acid introduced by viral or other vectors. The CnT may also be embedded in biopolymers or delivered by implanted pumps to release the CnT into solution over prolonged periods.

By "therapeutically effective amount" it is meant of purposes of this invention that the CnT is administered in a non-toxic amount sufficient to cause reduction in the occurrence or magnitude of the symptoms being targeted.

By "unit" it is meant the biological equivalent of the current unit measure used for botulinum toxin A marketed as Botox. At present BoNT is measured by biological assay; a unit of BoNT is the amount that causes death to 50% of mice when injected intraperitoneally. BoNT-A is marketed as Botox by Allergan Corp, Irvine Ca, and as
5 Dysport by Ipsen Ltd, Berks United Kingdom. Although the biological assay is done the same way the in vivo effect of Botox and Dysport vary. BoNT-B is marketed as Myobloc by Elan Pharmaceuticals, Dublin, Ireland. TeNT is not commercially available but other assays have compared the potency of the blocking effect of TeNT to BoNT. All serotypes of BoNT as well as TeNT are commercially available from List
10 Biological laboratories). A therapeutically effective amount of BoNT will vary depending on the organ to be treated, how much of the organ will be treated, the method of application and the exact preparation of BoNT used. A therapeutically effective amount will vary from a fraction of a unit to hundreds of units as is it currently does with intramuscular injections. The exact dosage will not require undo
15 experimentation by those skilled in the art.

Where solutions or suspensions of BoNT or CnT are referred to, unless indicated to the contrary, this means the designated number of units in 1 ml of Normal saline.

By "CnT" it is meant that any biological substance having essentially the
20 same biological effect within cells as the wild types of clostridia neurotoxins. Specifically, to block or decrease the activity of the SNARE family of proteins involved in secretion of allergy related neurohumors. Numerous substitutions for the major parts of the CnT have been disclosed and these are all included in this specification. This would include fragments, altered forms, and recombinant forms of
25 CnT. Also included are chimeras, hybrids and conjugates. Also included are the use of DNA and RNA sequences that are directly applied and translated in the allergic sites. Also included are "vectors", various compositions that deliver a botulinum or tetanus toxin light chain or its equivalent such as Protease A across cell membranes. These vectors include but are not limited to viruses, liposomes, noisomes, and
30 protein transduction domains (US Provisional Application 60/449,107).

Allergic "neurohumors" are neurotransmitters, neuropeptides and cytokines that participate in allergic reactions and whose secretion or action can be blocked by CnT. They include acetylcholine, noradrenaline, neuropeptide Y, substance P,

calcitonin gene reactive protein (CGRP), histamine, nerve growth factor, and interleukins.

The invention is directed to a method of blocking or reducing physiological reaction in a mammal, suitably but not limited to *H. sapiens*, to the interaction of IgE antibodies present in said mammal upon contact with the corresponding antigen. This blocking is achieved by the administration to said mammal of a therapeutically effective amount of a neurotoxin (CnT) derived from *Clostridia* sp. Suitably, the CnT is derived from a species of *Clostridia* selected from the group consisting of *C. botulinum*, *C. butyricum*, *C. beratti*, *C. tetani*. The neurotoxins (BoNT), derived from *C. botulinum*, are derived from serotypes A, B, C1, D, E, F and G, while neurotoxin (TeNT), is derived from *C. tetani*.

BoNT/A is marketed as Botox® by Allergan Inc and as Dysport® by Ipsen Ltd as a lyophilized powder that is reconstituted with preservative free normal saline prior to use. BoNT/B is marketed as Myobloc® by Elan Pharmaceuticals in normal saline solution. The light chains and holotoxins for each BoNT serotypes and TeNT can be obtained from List Biological Labs and/or Metabologics Inc.

CnT compositions of the present inventions are prepared in a variety of forms depending on whether the composition is injected or implanted, topically applied to respiratory mucosa of the nasal cavity or lungs, gastrointestinal mucosa, or to skin.

For all injectable CnT compositions fluid dosage forms are prepared utilizing the compound and a pyrogen-free sterile vehicle. The compound, depending on the vehicle and concentration used, can be either dissolved or suspended in the vehicle. In preparing solutions the compound can be dissolved in the vehicle, the solution being made isotonic if necessary by addition of sodium chloride and sterilized by filtration through a sterile filter using aseptic techniques before filling into suitable sterile vials or ampoules and sealing. Alternatively, if solution stability is adequate, the solution in its sealed containers may be sterilized by autoclaving. Advantageously additives such as buffering, solubilizing, stabilizing, preservative or bactericidal, suspending or emulsifying agents and/or local anaesthetic agents may be dissolved in the vehicle.

Dry powders, which are dissolved or suspended in a suitable vehicle prior to

use, may be prepared by filling pre-sterilized drug substance and other ingredients into a sterile container using aseptic technique in a sterile area. Alternatively the drug and other ingredients may be dissolved into suitable containers using aseptic technique in a sterile area. The product is then freeze-dried and the containers are
5 sealed aseptically.

In the respiratory and gastrointestinal systems, CnT binds to mucosal epithelial cells and is actively transcytosed across the mucosa. Compositions suitable for administration to the respiratory tract include aerosols, nebulisable
10 solutions or micro-fine powders for insufflation. In the latter case, particle size of less than 50 microns, especially less than 10 microns, is preferred.

Compositions suitable for topical mucosal application include normal saline solutions as described above for injections. Other suitable compositions include gels
15 and creams.

The skin presents a formidable barrier to the application of CnT. CnT may be mechanically propelled across the dermal barrier with air or water pressure injectors or in association with micro-pellets. Other suitable forms of transdermal delivery
20 include iontophoresis. CnT may be encapsulated into liposomes or niosomes to form suitable trans-dermal compositions.

The method of administration may take many forms, including topical, intra-dermal, sub-cutaneous, trans-cutaneous, intra cavital and by inhalation of the CnT in
25 a suitable carrier. Examples of such administration include, but are not limited to contact with absorbant pledgets having CnT absorbed thereon, contact with biodegradable micropellets having CnT embedded therein. Also included is injection, for example, injection to the nasal mucosa or injection into the pterygoplatine space through the palate, or injection into affected areas of the surface skin. More
30 invasively, by myringotomy and injection into the middle ear space. tympanic membranes. Alternatively less invasive methods include by drops into the inner eyelid and inhalation of an aqueous mist containing same.

The physiological reaction reactions dealt with herein include but are not limited to conditions such as allergic rhinitis, Infectious rhinitis, vasomotor rhinitis, serous otitis media, sinusitis, asthma, food allergies and allergic dermatitis.

5 The amount of CnT administered per administration may be, but is not limited to between about 0.1 and about 1000 units, suitably between about 1 and about 100 units per administration, preferably between about 1 and about 20 units.

10 The invention is also directed to use of a neurotoxin (CnT) derived from Clostridia sp for the production of a medicament for blocking or reducing physiological reaction in a mammal to the interaction of IgE antibodies present in said mammal upon contact with the corresponding antigen. The formulations of CnT, including BoNT and TeNT, which are suitable for the purposes designated herein are well known, but have not previously been designated for this purpose.

15 There is a great need for an effective treatment for allergic disorders. It has long been thought that the allergic reaction involved only histamine release by mast cells. Therefore first line therapy for allergy was antihistamines, or more recently the non-sedating antihistamines. Other therapies are directed to block the effects of the mast cell secretions with adrenergic agonists. It is not obvious to those skilled in the art that a central role in allergic disorders involves the autonomic nervous system and that this nerve activity can be blocked by CnT for a beneficial effect.

20 It is an object of the invention to provide a treatment for allergic conditions. Included particularly are allergy related rhinitis, asthma, gastroenteritis, serous otitis, sinusitis and dermatitis) and their related conditions (such as sinusitis and serous otitis media that occur secondary to allergy induced mucosal swelling). Treatment is by local application of therapeutically effective amounts of CnTs to the body structure and/or the nerves and nerve ganglia supplying these structures. CnT interfere with
25 the allergic process by:

- 1) Directly blocking neuroimmune secretions by the mast cell or other immune cell types including but not limited to eosinophils ()
- 2) Block the release of neurohumors by mast cells induced by autonomic
30 nerve activity.
- 3) Decrease neurohumoral release during axonal reflexes.

- 4) Decrease the parasympathetic effector arm of reflex allergic responses
- 5) Decrease the increased tonic activity of the autonomic system that is related to prior allergic reactions.
- 6) Decrease the enlargement and hypersensitivity of sensory nerves induced by nerve growth factor and other neurohumors released during allergic reactions.
- 7) Reverse certain complications of allergic reactions such as mucosal thickening by decreasing autonomic nerve activity.

The beneficial effect of this treatment in the:

- 1) Nasal area, is to decrease the symptoms of sneezing, itching, nasal congestion and post nasal drip, as well as related conditions including nasal polyps and mucosal thickening, and complications such as sinusitis and serous otitis.
- 2) Lungs, is to decrease coughing and wheezing (bronchoconstriction, edema) and the non-specific sensory hypersensitivity related to chronic allergic reactions.
- 3) Eye, is to decrease itching, tearing and redness.
- 4) Skin, is to decrease itching and swelling.
- 5) Gastrointestinal tract, is to decrease gastrointestinal dysmotility.

Examples

Example 1. Seasonal allergic rhinitis

1a) A 30-year-old male has seasonal allergic rhinitis. In May, prior to pollen formation, 30 units of BoNT topically applied in each nostril. Specifically, the nasal cavity is sprayed with a solution of 1% lidocaine and ½% neosynephrine to anesthetize and decongest the nasal mucosa, respectively. Then 1 cc of normal saline containing 30 units of BoNT is sprayed into each nasal cavity. This method of delivery, although commonly used for application of nasal medication, is inherently inefficient as a significant percentage of a sprayed medication will exit the posterior nasal cavity and be exhaled or swallowed.

1b) In another embodiment, the patient is treated by placing 1 x 3 cm² cotton pledgets impregnated with 20 units of BoNT onto the medial surface of the turbinates and left for one hour, then removed by the physician. This delivery method is more efficient than a spray, however a significant percentage of the BoNT will not diffuse from the pledgets to the mucosa.

1c) Alternatively, the patient has topical anesthesia applied only to a localized area, preferably the anterior end of the inferior turbinate. Then, patient has a 1cm² cotton pledget impregnated with 10 units of BoNT placed onto the mucosa of the anterior turbinate for one hour and then removed. Within the nasal cavity a mucociliary blanket transports fluids and particles posteriorly, thereby distributing the BoNT. This is an example of applying a BoNT to a localized region of the nasal cavity and using the normal physiology of the nasal cavity for distribution. The routes of mucociliary clearance of the nose and sinus cavities are known so that other variations of this method are apparent to those skilled in the art.

1d) In another embodiment, using a topical biodegradable depot to deliver BoNT over an extended time period to nasal mucosa is used for treating the patient. Various biodegradable compounds are known in the art that vary in consistency and rate of dissolution.

An example is oxidized cellulose (marketed as Surgicel® by Johnson & Johnson, New Brunswick, NJ). The oxidized cellulose can be manufactured with BoNT as an integral component, or the BoNT can be added to the oxidized cellulose before its clinical use. Surgicel is available in the form of a thin flexible sheet that is

often cut to fit the area of the body to which it will be applied. For intranasal use the size may vary from a few square millimeters to a 4 by 8 cm² sheet that could contact the entire exposed mucosa of the nasal cavity. BoNT can be added to the Surgicel as a lyophilized powder or after reconstitution into solution. If added as a powder it can homogeneously applied onto one side of the Surgicel and the material can be folded. The material is then moistened with normal saline to bind the material together and immobilize the BoNT prior to clinical use. In contrast the BoNT can first be constituted into solution and then absorbed into the material.

As an example a 2 x 6 cm² piece of oxidized cellulose is saturated with 1 cc of normal saline containing a total of 10 units of BoNT. Using a nasal speculum the nostril is dilated and the nasal cavity is visualized and the saturated cellulose placed therein. The cellulose will gradually dissolve over hours while releasing a small continual dose of BoNT directly onto the nasal mucosa.

Alternatively the patient is given 0.5 cc. of normal saline containing 5 units of BoNT is applied to the oxidized cellulose which is grasped with bayonet forceps and placed flat onto the medial surface of the anterior end of the inferior turbinate of each nasal cavity. As disclosed above the mucociliary action of the nasal mucosa transports liquids and particles from the anterior to posterior nasal cavity.

1e) In another embodiment the patient is injected with BoNT solution directly into the nasal mucosa. After anesthetizing and decongesting the mucosa, 5 units of BoNT in 1 cc of saline are injected beneath the mucosa throughout the length of the inferior turbinate with a 25 gauge spinal needle coupled to a 1 cc syringe.

1f) Alternatively the patient can be treated with TeNT.

Compositions of TeNT for intranasal administration, can range in dose from .1 to 1000 units in 0.1cc to 10 cc of solution. One preferable composition is 10 units of TeNT in 1 cc of normal saline.

As an example the same patient is treated by spraying each nostril with 1 cc of normal saline solution containing 10 units of TeNT.

Alternatively, if only decongestion is desired 10 units of TeNT can be topically applied.

In another embodiment, 1 unit of recombinant DNA coding for TeNT is pressure injected across the nasal mucosa to transfect mucosal cells. These cells then express the TeNT for months.

Example 2. Perennial allergic rhinitis

5 2a) Direct injection of the sphenopalatine ganglia.

A 40-year-old female has chronic nasal congestion due to perennial rhinitis. Skin testing demonstrates that she is allergic to numerous environmental antigens and intranasal examination shows enlarged turbinate mucosa and nasal polyps. Testing of nasal secretions shows eosinophilia. An injection of 20 units of BoNT in a
10 1cc solution of normal saline is made through the sphenopalatine canal into the area of the sphenopalatine ganglia.

In another embodiment, 100 units of BoNT embedded in 0.1 micron biodegradable pellets suspended in solution is injected into the mucosa of each turbinate to slowly release its contents over 6 months.

15 Alternatively a biodegradable carrier containing 5 units of BoNT is placed intranasally in the most superior and posterior aspect of the lateral nasal wall. This permits the BoNT to diffuse across the nasal wall to the underlying sphenopalatine ganglia.

20

Example 3. Serous otitis media

A 3-year male has a history of serous otitis media. Under general anesthesia a myringotomy is made into the tympanic membranes and 2 units of BoNT in .5 cc of normal saline is injected.

25

Example 4. Sinusitis

A fifty-year-old male has a history of allergic rhinitis and recurrent sinusitis. Ten units of BoNT are injected through the palate into the pterygopalatine space to block the sphenopalatine ganglion.

30

Example 5. Allergic dermatitis.

A seventy-year-old male has severe allergic dermatitis of the forearm skin. Each forearm is injected with 10 injections of 0.3 units BoNT in 0.1 cc of normal saline. Each injection is made intradermally at 3 cm intervals.

5

Example 6. Allergic asthma

A 13-year-old boy has severe allergic asthma. He is treated by bimonthly inhalation therapy of an aerosilized solution of 5 units of botulinum toxin in 5 cc of normal saline.

10 Alternatively the same botulinum solution can be injected directly into the trachea and bronchi. After injecting local anesthesia into the skin overlying the cricothyroid membrane a needle is passed directly through the skin and cricothyroid membrane and the BoNT solution is sprayed into the trachea. The solution drips down to reach the bronchial mucosa where it is topically absorbed. and is absorbed

15

Example 7 Allergic rhinitis

A 40 year old male has allergic rhinitis and an associated reflex chronic cough. Application of CnT to the nasal cavity as described above or alternatively injected or aerosilized topical application of BoNT to the lungs is used to treat the

20 cough.

Example 8. Food allergies

A 10-year-old boy with food allergies manifested by bloating and diarrhea is treated with a rectal suppository containing 50 units of BoNT. The suppository is composed

25 of biocompatible material designed to be solid at room temperature but to dissolve at body temperature. Sufficient materials for the composition are cocoa butter, glycerinated gelatin, hydrogenated vegetable oils, polyethylene glycols of various molecular weights and fatty esters of polyethylene glycol.

30 **Example 9. Infectious rhinitis**

Chronic allergic exposure causes the nervous system to become hyper responsive to non-allergic stimulation such as that caused by viral infections.

A patient with rhinitis is given 10 units of BoNT and 5 units of TeNT prior to spring.

I Claim

1. A method of blocking or reducing physiological reaction in a mammal to the interaction of IgE antibodies present in said mammal upon contact with the corresponding antigen, by the administration to said mammal of a therapeutically effective amount of a neurotoxin (CnT) derived from *Clostridia* sp.
5
2. The method of claim 1 wherein the mammal is a member of *H. sapiens*.
3. The method of claim 2 wherein the neurotoxin is derived from a species of *Clostridia* selected from the group consisting of *C. botulinum*, *C. butyricum*, *C. beratti*, *C. tetani* .
10
4. The method of claim 3 wherein the neurotoxins (BoNT), derived from *C. botulinum*, are derived from serotypes A, B, C1, D, E, F and G
15
5. The method of claim 3 wherein the neurotoxin (TeNT) is derived from *C. tetani*.
6. The method of claim 1 wherein CnT is administered by contact with absorbant pledgets having CnT absorbed thereon.
20
7. The method of claim 1 wherein CnT is administered by contact with biodegradable carrier containing CnT .
8. The method of claim 1 wherein CnT is administered by injection.
25
9. The method of claim 1 wherein CnT is administered by myringotomy into tympanic membranes.
10. The method of claim 1 wherein CnT is administered by injection into the pterygoplatine space through the palate.
30
11. The method of claim 7 wherein CnT is administered to pass through the nasal wall to the sphenopalatine ganglia .
- 35 12. The method of claim 1 wherein CnT is administered by inhalation of an aqueous mist containing same.

13. The method of claim 1 wherein CnT is administered by injection to the nasal mucosa.
- 5 14. The method of claim 1 wherein CnT is administered by application of a suppository containing same.
- 10 15. The method of claim 1 wherein the physiological reaction is manifested by a condition or symptoms selected from the group consisting of allergic rhinitis, infectious rhinitis, serous otitis media, sinusitis, pulmonary disease, food allergies, allergic dermatitis, and sneezing, coughing, itching and excess mucous secretion related to allergic reactions.
- 15 16. The method of claim 15 wherein the pulmonary disease is selected from the group consisting of bronchitis, emphysema and hypereactive asthma.
17. The method of claim 1 wherein CnT is administered by contact with absorbant pledgets having CnT absorbed thereon.
- 20 18. The method of claim 1 wherein the amount of CnT administered per administration is between about 0.1 and about 1000 units per administration.
- 25 19. The method of claim 1 wherein the amount of CnT administered per administration is between about 1 and about 100 units per administration.
- 30 20. The method of claim 1 wherein the amount of CnT administered per administration is between about 1 and about 20 units per administration.
- 35 21. The use of a neurotoxin (CnT) derived from Clostridia sp for the production of a medicament for blocking or reducing physiological reaction in a mammal to the interaction of IgE antibodies present in said mammal upon contact with the corresponding antigen.
22. The use of claim 21 wherein the physiological reaction is manifested by a condition selected from the group consisting of allergic rhinitis, infectious rhinitis, serous otitis media, sinusitis, pulmonary disease, food allergies , allergic

dermatitis and sneezing, coughing, itching and excess mucous secretion related to allergic reactions.

- 5 23. The use of claim 22 wherein the pulmonary disease is selected from the group consisting of asthma and/or the symptoms of broncho-constriction, bronchitis, mucosal edema, emphysema increased secretions and cough,
- 10 24. A medicament for blocking or reducing physiological reaction in a mammal to the interaction of IgE antibodies present in said mammal upon contact with the corresponding antigen comprising a neurotoxin (CnT) derived from *Clostridia* sp and a pharmacologically acceptable carrier.

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property
Organization
International Bureau



(43) International Publication Date
10 June 2004 (10.06.2004)

PCT

(10) International Publication Number
WO 2004/048519 A3

(51) International Patent Classification⁷: **A61K 39/00**,
39/395, 39/02, 38/00, C07K 1/00

LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW,
MX, MZ, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC,
SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA,
UG, UZ, VC, VN, YU, ZA, ZM, ZW.

(21) International Application Number:
PCT/US2003/037286

(22) International Filing Date:
20 November 2003 (20.11.2003)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
60/427,749 21 November 2002 (21.11.2002) US

(84) Designated States (*regional*): ARIPO patent (BW, GH,
GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW),
Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM),
European patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE,
ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE,
SI, SK, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA,
GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Declaration under Rule 4.17:

— *of inventorship (Rule 4.17(iv)) for US only*

Published:

— *with international search report*
— *before the expiration of the time limit for amending the
claims and to be republished in the event of receipt of
amendments*

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(88) Date of publication of the international search report:
1 July 2004

(81) Designated States (*national*): AE, AG, AL, AM, AT, AU,
AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU,
CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH,
GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC,

*For two-letter codes and other abbreviations, refer to the "Guid-
ance Notes on Codes and Abbreviations" appearing at the begin-
ning of each regular issue of the PCT Gazette.*

(54) Title: TREATMENT OF MAMMALIAN REACTION TO IGE INTERACTIONS

(57) Abstract: A method is disclosed for blocking or reducing physiological reaction in a mammal to the interaction of IgE antibodies present in said mammal upon contact with the corresponding antigen, by the administration to said mammal of a therapeutically effective amount of a neurotoxin (CnT) derived from Clostridia sp.

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US03/37286

A. CLASSIFICATION OF SUBJECT MATTER

IPC(7) : A61K 39/00, 39/395, 39/02, 39/08, 38/00; C07K 1/00

US CL : 424/236.1, 234.1, 239.1, 247.1, 810, 805; 530/825, 350; 514/2, 826, 886, 849

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 424/236.1, 234.1, 239.1, 247.1, 810, 805; 530/825, 350; 514/2, 826, 886, 849

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
Please See Continuation Sheet

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X --- Y	WO 95/28171 A1 (MOUNT SINAI SCHOOL OF MEDICINE OF THE CITY UNIVERSITY OF NEW YORK) 26 October 1995 (26.10.1995), claims; Examples; and Summary of the invention	1-4, 6-15, 17-22 and 24 ----- 5, 16 and 23
X --- Y	SHAARI, C.M. et al. Rhinorrhea is decreased in dogs after nasal application of botulinum toxin. Otolaryngology-Head and Neck Surgery. April 1995, Vol. 112, No. 4, 566-571, entire document.	1-4, 11-13, 15 and 24 ----- 5-10, 14, 16-23

☐ Further documents are listed in the continuation of Box C.

☐ See patent family annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search

14 April 2004 (14.04.2004)

Date of mailing of the international search report

24 MAY 2004

Name and mailing address of the ISA/US

Mail Stop PCT, Attn: ISA/US
Commissioner for Patents
P.O. Box 1450
Alexandria, Virginia 22313-1450

Facsimile No. (703)305-3230

Authorized officer

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Telephone No. (703) 308-0196

Form PCT/ISA/210 (second sheet) (July 1998)

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US03/37286

Box I Observations where certain claims were found unsearchable (Continuation of Item 1 of first sheet)

This international report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claim Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
2. ☐ Claim Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
3. ☐ Claim Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of Item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:
Please See Continuation Sheet

1. ☒ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐
☐

The additional search fees were accompanied by the applicant's protest.

No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Continuation of Item 4 of the first sheet:

The title shall be short and precise, PCT Rule 4.3, suggested new title follows: "TREATMENT OF MAMMALIAN REACTION TO IGE INTERACTIONS"

BOX II. OBSERVATIONS WHERE UNITY OF INVENTION IS LACKING

This application contains the following inventions or groups of inventions which are not so linked as to form a single general inventive concept under PCT Rule 13.1. In order for all inventions to be examined, the appropriate additional examination fees must be paid.

Group I, claims 1-20, drawn to a method of blocking physiological reaction to the interaction of IgE with the corresponding antigen in a mammal by administering a clostridial neurotoxin.

Group II, claims 21-23, drawn to the use of a clostridial neurotoxin for the production of a medicament.

Group III, claim 24, drawn to a medicament comprising a clostridial neurotoxin and a pharmaceutically acceptable carrier.

The inventions listed as Groups I-III do not relate to a single general inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, they lack the same or corresponding special technical features for the following reasons:

The special technical feature of invention I is a method of blocking physiological reaction to the interaction of IgE with the corresponding antigen in a mammal by administering a clostridial neurotoxin.

However, such a method is already disclosed in the prior art, for example, by Shaari *et al.* (*Otolaryngology-Head and Neck Surgery* 112 (4): April 1995. See abstract; Methods; Results; and Discussion. The special technical features of inventions II and III respectively are the use of a clostridial neurotoxin for the production of a medicament, and a medicament comprising a clostridial neurotoxin. These are also disclosed in the prior art, for example, by MOUNT SINAI SCHOOL OF MEDICINE OF THE CITY UNIVERSITY OF NEW YORK (WO 9528171). The special technical features do not define over the prior art.

Continuation of B. FIELDS SEARCHED Item 3:

DIALOG, WEST, MEDLINE, TOXLINE, BIOSIS, EMBASE, DERWENT

clostrid?, neurotoxin?, BOTOX, IgE, allerg?, rhinitis, otitis, sinusitis, dermatitis, sneez?, cough?, itch?

(19) World Intellectual Property
Organization
International Bureau



(43) International Publication Date
25 November 2004 (25.11.2004)

PCT

(10) International Publication Number
WO 2004/101028 A2

(51) International Patent Classification⁷: **A61M**
(21) International Application Number:
PCT/US2004/015222
(22) International Filing Date: 13 May 2004 (13.05.2004)
(25) Filing Language: English
(26) Publication Language: English

(30) Priority Data:
10/437,882 13 May 2003 (13.05.2003) US

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(81) Designated States (unless otherwise indicated, for every
kind of national protection available): AE, AG, AL, AM,
AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN,
CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI,
GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE,
KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD,
MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG,
PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM,
TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM,
ZW.

(84) Designated States (unless otherwise indicated, for every
kind of regional protection available): ARIPO (BW, GH,
GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM,
ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM),
European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI,
FR, GB, GR, HU, IE, IT, LU, MC, NL, PL, PT, RO, SE, SI,
SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ,
GW, ML, MR, NE, SN, TD, TG).

Published:

— without international search report and to be republished
upon receipt of that report

For two-letter codes and other abbreviations, refer to the "Guid-
ance Notes on Codes and Abbreviations" appearing at the begin-
ning of each regular issue of the PCT Gazette.

(54) Title: APPARATUS AND METHODS FOR TREATING ASTHMA USING NEUROTOXIN

(57) Abstract: Apparatus providing intrabronchial delivery of neurotoxin to control the effects of asthma comprises a shaft having proximal and distal ends and a neurotoxin applicator assembly disposed on the distal end, wherein the neurotoxin applicator assembly comprises a deployable needle assembly, a rotating needle assembly, a needle-less injection assembly, a nebulizer assembly or a microporous tip. Further embodiments involve apparatus comprising drug-eluting bioabsorbable stents having one or more layers of asthma-fighting drugs.

APPARATUS AND METHODS FOR TREATING ASTHMA
USING NEUROTOXIN

Field of the Invention

[0001] The present invention relates to apparatus for treating asthma by controlled delivery of neurotoxin
5 using a neurotoxin applicator assembly.

Background of the Invention

[0002] The lung is made up of progressively smaller bronchial bifurcations stemming downward from the trachea. The trachea and proximal bronchi are lumens
10 consisting of an outer layer of fascia surrounding a U-shaped inner cartilaginous layer, wherein the open portion of the U is spanned by smooth muscle. Inside the cartilaginous layer are a collagenous elastic layer and an innermost epithelial layer. Mucus secreting goblet
15 cells and transport ciliary cells are interspersed within these inner layers.

[0003] As the bronchi branch and get smaller, the cartilaginous layer changes from a U-shape to irregular and helical shapes. In addition, the smooth muscle layer
20 becomes helical bands surrounding the entire circumference of the bronchi, the goblet cells gradually decrease in numbers and the ciliated cells get smaller

and fewer in number. In the most distal bronchi, the outer cartilaginous layer disappears completely, the smooth muscle layer becomes the outermost layer and goblet cells and ciliated cells disappear completely.

5 **[0004]** Asthma is a complex disease of the bronchial tree, characterized by airway hyperresponsiveness to allergens, stress and environmental triggers. Environmental triggers include irritants such as pollutants and non-allergenic triggers such as exposure
10 to cold air. Airway hyperresponsiveness results in acute narrowing of the entire bronchial tree reducing airflow through the lungs, compromising respiration and limiting gas exchange in the alveoli. The narrowing of the bronchial tree is a result of three basic characteristic
15 physiologic responses: (1) smooth muscle contraction; (2) increased mucus production; and (3) edema caused by arterial dilatation and increased arterial permeability. The triggering mechanisms for these physiologic responses are part of the body's inflammatory response system.

20 **[0005]** Chronic uncontrolled asthma can result in structural changes to the bronchial wall itself. Smooth muscle hyperplasia results in thickening of the smooth muscle components of the bronchial wall. Thickening of the subepithelial collagen layer that lies between the
25 airway epithelium and the smooth muscle layer results in progressive stiffening of the wall of the bronchi. Studies have shown that stiffening of the airway wall results in more profound narrowing of the airway for a given asthma attack. This is due to changes in the
30 ability of the mucosal layer to fold in response to the smooth muscle layer contraction.

[0006] Recently, the controlled injection of neurotoxin has become a common procedure for controlling

skeletal muscle spasms. A frequently used neurotoxin for this procedure is the botulinum toxin, serotype A, sold commercially by Allergan, Inc. as Botox™. Botulinum toxin blocks the release of neurotransmitter from the nerves that control the contraction of the target muscles. Many applications for botulinum toxin have been proposed and/or clinically tested, including cervical dystonia, cosmetic relief of frown lines and tremor associated with cerebral palsy. Recently, botulinum toxin has become the subject of clinical study for the relief of hyperhidrosis (profuse sweating) and hypersalivation. These studies indicate that botulinum toxin can be used to control the action of cholinergic parasympathetic nerves as well as large skeletal muscle groups. The recent findings open the possibility of using neurotoxins such as botulinum toxin to control some of the main mechanisms of airway narrowing in asthmatic attacks, specifically smooth muscle contraction and hypersecretion of mucus from the goblet cells. Additionally, there is evidence that some part of the inflammatory response of asthma is stimulated by the release of the neurotransmitters that botulinum toxin inhibits. This opens the possibility that botulinum toxin also may work to mitigate the inflammatory cycle itself.

[0007] The use of neurotoxin for the control of asthma is described in U.S. Patent No. 6,063,768 to First, wherein asthma is included in a list of neurogenic inflammatory disorders that may be controlled through the action of neurotoxins such as botulinum toxin but does not describe the methods or devices used to do so. An earlier patent, U.S. Patent No. 5,766,605 to Sanders, et.al., describes the use of botulinum toxin to treat

asthma and COPD. That patent also describes that botulinum toxin could be aerosolized and introduced into the lungs. Further mention of botulinum toxin in connection with asthma is provided in a press release
5 dated February 7, 2003 by the University of Alberta in describing the work of Dr. Redwan Mogbel. The release mentions that Dr. Mogbel and others are researching the possible use of neurotoxins such as tetanus and botulinum toxin to prevent eosinophils from activating and starting
10 the inflammatory cascade that results in an asthma attack.

[0008] While it may be possible to simply aerosolize neurotoxins for introduction into the lungs, introducing it into the patient through traditional inhalation means
15 would expose the mouth, tongue, epiglottis, vocal cords, etc. to the actions of the neurotoxin, with obvious deleterious results. Much more controlled and direct application of the neurotoxin to the desired tissue is required for safe and effective therapy.

20 [0009] Accordingly, it would be desirable to provide apparatus that enables controlled delivery of a neurotoxin to target treatment areas within a patient's bronchial airways.

[0010] It also would be desirable to provide an
25 apparatus permitting the controlled injection of neurotoxin into the bronchial wall of a patient.

[0011] It would further be desirable to provide a needle-less injection apparatus to eliminate potential complications related to the presence of needles within a
30 patient's bronchial airways.

[0012] Additionally, it would be desirable to provide an apparatus permitting the application of neurotoxin

onto a target treatment area within a patient's bronchial airways.

[0013] In addition, implantable drug eluting devices for treating various diseases also have been developed. Examples include drug eluting coronary stents such as those under clinical investigation and commercial sale from such companies as Boston Scientific and Cordis Corporation. Bioabsorbable devices for drug delivery have likewise been contemplated, such as those under development by Synecor, Inc. (recently acquired by Guidant), and by numerous university and hospital-based development efforts. Examples of such efforts are provided in Blindt, et al., *Development of a New Biodegradable Intravascular Polymer Stent with Simultaneous Incorporation of Bioactive Substances*, Int'l J. Artif. Organs, 22(12):843-853 (1998) and Tsuji, et al., *Biodegradable Stents as a Platform to Drug Loading*, Int'l J. Cardio. Interv., 13-16 (2003).

[0014] Other uses for biodegradable stents include restoring patency of the urethra following treatment of prostatic hyperplasia and maintaining the patency of bronchial airways after impingement by lung tumors. Biodegradable and non-biodegradable implants for the controlled release of neurotoxin for the treatment of various diseases is described in U.S. Patent Nos. 6,306,423, 6,506,399 and 6,383,509. Further, U.S. Patent No. 5,766,605 describes the use of neurotoxin to treat autonomic nerve dysfunction, including specific claims involving treating asthma and chronic obstructive pulmonary disease (COPD). Additionally, U.S. Patent Publication No. 2002/0082197 describes the use of neurotoxin for treating mucus secreting disease, such as asthma and COPD, as does WO 00/10598.

[0015] It further would be desirable to provide implantable apparatus that provides a sustained or periodic dosage of asthma-fighting drugs to a target treatment area within a patient's bronchial airways.

5 Summary of the Invention

[0016] In view of the foregoing, it is an object of the present invention to provide apparatus that enables the controlled delivery of a neurotoxin to target treatment areas within a patient's bronchial airways.

10 [0017] It is a further object of the present invention to provide an apparatus permitting the controlled injection of neurotoxin into the bronchial wall of a patient.

[0018] It is an additional object of the present
15 invention to provide a needle-less injection apparatus to eliminate potential complications related to the presence of needles within a patient's bronchial airways.

[0019] It is another object of the present invention to provide an apparatus permitting the application of
20 neurotoxin onto a target treatment area within a patient's bronchial airways.

[0020] It still further is an object of this invention to provide implantable apparatus that provides a sustained or periodic dosage of asthma-fighting drugs to
25 a target treatment area within a patient's bronchial airways.

[0021] These and other objects of the present invention are accomplished by providing an intrabronchial neurotoxin delivery system for controlled delivery of
30 neurotoxin to a target treatment area within a patient's bronchial airways to lessen the effects of asthma. The introduction of neurotoxin into the bronchial airways

disables the hyperresponsive smooth muscle layer and controls the hypersecretion of mucus.

[0022] In accordance with a first aspect of the present invention, the intrabronchial neurotoxin delivery system comprises neurotoxin applicator assembly. The distal end of the neurotoxin applicator assembly may comprise a needle tip, a rotating needle assembly, a needle-less injection assembly, a nebulizer, or a micro-porous tip. This and all following applicator embodiments may be designed to work through or in concert with a standard bronchoscope, or may be incorporated into a stand-alone system for accessing and treating the airways.

[0023] In accordance with this aspect of the invention, the neurotoxin applicator assembly comprises an elongated shaft having a lumen in fluid communication with a source of liquid neurotoxin. The distal end of the shaft includes one or more needles that are preformed to contract radially when disposed within a lumen of the bronchoscope, but may be extended to penetrate and inject small doses of neurotoxin into the bronchial wall of a patient.

[0024] Alternatively, the distal end of the neurotoxin applicator assembly may carry a rotating needle assembly including plural needles disposed along the circumference of a wheel, so that the wheel may be rolled across a target treatment area. Optionally, the rotating needle assembly may include a fender to protect a portion of the bronchial wall substantially opposite the target treatment area.

[0025] In another alternative embodiment, the distal end of the neurotoxin applicator assembly may comprise a needle-less injection assembly that may be used to inject

neurotoxin into the bronchial wall without needle penetration. An inflatable balloon optionally may be provided to help position a port of the needle-less injection assembly adjacent to the target treatment area.

5 **[0026]** In a further alternative embodiment, the distal end of the neurotoxin applicator assembly comprises a nebulizer assembly having an atomizer that converts the liquid neurotoxin into a fine spray or mist that is directed onto the target treatment area. The particle
10 size of the mist can be controlled using injection pressure or atomizer head design to access specific portions of the lung adjacent to or downstream of the treatment device. An inflatable balloon optionally may be provided to facilitate positioning the atomizer
15 adjacent the target treatment area, and further serves to isolate the lung segment downstream of the device to prevent reflux of the mist into undesired portions of the airway. In addition, lumens optionally may be disposed between the balloon and atomizer to provide a ventilation
20 system that allows pressure control of the treatment area to prevent over-inflation of the lung, mixing of the atomized fluid, and evacuation of remaining mist at termination of therapy, prior to balloon deflation.

[0027] In a still further embodiment, the distal end
25 of the neurotoxin applicator assembly may comprises an articulable region of the shaft including a micro-porous tip that mediates flow of asthma-fighting solution through the lumen and out of the distal tip.

[0028] In accordance with another aspect of the
30 present invention, the intrabronchial neurotoxin delivery system comprises a drug-eluting bioabsorbable stent comprising one or more layers of asthma-fighting drugs.

Brief Description of the Drawings

[0029] The above and other objects and advantages of the present invention will be apparent upon consideration of the following detailed description, taken in
5 conjunction with the accompanying drawings, in which like reference characters refer to like parts throughout, and in which:

[0030] FIG. 1 is a side view of an intrabronchial neurotoxin delivery system of the present invention;

10 [0031] FIG. 2 is a perspective view of an illustrative embodiment of a neurotoxin applicator assembly of the present invention;

[0032] FIGS. 3A and 3B are cross-sectional views of the neurotoxin applicator assembly of FIG. 2 in retracted
15 and extended positions, respectively;

[0033] FIG. 4 is a perspective view of an alternative embodiment of a neurotoxin applicator assembly of the present invention;

[0034] FIGS. 5A and 5B are partial cross-sectional
20 views of the neurotoxin applicator assembly of FIG. 4 in retracted and extended positions, respectively;

[0035] FIG. 6 is a perspective view of another alternative embodiment of a neurotoxin applicator assembly of the present invention;

25 [0036] FIG. 7A and 7B are partial cross-sectional views of the neurotoxin applicator assembly of FIG. 6 in retracted and extended positions, respectively;

[0037] FIG. 8 is a perspective view of a yet further alternative embodiment of a neurotoxin applicator
30 assembly of the present invention;

[0038] FIGS. 9A and 9B are partial cross-sectional views of the neurotoxin applicator assembly of FIG. 8 in retracted and extended positions, respectively;

[0039] FIG. 10 is a side view of a distal end of a neurotoxin applicator assembly for topically applying an asthma-fighting solution to a patient's bronchi;

[0040] FIGS. 11A-11C are side views of the applicator of FIG. 10 depicting the curved distal segment in different configurations;

[0041] FIG. 12 is a perspective view of a syringe that is employed to provide pressurization at the proximal end of the applicator of FIG. 10;

10 [0042] FIG. 13 is a perspective view of an alternative syringe that is employed to provide pressurization at the proximal end of the applicator of FIG. 10;

[0043] FIG. 14 is a side view of a drug-eluting bioabsorbable stent of the present invention;

15 [0044] FIG. 15 is a side view of another drug-eluting bioabsorbable stent of the present invention;

[0045] FIG. 16 is a cross-sectional view of the drug-eluting bioabsorbable stent of FIG. 14;

[0046] FIG. 17 is a perspective view depicting the delivery of drug-eluting bioabsorbable stents within a patient's bronchi;

[0047] FIG. 18 is a perspective view depicting the delivery of alternative drug-eluting bioabsorbable stents within a patient's bronchi; and

25 [0048] FIG. 19 is a perspective view depicting the delivery of further alternative drug-eluting bioabsorbable stents within a patient's bronchi.

Detailed Description of the Invention

[0049] Referring to FIG. 1, apparatus for controlled delivery of neurotoxin to a target treatment area within a patient's bronchial airways to lessen the effects of asthma is described. Preferably, the apparatus comprises bronchoscope 10 and neurotoxin applicator assembly 20.

Bronchoscope 10 has proximal end 12, distal end 13, and lumen 14. As is conventional, bronchoscope 10 also includes a light source for illuminating the interior of a patient's lung and optics, such as a miniature camera, 5 that enables the physician to view the interior of the patient's lung. Alternatively, bronchoscope 10 may omit the light source and optics, and instead comprise an outer sheath. In this latter case, device 10 and neurotoxin applicator 20 would be observed using a 10 separate conventional bronchoscope or through a light source and optics that are built into the neurotoxin applicator 20.

[0050] In accordance with the principles of the present invention, neurotoxin applicator assembly 20, of 15 which various illustrative embodiments are described hereinbelow, enables the physician to selectively administer controlled doses of neurotoxin to or within selected treatment sites in the patient's lung. More specifically, neurotoxin applicator assembly 20 may be 20 selectively advanced through lumen 14 of bronchoscope 10 to deliver a neurotoxin, such as botulinum toxin, serotype A, to a target treatment area.

[0051] Neurotoxin applicator assembly 20 includes shaft 21 coupled to at its proximal end to handle 22, 25 distal end 23 having neurotoxin applicator 24, and lumen 25. Lumen 25 provides fluid communication between proximal end and handle 22 and applicator 24. Syringe 26 having plunger 27 is coupled to a port on proximal end 22. Syringe 26 is filled with neurotoxin in liquid form, 30 and applies the neurotoxin to applicator 24 via lumen 25 when plunger 27 is actuated.

[0052] Handle 22 enables the physician to extend and retract applicator 24 from within lumen 14 of

bronchoscope 10, and to manipulate distal end 23 of neurotoxin applicator assembly 20 under direct visual observation using the optics of bronchoscope 10.

The neurotoxin applicator assembly preferably remains retracted within lumen 14 of the bronchoscope during insertion of the catheter into the patient's bronchial airways, and is deployed once the applicator is in a desired position. Alternatively, applicator 20 may be housed inside of a retaining sheath, and both units can be advanced through lumen 14 together.

[0053] Referring now to FIGS. 2-3, a first illustrative embodiment of applicator 24 of neurotoxin applicator assembly 20 constructed in accordance with the principles of the present invention is described. Applicator 24 comprises needle assembly 28 having at least one needle 30 with lumen 31 in fluid communication with lumen 25. The needles are configured to penetrate the airway epithelium and directly inject small amounts of neurotoxin from the syringe into the collagenous and smooth muscle layers of bronchial wall B.

[0054] In FIG. 3A, needle assembly 28 is depicted retracted with lumen 14 of bronchoscope 10. Alternatively, device 10 may comprise an outer sheath that is dimensioned to be slidably accept neurotoxin applicator assembly 20, and which is selectively retractable to expose needle assembly 28. Again, in the case where device 10 is an outer sheath, visualization could be achieved through a separate bronchoscope or through built-in optics. In a further embodiment, a retaining sheath housed within lumen 14 and covering applicator 20 is selectably retractable to expose needle assembly 28. As depicted in FIG. 3B, needles 30 comprise a material capable of retaining a preformed shape, such

as nickel-titanium, and are preformed to deflect radially outward when extended beyond distal end 13 of bronchoscope 10 (or the distal end of the outer sheath, if present). Each needle 30 optionally includes hilt 36 disposed a pre-selected distance from the distal end of the needle to control the depth of penetration of the needle tip into the bronchial wall.

[0055] When needle assembly 30 is deployed, as illustrated in FIGS. 2 and 3B, needles 30 penetrate target treatment area T of bronchial wall B so that neurotoxin may be injected in the bronchial wall. Syringe 26 may include graduations that enable the physician to inject a pre-determined amount of neurotoxin at each target treatment area.

[0056] Referring now to FIGS. 4 and 5, an alternative embodiment of applicator 24 of neurotoxin applicator assembly 20 is described. Applicator 24 in this embodiment comprises rotating needle assembly 38, including wheel 39 mounted to rotate about hub 40. While wheel 39 illustratively is round, it alternatively may comprise an ellipse or hexagon or other polygonal shape. Plurality of needles 41 is disposed around the circumference of the wheel, each needle 41 having lumen 42 in fluid communication with lumen 25 via a passageway in hub 40. Optional fender 45 protects a portion of the bronchial wall substantially opposite the target treatment area.

[0057] In FIG. 5A, rotating needle assembly 38 is shown retracted within outer sheath 37. Outer sheath 37 is dimensioned to fit within lumen 14 of bronchoscope 10, and may be selectively retracted to expose rotating needle assembly 38. Alternatively, rotating needle assembly 38 extends through lumen 14 and past the tip of

bronchoscope 10. In this embodiment, the wheel is covered by a retractable protection sheath which covers the wheel during insertion of the system. In FIGS. 4 and 5B, rotating needle assembly 38 is shown in the extended position. When so deployed, wheel 39 may be rolled across target treatment area **T**, so that as the wheel rotates needles 41 alternately penetrate and inject neurotoxin into bronchial wall **B**.

[0058] Suitable needles materials for needle assembly 28 of FIGS. 2-3 and rotating needle assembly 38 of FIGS. 4-5 include shape memory alloys such as nickel titanium alloys and spring tempered stainless steel alloys. Advantageously, either needle assembly permits direct injection of neurotoxin into the bronchial wall. This prevents the ciliary transport system from trapping the neurotoxin and transporting it to other regions of the respiratory system, e.g., the oropharynx, where potentially unintended targets may be exposed to the neurotoxin, and prevents accidental exhalation of aerosolized neurotoxin.

[0059] Referring now to FIGS. 6 and 7, another alternative embodiment of applicator 24 of the neurotoxin applicator assembly of the present invention is described. Applicator 24 of FIGS. 6-7 comprises a needle-less injection assembly 46, which uses pressurized injection to deliver neurotoxin from the proximal controller to target treatment area **T**. Advantageously, the needle-less injection assembly allows controlled introduction of neurotoxin across the airway epithelium without the potential complications of introducing needles proximate to the delicate bronchial tissues, and may allow a lower profile system.

[0060] Needle-less injection assembly 46 comprises shaft 47 including at least one port 48 in fluid communication with lumen 25. Inflatable balloon 49 optionally may be coupled to shaft 47, and used to position the shaft adjacent target treatment area T. Balloon 49 is inflated with a fluid introduced through a lumen of shaft 47. When the shaft is aligned with the target treatment area, pulses of pressurized gas may be employed to inject predetermined amounts of neurotoxin across the airway wall and into the collagenous and smooth muscle layers.

[0061] In FIG. 7A, needle-less injection assembly 46, with balloon 49 deflated, is depicted housed within the lumen 14 of bronchoscope 10 (or a separate outer sheath). FIGS. 6 and 7B depict needle-less injection assembly 46 with balloon 49 inflated to place ports 48 in apposition to target treatment area T. Once the physician has confirmed placement of needle-less injection assembly 46, e.g., by visualization using the optics of bronchoscope 10, x-ray, fluoroscopy or other suitable means, a controller attached to the proximal end of neurotoxin applicator assembly 20 (instead of syringe 26), may be activated to deliver the desired doses of neurotoxin to the bronchial wall. As an alternative to the balloon 49, the assembly may have 2 or more needle-less injectors arranged to position against opposite walls of the bronchial passage. For instance, they might be spring loaded to expand the sections away from the midline and contact the bronchial wall. As a further alternative, the shaft of the assembly may be pre-curved or actively curved with an activation mechanism to urge the injector against the wall of the bronchial passage. Yet another alternative includes lower-pressure injection of

neurotoxin through port(s) 48, creating a weeping-balloon applicator. In this case, transport of neurotoxin across the epithelial surface is achieved by cellular endocytosis of the neurotoxin.

5 [0062] With respect to FIGS. 8 and 9, a yet further alternative embodiment of applicator 24 of the neurotoxin applicator assembly constructed in accordance with the present invention is described. Applicator 24 comprises nebulizer assembly 50 having shaft 55 with atomizer 51
10 disposed at its distal end and in fluid communication with central lumen 25. Atomizer 51 converts the liquid neurotoxin from the syringe into a fine spray or mist. Particle size of the mist can be controlled through nebulizer head design or by varying injection pressure in
15 order to control the depth of penetration of the mist into the target segment.

[0063] Nebulizer assembly 50 may also include optional inflatable balloon 52 disposed on shaft 55 proximal of atomizer 51. Selective inflation of balloon 52 allows
20 positioning of atomizer 51 so that aerosolized neurotoxin may be directly sprayed onto target treatment area T. Balloon 52 also acts to isolate the treatment area from the rest of the lung, preventing reflux of mist into unintended areas. As for the embodiment of FIGS. 6-7,
25 balloon 52 may be inflated using a fluid introduced through an auxiliary lumen in shaft 55.

[0064] In FIG. 9A, the nebulizer assembly, including deflated balloon 52, is disposed within lumen 14 of bronchoscope 10, or alternatively, in an outer sheath
30 that is slidably received in lumen 14. Alternatively, the nebulizer assembly may be inserted within a separate delivery sheath, with the bronchoscope inserted separately or with the optics and/or steering mechanisms

built into the nebulizer assembly. In FIGS. 8 and 9B, nebulizer assembly 50 is depicted deployed from lumen 14 (or the outer sheath, if present), with balloon 52 inflated. Advantageously, nebulizer assembly 50 can be dimensioned to access very small bronchial passageways, and also may be used to deliver neurotoxin to upstream regions of the lung.

[0065] Still referring to FIGS. 9A and 9B, shaft 55 optionally also may include an additional auxiliary lumen or lumens coupled to inlet port 53 and outlet port 54 disposed between the balloon and the atomizer. Inlet port 53 allows the introduction of gas (such as fresh air) near the target treatment area, while outlet port 54 allows air or gas mixed with atomized neurotoxin to be removed. Inlet and outlet ports 53 and 54 therefore provide a ventilation system that shields tissue adjacent and proximal to target treatment area T from being inadvertently exposed to the atomized neurotoxin. Inlet and outlet ports 53 and 54 further serve to either actively inflate and deflate the isolated segment, or simply to normalize pressure within the lung near the target treatment area. A control unit may be connected to the proximal outlets of ports 53 & 54 to control the introduction and removal of gases from the lung without allowing escape of atomized neurotoxin to the environment or patient.

[0066] According to some embodiments, the nebulizer assembly may be built into a single, disposable fiberoptic unit having a unidirectional tip-deflection element having an integral isolation balloon and aerosolizing tip. A neurotoxin containing canister can also be provided integral with the nebulizer assembly. Advantageously, such an assembly permits a much lower

profile, user-friendly system suitable for trans-nasal introduction past the vocal cords and into the lung.

[0067] With respect to FIGS. 10-13, another alternative embodiment of a neurotoxin applicator of the present invention is described. In this embodiment, neurotoxins or other therapeutic drugs are delivered to the patient's bronchial tree via sub-selective topical application of toxin to the bronchial lining. The applicator assembly may be inserted through the working channel of a bronchoscope (as in FIG. 1) and used to paint a solution containing neurotoxins onto the epithelial surface of the airways of the lung.

[0068] Referring now to FIG. 10, neurotoxin applicator assembly 60 comprises proximal shaft 62, spring-reinforced distal segment 64, and beveled distal tip 66 comprising a micro-porous filter material that functions as a topical applicator for the asthma-fighting solution. Distal segment 64 preferably is bendable into an infinite number of configurations having various radii of curvature. Additionally, torsional rotation of distal tip 66 is provided in response to torque applied to proximal shaft 62. In the illustrated embodiment, neurotoxin applicator assembly 60 comprises a wire-braid reinforced tube that provides desirable characteristics of high burst strength and good torque response, and may be formed of a nickel-titanium alloy.

[0069] Referring to FIGS. 11A-11C, curved distal segment 64 of neurotoxin applicator assembly 60 extends out of the tip of bronchoscope 70. Neurotoxin applicator assembly 60 preferably may be rotated with respect to and in conjunction with bronchoscope 70. The variable curve of distal segment 64 and the beveled termination of distal tip 66 provide intimate contact of distal tip 66

against bronchial walls having different diameters. The beveled distal tip 66 allows for easy introduction through the working channel of the bronchoscope 70. Distal segment 64 preferably is spring-biased into a curved configuration to permit self-adjustment of the device to a wide range of inner bronchial diameters. FIGS. 11 demonstrate that the curved distal segment will remain in contact with the walls of very small bronchi having a diameter of 5 mm or less (FIG. 11A), average bronchi having a diameter of 5 mm to 15 mm (FIG. 11B), as well as very large bronchi having a diameter of 15 mm or more (FIG. 11C).

[0070] In operation, the asthma-fighting solution is induced to flow through a central lumen running through neurotoxin applicator assembly 60. According to some embodiments, the rotation of distal tip 66 using torque applied at the proximal end of proximal shaft 62, in addition to proximal end pressure, is used to control the flow of solution through distal tip 66. This flow control aspect, in combination with the variable curve of distal segment 64, allows a rotational "painting" onto the walls of the bronchi.

[0071] Referring to FIG. 12, syringe 72 is employed to provide pressurization at the proximal end of neurotoxin applicator assembly 60 for controlling the flow of asthma-fighting solution through the central lumen and distal tip of the device. Syringe 72 comprises syringe barrel 73 and threaded plunger 74, which terminates in finger slot 75. A proximal end of syringe barrel 73 terminates in an outwardly-projecting rim 76, whereas a distal end of syringe barrel 73 is fixedly attached to the proximal end of torque-responsive neurotoxin applicator assembly 60. Syringe 73 preferably further

comprises a threaded half-collar 77 adapted to slide into place over syringe barrel 73 and threaded plunger 74. Half-collar 77 preferably comprises internal threads corresponding to the threads on threaded plunger 74.

- 5 Moreover, half-collar 77 preferably further comprises a recess that engages rim 76. When slid into place over syringe 72, threaded half-collar 77 locks the threaded plunger in place with respect to the barrel.

[0072] When collar 77 is in place, rotation of syringe
10 barrel 73 (e.g., in a clockwise direction) results in a controlled deflection of plunger 74 relative to barrel 73. The deflection of plunger 74 increases the pressure within the central lumen of neurotoxin applicator assembly 60, thereby causing a controlled amount of
15 solution to be dispensed from distal tip 66. By altering the pitch of the thread on the plunger and half-collar, the volume of fluid dispensed per revolution may be varied. Since syringe barrel 73 is fixedly attached to torque-responsive neurotoxin applicator assembly 60,
20 rotation of syringe barrel 73 results in corresponding rotation of distal tip 66. The half-collar may be removed from the assembly to allow conventional syringe operation for rapid filling or emptying of syringe 72.

[0073] Referring to FIG. 13, standard syringe 80 is
25 attached to the proximal end of torque-responsive neurotoxin applicator assembly 60, which is disposed within bronchoscope 85. Syringe comprises syringe barrel 82 and non-threaded plunger 83. In this embodiment, a collar is not provided, and flow control is provided by
30 manually modulating the force applied to plunger 83. The force applied to plunger 83, in addition to the rotation of syringe 80 (which causes corresponding rotation of

neurotoxin applicator assembly 60) dispenses the asthma-fighting solution onto the patient's bronchial walls.

[0074] In accordance with another aspect of the present invention, implantable devices and methods for treating asthma are described with respect to FIGS. 14-19. The bioabsorbable implants are employed to controllably introduce one or more neurotoxins into the walls of a patient's bronchial tree, which control asthma by disabling the hyperresponsive smooth muscle layer and controlling hypersecretion of mucus.

[0075] More specifically, delivery of neurotoxins or other therapeutic drugs to the bronchial tree is achieved through drug elution from bioabsorbable implants placed within the bronchial passages. The implants preferably are bioabsorbable, but alternatively may comprise permanent devices with refillable reservoirs as well as elution devices that may be removed and replaced at periodic intervals, e.g., when drug supplies are determined be depleted.

[0076] In accordance with the principles of the present invention, a system for treating asthma comprises one or more drug-eluting bioabsorbable stents. Referring to FIG. 14, stent 102 comprises a single wire 104 including a plurality of turns 106. According to some embodiments, the stent system comprises one or more discrete-length coiled stents. Alternatively, the stent system comprises one or more custom-length coiled stents, which are deployed and cut to length at the end point of delivery by a cutting mechanism that is part of the stent delivery system. Bioabsorbable stent 102 preferably is loaded with neurotoxin and/or other asthma-fighting drugs. Gradual elution of the neurotoxin and/or other asthma-fighting drugs treats the underlying inflammatory

disease that causes the asthmatic response.

Advantageously, stent 102 also lends mechanical reinforcement to the patient's bronchi.

[0077] Referring to FIG. 15, alternative drug-eluting
5 bioabsorbable stent 108 is shown, and comprises a plurality of wires 110 that are intertwined to form a slotted or knitted tube. As will be appreciated by those of skill in the art, many other known stent designs may be used to deliver the asthma-fighting drugs without
10 departing from the scope of the present invention. Suitable materials for stents 102, 108 include PEG, PLLA, collagen and copolymers of these materials. Appropriate drugs include the array of steroids and bronchodilators that are currently used systemically to treat asthmatic
15 conditions. Examples of other suitable asthma-fighting drugs include corticosteroid and albuterol.

[0078] Additionally, a neurotoxin composition such as botulinum toxin or tetanus may be delivered using the stent. According to some embodiments, stents 102
20 encapsulate the neurotoxin, releasing it gradually onto the bronchial wall, thereby greatly extending the effective working life of the neurotoxin past its usual 3+ month active lifespan.

[0079] Since the effect of neurotoxin on the smooth
25 muscle and inflammatory responses related to asthma are not permanent, it is desirable to provide doses of neurotoxin that are automatically delivered at predetermined intervals. FIG. 16 is a cross-sectional view of stent wire 104 of drug-eluting bioabsorbable
30 stent 102. Wire 110 forming drug-eluting bioabsorbable stent 108 may comprises a substantially similar cross-section.

[0080] In the illustrated embodiment, stent wire comprises alternating layers of drug-loaded and non-drug-loaded resorbable materials. More particularly stent wire 104 comprises inner drug-eluting layer 114 that is substantially circular in cross-section and barrier layer 116 disposed around the perimeter of inner layer 114. Stent wire 104 further comprises outer drug-eluting layer 118 surrounding barrier layer 116, and protective outer coating 120 surrounding outer layer 118. In this manner, the drug is loaded into the implant in discrete dosing layers 114, 118 and delivered at predetermined intervals.

[0081] After the drug-eluting stent is implanted within a patient's bronchial airways, protective outer coating 20 dissolves, thereby exposing outer drug-eluting layer 118. The outer layer is slowly absorbed, thus providing a first dose of asthma-fighting drugs to a target treatment area within the patient's bronchi. After outer layer 118 is absorbed, barrier layer 116 dissolves within the bronchi over a predetermined amount of time. Then, inner layer 114 is slowly absorbed, thereby providing a second dose of asthma-fighting drugs to the target treatment area. Of course, as would be understood by those of ordinary skill in the art, additional drug-eluting layers (and barrier layers) may be employed to deliver additional doses of asthma-fighting drugs at predetermined intervals without departing from the scope of the present invention. In this manner, the first dose is administered shortly after implantation, and then subsequent doses are released at predetermined intervals, for example every 3 months.

[0082] Delivery of the drug-eluting stents of the present invention preferably is achieved through the working channel of a conventional bronchoscope, either

oral or nasal, or through a custom device specifically designed for placing the loaded stents. Referring to FIG. 17, one or more drug-eluting bioabsorbable stents 102 are delivered to target treatment area within a patient's bronchi B through the working channel of bronchoscope 122. Stent 102 is a continuous length of coiled drug-loaded wire 104 that is initially delivered at the distal end of a target bronchial passage. Then, stent 102 is unwound along the target bronchial passage to the desired proximal termination point. Manipulation of the bronchoscope during deployment allows the physician to avoid placing coils across side branches of the bronchial tree. When the proximal termination point is reached, a cutting mechanism is used to cut the implant coil.

[0083] Alternatively, as depicted with respect to FIGS. 18 and 19, one or more discrete length drug-eluting bioabsorbable coiled stents 108, 130, may be deployed within the patient's bronchi B. Stents 108 and 130 are formed of wire segments that preferably include alternating layers of drug-loaded and non-drug-loaded materials, such as described with respect to FIG. 16. Stents 108 and 130 preferably are delivered through the working channel of a bronchoscope or through another delivery device. As would be understood by those of skill in the art, stents 108 and 130 may comprise any number of different sizes and configurations without departing from the scope of the present invention.

[0084] Deployment of the inventive stents described hereinabove may be accomplished using conventional stent delivery catheters and procedures, via either self-expansion or balloon expansion of the stents, by heating and setting a final size with a purpose-built delivery

system, or any other suitable procedure. Delivery may be achieved one stent at a time, or multiple implants may be placed from a single multi-stent delivery system.

[0085] Although preferred illustrative embodiments of the present invention are described above, it will be evident to one skilled in the art that various changes and modifications may be made without departing from the invention. It is intended in the appended claims to cover all such changes and modifications that fall within the true spirit and scope of the invention.

What is claimed is:

1. Apparatus for intrabronchial delivery of medication to treat lung disease, the apparatus comprising:

a shaft having a proximal end including at least one inlet port, a distal end and a lumen extending between the inlet ports and the distal end; and

a medication applicator disposed on the distal end of the shaft in fluid communication with the lumen.

2. The apparatus of claim 1, wherein the medication is a neurotoxin.

3. The apparatus of claim 1, further comprising a bronchoscope having proximal and distal ends, and a lumen extending therebetween, and wherein the shaft is dimensioned to slidably pass through the lumen of the bronchoscope.

4. The apparatus of claim 1, wherein the neurotoxin applicator includes a needle assembly.

5. The apparatus of claim 4, wherein the needle assembly has a retracted delivery position and a deployed position wherein at least one needle extends radially outward from the shaft to penetrate bronchial tissue.

6. The apparatus of claim 4, wherein the needle assembly comprises a wheel having a circumference and a plurality of needles disposed around the

circumference, wherein the plurality of needles are in fluid communication with the lumen of the shaft.

7. The apparatus of claim 6, wherein the wheel further comprises a hub that forms an axis of rotation for the wheel.

8. The apparatus of claim 6, wherein the wheel is adapted to be rolled across a target treatment area within a patient's bronchial airways.

9. The apparatus of claim 8, wherein the needle assembly further comprises a fender that protects an area of the patient's bronchial airways opposite the target treatment area.

10. The apparatus of claim 2, wherein the neurotoxin is a serotype of botulinum toxin.

11. The apparatus of claim 10, wherein the serotype of botulinum toxin is selected from the group consisting of serotype A and serotype B.

12. The apparatus of claim 2, wherein the neurotoxin is tetanus or a tetanus derivative.

13. The apparatus of claim 1, wherein the applicator uses pressurized fluid to inject neurotoxin into a target treatment area.

14. The apparatus of claim 13, wherein the shaft includes a portion defining a port in fluid communication with the lumen.

15. The apparatus of claim 13, further comprising a deflection means disposed on the shaft to position the port adjacent to the target treatment area.

16. The apparatus of claim 15, wherein the deflection means is an inflatable balloon.

17. The apparatus of claim 13, wherein the applicator further comprises an atomizer in fluid communication with the lumen.

18. The apparatus of claim 17, further comprising an inflatable balloon disposed proximal to the atomizer.

19. The apparatus of claim 18, further comprising at least one lumen disposed between the balloon and the atomizer to ventilate tissue adjacent the target treatment area.

20. The apparatus of claim 1 wherein the medication applicator comprises a micro-porous filter material.

21. The apparatus of claim 1 wherein the shaft is selectively bendable.

22. The apparatus of claim 1 wherein the shaft is steerable.

23. The apparatus of claim 1 further comprising an optical component disposed in operative relation to the medication applicator.

24. The apparatus of claim 20 further comprising a syringe coupled to the proximal end of the shaft for controlling the flow of medication.

25. Apparatus for treating lung disease by intrabronchial delivery of medication, the apparatus comprising:

an elongate shaft having a proximal end including at least one inlet port, a distal end and a lumen extending between the inlet port and the distal end; and

a medication applicator disposed on the distal end of the shaft in fluid communication with the lumen, the medication applicator having a contracted delivery position, and a deployed position adapted to deliver medication to a target tissue area of a patient's bronchial wall.

26. The apparatus of claim 25, wherein the neurotoxin applicator includes a needle assembly.

27. The apparatus of claim 25, wherein the needle assembly comprises at least one needle that extend radially outward from the shaft to penetrate bronchial tissue.

28. The apparatus of claim 25, wherein the needle assembly comprises a wheel having a circumference and a plurality of needles disposed around the circumference, wherein the plurality of needles are in fluid communication with the lumen of the shaft.

29. The apparatus of claim 28, wherein the needle assembly further comprises a fender that protects an area of the patient's bronchial airways opposite the target treatment area.

30. The apparatus of claim 25, wherein the neurotoxin is botulinum toxin.

31. The apparatus of claim 25, wherein the applicator uses pressurized fluid to inject neurotoxin into a target treatment area.

32. The apparatus of claim 31, wherein the shaft includes a portion defining at least one port in fluid communication with the lumen.

33. The apparatus of claim 25, wherein the applicator further comprises an atomizer in fluid communication with the lumen.

34. The apparatus of claim 25 wherein the medication applicator comprises a micro-porous filter material.

35. The apparatus of claim 25 wherein a distal portion of the elongated shaft is selectively bendable.

36. The apparatus of claim 25 further comprising a syringe coupled to the proximal end of the shaft for controlling the flow of medication.

37. Apparatus for intrabronchial delivery of medication to treat asthma, the apparatus comprising:

a drug-eluting bioabsorbable stent comprising one or more layers of asthma-fighting drugs.

38. The apparatus of claim 37, wherein the stent comprises a single wire including a plurality of turns.

39. The apparatus of claim 37, wherein the stent comprises a plurality of wires that are intertwined to form a slotted or knitted tube.

40. The apparatus of claim 37, wherein the asthma-fighting drug is a neurotoxin.

41. The apparatus of claim 40, wherein the neurotoxin is botulinum toxin

42. The apparatus of claim 40, wherein the neurotoxin is tetanus.

43. The apparatus of claim 37, wherein the asthma-fighting drug is a steroid or bronchodilator.

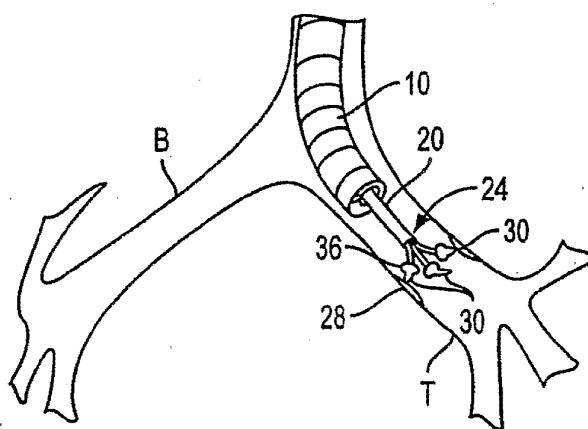
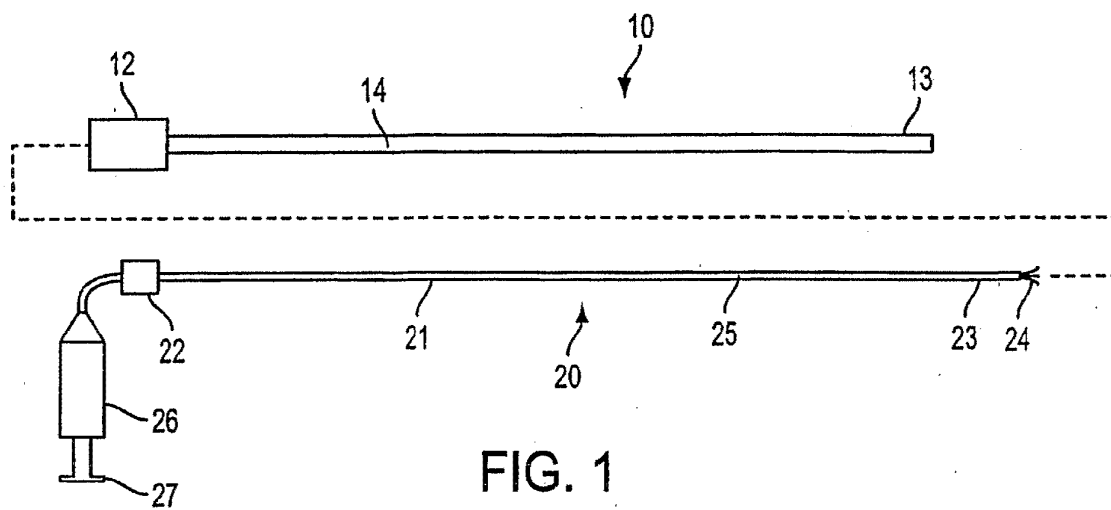
44. The apparatus of claim 37, wherein the stent comprises alternating layers of drug-loaded and non-drug-loaded resorbable materials.

45. The apparatus of claim 44, wherein the material for the non-drug-loaded resorbable materials is chosen from the group consisting of PLLA, collagen and copolymers of these materials.

46. The apparatus of claim 44, wherein the non-drug-loaded resorbable materials encapsulate the drug-loaded resorbable materials such that the asthma-fighting drug is released gradually into the bronchial airways.

47. The apparatus of claim 37, wherein the stent comprises:
an inner drug-eluting layer; and
a barrier layer disposed around the perimeter of the inner layer.

48. The apparatus of claim 47, further comprising:
an outer drug-eluting layer surrounding the barrier layer; and
a protective outer coating surrounding the outer layer.



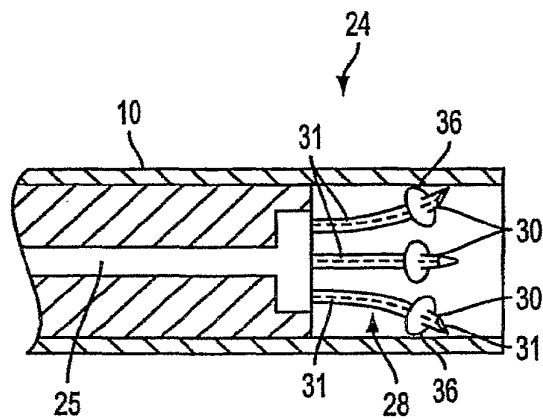


FIG. 3A

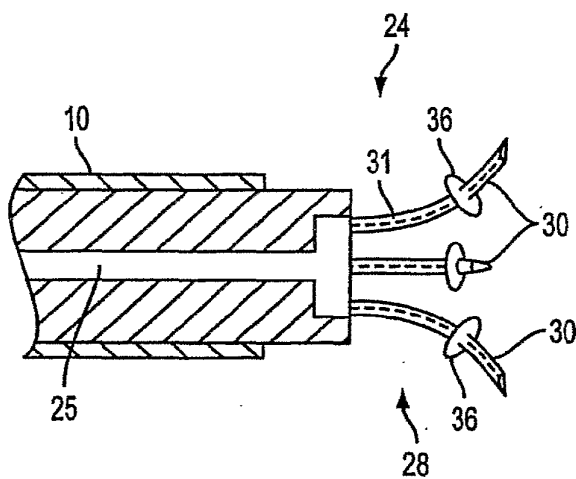


FIG. 3B

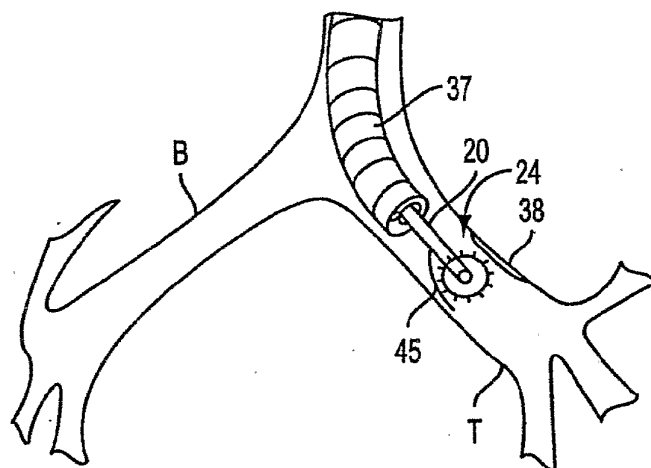


FIG. 4

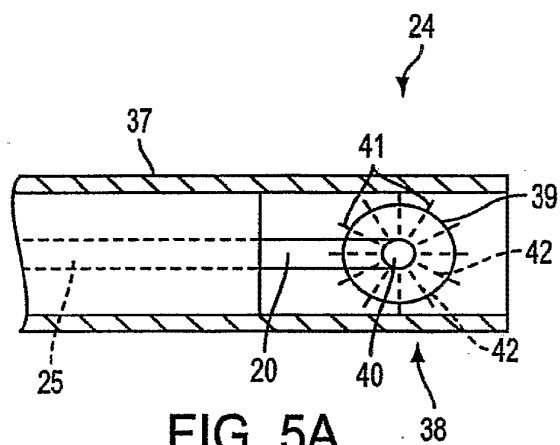


FIG. 5A

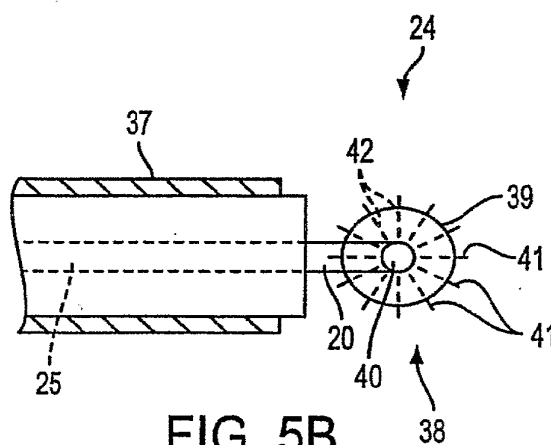


FIG. 5B

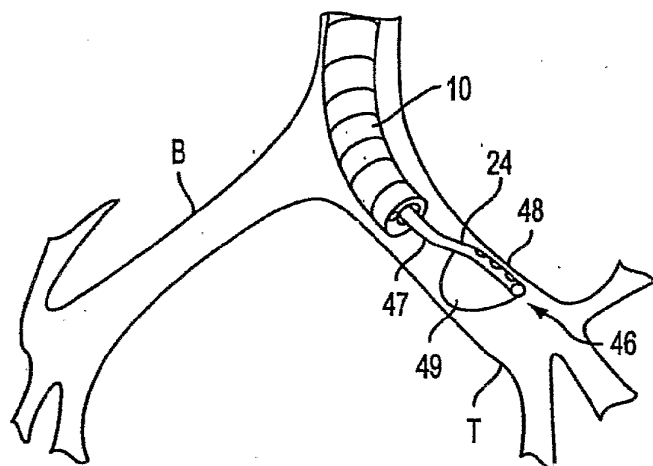


FIG. 6

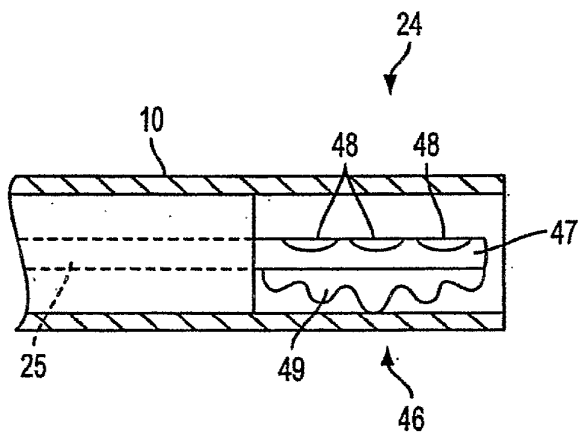


FIG. 7A

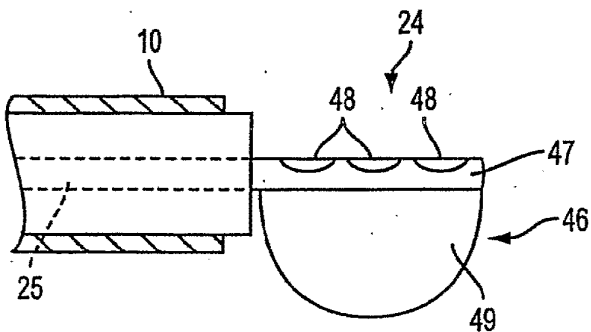


FIG. 7B

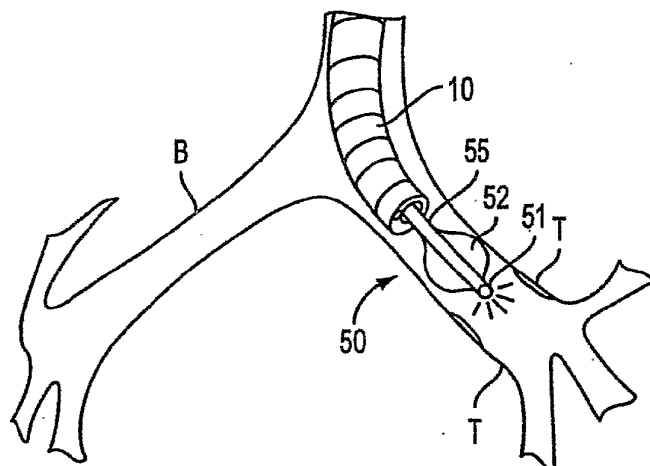


FIG. 8

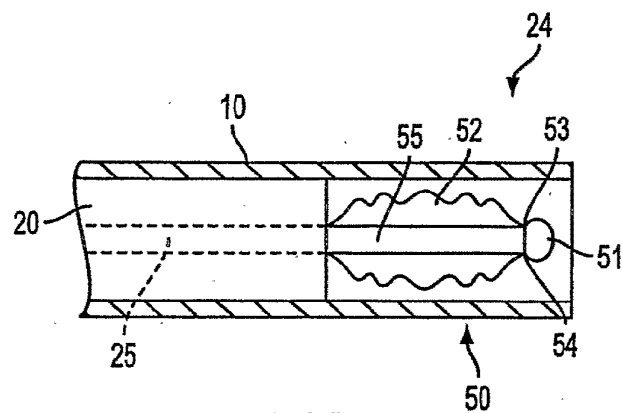


FIG. 9A

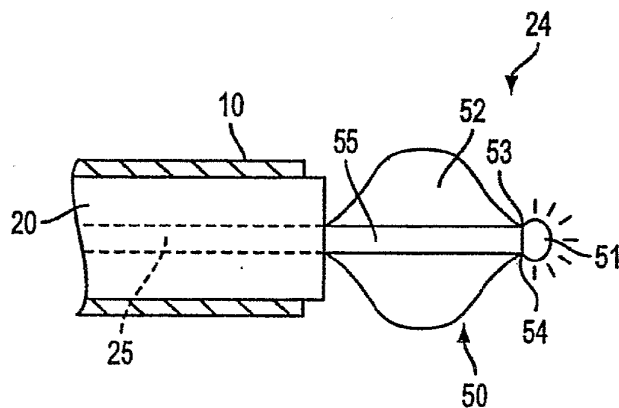


FIG. 9B

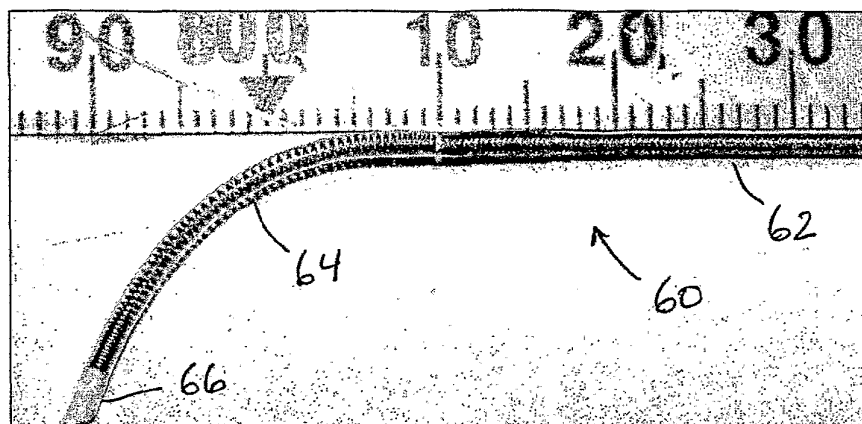


FIG. 10

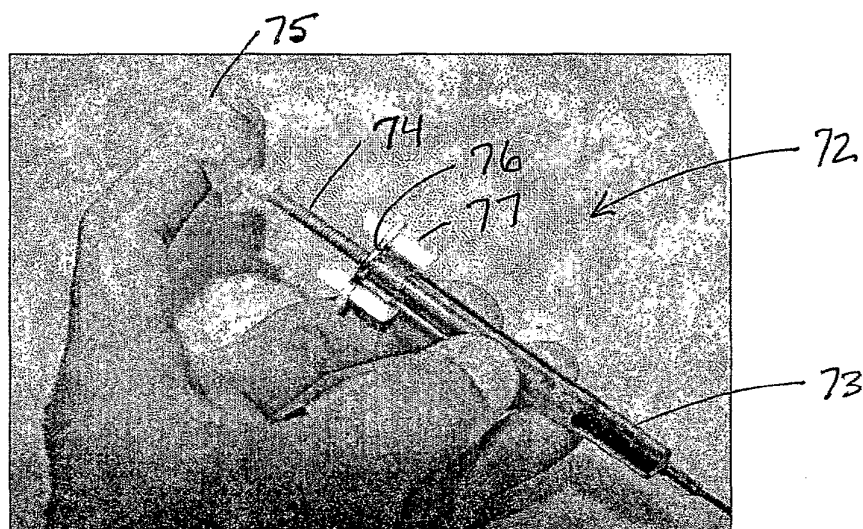


FIG. 12

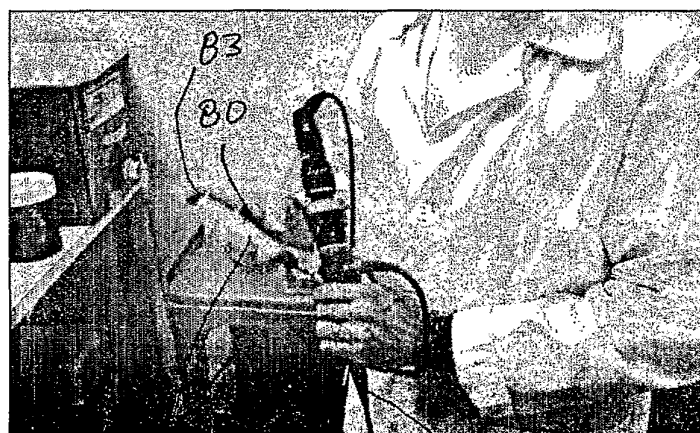


FIG. 13

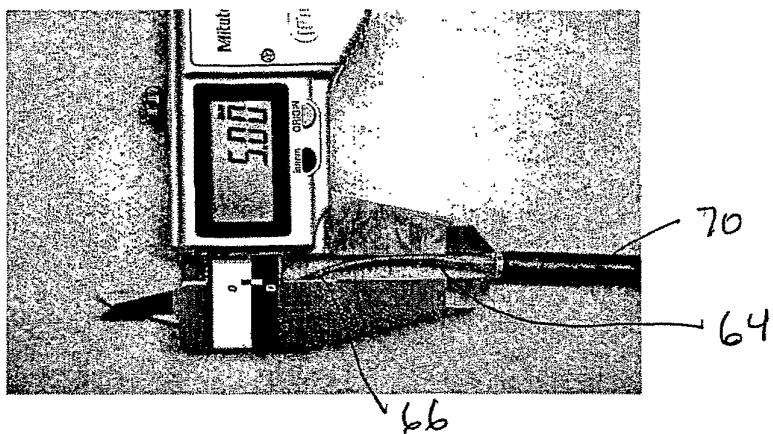


FIG. 11A

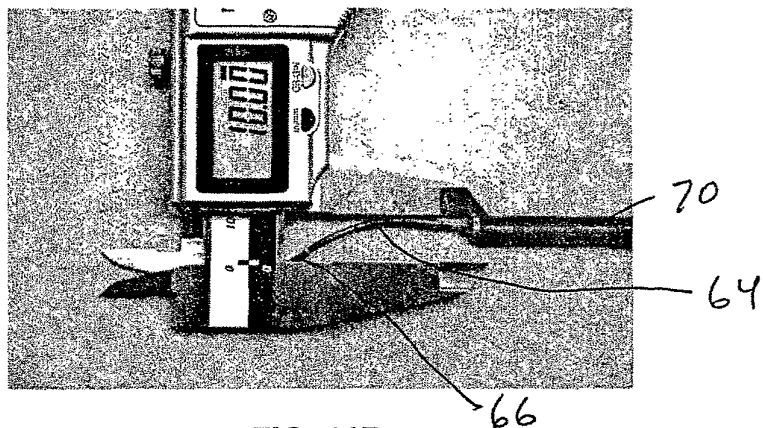


FIG. 11B

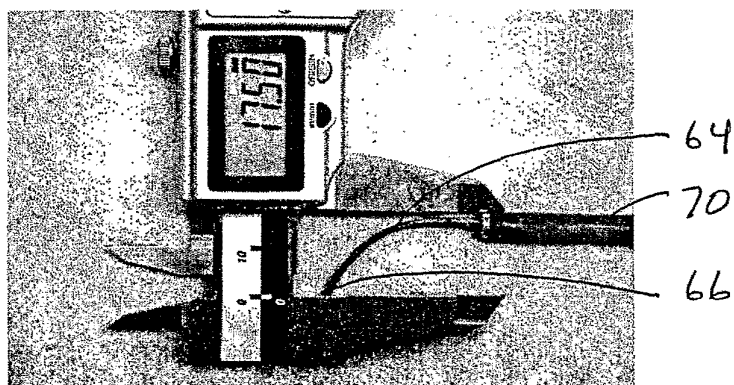


FIG. 11C

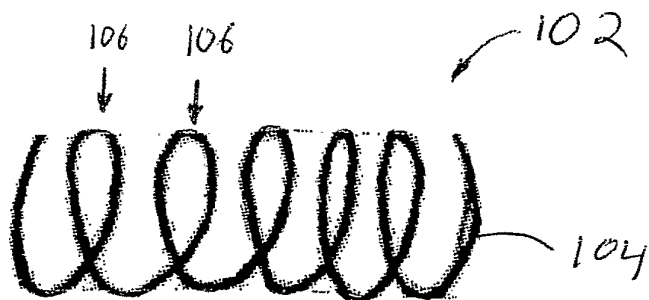


FIG. 14

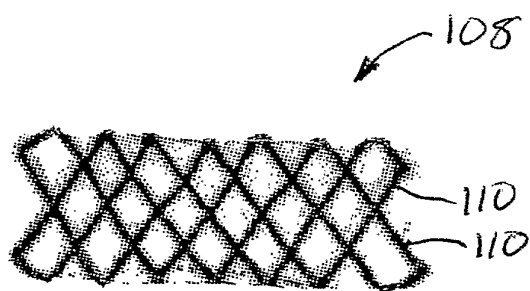


FIG. 15

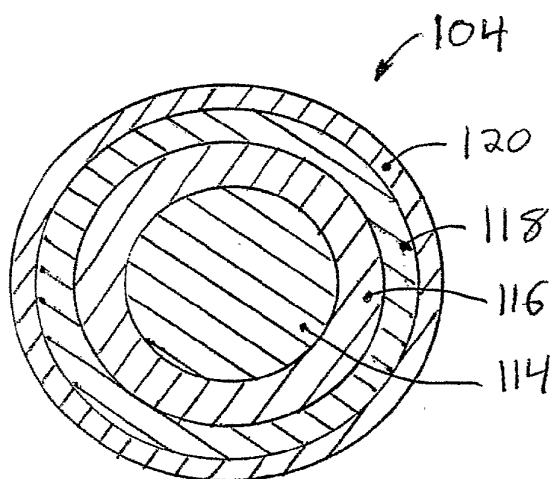


FIG. 16

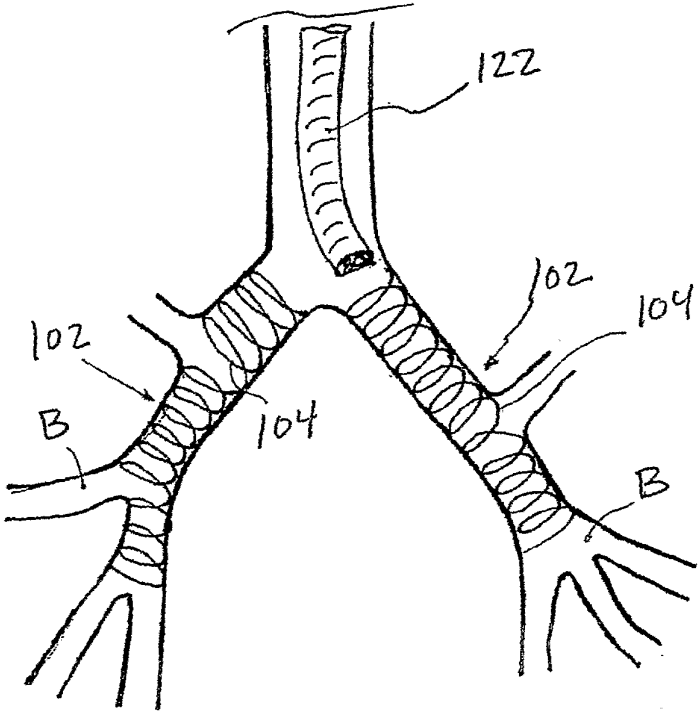


FIG. 17

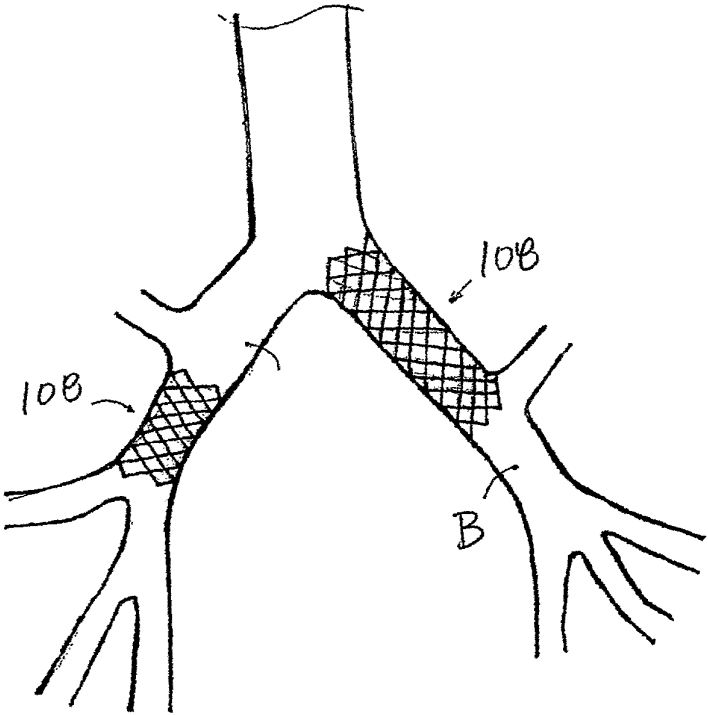


FIG. 18

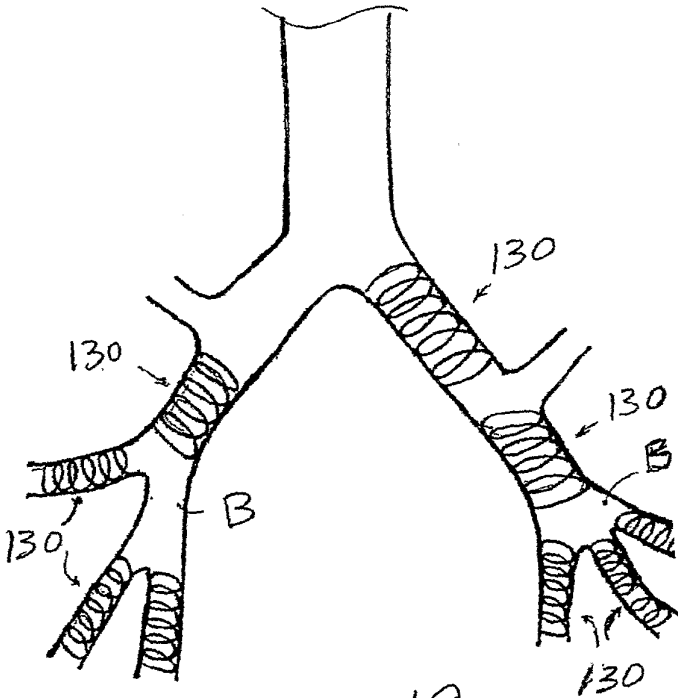


FIG. 19

(19) World Intellectual Property Organization
International Bureau



(43) International Publication Date
25 November 2004 (25.11.2004)

PCT

(10) International Publication Number
WO 2004/101028 A3

(51) International Patent Classification:
A61M 16/00 (2006.01)

(21) International Application Number:
PCT/US2004/015222

(22) International Filing Date: 13 May 2004 (13.05.2004)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
10/437,882 13 May 2003 (13.05.2003) US

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(81) Designated States (unless otherwise indicated, for every
kind of national protection available): AE, AG, AL, AM,

AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN,
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TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM,
ZW.

(84) Designated States (unless otherwise indicated, for every
kind of regional protection available): ARIPO (BW, GH,
GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM,
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European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI,
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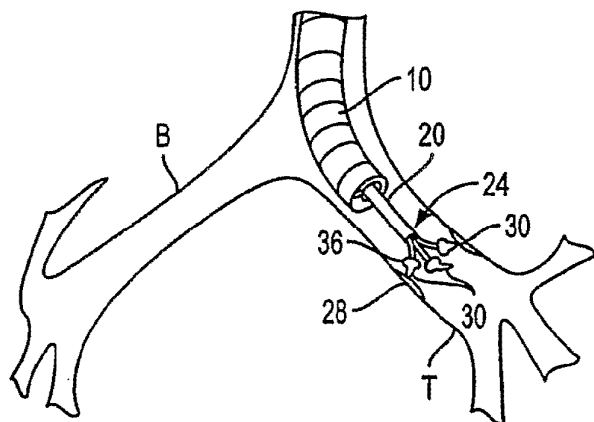
Published:

- with international search report
- before the expiration of the time limit for amending the
claims and to be republished in the event of receipt of
amendments

(88) Date of publication of the international search report:
14 December 2006

For two-letter codes and other abbreviations, refer to the "Guid-
ance Notes on Codes and Abbreviations" appearing at the begin-
ning of each regular issue of the PCT Gazette.

(54) Title: APPARATUS AND METHODS FOR TREATING ASTHMA USING NEUROTOXIN



(57) Abstract: Apparatus providing intrabronchial
delivery of neurotoxin to control the effects of asthma
comprises a shaft having proximal and distal ends and a
neurotoxin applicator assembly disposed on the distal end,
wherein the neurotoxin applicator assembly comprises a
deployable needle assembly, a rotating needle assembly,
a needle-less injection assembly, a nebulizer assembly or a
microporous tip. Further embodiments involve apparatus
comprising drug-eluting bioabsorbable stents having one
or more layers of asthma-fighting drugs.

WO 2004/101028 A3

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US04/15222

A. CLASSIFICATION OF SUBJECT MATTER

IPC: A61M 16/00(2006.01)

USPC: 128/207.14

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 128/207.14, 207.15, 207.16, 200.14, 200.21, 200.18, 200.24

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X --- Y	US 5,964,223 (BARAN) 12 October 1999 (12.10.1999), See Figures.	1, 3, 25
Y	US 5,766,605 A (SANDERS et al) 16 June 1998 (16.06.1998), column 7, lines 10-13 & column 10, lines 46-50.	2, 4, 10-24, 26, 30-36
A	US 6,546,932 B1 (NAHON et al) 15 April 2003 (15.04.2003), Figure 10.	1-36
A	US 2002/0111620 A1 (COOPER et al) 15 August 2002 (15.08.2002), Figure 5J.	1-36

☐ Further documents are listed in the continuation of Box C.

☐ See patent family annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"I"

later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X"

document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y"

document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&"

document member of the same patent family

Date of the actual completion of the international search

06 April 2006 (06.04.2006)

Date of mailing of the international search report

05 OCT 2006

Name and mailing address of the ISA/US

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Commissioner of Patents
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Alexandria, Virginia 22313-1450

Facsimile No. (571) 273-3201

Authorized officer

FOR
Henry Bennett

Telephone No. (571) 272-0000

Form PCT/ISA/210 (second sheet) (July 1998)

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US04/15222

Box I Observations where certain claims were found unsearchable (Continuation of Item 1 of first sheet)

This international report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claim Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
2. ☐ Claim Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
3. ☐ Claim Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of Item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:
Please See Continuation Sheet

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☒ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.: 1-36

Remark on Protest

☐
☐

- The additional search fees were accompanied by the applicant's protest.
- No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

PCT/US04/15222

BOX II. OBSERVATIONS WHERE UNITY OF INVENTION IS LACKING

This application contains claims directed to more than one species of the generic invention. These species are deemed to lack unity of invention because they are not so linked as to form a single general inventive concept under PCT Rule 13.1.

In order for more than one species to be examined, the appropriate additional examination fees must be paid. The species are as follows:

Group I, claim(s) 1-36, drawn to an apparatus for intrabronchial delivery of a medication using a medication applicator disposed on the distal end of a shaft.

Group II, claim(s) 37-48, drawn to an apparatus for intrabronchial delivery of medication using a drug-eluting bioabsorbable stent comprising one or more layers of drugs.

The species listed above do not relate to a single general inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, the species lack the same or corresponding special technical features for the following reasons: each group corresponds to a distinctly different means for intrabronchial delivery of medication.

(19) World Intellectual Property Organization
International Bureau



(43) International Publication Date
1 February 2007 (01.02.2007)

PCT

(10) International Publication Number
WO 2007/014003 A2

(51) International Patent Classification:

A61L 9/04 (2006.01) A61K 39/02 (2006.01)
A61K 39/08 (2006.01) A61K 36/47 (2006.01)

(21) International Application Number:

PCT/US2006/028310

(22) International Filing Date: 21 July 2006 (21.07.2006)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:

60/702,077 22 July 2005 (22.07.2005) US
60/747,771 19 May 2006 (19.05.2006) US

(71) Applicant (for all designated States except US): **THE
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(74) Agents: **HESLIN, James, M.** et al.; Two Embarcadero
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(81) Designated States (unless otherwise indicated, for every
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AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN,
CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI,
GB, GD, GE, GH, GM, HN, HR, HU, ID, IL, IN, IS, JP,
KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT,
LU, LV, LY, MA, MD, MG, MK, MN, MW, MX, MZ, NA,
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SD, SE, SG, SK, SL, SM, SY, TJ, TM, TN, TR, TT, TZ,
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GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Declaration under Rule 4.17:

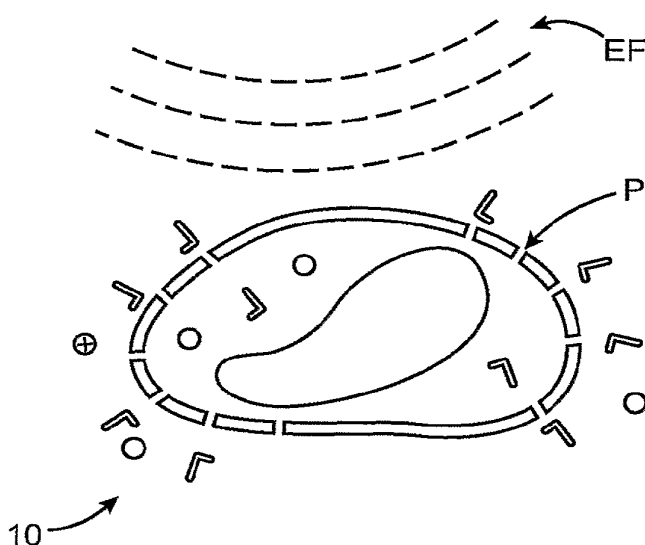
— as to applicant's entitlement to apply for and be granted a
patent (Rule 4.17(ii))

Published:

— without international search report and to be republished
upon receipt of that report

For two-letter codes and other abbreviations, refer to the "Guid-
ance Notes on Codes and Abbreviations" appearing at the begin-
ning of each regular issue of the PCT Gazette.

(54) Title: SYSTEMS AND METHODS FOR DELIVERY OF A THERAPEUTIC AGENT



(57) Abstract: Methods and apparatus are provided for ap-
plying 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 per-
meabilization of targeted cell membranes to enable translo-
cation of the botulinum neurotoxin light chain (BoNT-LC)
molecule across the targeted cell membrane to the cell cy-
tosol where a therapeutic response is produced in a mam-
malian system. The methods and apparatus include use of
catheter based delivery systems, non-invasive delivery sys-
tems, and transdermal delivery systems.

SYSTEMS AND METHODS FOR DELIVERY OF A THERAPEUTIC AGENT

BACKGROUND OF THE INVENTION

5 [0001] 1. Field of the Invention. The present invention relates to methods and apparatus for the control of autonomic nerve function comprising delivery via permeabilization of targeted cell membranes a therapeutically effective amount of a portion or fragment of a neurotoxin such as botulinum toxin (BoNT), the active portion known as the light chain (LC), to cause a clinical benefit in various regions within the body.

10 [0002] First used for medical purposes over 20 years ago for treatment of blepharospasm and strabismus and other skeletal muscle abnormalities, certain neurotoxins have found widespread use in millions of patients worldwide for a variety of conditions.

[0003] Controlled injection of neurotoxins has become a common procedure to control skeletal muscle spasms. While the primary application of neurotoxins such as BOTOX®,
15 commercially sold by Allergan, Inc. (Irvine, CA), has been focused on cosmetic applications, such as treatment of facial wrinkles, other uses for the compound are now common. Certain applications include treatment of cervical dystonia, tremor, headache (migraine), spasticity, torticollis, hemifacial spasm, blepharospasm, meige syndrome, spastic dysphonia, writers cramp, hyperhidrosis, hypersalivation, bladder dysfunction multiple sclerosis, spinal cord
20 injury, cystic fibrosis, stroke paralysis, stuttering, and all types of pain.

[0004] *Clostridium botulinum* neurotoxins (BoNTs) block the release of acetylcholine from peripheral cholinergic nerve endings thereby disabling the release of neurotransmitters from the cells (Bigalke, H. and Shoer, L.F. (1999) *Clostridial Neurotoxins in Handbook of Experimental Pharmacology* 45, 407-443). This mechanism of action is well defined. Seven
25 immunologically distinct serotypes of neurotoxin, designated types A through G, have been identified as discussed by Simpson, L.L., Schmidt, J.J. and Middlebrook, J.L. (1988) in *Methods Enzymol.* 165, 76-85. There are general structural and functional similarities among the various types of neurotoxins, but they all have preferred recipients, for example some favor use in humans and other in non-human species.

[0005] A frequently used neurotoxin for many applications in the human body is Botulinum Toxin Type A (BoNT\A), a protein produced by the bacterium *Clostridium botulinum* and sold commercially by Allergan, inc., as BOTOX®. Botulinum toxin blocks the release of neurotransmitter from the nerves that control the contraction of the target muscles. When used in medical settings, small doses of the toxin are injected into the affected muscles and block the release of a chemical acetylcholine that signals the muscle to contract. The toxin thus paralyzes or weakens the injected muscle.

[0006] In addition, use of neurotoxin for control of the following conditions has been proposed in United States Patents 6,063,768 to First, and 5,766,605 to Sanders, including: rhinorrhea, asthma, COPD, excessive stomach acid secretion, spastic colitis, otitis media, arthritis, tenosynovitis, lupus, connective tissue disease, inflammatory bowel disease, gout, tumors, musculo-skeletal abnormalities, reflex sympathetic dystrophies, tendonitis, bursitis, and peripheral neuropathy. Various other patents contemplate the use of a neurotoxin for additional applications such as, neuromuscular disorders (6,872,397), essential tremor (6,861,058), pancreatitis (6,843,998), muscle spasm (6,841,156), sinus headache (6,838,434), endocrine disorders (6,827,931), priapism (6,776,991), thyroiditis (6,773,711), cardiovascular disease (6,767,544), thyroid disorders (6,740,321), hypocalcemia (6,649,161), hypercalcemia (6,447,785), tardive dyskinesia (6,645,496), fibromyalgia (6,623,742), Parkinson's Disease (6,620,415) cerebral palsy (6,448,231), inner ear disorders (6,358,926), cancers (6,139,845), otic disorders (6,265,379), appetite reduction ((US2004/0253274), compulsive disorders (US2004/0213814, US2004/0213813), uterine disorders ((US2004/0175399), neuropsychiatric disorders (US2003/0211121), dermatological or transdermal applications (US2004/00091880), focal epilepsy (US2003/0202990) the contents of which are expressly incorporated herein by reference in their entirety.

[0007] The patent authors have further detailed devices and methods for treating asthma with local delivery of the intact botulinum toxin in United States Patent Application 10/437,882, filed on May 13, 2003, the contents of which are expressly incorporated by reference herein in its entirety.

[0008] Due to their extreme toxicity, neurotoxins are highly controlled and can have disastrous consequences if not used and controlled properly, especially when used *in vivo*. In addition, due to their toxicity, the body tends to build up a resistance to their use, resulting in

lower efficacy, the need for increased treatments, or the need to discontinue their use all together in certain patients.

[0009] In light of the foregoing, it would be desirable to provide methods and apparatus for delivering neurotoxins such as botulinum toxins non-toxically.

5 [0010] It would also be desirable to provide methods and apparatus for treating various conditions with a neurotoxin such as botulinum toxin fragments via *in vivo* cell permeabilization.

[0011] It would also be desirable to provide a system of devices, including catheters, trocars, needles, endoscopes, inhalers, nebulizers and aerosolizers and other mechanisms to
10 deliver fragmented neurotoxins non-toxically.

[0012] Further, it would be desirable to couple energy delivery devices with the delivery of fragmented neurotoxins to deliver active neurotoxins, non-toxically, including catheter based energy systems, and non-invasive energy systems.

[0013] All publications and patents or patent applications mentioned in this specification
15 are herein incorporated by reference to the same extent as if each individual publication, patent or patent application was specifically and individually so incorporated by reference.

BRIEF SUMMARY OF THE INVENTION

[0014] According to the present invention, an active fragment (sometimes referred to as a catalytic portion) of a neurotoxin such as the botulinum neurotoxin (BoNT), preferably the
20 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
25 the methods and systems of the present invention include ricin and its active fragments, exotoxin A and its active fragments, diphtheria toxin and its active fragments, cholera toxin and its active fragments, tetanus toxin and its active fragments, and the like.

[0015] The present invention contemplates application to all of the conditions listed herein, collectively defined as "therapeutic target conditions", and any other conditions for which
30 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.

5 [0016] In one aspect of the present invention, BoNT-LC or other active neurotoxin fragment is delivered with the application of energy to achieve cell membrane permeabilization.

[0017] In another aspect of the present invention methods and apparatus are provided for altering autonomic nerve function by utilizing an electric field or ultrasonic energy generated
10 by a pulse or pulses of a designated duration and amplitude to alter tissue at the cellular level via permeabilization of the cell membrane to facilitate the translocation of the BoNT-LC or other active neurotoxin fragment to the cell cytosol.

[0018] A further aspect of the invention is to provide methods and apparatus for treating or inhibiting a variety of diseases or syndromes that have an underlying neurogenic component,
15 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
20 the BoNT-LC fragment to the cell cytosol, its catalytic environment.

[0019] In addition to the methods described thus far, the present invention further provides systems for delivering toxins to target cells in a mammalian host. The target cells may be in any of the target regions described above or in any other target region which may benefit from the specific and enhanced delivery of a neurotoxin to cells within the region. Systems
25 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
30 catheter or other delivery structure.

[0020] The energy applicator will typically be adapted to selectively apply energy to target cells within the region where the toxin is to be introduced, e.g., by focusing energy

distribution to the particular target cells or regions which are rich with the target cells. Alternatively, the energy applicator may be adapted to apply energy non-selectively within the target region where both target cells and other cell types may receive the energy.

[0021] In some instances, the toxin may comprise an intact toxin, but more usually will comprise an active toxin fragment as defined elsewhere in this application. In the exemplary embodiments, the active toxin fragment is the light chain fragment of the botulinum toxin (BoNT-LC). The light chain fragment may be derived from any one of at least botulinum toxins A, B, C, D, E, F, and G.

[0022] The energy applicators of the systems of the present invention may be adapted to apply electric energy, typically pulses between 1 V and 500 V to the targeted region. The electric energy may be radiofrequency (RF) energy, where the energy may be pulsed for durations between 5 microseconds to 100 milliseconds. Alternatively, the electrical energy can be direct current (DC), alternating current (AC), or combinations thereof.

[0023] In addition to electrical energy, the energy applicator may be adapted to deliver ultrasonic energy, X-ray beam energy, microwave energy, or any other energy type which can achieve a reversible poration of the target cell walls.

[0024] There are at least two general power categories of medical ultrasound waves which may be utilized in the present invention. One category of medical ultrasound wave is high acoustic pressure ultrasound. Another category of medical ultrasound wave is low acoustic pressure ultrasound. Acoustic power is expressed in a variety of ways by those skilled in the art. One method of estimating the acoustic power of an acoustic wave on tissue is the Mechanical Index. The Mechanical Index (MI) is a standard measure of the acoustic output in an ultrasound system. High acoustic pressure ultrasound systems generally have a MI greater than 10. Low acoustic pressure systems generally have a MI lower than 5. For example, diagnostic ultrasound systems are limited by law to a Mechanical Index not to exceed 1.9. Another measurement used by those skilled in the art is the spatial peak, peak average intensity (Isppa). The intensity of an ultrasound beam is greater at the center of its cross section than at the periphery. Similarly, the intensity varies over a given pulse of ultrasound energy. Isppa is measured at the location where intensity is maximum averaged over the pulse duration. Isppa for high acoustic pressure or high intensity focused ultrasound (HIFU) applications ranges from approximately 1500W/cm². to 9000 W/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 10MPa. Low acoustic pressure ultrasound will generally have peak negative pressures in the range of 0.01 to 5.0 MPa . Diagnostic ultrasound equipment, for example, will generally have a peak amplitude less than 3.0MPa. Both high and low acoustic pressure ultrasound systems generally operate within the frequency range of 20KHz – 10.0 MHz. Interventional applications (such as in blood vessels) operate clinically up to about 50 MHz. Also ophthalmologic applications up to about 15 MHz. Diagnostic imaging typically uses frequencies of about 3 to about 10 MHz. Physical therapy ultrasound systems generally operate at frequencies of either 1.0MHz or 3.3MHz. High acoustic pressure ultrasound or high intensity focused ultrasound has been used for tissue disruption, for example for direct tumor destruction. High intensity focused ultrasound using high acoustic pressure ultrasound is most commonly focused at a point in order to concentrate the energy from the generated acoustic waves in a relatively small focus of tissue.

[0025] Systems and methods for permeabilization of target tissue cell membranes according to the present invention may employ either high acoustic pressure or low acoustic pressure ultrasound. Some embodiments may preferably employ relatively low acoustic pressure, for example the systems described herein where the transducers are mounted on the delivery devices and operate inside the body. Other systems may operate at interim acoustic pressure ranges. For example, systems described herein which employ an external ultrasound generator and transducer and which conduct the ultrasound to the target tissues through the use of a wave guide. In these systems, losses due to transduction through the wave guide can be compensated for by increasing the input power to the wave guide until adequate power is delivered to the target tissue. Finally, some systems described herein may employ focused or partially focused higher pressure ultrasound, for example the systems which employ an external mask to conduct the ultrasonic power through the tissues to the target tissues. It should be appreciated that combinations of high and low acoustic pressure systems may also be employed.

[0026] The catheter or other structure may be adapted to introduce the toxin to the target cells in a variety of ways. For example, catheters may comprise a needle for injecting the toxin, optionally a needle which is deployable axially or radially from the catheter body.

Alternatively or additionally, catheters may be provided with nozzles or other ports for aerosolizing the toxin, particularly within regions of the lung as described herein. Still further alternatively or additionally, the catheters may comprise balloons or other expandable elements for deflecting an end of the catheter to engage one or more ports on the catheter

5 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.

10 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

15 radiofrequency or other electroporation energy.

[0027] In a further aspect of the invention, it may be desirable to provide methods and devices that utilize a non-toxic delivery mechanism to target cells to reduce the potential for an immunogenic response to the delivered toxin over time.

[0028] In a further aspect of the invention, it may be desirable to deliver the therapeutic

20 neurotoxin fragment and energy via a catheter.

[0029] In a further aspect of the invention, it may be desirable to deliver the therapeutic neurotoxin fragment via an aerosolizer or nebulizer.

[0030] In a further aspect of the invention, it may be desirable to deliver the therapeutic neurotoxin fragment via an inhaler.

25 [0031] In a further aspect of the invention, it may be desirable to deliver the therapeutic neurotoxin fragment and membrane transport energy transdermally.

[0032] In a further aspect of the invention, it may be desirable to deliver the therapeutic neurotoxin fragment via a catheter, or aerosolizer or inhaler, and the energy via a catheter placed in the vicinity of the targeted cell.

[0033] In a further aspect of the invention, it may be desirable to delivery the therapeutic neurotoxin fragment and the membrane transport energy via an implantable generator and drug delivery pump.

[0034] In a further aspect of the invention, it may be desirable to deliver the therapeutic neurotoxin fragment via a catheter, or aerosolizer (nebulizer) or inhaler, and the energy via an external energy source adapted to target the applied energy in the vicinity of the targeted cell.

BRIEF DESCRIPTION OF THE DRAWINGS

[0035] Further features of the invention, its nature and various advantages will be more apparent from the accompanying drawings and the following detailed description, in which:

[0036] Figure 1 – depicts a schematic of the creation of neurotoxin Botulinum Toxin Type A (BoNT/A), including the light chain (LC) fragment or portion.

[0037] Figure 2A – depicts a schematic of a target cell, including the cell membrane, and inner cellular matrices.

[0038] Figure 2B – depicts a schematic of the target cell wherein LC molecule has been introduced.

[0039] Figure 3A-3B – depicts a the target cell of Figure 2 showing application of an energy field (EF) to produce permeabilization or pores (P) in the cell membrane, and introduction of the LC fragment therethrough.

[0040] Figure 4 – depicts a schematic of a cell wherein the energy field has been discontinued, and neurotransmission of the cell has been effectively blocked.

[0041] Figures 5, 5A-5B – depicts various embodiments of a delivery device of the present invention utilizing multiple energy transmission elements and an energy transmission system.

[0042] Figures 6A-D, 6AA, and 6CC – depict various electrode catheter configurations adapted to deliver energy or energy and therapeutic agents to target tissue.

[0043] Figure 7 – depicts an alternative embodiment of the present invention wherein one of the multiple energy transmission elements is placed at the targeted cell site, and the other in a location remote therefrom.

[0044] Figure 8 - depicts an embodiment of the present invention utilizing an ultrasound element on a catheter device.

[0045] Figure 9 - depicts an embodiment of the present invention utilizing an inhaler with an *in vivo* energy delivery source.

[0046] Figure 10 - depicts an interstitial method of use of the present invention.

5 [0047] Figure 11 – depicts an embodiment of the present invention utilizing an aerosolizing element.

[0048] Figure 12 – depicts a fully implantable pulse generator, lead and agent delivery pump of the present invention.

10 [0049] Figure 13 – depicts an embodiment of the present invention utilizing an external energy delivery source applied to the therapeutic agent applied in the vicinity of a targeted cell.

[0050] Figure 14 – depicts an embodiment of the present invention wherein the energy and therapeutic agent are delivered transdermally.

[0051] Figure 15 – depicts a method of use of a noninvasive agent delivery device coupled with a non-invasive energy source for treating a lumen or tract of the respiratory system.

15 [0052] Figures 15A and 15B – depict use of a balloon for delivering toxin fragments in a lung.

[0053] Figures 16A and 16B – depict use of a deflected catheter tip for delivering toxin fragments in a lung.

DETAILED DESCRIPTION OF THE INVENTION

20 [0054] The present invention is directed to methods and apparatus for targeting the non-toxic delivery of a fragment of a neurotoxin, while still maintaining the catalytic or toxic effect of the neurotoxin fragment once it is non-toxically delivered to its targeted cell. For purposes of this specification, the term “non-toxic”, “non-toxically” and the like refer to the state of the fragment molecule prior to delivery to a target location. In this description, the
25 fragment neurotoxin is intended to retain its toxic effect once delivered to its catalytic environment; the intracellular matrix or cytosol of the targeted cell.

[0055] Devices and methods of the present invention may be directed to suitable “targeted regions” such as muscle cells in various regions of the body related to the various “therapeutic target conditions” or syndromes to be treated, as detailed in this specification

above. Some particular examples include targeting mucosal and muscular lining of the lung, cholinergic cells in the region of tumors, myofacial regions, vascular smooth muscle cells, musculoskeletal regions and the like.

[0056] According to the present invention, energy fields (EF) may be applied to target

5 regions in conjunction with the delivery of a fragmented neurotoxin such as BoNT-LC to facilitate the transfer of the neurotoxin fragment into the targeted cell, non-toxically via *in vivo* target cell permeabilization.

[0057] Use of Isolated Light Chain of Botulinum Neurotoxins. Generally, the BoNT

10 molecule is synthesized as a single polypeptide chain of 150kD molecular weight. The neurotoxin is then exposed to enzymes, either during cultivation of the *Clostridium botulinum* organism or subsequent to purification of the toxin, wherein specific peptide bonds are cleaved or "nicked" resulting in the formation of a dichain molecule referred to as BoNT. As shown in Figure 1, dichain neurotoxin is composed of a light chain (LC) region 50kD molecular weight linked by disulfide bonds to a heavy chain (HC) 100kD molecular weight
15 (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.
20 (1981) *Pharmacol. Rev.* 33, 155-188.) Focusing on the light chain, the isolation or separation process essentially renders the light chain "non-toxic" in a general environment, while still maintaining its effect or toxicity, once it is transported through the target cell membrane.

[0058] Over the past several years, the separation and purification of the light chain and

25 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
30 to isolate and purify the light chain (LC) of the botulinum molecule. In its isolated and purified form, all HC elements are removed, rendering the LC incapable of crossing the cell

membrane without assistance. Thus, the LC is non-toxic until delivered to the target cell cytosol by the delivery protocols of the present invention.

[0059] Various groups have been active in the area of isolation and purification. For example, companies such as Metabiologics, a group affiliated with the University of Wisconsin, the Center for Applied Microbiology and Research (CAMR), a division of the UK Health Protection Agency, List Biological Laboratories, Inc. of California, and other research groups throughout the world. Many of these companies provide purified preparations of botulinum neurotoxins from *Clostridium botulinum* types A and B. List Laboratories in particular provides recombinantly produced light chains from both types A, B, C, D and E.

[0060] According to the present invention, the therapeutic use and delivery of the light chain only may significantly improve the safety profile of certain applications of therapies utilizing BoNT. BoNT are some of the most lethal toxins known to man. All concerns about migration of the neurotoxin into unintended regions, and harm or toxicity to the patient or physician are eliminated by storing, handling, injecting and metabolizing the light chain only. In the absence of a specific membrane binding technology, the LC is completely non-toxic. In certain applications, such as the treatment of asthma, this is of critical import. In using BoNT to treat asthma, a large quantity of the purified LC substance may be introduced directly into the lung, and then specifically transported to target cells in the exact location and only during the period of use of application of the membrane transport technology, such as cell membrane permeabilization by energy. Once the membrane transport technology has been removed, turned off or otherwise inactivated, the remaining LC which has not been transported into target cells can simply be removed from the body by standard biologic processes for expelling foreign materials, e.g. coughing, immune system or lymphatic system transport and the like.

[0061] In addition, therapeutic use of only the LC of the neurotoxin BoNT may reduce the likelihood of the body developing an immunogenic response to the therapy that is seen with delivery of the intact toxin. This could be a major advantage in light of the repetitive application or injection of the toxin that is required to maintain a therapeutic effect.

[0062] Non-Toxic Membrane Transport Mechanisms. To date, the main application of purified or isolated light chain has been the study of its mechanism of action. To further this research, literature has reported the use of certain detergent based permeabilization

techniques to deliver fragment BoNT (Bittner MA, DasGupta BR, Holz RW. Isolated light chains of botulinum neurotoxins inhibit exocytosis. Studies in digitonin-permeabilized chromaffin cells. J Biol Chem 1989 Jun 25; 264(18):10354–10360.) Further reference to the mechanism of permeability of cell membranes to deliver botulinum toxin are mentioned in United States Patent 6,063,768 to First, and United States Patent No. 6,632,440 to Quinn, Chaddock, et al “Expression and Purification of Catalytically Active Non-Toxic Endopeptidase Derivatives of Clostridium botulinum toxin type A”, *Protein Expression and Purification*, 25 (2002) 219-228, contemplating the insertion of the light chain of BoNT into a target cell without the heavy chain for purposes of deriving vaccines or in bench top studies of cell mechanisms of action. The contents of these references are expressly incorporated by reference in their entirety. None of the teachings contemplate a delivery of a fragment of neurotoxin using a clinically acceptable permeabilization technique *in vivo* for therapeutic uses as is contemplated by the present invention.

[0063] For purposes of this specification, the term “poration” includes various forms of electroporation, such as the use of pulsed electric fields (PEFs), nanosecond pulsed electric fields (nsPEFs), ionophoresis, electrophoresis, electroporation, as well as other energy mediated permeabilization, including sonoporation (mediated by ultrasonic or other acoustic energy), and/or combinations thereof, to create temporary pores in a targeted cell membrane. Similarly, the term “electrode” or “energy source” used herein, encompasses the use of various types of energy producing devices, including x-ray, radiofrequency (RF), DC current, AC current, microwave, ultrasound, adapted and applied in ranges to produce membrane permeabilization in the targeted cell.

[0064] Reversible electroporation, first observed in the early 1970’s, has been used extensively in medicine and biology to transfer chemicals, drugs, genes and other molecules into targeted cells for a variety of purposes such as electrochemotherapy, gene transfer, transdermal drug delivery, vaccines, and the like.

[0065] In general, electroporation may be achieved utilizing a device adapted to activate an electrode set or series of electrodes to produce an electric field. Such a field can be generated in a bipolar or monopolar electrode configuration. When applied to cells, depending on the duration and strength of the applied pulses, this field operates to increase the permeabilization of the cell membrane and reversibly open the cell membrane for a short period of time by causing pores to form in the cell lipid bilayer allowing entry of various therapeutic elements

or molecules, after which, when energy application ceases, the pores spontaneously close without killing the cell after a certain time delay. As characterized by Weaver, *Electroporation: A General Phenomenon for Manipulating Cells and Tissues* Journal of Cellular Biochemistry, 51:426-435 (1993), short(1-100 μ s) and longer (1-10ms) pulses have induced electroporation in a variety of cell types. In a single cell model, most cells will exhibit electroporation in the range of 1-1.5V applied across the cell (membrane potential).

[0066] In addition, it is known in the art that macromolecules can be made to cross reversibly created pores at voltages of 120V or less applied to cells for durations of 20 microseconds to many milliseconds. For applications of electroporation to cell volumes, ranges of 10 V/cm to 10,000 V/cm and pulse durations ranging from 1 nanosecond to 0.1 seconds can be applied. In one example, a relatively narrow (μ sec) high voltage (200V)pulse can be followed by a longer (>msec) lower voltage pulse (<100V). The first pulse or series of pulses open the pores and the second pulse or series of pulses assist in the movement of the BoNT-LC across the cell membrane and into the cell.

[0067] Certain factors affect how a delivered electric field will affect a targeted cell, including cell size, cell shape, cell orientation with respect to the applied electric field, cell temperature, distance between cells (cell-cell separation), cell type, tissue heterogeneity, properties of the cellular membrane and the like.

[0068] Various waveforms or shapes of pulses may be applied to achieve electroporation, including sinusoidal AC pulses, DC pulses, square wave pulses, exponentially decaying waveforms or other pulse shapes such as combined AC/DC pulses, or DC shifted RF signals such as those described by Chang in *Cell Poration and Cell Fusion using and Oscillating Electric Field*, Biophysical Journal October 1989, Volume 56 pgs 641-652, depending on the pulse generator used or the effect desired. The parameters of applied energy may be varied, including all or some of the following: waveform shape, amplitude, pulse duration, interval between pulses, number of pulses, combination of waveforms and the like.

[0069] A schematic example of the methods of the present invention are shown in Figures 2-4 in a simplified single cell model. A targeted cell 10 is shown in Figure 2A. Fragmented neurotoxin such as BoNT-LC (LC) is introduced into the vicinity of the targeted cell as depicted in Figure 2B. An energy field (EF) is applied in accordance with the present invention resulting in the transfer of the BoNT-LC through pores P to the intracellular matrix (cytosol) as shown in Figures 3A and 3B. Once this transfer has occurred, the release of

neurotransmitters of the target cell are then blocked or disrupted, and once energy application is discontinued, the pores P in the cell membrane recover or close as depicted in Figure 4.

[0070] Of particular interest for application in certain therapeutic target conditions is the developing field of sonoporation. Just as pulses of high voltage electricity can open transient pores in the cell membrane, ultrasonic energy can do the same. See for example Guzman et al. "Equilibrium Loading of Cells with Macromolecules by Ultrasound: Effects of Molecular Sizing and Acoustic Energy," *Journal of Pharmaceutical Sciences*, 91:7, 1693-1701, which examines the viability of ultrasound to deliver molecules of a variety of sizes into target cells. In addition, techniques for nebulizing fluids and aqueous drugs are well known in the art, and as such, devices of the present invention may be adapted to introduce a BoNT-LC solution to a target region, such as the lung and then effect selective membrane transport of the BoNT-LC into the cell using sonoporation.

[0071] For example, United States Patent 6,601,581 to Babaev, hereby incorporated by reference in its entirety, describes certain techniques for delivering therapeutic agents using ultrasound for pulmonary delivery via an aerosolizing technique. Further, Guzman, et al, depicts delivery of molecules from a low of 62Da up to 464 kDa (a range of 0.6-18.5nm radius). Since the LC of the botulinum toxin is in the 50kDa range, the LC would be very susceptible to sonoporetic delivery. Furthermore, Guzman, et al also showed that for all size ranges tested, levels of macromolecule within the cell reached thermodynamic equilibrium with the extracellular environment, and the cell uptake also depended on the energy delivered, as expressed in J/cm^2 . As such, the sonoporetic delivery of LC to the targeted regions may be controlled by adjusting the concentration of the LC exposed to the target region (e.g. wall or membrane of the lung), the energy delivered to the target region, or both.

[0072] Catheter Devices. To achieve the goals of the present invention, it may be desirable to employ methods and apparatus for achieving cell membrane permeabilization via the application of an energy source, either from a catheter located directly in the vicinity of the targeted cells, or an externally focused energy system. For purposes of this specification, the term "catheter" may be used to refer to an elongate element, hollow or solid, flexible or rigid and capable of percutaneous introduction to a body (either by itself, or through a separately created incision or puncture), such as a sheath, a trocar, a needle, a lead. Further descriptions of certain electroporation catheters are described in United States Patent Application

60/701,747 (Attorney Docket No. 020979-003500US), filed on July 22, 2005, the full disclosure of which is expressly incorporated herein by reference.

[0073] Figures 5 and 5A-5B depict a system 20 utilizing an electroporation catheter 22 for selective electroporation of targeted cells. In certain configurations of the present invention, voltages may be applied via the electroporation catheter 22 to induce reversible electroporation at the same time as the catheter delivers the fragmented neurotoxin to the targeted region.

[0074] Referring to Figure 5, electroporation catheter system 20 further comprises a pulse generator 24 such as those generators available from Cytropulse Sciences, Inc. (Columbia, MD) or the Gene Pulser Xcell (Bio-Rad, Inc.), or IGEA (Carpi, Italy), electrically connected to a catheter having a proximal end and a distal end and adapted for minimally invasive insertion into the desired region of the body as described herein. The catheter further comprises an electroporation element 26 at a distal 28 end thereof. The electroporation element may include for example a first and second electrode 30 and 32 operatively connected to the pulse generator for delivering the desired number, duration, amplitude and frequency of pulses to affect the targeted cells. These parameters can be modified either by the system or the user, depending on the location of the catheter within the body (intervening tissues or structures), and the timing and duration of reversible cell poration desired. Figure 5A depicts an arrangement of electrodes 30 and 32 that produces an electric field concentrated in a lateral direction from the catheter body whereas, Figure 5B shows a device constructed to create a more uniform electric field about the shaft of the catheter body.

[0075] Further catheter device and electrode configurations are shown in Figures 6A-6D. Figure 6A depicts an elongate catheter 40 having first and second electrodes 42 and 44 near the distal tip thereof, and including a monitoring or stimulation electrode 46 in the vicinity of the active porating electrodes for localizing the treatment area. In some embodiments, the monitoring or stimulating function may be performed by one or more of the treatment electrodes. The catheter device may have an optional sharp tip 48 to facilitate percutaneous introduction. Cross-sectional view Figure 6AA shows various lumens provided for neurotoxin fragment delivery and other purposes.

[0076] Figure 6B is a similar catheter device 50 having electrodes 52, 54, and 56, but is further adapted to be steerable, or articulate at a region 53 near the distal end of the device, e.g., including a pull wire for deflecting the tip. Such steering ability enables the operator to

introduce the device into tight or tortuous spaces (such as the bronchial passages or cardiovascular vessels) so that optimal placement of the device at the target location may be achieved.

[0077] Figure 6C depicts a catheter device 60 having a needle 62 or other injection element to allow for the injection of a therapeutic agent such as a fragmented neurotoxin before, during or after the application of the pulsed energy or electroporation. The catheter 60 further includes electrodes 64 and 66 or other poration components as discussed herein. The injection element may be a needle 62 as shown in Figure 6C, an infusion port, or other infusion means. Needle 62 may also be used as an electrode in addition to an injection port. Electrode 68 comprises a monitoring or stimulating electrode. Figure 10 depicts the use of a catheter of Figure 6C to treat bronchial tissue in the lung for a variety of respiratory ailments such as asthma. Figure 6CC is a cross-sectional view taken along line 6CC-6CC in Figure 6, showing a co-axial sleeve design.

[0078] Figure 6D depicts a catheter device 70 having electrode elements 72 and 74 that are adapted to extend laterally from the main catheter body, and in some cases, penetrate the surrounding tissue prior to application of energy. In doing so the depth and direction of the energy field created by the electroporative process, may be further controlled. A monitoring/stimulating electrode 76 will usually also be provided. Elements 72 and 74 may also be used as injection ports for introduction of toxin or toxin fragments.

[0079] Figure 7 depicts the use of a catheter device 80 of the present invention for treatment of a respiratory tract, by positioning at least one electrode (82) at the target region, and a second electrode (84) remote from the target region, the target region being positioned between 82 and 84, such that activation of the electrodes produces an energy field (EF) therebetween, the size and intensity of which can be controlled by the placement of the electrodes relative to each other and the targeted region.

[0080] Figure 8 depicts catheter 90 constructed in accordance with the principles of the present invention utilizing an ultrasonic element 92 that may be particularly useful in delivery of the BoNT-LC to bronchial tissue (lung) that provides a broad but targeted transport of the LC across the target cell walls, for example, epithelial and goblet cell walls. In this device, ultrasound energy is delivered to the distal end of the catheter device via an ultrasonic waveguide 94 that is operatively connected to an ultrasound energy source (U/SES). The LC fragment would be delivered from a receptacle 96 via the same lumen as the waveguide via a

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

[0081] Since air is a very effective insulator against transmission of ultrasonic energy, the treatment area in the lung may be more precisely controlled by the concentration of the LC mist and the intensity of the ultrasonic energy. A fairly steep drop off in energy delivery would occur as mist concentration diffused, effectively protecting areas outside the predetermined radius surrounding the distal end of the delivery device. According to the present invention, since no functional neurotoxin exists without an effective membrane transport technology, terminating the energy application leaves a harmless mist that is then coughed up (if resident in the lungs) or otherwise metabolized and excreted by the body.

[0082] Any of the catheter devices described herein, or described in the contemporaneously filed United States Patent Application 60/701,747 (Attorney Docket No. 020979-003500US), previously incorporated by reference in its entirety, may be adapted to include an energy delivery element such as those described herein for purposes of providing a membrane transport system for delivery of a fragment of neurotoxin. In addition, certain catheter devices and methods such as those set forth in United States Patents 5,964,223 and 6,526,976 to Baran may be adapted to include energy transmission elements capable of producing a porative effect at the cellular level, including electrodes, ultrasonic elements and the like, for treatment in the respiratory tract.

[0083] Furthermore, any of the foregoing systems may include electrodes or other monitoring systems either located on the treatment catheter, or external to the patient, to determine the degree of treatment to the region, including, thermocouple, ultrasound transducers, fiberoptics, sensing or stimulating electrodes. Further, it may be desirable to

incorporate multiple pairs of electrodes that may be activated in pairs, in groups, or in a sequential manner in order to maximize the desired shape of the energy field (EF) while minimizing the field strength requirements.

[0084] Implantable Devices. Just as energy may be delivered to a targeted region to facilitate the delivery of fragmented neurotoxin via a catheter system, it is also within the scope of the present invention to deliver neurotoxins via an implantable system, including a pulse generator, lead and drug pump as depicted in Figures 12. A neuromodulation system 200 may be fully implantable, having a pulse generator and a power supply or battery and be operatively connected to a programmable drug delivery pump all housed within a module 202, including a reservoir in which the BoNT-LC is stored for delivery over time using the principles of the present invention and technology of the programmable drug pump. A catheter 204 can be adapted to deliver the drug and poration energy to a desired target location in the patient's body.

[0085] Examples of useful implantable devices of the present invention are, devices such as those set forth in United States Patent 5,820,589 to Torgerson et al, the entire contents of which are hereby incorporated by reference, the SynchroMed® programmable pump available from Medtronic, Inc. (Minneapolis, MN), and the neurostimulation units such as the RESTORE® or SynergyPlus® available from Medtronic, Inc., modified if necessary to delivery the desired voltage range for cell membrane permeabilization. Implantation of the neurostimulation device is further described in US Patent 6,847,849, incorporated herein by reference in its entirety.

[0086] The non-toxic nature of the BoNT in the absence of applied energy makes it possible to contemplate placing a bolus of neurotoxin in the body of a patient in what might otherwise be a toxic amount. This is particularly advantageous, since the traditional treatment regime using neurotoxins, is typically repeat injections of the toxins every 3 to 6 months and sometimes more frequently depending on the application. Certainly in more chronic conditions such as chronic pain, tremor, spasm, palsy and the like, such a fully implantable system may be highly desirable.

[0087] Non-Invasive Devices. It is within the scope of the invention to deliver either the energy or the therapeutic BoNT-LC non-invasively, or both. For example, Figure 13 depicts delivery of the BoNT-LC via a catheter 100 placed in the bronchial passageway with the energy field (EF) delivered from outside the patient in the form of an energy system 102 such

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

[0088] A combination of these non-invasive approaches may also be advantageous as shown in Figure 15, wherein a non-invasive inhaler 110 is used to deliver the BoNT-LC to the target region (such as the lung), and the energy is delivered to the target region by the non-invasive source 102 such as the focused ultrasound (HIFU), stereotactic x-ray, or magnetic resonance transmission as previously described. Due to its non-invasive technique, this approach may have broad appeal to a large patient population, including pediatric use, on an outpatient basis in a clinic designated for the treatment of specific respiratory ailments.

[0089] In a further aspect of the present invention, the fragmented molecule BoNT-LC may be delivered intravenously to a patient to achieve a systemic effect. A non-invasive energy application device, such as those described above, may then be targeted at the area of interest to porate the target area, thereby locally delivering the BoNT-LC to the region sufficiently porated by the applied energy.

[0090] Cosmetic and Myofacial Applications. For some conditions, it may be desirable to apply the energy field from the surface of the skin to produce a porative effect, while injecting the BoNT-LC fragment into the targeted facial muscles as shown in Figure 14. In

operation, an injection device 220 places the BoNT-LC in the muscle to be treated (target region), and an energy transmission device such as an ultrasonic pen 222 with a single, or a series of ultrasonic elements located on the distal end and coupled to an energy transmission system 224, follows along the target region to controllably discharge the BoNT-LC fragments to the targeted cells leaving a highly controlled treated region. In some instances for treatments around the eye, it may be desirable to limit the penetration of the BoNT-LC to dermal or subdermal layers. In these applications, BoNT-LC may be applied transdermally with ultrasound assistance using techniques similar to those set forth in US Patent 4,767,402 to Kost the contents of which is expressly incorporated herein in its entirety or through transdermal electroporation.

[0091] Intraluminal Devices. It may further be advantageous to position catheters of the present invention through vessels in the body to direct them to various regions to affect neurotransmitters in the cardiovascular system. Intraluminal catheters such as those shown in United States Patent Applications 2001/0044596 to Jaafar and 2002/0198512 to Seward, hereby incorporated by reference in their entirety, may be used in this application of the present invention.

[0092] Treatment Enhancements. In some applications of the present invention, it may be desirable to 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.

[0093] 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.

[0094] In a further aspect of the present invention, the method of delivering the LC fragment of the BoNT molecule may include the use of a media that contains microspheres or microbubbles, such as OptisonTM sold by GE Healthcare (www.amershamhealth-

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

[0095] In a further aspect of the present invention, it may be advantageous to heat the targeted cells or surrounding tissue by either applying thermal energy directly to the region, or directing a heated fluid, such as saline to the region through an injection element, to aid the cell poration process. Other substances may also be injected to aid in the transmission of the BoNT-LC into the intracellular membrane, such as amino acids, detergents or other agents that may facilitate the catalytic activity of the LC, in addition to the applied energy.

[0096] Referring now to Figs. 15A and 15B, a balloon catheter 300 may be delivered to a target site in the bronchus B of a lung (Fig. 15B). Typically, the catheter 300 will be delivered through an endoscope E, and the shaft 302 of the catheter will comprise at least one lumen for inflating the balloon 304. The inflation medium may carry the toxin fragment which is released through ports 306 formed in the balloon itself. Thus, inflation of the balloon both engages the ports against the wall of the bronchus B and provides the pressure necessary to infuse the neurotoxin fragments into the wall of the bronchus B. Usually, energy will be applied from electrodes 308 or other transducers located within the balloon 304.

[0097] Referring now Figs. 16A and 16B, the catheter 400 may also be delivered to a bronchus B of a lung through an endoscope E. Catheter shaft 402 terminates with a delivery port 404 near its distal end. A deflection balloon 406 (or other expandable element capable of pressing against the wall of the bronchus B to engage the port 404 against target tissue) is provided on a side of the catheter shaft 402 which is opposite to that of the port 404. Electrodes 408 are provided on either side of the port 404 in order to deliver the poration energy into the target tissue.

[0098] Although various illustrative embodiments of the present invention are described above, it will be evident to one skilled in the art that various changes and modifications may be made without departing from the scope of the invention. It will also be apparent that various changes and modifications may be made herein without departing from the invention.

5 The appended claims are intended to cover all such changes and modifications that fall within the true spirit and scope of the invention.

WHAT IS CLAIMED IS:

1 1. A method for treating conditions affected by neurogenic function in a
2 targeted region of mammalian cells, said method comprising:
3 delivering an active neurotoxin fragment to cells in the targeted region;
4 applying energy to the cells under conditions which cause a reversible
5 poration in the cell membranes to permit delivery of the active fragment.

1 2. A method as in claim 1, wherein the active fragment is selected from
2 the group consisting of botulinum toxin fragments, ricin fragments, exotoxin A fragments,
3 diphtheria toxin fragments, cholera toxin fragments, and tetanus toxin fragments.

1 3. A method as in claim 2, wherein the active fragment comprises the
2 botulinum light chain (BoNT-LC).

1 4. A method of claim 3, wherein the active fragment comprises an
2 amount of BoNT-LC therapeutically effective to inhibit a neurogenic pathway associated
3 with the neurogenic function.

1 5. A method of claim 4, wherein the active fragment is BoNT-LC derived
2 from at least one of the botulinum toxins A, B, C, D, E, F or G.

1 6. A method of claim 1, wherein the neurogenic pathway is associated
2 with and contributes to at least one symptom of asthma.

1 7. A method of claim 1, wherein delivering comprises advancing a
2 catheter to said vicinity and releasing the active neurotoxin fragments from the catheter while
3 applying energy from an applicator on the catheter.

1 8. A method of claim 7, wherein delivering comprises aerosolizing the
2 fragment from the catheter.

1 9. A method as in claim 7, wherein delivering comprises injecting the
2 fragment from a needle on the catheter.

1 10. A method as in claim 7, wherein delivery comprises engaging one or
2 more ports on the catheter against tissue and releasing the fragments from the port(s).

- 1 11. A method as in claim 10, wherein engaging comprises inflating a
2 balloon on the catheter to deflect the catheter.
- 1 12. A method of claim 1, wherein the delivering is achieved using an
2 inhaler.
- 1 13. A method of claim 1, wherein the delivering is achieved transdermally
- 1 14. A method of claim 1, wherein the energy applied to the targeted region
2 is an electric pulse.
- 1 15. A method of claim 14, wherein the electric pulse has a voltage between
2 1V and 500V.
- 1 16. A method of claim 14, wherein the electric pulse comprises
2 radiofrequency energy.
- 1 17. A method of claim 16, wherein the radiofrequency energy is pulsed for
2 durations between 5 microseconds to 100 milliseconds.
- 1 18. A method of claim 13, wherein the electric pulse comprises a direct
2 current pulse.
- 1 19. A method of claim 13, wherein the electric pulse comprises an
2 alternating current pulse.
- 1 20. A method of claim 1, wherein the energy applied to the targeted region
2 comprises ultrasonic energy.
- 1 21. A method of claim 20, wherein the ultrasonic energy applied to the
2 targeted region comprises focused ultrasound energy.
- 1 22. A method of claim 1, wherein the energy applied to the targeted region
2 comprises an x-ray beam.
- 1 23. A method of claim 1, wherein the energy applied to the targeted region
2 comprises microwave energy.

1 24. A method of claim 4, wherein the neurogenic pathway is associated
2 with and contributes to at least one symptom of pain.

1 25. A method of treating a respiratory ailment, comprising the steps of:
2 providing a therapeutically effective amount of BoNT-LC, and
3 delivering the amount of BoNT-LC to a region of the respiratory system under
4 conditions selected to permeabilize target cells within the region and allow entry of the
5 BoNT-LC to enter the cells.

1 26. A system for delivering toxins to target cells in a mammalian target,
2 said system comprising:
3 a catheter or other structure adapted to introduce a toxin to a region adjacent
4 the target cells;
5 an energy applicator for applying energy to the target cells under conditions
6 which cause poration of the cell membranes to enhance delivery of the toxin; and
7 a source of toxin suitable for introduction from the catheter.

1 27. A system as in claim 26, wherein the energy applicator is adapted to
2 selectively apply energy to target cells within the region where toxin has been introduced.

1 28. A system as in claim 26, wherein the energy applicator is adapted to
2 apply energy non-selectively within the region where toxin has been introduced.

1 29. A system as in claim 26, wherein the toxin comprises an intact toxin.

1 30. A system as in claim 29, wherein the toxin is an active toxin fragment.

1 31. A system as in claim 30, wherein the fragment is a light chain
2 fragment.

1 32. A system as in claim 31, wherein the active fragment is selected from
2 the group consisting of botulinum toxin fragments, ricin fragments, exotoxin A fragments,
3 diphtheria toxin fragments, cholera toxin fragments, and tetanus toxin fragments.

1 33. A system as in claim 32, wherein the active fragment comprises the
2 botulinum light chain (BoNT-LC).

- 1 34. A system as in claim 33, wherein the light chain fragment is derived
2 from at least one of botulinum toxins A, B, C, D, E, F, and G.
- 1 35. A system as in claim 26, wherein the energy applicator is adapted to
2 apply an electric pulse of between 1V and 500V to the target region.
- 1 36. A system as in claim 35, wherein the electric pulse is radiofrequency
2 (RF) energy.
- 1 37. A system as in claim 35, wherein the RF energy is pulsed for durations
2 between 5 microseconds to 100 milliseconds.
- 1 38. A system as in claim 35, wherein the electric pulse is produced by a
2 DC power source.
- 1 39. A system as in claim 35, wherein the electric pulse is produced by an
2 AC power source.
- 1 40. A system as in claim 26, wherein the energy applicator is adapted to
2 apply ultrasonic energy to the targeted region.
- 1 41. A system as in claim 40, wherein the energy applicator is adapted to
2 apply focused ultrasound to the targeted region.
- 1 42. A system as in claim 26, wherein the energy applicator is adapted to
2 apply an x-ray beam to the targeted region.
- 1 43. A system as in claim 26, wherein the energy applicator is adapted to
2 apply microwave to the targeted region.
- 1 44. A system as in claim 26, wherein the catheter comprises a needle for
2 delivering the toxin.
- 1 45. A system as in claim 26, wherein the catheter comprises a port for
2 aerosolizing the toxin.
- 1 46. A system as in claim 28, wherein the catheter comprises a balloon for
2 deflecting one or more ports against target tissue.

- 1 47. A system as in claim 46, wherein the balloon comprises the one or
2 more ports.
- 1 48. A system as in claim 26, wherein the energy applicator is on the
2 catheter.
- 1 49. A system as in claim 48, wherein the energy applicator applies acoustic
2 energy from a transducer on the catheter.
- 1 50. A system as in claim 48, wherein the energy applicator applies
2 electrical energy from an electrode on the catheter.
- 1 51. A system as in claim 26, wherein the applicator applies energy from a
2 source external to the patient.
- 1 52. A system as in claim 51, wherein the source is an acoustic energy
2 transducer.
- 1 53. A system as in claim 52, wherein the acoustic energy transducer is
2 focused ultrasound transducer.

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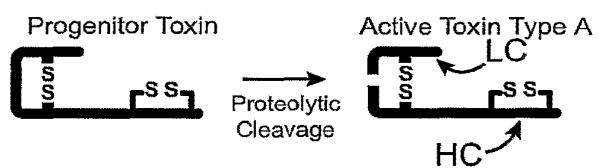
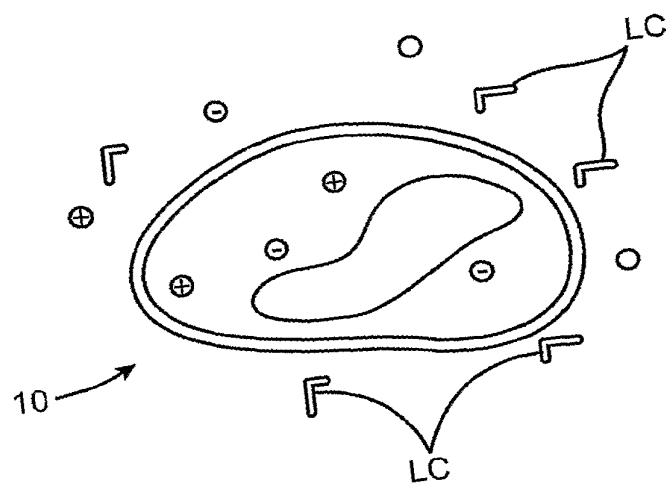
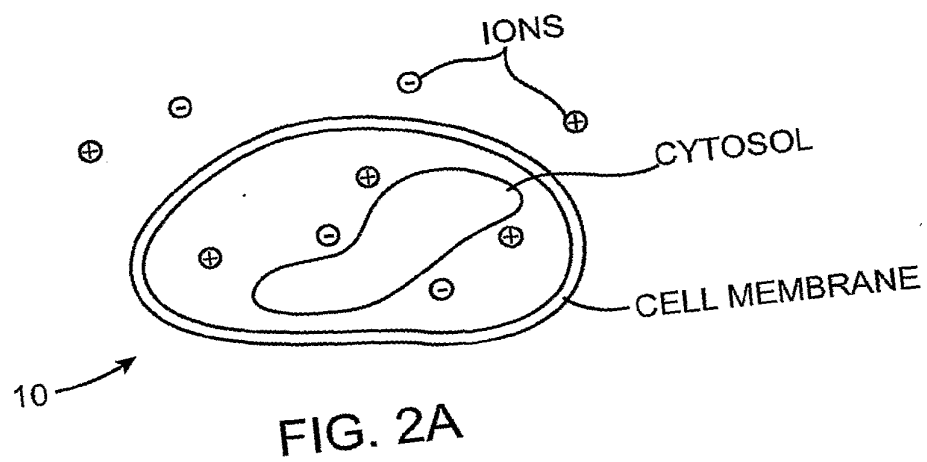
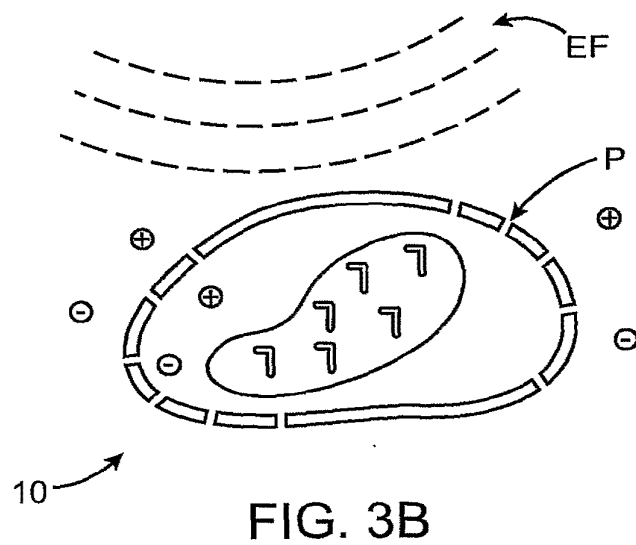
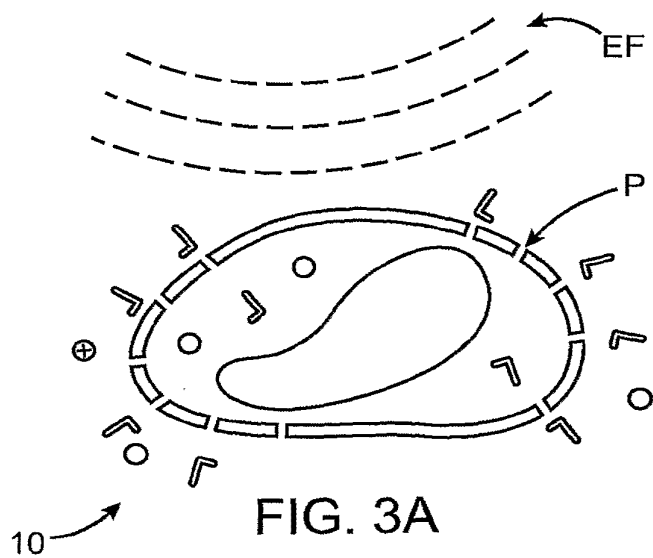


FIG. 1

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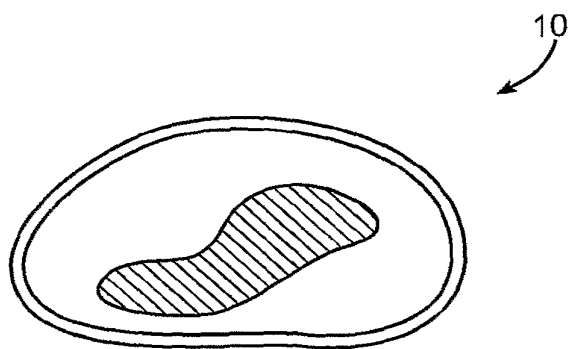
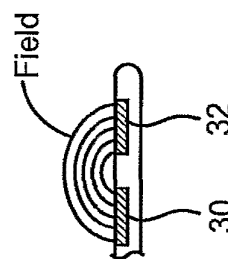
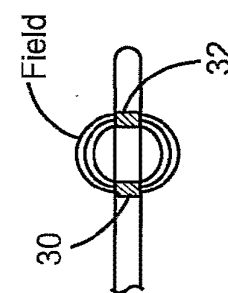
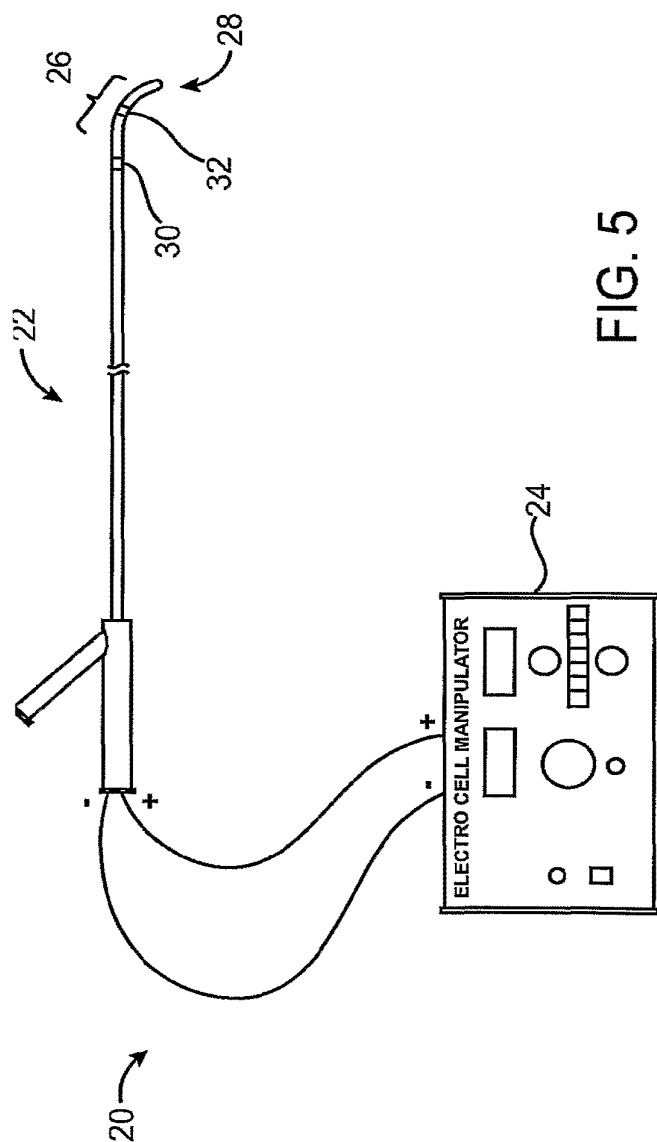


FIG. 4

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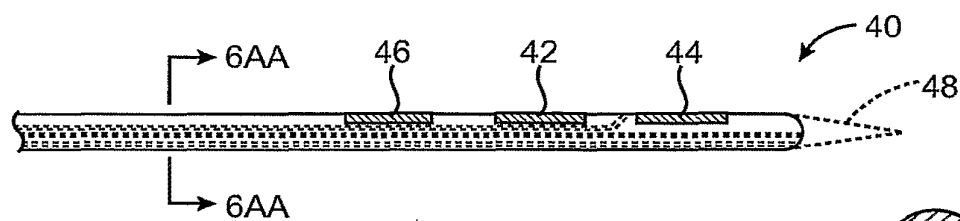


FIG. 6A

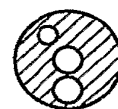


FIG. 6AA

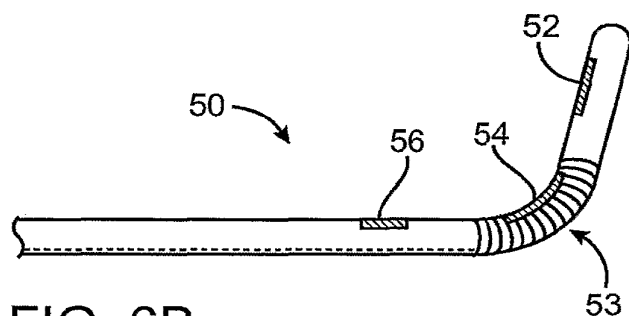


FIG. 6B

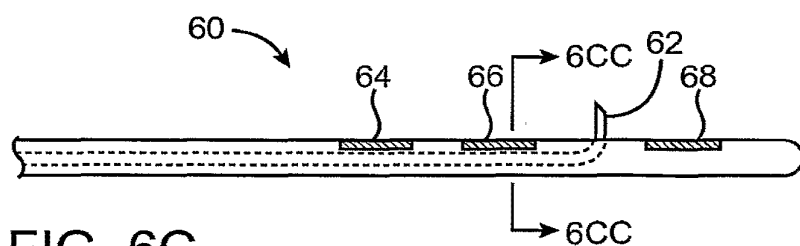


FIG. 6C



FIG. 6CC

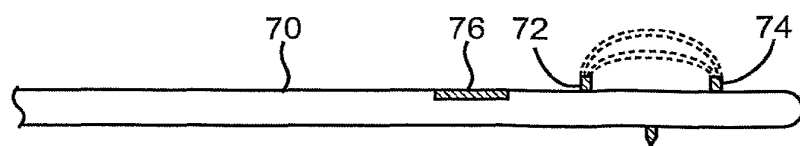


FIG. 6D

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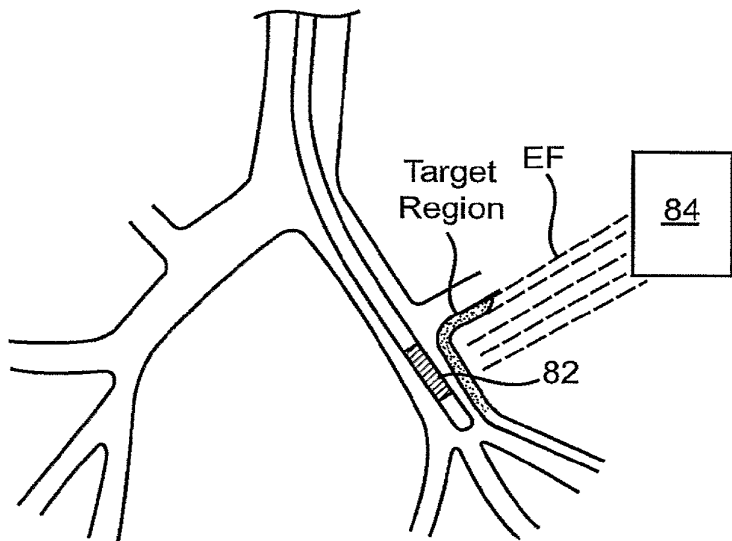


FIG. 7

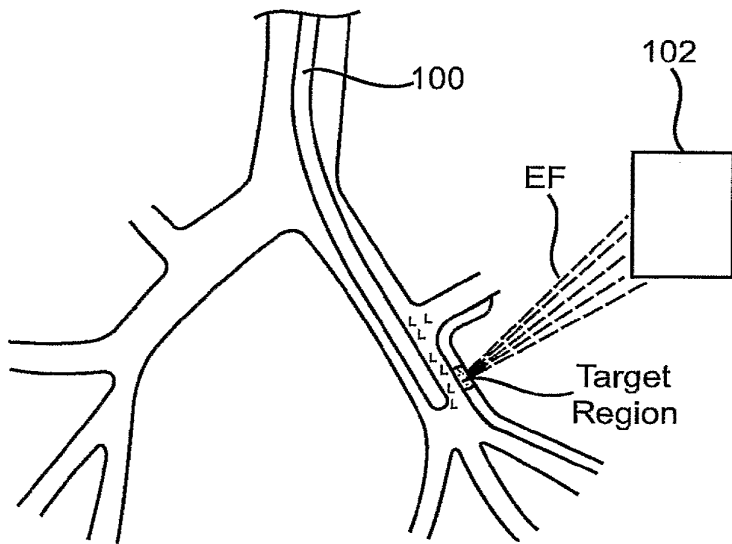


FIG. 13

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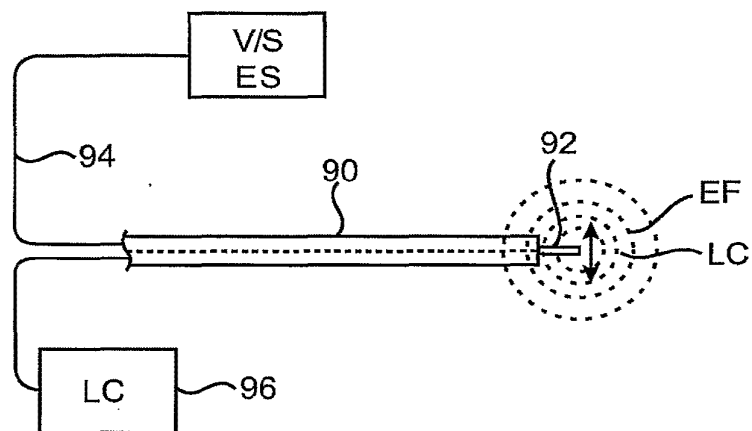


FIG. 8

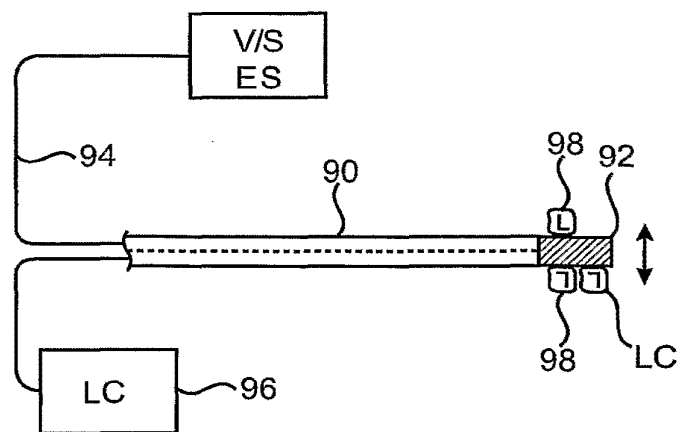


FIG. 11

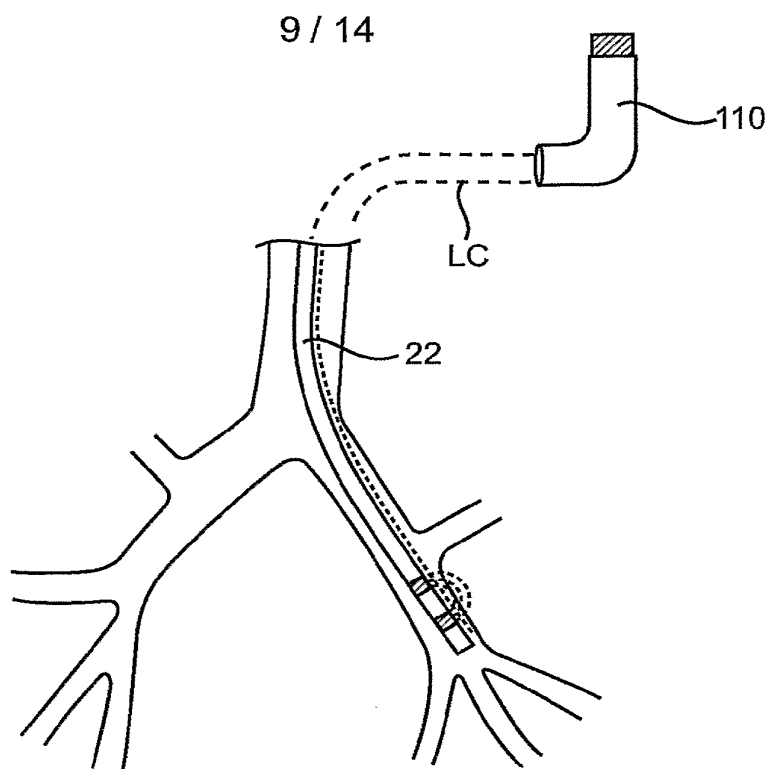


FIG. 9

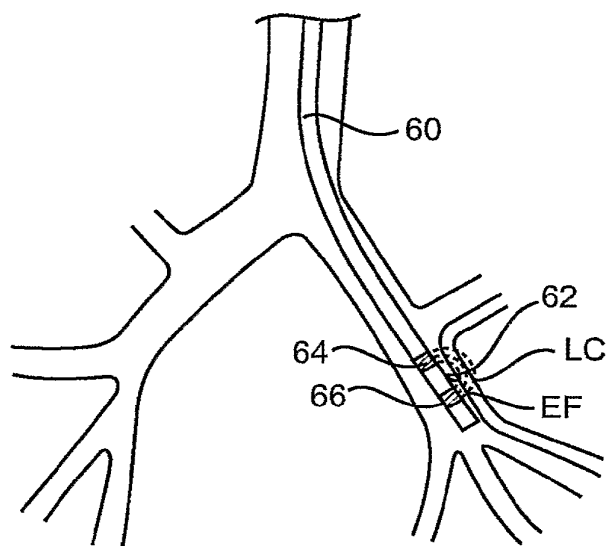
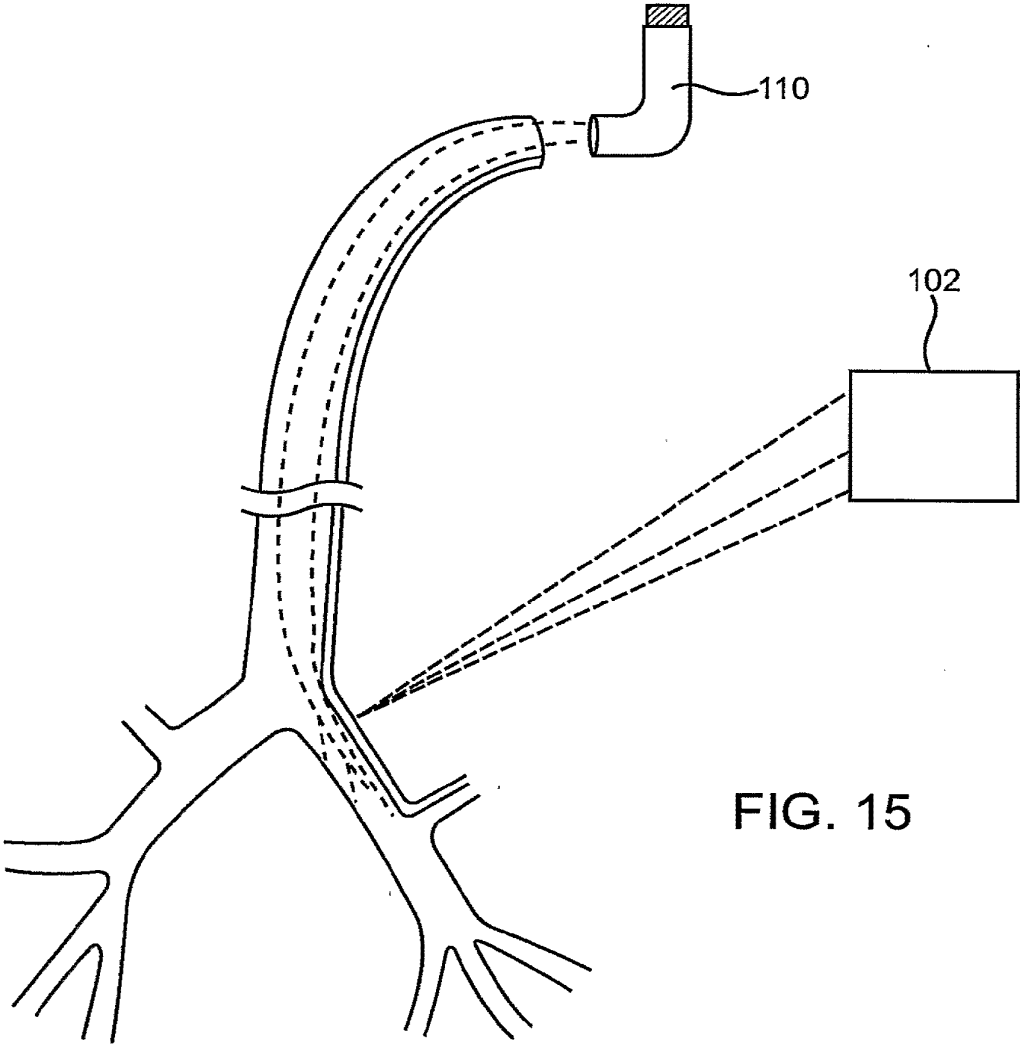
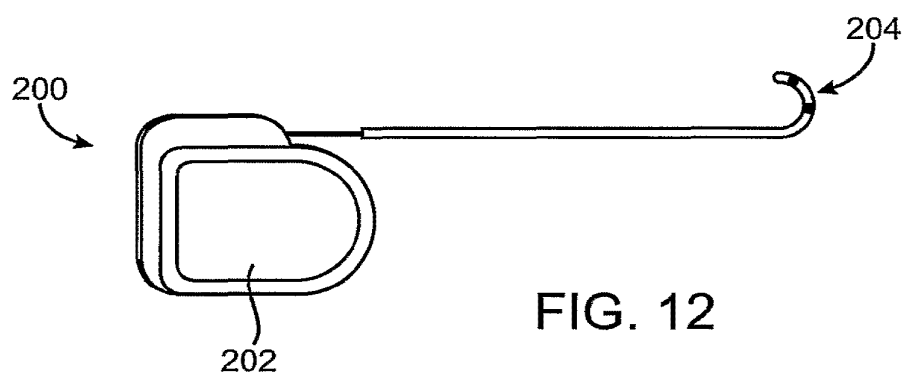


FIG. 10

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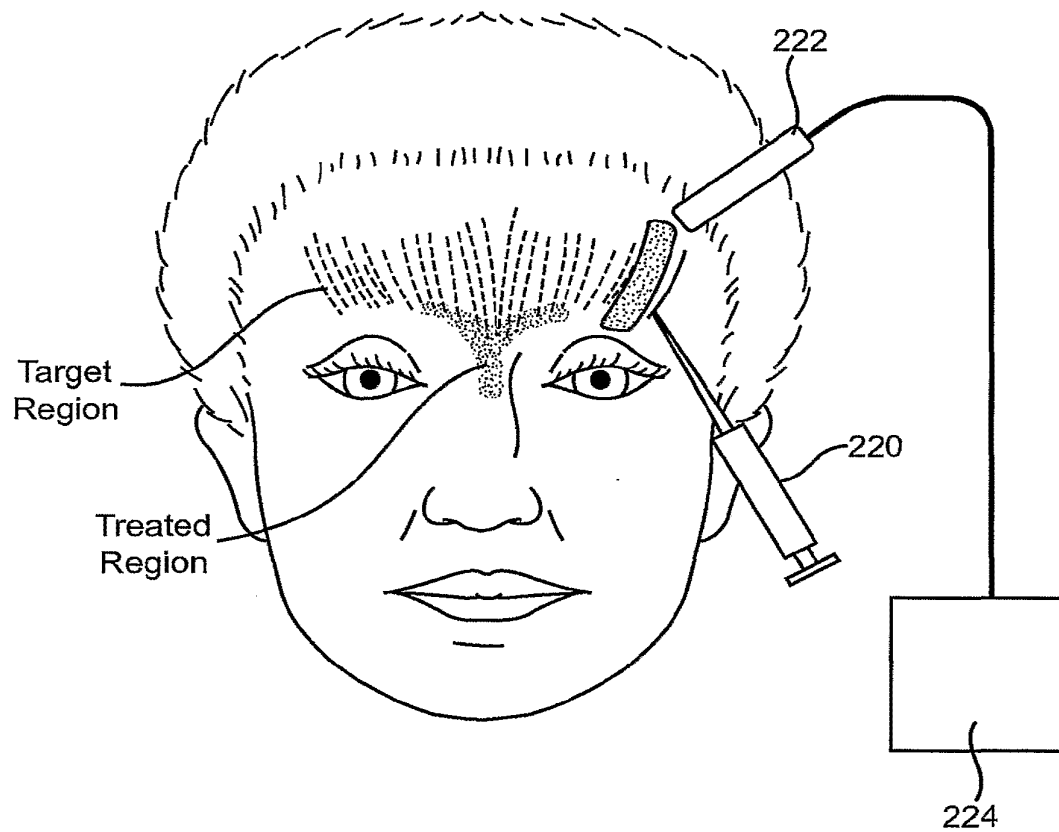


FIG. 14

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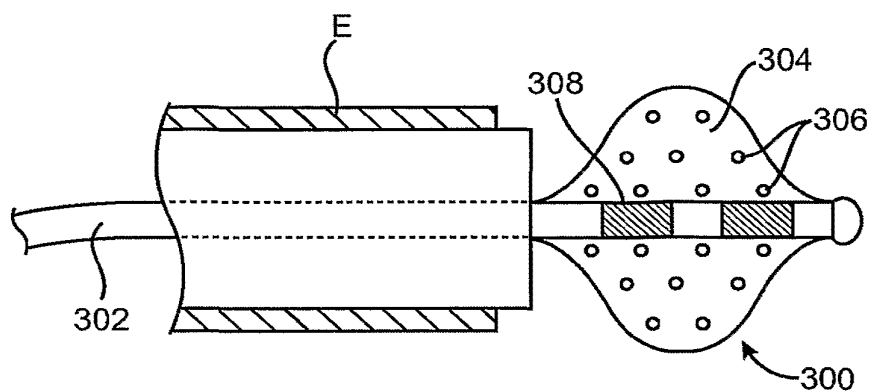


FIG. 15A

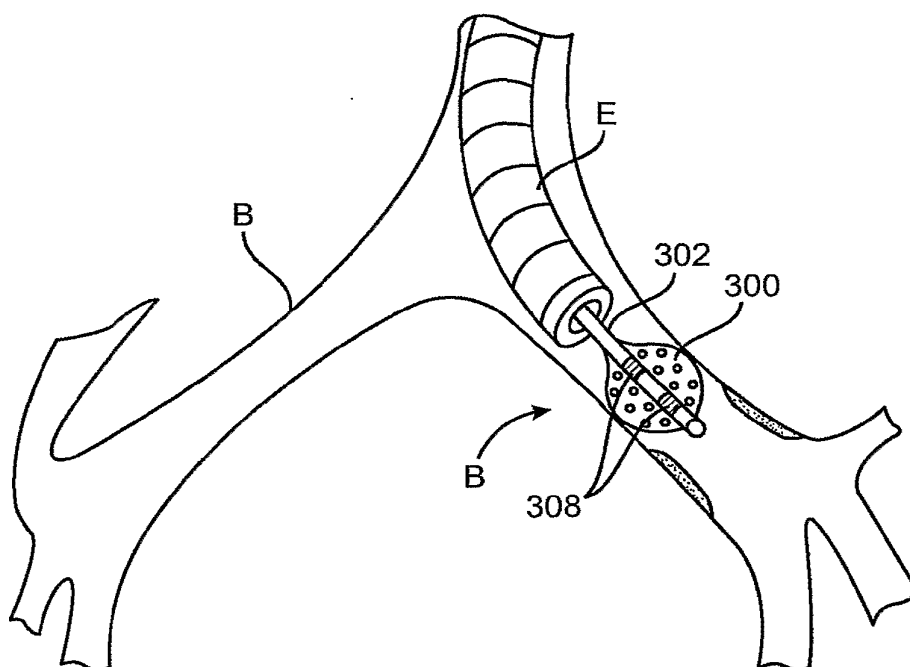


FIG. 15B

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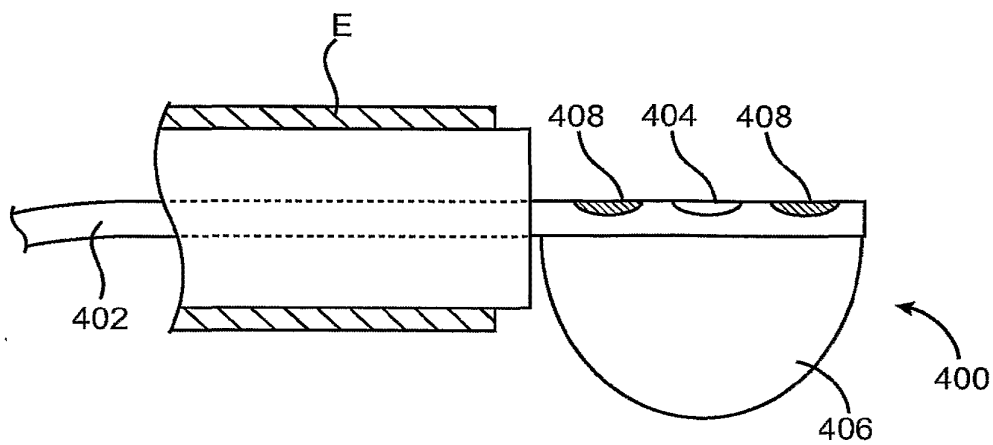


FIG. 16A

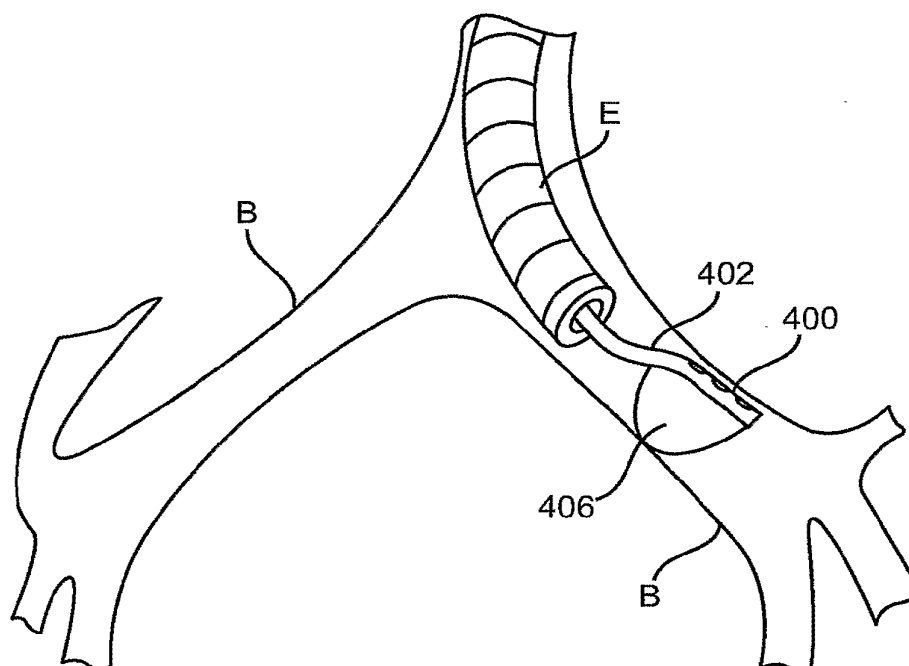


FIG. 16B

(19) World Intellectual Property Organization
International Bureau



(43) International Publication Date
1 February 2007 (01.02.2007)

PCT

(10) International Publication Number
WO 2007/014003 A3

(51) International Patent Classification:
A61K 9/12 (2006.01) *A61K 39/02* (2006.01)

(21) International Application Number:
PCT/US2006/028310

(22) International Filing Date: 21 July 2006 (21.07.2006)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
60/702,077 22 July 2005 (22.07.2005) US
60/747,771 19 May 2006 (19.05.2006) US

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(81) Designated States (unless otherwise indicated, for every kind of national protection available): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN,

CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LV, LY, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

(84) Designated States (unless otherwise indicated, for every kind of regional protection available): ARIPO (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, LV, MC, NL, PL, PT, RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Declaration under Rule 4.17:

— as to applicant's entitlement to apply for and be granted a patent (Rule 4.17(ii))

Published:

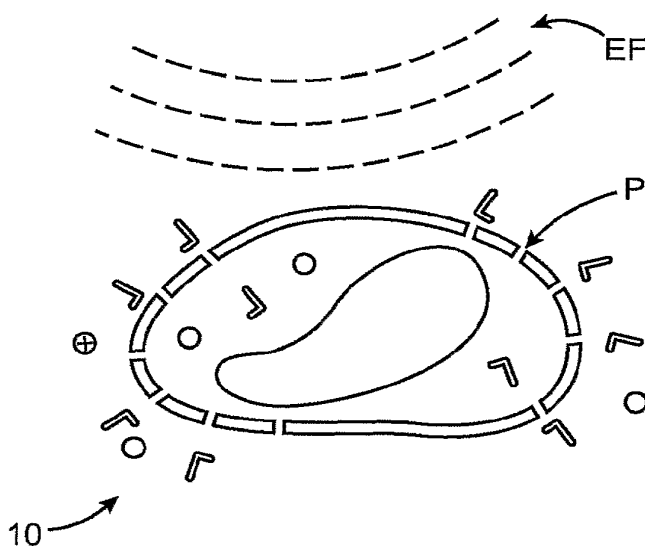
— with international search report
— before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments

(88) Date of publication of the international search report:

4 October 2007

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: SYSTEMS AND METHODS FOR DELIVERY OF A THERAPEUTIC AGENT



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

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US 06/28310

A. CLASSIFICATION OF SUBJECT MATTER

IPC(8) - A61K 9/12; A61K 39/02 (2007.01)

USPC 424/45; 424/236.1

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC(8) - A61K 9/12; A61K 39/02 (2007.01)

USPC 424/45; 424/236.1

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

PUBWEST(PGPB,USPT,USOC,EPAB,JPAB), GOOGLE SCHOLAR: BOTULINUM, TOXIN, NEUROTOXIN, LIGHT CHAIN, ELECTROPORATION, X-RAY, MICROWAVE, ULTRASONIC, ULTRASOUND, PERMEABLE, DELIVERY, CATHETER, NEUROTOXIN,

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X — Y	US 2004/0142005 A1 (Brooks et al.) 22 Jul 2004 (22.07.2004); para [0011], [0012], [0013] and [0036]	1-5 6-53
Y	WO 2004/101028 A2 (Deem et al.) 25 Nov 2004 (25.11.2004); para [0006], [0008], [0015], [0019], [0022], [0052], [0061], [0063], [0063] and [0065], Fig 9B	6, 8-11, 25, and 44-47
Y	US 2004/0010290 A1 (Schroeppel et al.) 15 Jan 2004 (15.01.2004); para [0011], [0067], [0074], [0103], [0116], [0149], [0188], [0192], [0237], [0239] and [0297]	7-11, 13-19, and 26-53
Y	US 5,766,605 A (Sanders) 16 Jun 1998 (16.06.1998); col 10, ln 45-50	12
Y	US 2003/0050591 A1 (McHale) 13 Mar 2003 (13.03.2003); para [0011], [0044], [0092] and [0093]	20-23, 40-43, 49, 52, and 53
Y	RAJ. Editorial Pain Practice. March 2004, 4(S1):S1-S3; pg S1, col 2; and pg S2, col 1	24

☐ Further documents are listed in the continuation of Box C.

* Special categories of cited documents:

“A” document defining the general state of the art which is not considered to be of particular relevance

“E” earlier application or patent but published on or after the international filing date

“L” document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

“O” document referring to an oral disclosure, use, exhibition or other means

“P” document published prior to the international filing date but later than the priority date claimed

“T” later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

“X” document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

“Y” document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

“&” document member of the same patent family

Date of the actual completion of the international search

23 Jun 2007 (23.06.2007)

Date of mailing of the international search report

08 AUG 2007

Name and mailing address of the ISA/US

Mail Stop PCT, Attn: ISA/US, Commissioner for Patents

P.O. Box 1450, Alexandria, Virginia 22313-1450

Facsimile No. 571-273-3201

Authorized officer:

Lee W. Young

PCT Helpdesk: 571-272-4300

PCT OSP: 571-272-7774

Form PCT/ISA/210 (second sheet) (April 2005)

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US 07/69391

A. CLASSIFICATION OF SUBJECT MATTER IPC(8) - A61K 39/08 (2007.01) USPC - 424/239.1; 514/8 According to International Patent Classification (IPC) or to both national classification and IPC		
B. FIELDS SEARCHED Minimum documentation searched (classification system followed by classification symbols) IPC(8) - A61K 39/08 (2007.01) USPC - 424/239.1; 514/8 Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched Electronic data base consulted during the international search (name of data base and, where practicable, search terms used) PubWEST(USPT,PGPB,EPAB,JPAB); Google Patents; Google Scholar Search terms: botulinum, toxin, nasal cavity, deliver or administer or administration, rhinorrhea, headache, handle, first, second, spring, actuator, applicator, nostril, electric, ultrasound, x-ray, microwave, electromagnetic, poration, transdermal		
C. DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US 2006/0106361 A1 (MUNI et al.) 18 May 2006 (18.05.2006) para [0010], [0014]-[0016], [0075], [0077], [0095], [0102], [0104], [0105], [0107] and [0161]	1-43, 68-78
Y	US 1,695,107 A (KAHL) 11 December 1928 (11.12.1928) col 1, ln 1-4, 22-35 and 49-55; col 2, ln 56-60 and 65-75	1-30, 41-43
Y	US 5,766,605 A (SANDERS et al.) 16 June 1998 (16.06.1998) col 2, ln 34-38 and 45; col 8, ln 29 and 33; col 10, ln 16-18	1-78
Y	US 2005/0152924 A1 (VOET) 14 July 2005 (14.07.2005) para [0013]-[0014], [0043], [0055], [0065] and [0074]	24-30, 52-53, 55-57
Y	US 2004/0009180 A1 (DONOVAN) 15 January 2004 (15.01.2004) para [0081]-[0083]	26-30, 44-78
Y	US 2005/0107853 A1 (KRESPI et al.) 19 May 2005 (19.05.2005) para [0037], [0060], [0108]-[0109] and [0115]	29, 59-67
☐ Further documents are listed in the continuation of Box C. ☐		
* Special categories of cited documents: "A" document defining the general state of the art which is not considered to be of particular relevance "E" earlier application or patent but published on or after the international filing date "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified) "O" document referring to an oral disclosure, use, exhibition or other means "P" document published prior to the international filing date but later than the priority date claimed "T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention "X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone "Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art "&" document member of the same patent family		
Date of the actual completion of the international search 30 December 2007 (30.12.2007)		Date of mailing of the international search report 03 MAR 2008
Name and mailing address of the ISA/US Mail Stop PCT, Attn: ISA/US, Commissioner for Patents P.O. Box 1450, Alexandria, Virginia 22313-1450 Facsimile No. 571-273-3201		Authorized officer: Lee W. Young PCT Helpdesk: 571-272-4300 PCT OSP: 571-272-7774

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US 07/69391

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

-- see extra sheet

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying additional fees, this Authority did not invite payment of additional fees.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☒ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:
1-78

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.
- ☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.
- ☐ No protest accompanied the payment of additional search fees.

Form PCT/ISA/210 (continuation of first sheet (2)) (April 2007)

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US 07/69391

Continuation of Box No. III - Observations where unity of invention is lacking

This application contains the following inventions or groups of inventions which are not so linked as to form a single general inventive concept under PCT Rule 13.1.

Group I: claims 1-78 are directed to an apparatus for treating inflammation of a nasal membrane of a patient comprising: a handle comprising a proximal section, a first member and a second member, wherein the first member and second member are connected at the proximal section; a first applicator tip coupled to the first member; and a second applicator tip coupled to the second member; wherein the first applicator tip and second applicator tip are each configured for insertion into a nostril of the patient and placement within a nasal passageway of the patient and wherein each applicator tip is configured for delivering a toxin to a region of nasal tissue within the nasal cavity of the patient, thereby treating the inflammation.

Group II: claims 79-112 are directed to a system for delivering toxins to target cells in a nasal membrane, said system comprising: a catheter adapted to introduce a toxin to a region proximate the target cells; an energy applicator configured for applying energy to the target cells under conditions which cause portion of the cell membranes to enhance delivery of the toxin; and a source of toxin suitable for introduction from the catheter.

The inventions listed as Groups I-II do not relate to a single general inventive concept under PCT Rule 13.1 because under PCT Rule 13.2 they lack the same or corresponding technical features for the following reasons:

Group II does not include the inventive concept of an applicator of the type as disclosed in claim 1 of Group I.

Group I does not include the inventive concept of an energy applicator configured for applying energy to the target cells as disclosed in Group II.

Neither of these technical features is common to the other group, nor do they correspond to a special technical feature in the other group. Therefore, unity of invention is lacking.

From the
INTERNATIONAL SEARCHING AUTHORITY

To: James M. Heslin
Two Embarcadero Center, 8th Floor
San Francisco, CA 94111-3834

PCT

WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY

(PCT Rule 43bis.1)

Date of mailing
(day/month/year)

03 MAR 2008

Applicant's or agent's file reference
20979-37-3PC

FOR FURTHER ACTION

See paragraph 2 below

International application No.

PCT/US 07/69391

International filing date (day/month/year)

21 May 2007 (21.05.2007)

Priority date (day/month/year)

19 May 2006 (19.05.2006)

International Patent Classification (IPC) or both national classification and IPC

IPC(8) - A61K 39/08 (2008.01)

USPC - 424/239.1; 514/8

Applicant **The Foundry Inc.**

1. This opinion contains indications relating to the following items:

- ☒ Box No. I Basis of the opinion
- ☐ Box No. II Priority
- ☐ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☒ Box No. IV Lack of unity of invention
- ☒ Box No. V Reasoned statement under Rule 43bis.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- ☐ Box No. VI Certain documents cited
- ☐ Box No. VII Certain defects in the international application
- ☐ Box No. VIII Certain observations on the international application

2. FURTHER ACTION

If a demand for international preliminary examination is made, this opinion will be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA") except that this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notified the International Bureau under Rule 66.1bis(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of 3 months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

3. For further details, see notes to Form PCT/ISA/220.

Name and mailing address of the ISA/US
Mail Stop PCT, Attn: ISA/US
Commissioner for Patents
P.O. Box 1450, Alexandria, Virginia 22313-1450
Facsimile No. 571-273-3201

Date of completion of this opinion

30 December 2007 (30.12.2007)

Authorized officer:

Lee W. Young

PCT Helpdesk: 571-272-4300
PCT OSP: 571-272-7774

Form PCT/ISA/237 (cover sheet) (April 2007)

WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY

International application No.

PCT/US 07/69391

Box No. I Basis of this opinion

1. With regard to the **language**, this opinion has been established on the basis of:
 - ☒ the international application in the language in which it was filed.
 - ☐ a translation of the international application into _____ which is the language of a translation furnished for the purposes of international search (Rules 12.3(a) and 23.1(b)).
2. ☐ This opinion has been established taking into account the **rectification of an obvious mistake** authorized by or notified to this Authority under Rule 91 (Rule 43bis.1(a))
3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, this opinion has been established on the basis of:
 - a. type of material
 - ☐ a sequence listing
 - ☐ table(s) related to the sequence listing
 - b. format of material
 - ☐ on paper
 - ☐ in electronic form
 - c. time of filing/furnishing
 - ☐ contained in the international application as filed
 - ☐ filed together with the international application in electronic form
 - ☐ furnished subsequently to this Authority for the purposes of search
4. ☐ In addition, in the case that more than one version or copy of a sequence listing and/or table(s) relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.
5. Additional comments:

WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY

International application No.

PCT/US 07/69391

Box No. IV Lack of unity of invention

1. ☒ In response to the invitation (Form PCT/ISA/206) to pay additional fees the applicant has, within the applicable time limit:
- ☐ paid additional fees
 - ☐ paid additional fees under protest and, where applicable, the protest fee
 - ☐ paid additional fees under protest but the applicable protest fee was not paid
 - ☒ not paid additional fees
2. ☐ This Authority found that the requirement of unity of invention is not complied with and chose not to invite the applicant to pay additional fees.
3. This Authority considers that the requirement of unity of invention in accordance with Rule 13.1, 13.2 and 13.3 is
- ☐ complied with
 - ☒ not complied with for the following reasons:

This application contains the following inventions or groups of inventions which are not so linked as to form a single general inventive concept under PCT Rule 13.1.

Group I: claims 1-78 are directed to an apparatus for treating inflammation of a nasal membrane of a patient comprising: a handle comprising a proximal section, a first member and a second member, wherein the first member and second member are connected at the proximal section; a first applicator tip coupled to the first member; and a second applicator tip coupled to the second member; wherein the first applicator tip and second applicator tip are each configured for insertion into a nostril of the patient and placement within a nasal passageway of the patient and wherein each applicator tip is configured for delivering a toxin to a region of nasal tissue within the nasal cavity of the patient, thereby treating the inflammation.

Group II: claims 79-112 are directed to a system for delivering toxins to target cells in a nasal membrane, said system comprising: a catheter adapted to introduce a toxin to a region proximate the target cells; an energy applicator configured for applying energy to the target cells under conditions which cause portion of the cell membranes to enhance delivery of the toxin; and a source of toxin suitable for introduction from the catheter.

The inventions listed as Groups I-II do not relate to a single general inventive concept under PCT Rule 13.1 because under PCT Rule 13.2 they lack the same or corresponding technical features for the following reasons:

Group II does not include the inventive concept of an applicator of the type as disclosed in claim 1 of Group I.

Group I does not include the inventive concept of an energy applicator configured for applying energy to the target cells as disclosed in Group II.

Neither of these technical features is common to the other group, nor do they correspond to a special technical feature in the other group. Therefore, unity of invention is lacking.

4. Consequently, this opinion has been established in respect of the following parts of the international application:

- ☐ all parts
- ☒ the parts relating to claims Nos. 1-78

**WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY**

International application No.

PCT/US 07/69391

Box No. V Reasoned statement under Rule 43bis.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Claims	1-78	YES
	Claims	None	NO
Inventive step (IS)	Claims	None	YES
	Claims	1-78	NO
Industrial applicability (IA)	Claims	1-78	YES
	Claims	None	NO

2. Citations and explanations:

Claims 31-40 lack an inventive step under PCT Article 33(3) as being obvious over US 2006/0106361 A1 to Muni et al. (hereinafter 'Muni') in view of US 5,766,605 A to Sanders et al. (hereinafter 'Sanders').

Regarding claim 31, Muni discloses an apparatus comprising: an applicator configured for (a) insertion into a nostril of the patient (para [0102]), (b) placement within a nasal passageway of the patient (para [0075]), and (c) delivering a therapeutically effective amount of a drug (para [0015]) to a region of nasal tissue within the nasal cavity of the patient (para [0075]); wherein the applicator comprises an inner member and an outer member (para [0016]). Muni does not expressly disclose wherein the drug is a toxin for treating a condition associated with inflammation of a nasal membrane of a patient selected from rhinorrhea. However, Sanders discloses wherein the drug is a toxin for treating a condition associated with inflammation of a nasal membrane of a patient selected from rhinorrhea (col 2, ln 34-36). It would have been obvious to one of ordinary skill in the art to combine the disclosures of Muni and Sanders because Muni states that the substance delivered by its apparatus may be any feasible drug (para [0077]) and Sanders discloses botulinum toxin used as a drug (col 2, ln 34-38).

Regarding claim 32, Muni discloses the apparatus of claim 31, wherein the applicator further comprises an impermeable lining configured for separating the inner member and outer member (para [0016]).

Regarding claim 33, Muni discloses the apparatus of claim 31, wherein the applicator is configured to be arranged in a low volume configuration for placement within the nasal passageway and an expanded volume configuration for delivering the toxin to the nasal tissue (para [0105]).

Regarding claim 34, Muni discloses the apparatus of claim 33, wherein wherein the inner member comprises a balloon (para [0161] - 'inflatable balloon').

Regarding claim 35, while Muni does not expressly disclose the apparatus of claim 33, wherein the inner member comprises a sponge, Muni discloses an inner core that contains a substance (para [0016]) and also discloses that a substance may be loaded within a sponge (para [0010]). Therefore it would have been obvious to one of ordinary skill in the art wherein the inner member comprises a sponge.

Regarding claim 36, while Muni does not expressly disclose the apparatus of claim 35, wherein the inner member further comprises a spring element, Muni discloses wherein the inner member is capable of causing an outer layer to expand (para [0161]). Since a spring may be employed to cause an outer layer to expand, it would have been obvious to one of ordinary skill in the art wherein the inner member further comprises a spring element.

Regarding claim 37, Muni discloses the apparatus of claim 31, wherein the outer member comprises a bioresorbable coating (para [0161] - 'biodegradable').

Regarding claim 38, Muni does not expressly disclose the apparatus of claim 31, wherein the outer member comprises a balloon and a sponge. However, Muni discloses wherein the outer member elutes a substance (para [0016]) and further discloses a balloon that releases a substance (para [0095]) and a sponge that releases a substance (para [0010]). Therefore, it would have been obvious to one of ordinary skill in the art wherein the outer member comprises a balloon and a sponge.

Regarding claim 39, Muni discloses the apparatus of claim 31, wherein the inner member is configured to expand (para [0161]).

Regarding claim 40, Muni discloses the apparatus of claim 39, wherein expansion of the inner member facilitates delivery of the toxin to the nasal tissue (para [0161] - 'inflatable balloon 418 is inflated by a user. This causes stent 410 to expand'; and para [0162] - 'material of stent 410 comprises . . . one or more substances to be delivered').

(see continuation of citations and explanations in first supplemental box)

Supplemental Box

In case the space in any of the preceding boxes is not sufficient.

Continuation of:

Box No. V(2) -- citations and explanations

Claims 44-51, 54 and 58 lack an inventive step under PCT Article 33(3) as being obvious over Sanders in view of US 2004/0009180 A1 to Donovan (hereinafter 'Donovan').

Regarding claim 44, Donovan discloses a method for delivering toxins to target cells, said method comprising: introducing a toxin to a region proximate the target cells; and applying energy to the target cells to enhance delivery of the toxins to the cells (para [0083]). Donovan does not disclose wherein the target cells are in a nasal membrane. However, Sanders discloses wherein the target cells are in a nasal membrane (col 2, ln 34-36). It would have been obvious to one of ordinary skill in the art to combine the disclosures of Donovan and Sanders because Sanders suggests delivering botulinum toxin via a topical route (col 2, ln 34-36) and Donovan describes an improved topical method to deliver botulinum toxin (para [0083]).

Regarding claim 45, Sanders discloses the method of claim 44, wherein the region comprises at least a main nasal passage (col 10, ln 17).

Regarding claim 46, Sanders discloses the method of claim 44, wherein the region comprises substantially the entire nasal cavity (col 8, ln 29 and 33).

Regarding claim 47, while Sanders does not expressly disclose the method of claim 44, wherein the region comprises the nasopharynx, it would have been obvious to one of ordinary skill in the art that the nasopharynx comprises a nasal membrane and wherein the region comprises the nasopharynx.

Regarding claim 48, while Sanders does not expressly disclose the method of claim 44, wherein the target cells comprise epithelial or goblet cells, Sanders discloses wherein the toxin is targeted to the nasal mucosa (col 2, ln 34-36). Since epithelial or goblet cells function to secrete mucus, it would have been obvious to one of ordinary skill in the art that Sanders implies wherein the target cells comprise epithelial or goblet cells.

Regarding claim 49, Donovan discloses the method of claim 44, wherein the energy is selectively applied to target cells within the region where toxin has been introduced (para [0083]).

Regarding claim 50, while Donovan does not expressly disclose the method of claim 44, wherein the energy is applied non-selectively within the region where toxin has been introduced; it would have been obvious to one of ordinary skill in the art wherein the energy is applied non-selectively within the region where toxin has been introduced.

Regarding claim 51, Sanders discloses the method of claim 44, wherein the patient suffers from or is at risk of suffering from rhinorrhea (col 2, ln 34-36).

Regarding claim 54, Sanders discloses the method of claim 44, wherein the toxin comprises botulinum toxin (col 2, ln 35-36).

Regarding claim 58, Donovan discloses the method of claim 44, wherein the energy applied to the targeted region is an electric pulse (para [0083]).

Claims 1-23 and 41-43 lack an inventive step under PCT Article 33(3) as being obvious over Muni in view of Sanders and further in view of US 1,695,107 A to Kahl (hereinafter 'Kahl').

Regarding claim 1, Muni discloses an apparatus comprising: a handle (para [0095] - 'tube or elongate shaft') comprising a proximal section, a first member (para [0095]), wherein the first member is connected at the proximal section; and an applicator tip coupled to the first member (para [0095] - 'substance reservoir'); wherein the first applicator tip are each configured for insertion into a nostril of the patient and placement within a nasal passageway of the patient (para [0075]) and wherein the first applicator tip is configured for delivering a drug (para [0077]) to a region of nasal tissue within the nasal cavity of the patient (para [0075]). Muni does not expressly disclose wherein the apparatus has a second member and a second applicator tip coupled to the second member. However, Kahl discloses a second member (col 1, ln 22-35 - 'links') and a second applicator tip coupled to the second member (col 1, ln 22-35 - 'lamps'). It would have been obvious to one of ordinary skill in the art to combine the disclosures of Muni and Kahl because Muni suggests that its apparatus may be inserted into the nasal passage (para [0075]) and Kahl discloses an apparatus that is adapted for insertion into the nasal passage (col 1, ln 1-4). Moreover, it would have been obvious to one of ordinary skill in the art that a nose has two nostrils and that each nostril may require a member and an applicator tip. Muni also does not expressly disclose wherein the drug delivered is a toxin and that toxin delivery treats the inflammation. However, Sanders discloses wherein the drug delivered is a toxin and that toxin delivery treats the inflammation (col 2, ln 34-38). It would have been obvious to one of ordinary skill in the art to combine the disclosures of Muni and Sanders because Muni states that the substance delivered by its apparatus may be any feasible drug (para [0077]) and Sanders discloses botulinum toxin used as a drug (col 2, ln 34-38).

Regarding claim 2, Kahl discloses the apparatus of claim 1, wherein the handle further comprises a spring element (col 2, ln col 65-66).

Regarding claim 3, while Kahl does not expressly disclose the apparatus of claim 2, wherein the spring element is either a v-shaped spring or closed-loop spring, it would have been obvious to one of ordinary skill in the art that a v-shaped spring or closed-loops spring may act as the 'pressure spring' disclosed in Kahl.

(see continuation of citations and explanations in second supplemental box)

Supplemental Box

In case the space in any of the preceding boxes is not sufficient.

Continuation of:

citations and explanations from first supplemental box

Regarding claim 4, Kahl discloses the apparatus of claim 2, wherein the handle is configured to be arranged in a compressed delivery configuration for placement of the applicator tips within the nasal passageway and an expanded treatment configuration for delivering a therapeutic to the region of nasal tissue (col 2, In 65-75) and Sanders discloses wherein the therapeutic is a toxin (col 2, In 34-38), as discussed above.

Regarding claim 5, Sanders discloses the apparatus of claim 1, wherein each applicator tip comprises gauze (col 10, In 16-18) but does not expressly disclose a sponge. However, it would have been obvious to one of ordinary skill in the art to substitute one absorbent material, a sponge, for another absorbent material, gauze.

Regarding claim 6, Muni discloses the apparatus of claim 5, wherein each applicator tip is configured to be arranged in a low volume delivery configuration for placement within the nasal passageway and an expanded volume treatment configuration for delivering a drug to the region of nasal tissue (para [0105]) and Sanders discloses wherein the therapeutic is a toxin (col 2, In 34-38), as discussed above.

Regarding claim 7, Muni discloses the apparatus of claim 6, wherein each applicator tip in the expanded volume treatment configuration is adapted to fit substantially within the nasal cavity of the patient (para [0104]).

Regarding claim 8, Kahl discloses the apparatus of claim 5, wherein each applicator tip further comprises a spring element (col 1, In 49-55; col 2, In 56-60).

Regarding claim 9, Kahl discloses the apparatus of claim 8, wherein each applicator tip is configured to be arranged in a compressed delivery configuration for placement within the nasal passageway and an expanded treatment configuration for delivering toxin to the region of nasal tissue (col 1, In 49-55; col 2, In 56-60).

Regarding claim 10, Muni discloses the apparatus of claim 9, wherein each applicator tip (para [0161] - 'self-expanding stent') further comprises an actuator (para [0161] - 'hollow guide or sheath'), wherein the actuator is configured for movement from an engaged position and a retracted position (para [0161]).

Regarding claim 11, Muni discloses the apparatus of claim 10, wherein the applicator tip is in a compressed delivery configuration when the actuator is in the engaged position (para [0161] - 'self-expanding stent . . . introduced through a hollow guide or sheath into an anatomical region').

Regarding claim 12, Muni discloses the apparatus of claim 10, wherein the applicator tip is in the expanded delivery configuration when the actuator is in the retracted position (para [0161] - 'Stent may be pushed out of the hollow sheath or guide').

Regarding claim 13, Muni discloses the apparatus of claim 10, further comprising an engagement element, wherein the engagement element is configured to control the movement of an actuator (para [0161] - 'pusher'). Muni does not expressly disclose wherein the engagement element controls the movement of both actuators simultaneously. However, since toxin is being delivered into both nostrils, it would have been obvious to one of ordinary skill in the art wherein the engagement element controls the movement of both actuators simultaneously.

Regarding claim 14, Muni discloses the apparatus of claim 5, wherein each applicator tip further comprises an impermeable lining (para [0016]).

Regarding claim 15, Sanders discloses the apparatus of claim 1, wherein each applicator tip further comprises a muco-adhesive pad (col 10, In 18 - 'gauze').

Regarding claim 16, Muni discloses the apparatus of claim 1, wherein the toxin is carried by a bioresorbable coating (para [0010]).

Regarding claim 17, Muni discloses the apparatus of claim 1, further comprising an infusion channel for delivering the drug to the applicator tips (para [0107] - 'substance introducing lumen') and Sanders discloses wherein the therapeutic is a toxin (col 2, In 34-38), as discussed above.

Regarding claim 18, Muni discloses the apparatus of claim 17, further comprising an access port, wherein the apparatus is in fluid communication with a drug source via the access port (para [0107]) and Sanders discloses wherein the therapeutic is a toxin (col 2, In 34-38), as discussed above.

Regarding claim 19, Sanders discloses the apparatus of claim 17, wherein the applicator tips are configured to receive the toxin prior to being positioned in the nasal passageway (col 10, In 17-18 - 'gauzed soaked with a saline solution of botulinum toxin').

Regarding claim 20, Muni discloses the apparatus of claim 17, wherein the applicator tips are configured to receive the toxin after being positioned in the nasal passageway (para [0095]).

Regarding claim 21, Sanders discloses the apparatus of claim 1, wherein the toxin comprises a liquid (col 10, In 18 - 'solution').

Regarding claim 22, Sanders discloses the apparatus of claim 1, wherein the toxin comprises botulinum toxin (col 10, In 18).

Regarding claim 23, Sanders discloses the apparatus of claim 22, wherein the botulinum toxin is botulinum toxin D (col 10, In 18).

(see continuation of citations and explanations in third supplemental box)

Supplemental Box

In case the space in any of the preceding boxes is not sufficient.

Continuation of:

citations and explanations from second supplemental box

Regarding claim 41, Muni discloses an apparatus comprising: a handle (para [0095] - 'tube or elongate shaft') comprising a proximal section, a first member (para [0095]), wherein the first member is connected at the proximal section; and an applicator tip coupled to the first member (para [0095] - 'substance reservoir'); wherein the first applicator tip are each configured for insertion into a nostril of the patient and placement within a nasal passageway of the patient (para [0075]) and wherein the first applicator tip is configured for delivering a drug (para [0077]) to a region of nasal tissue within the nasal cavity of the patient (para [0075]). Muni does not expressly disclose wherein the apparatus has a second member and a second applicator tip coupled to the second member. However, Kahl discloses a second member (col 1, ln 22-35 - 'links') and a second applicator tip coupled to the second member (col 1, ln 22-35 - 'lamps'). It would have been obvious to one of ordinary skill in the art to combine the disclosures of Muni and Kahl because Muni suggests that its apparatus may be inserted into the nasal passage (para [0075]) and Kahl discloses an apparatus that is adapted for insertion into the nasal passage (col 1, ln 1-4). Moreover, it would have been obvious to one of ordinary skill in the art that a nose has two nostrils and that each nostril may require a member and an applicator tip. Muni also does not expressly disclose wherein the drug delivered is a toxin and that the toxin treats a condition associated with inflammation of a nasal membrane of a patient selected from rhinorrhea. However, Sanders discloses wherein the drug delivered is a toxin and that the toxin treats a condition associated with inflammation of a nasal membrane of a patient selected from rhinorrhea (col 2, ln 34-38). It would have been obvious to one of ordinary skill in the art to combine the disclosures of Muni and Sanders because Muni states that the substance delivered by its apparatus may be any feasible drug (para [0077]) and Sanders discloses botulinum toxin used as a drug (col 2, ln 34-38).

Regarding claim 42, Kahl discloses the apparatus of claim 41, further comprising a spring element, wherein the spring element is configured to provide the applicator tips with an outward bias with the applicator tips are placed within the nasal passageway (col 1, ln 49-55; col 2, ln 56-60).

Regarding claim 43, while Kahl does not expressly disclose the apparatus of claim 42, wherein the outward bias presses each applicator tip against a turbinate in the nasal cavity, Kahl discloses wherein the springs exert pressure on the inner walls of the nose (col 2, ln 56-60). Since the nasal turbinates are the walls of the nasal cavity, it would have been obvious to one of ordinary skill in the art wherein the outward bias presses each applicator tip against a turbinate in the nasal cavity.

Claims 52-53 and 55-57 lack an inventive step under PCT Article 33(3) as being obvious over Sanders in view of Donovan and further in view of US 2005/0152924 A1 to Voet (hereinafter 'Voet').

Regarding claim 52, neither Sanders nor Donovan discloses the method of claim 44, wherein the patient suffers from or is at risk of suffering from sinus headaches. However, Voet discloses wherein the patient suffers from or is at risk of suffering from sinus headaches (para [0074]). It would have been obvious to one of ordinary skill in the art to combine the disclosure of Voet with the combination of Sanders and Donovan because Voet expressly makes reference to Sanders (para [0043]) and sinus headaches are a common ailment for which a therapeutic composition is used.

Regarding claim 53, Voet discloses the method of claim 44, wherein the patient suffers from or is at risk of suffering from migraine headaches (para [0043]).

Regarding claim 55, Voet discloses the method of claim 54, wherein the toxin is a fragment of botulinum toxin (para [0065]).

Regarding claim 56, Voet discloses the method of claim 55, wherein the fragment is a light chain fragment of botulinum toxin (para [0065] and [0013]-[0014]).

Regarding claim 57, Voet discloses the method of claim 56, wherein the light chain fragment is derived from at least one of botulinum toxins A, B, C, D, E, F and G (para [0055]).

Claims 59-67 lack an inventive step under PCT Article 33(3) as being obvious over Sanders in view of Donovan and further in view of US 2005/0107853 A1 to Krespi et al. (hereinafter 'Krespi').

Regarding claim 59, Donovan discloses the method of claim 58, wherein the energy applied to the target region is an electric pulse (Donovan para [0083]), but does not expressly disclose wherein the electric pulse is applied from between 1V to 500V. However, Krespi discloses wherein the electric pulse is applied from between 1V to 500V (para [0109] - '0.1 to about 5 J/cm²'). It would have been obvious to one of ordinary skill in the art to combine the disclosure of Krespi with the combination of Sanders and Donovan because Sanders suggests delivering botulinum toxin to the nasal passages (col 2, ln 34-36), Donovan describes an improved method for delivering botulinum toxin that uses application of energy (para [0083]), and Krespi discloses application of energy to the nasal passages (para [0037]).

Regarding claim 60, Krespi discloses the method of claim 58, wherein the electric pulse is an RF signal (para [0115]).

Regarding claim 61, Krespi discloses the method of claim 58, wherein the electric pulse is pulsed for durations between 5 microseconds to 100 milliseconds (para [0108]).

Regarding claim 62, Krespi discloses the method of claim 58, wherein the electric pulse is produced by a DC power source (para [0060]).

Regarding claim 63, Krespi discloses the method of claim 58, wherein the electric pulse is produced by an AC power source (para [0060]).

(see continuation of citations and explanations in fourth supplemental box)

Supplemental Box

In case the space in any of the preceding boxes is not sufficient.

Continuation of:

citations and explanations from third supplemental box

Regarding claim 64, Donovan discloses the method of claim 44, wherein the energy applied to the target region is ultrasonic (para [0081]).

Regarding claim 65, Krespi does not expressly disclose the method of claim 44, wherein the energy applied to the targeted region is an x-ray beam, but discloses using electromagnetic energy (para [0037]). Since x-rays are a form of electromagnetic energy, it would have been obvious to one of ordinary skill in the art wherein the energy applied to the targeted region is an x-ray beam.

Regarding claim 66, Donovan discloses the method of claim 44, wherein the energy applied to the target region is ultrasonic (para [0081]) but does not expressly disclose focused ultrasound. However, it would have been obvious to one of ordinary skill in the art wherein the ultrasound used in the method is focused ultrasound.

Regarding claim 67, Krespi discloses the method of claim 44, wherein the energy applied to the targeted region is microwave (para [0115]).

Claims 68-78 lack an inventive step under PCT Article 33(3) as being obvious over Sanders in view of Donovan and further in view of Muni.

Regarding claim 68, neither Sanders nor Donovan discloses the method of claim 44, wherein the toxin is introduced to the target region through a catheter. However, Muni discloses wherein the toxin is introduced to the target region through a catheter (para [0095]). It would have been obvious to one of ordinary skill in the art to combine the disclosure of Muni with the combination of Sanders and Donovan because Muni states that the substance delivered by its apparatus may be any feasible drug (para [0077]) and Sanders discloses botulinum toxin used as a drug (col 2, ln 34-38).

Regarding claim 69, Muni discloses the method of claim 68, wherein the toxin is introduced through a balloon on the catheter (para [0095]).

Regarding claim 70, Muni discloses the method of claim 69, wherein the balloon is porous and the toxin is introduced through the balloon (para [0095]).

Regarding claim 71, Muni discloses the method of claim 68, wherein the toxin is introduced through a needle on the catheter (para [0014]).

Regarding claim 72, neither Sanders nor Donovan discloses the method of claim 68, wherein the toxin is introduced to the target region through a catheter. However, Muni discloses a catheter (para [0095]) and Sanders suggests aerosolizing the toxin (col 2, ln 45). Therefore it would have been obvious to one of ordinary skill in the art wherein the toxin is aerosolized from the catheter. It would have been obvious to one of ordinary skill in the art to combine the disclosure of Muni with the combination of Sanders and Donovan because Muni states that the substance delivered by its apparatus may be any feasible drug (para [0077]) and Sanders discloses botulinum toxin used as a drug (col 2, ln 34-38).

Regarding claim 73, neither Sanders nor Donovan discloses the method of claim 68, wherein energy is applied from a source on the catheter. However, Donovan suggests applying energy from a source close to the source for introducing the toxin (para [0081]). Muni discloses wherein the source for introducing the toxin is a catheter (para [0095]). Therefore it would have been obvious to one of ordinary skill in the art wherein energy is applied from a source on the catheter. It would have been obvious to one of ordinary skill in the art to combine the disclosure of Muni with the combination of Sanders and Donovan because Muni states that the substance delivered by its apparatus may be any feasible drug (para [0077]) and Sanders discloses botulinum toxin used as a drug (col 2, ln 34-38).

Regarding claim 74, neither Sanders nor Donovan discloses the method of claim 73, wherein acoustic energy is applied from a transducer on the catheter. However, Donovan suggests applying energy from a source close to the source for introducing the toxin (para [0081]) and also discloses wherein the energy is in the form of ultrasound (para [0081]). Muni discloses wherein the source for introducing the toxin is a catheter (para [0095]). Therefore it would have been obvious to one of ordinary skill in the art wherein acoustic energy is applied from a transducer on the catheter. It would have been obvious to one of ordinary skill in the art to combine the disclosure of Muni with the combination of Sanders and Donovan because Muni states that the substance delivered by its apparatus may be any feasible drug (para [0077]) and Sanders discloses botulinum toxin used as a drug (col 2, ln 34-38).

Regarding claim 75, neither Sanders nor Donovan discloses the method of claim 74, wherein electrical energy is applied from an electrode on the catheter. However, Donovan suggests applying energy from a source close to the source for introducing the toxin (para [0081]) and also discloses wherein the energy is in the form of electricity (para [0083]). Muni discloses wherein the source for introducing the toxin is a catheter (para [0095]). Therefore it would have been obvious to one of ordinary skill in the art wherein electrical energy is applied from an electrode on the catheter. It would have been obvious to one of ordinary skill in the art to combine the disclosure of Muni with the combination of Sanders and Donovan because Muni states that the substance delivered by its apparatus may be any feasible drug (para [0077]) and Sanders discloses botulinum toxin used as a drug (col 2, ln 34-38).

Regarding claim 76, Donovan discloses the method of claim 44, wherein the energy is delivered from a source external to the patient (para [0082] - 'to the skin').

Regarding claims 77 and 78, Donovan discloses the method of claim 76, wherein the energy is ultrasound (para [0081]-[0082]), therefore it would have been obvious to one of ordinary skill in the art wherein the source is an acoustic energy transducer and wherein the acoustic energy transducer is a focused ultrasound transducer.

(see continuation of citations and explanations in fourth supplemental box)

WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY

International application No.

PCT/US 07/69391

Supplemental Box

In case the space in any of the preceding boxes is not sufficient.

Continuation of:

citations and explanations from third supplemental box

Claims 24-25 lack an inventive step under PCT Article 33(3) as being obvious over Muni in view of Sanders and in view of Kahl and further in view of Voet.

Regarding claim 24, Sanders discloses the apparatus of claim 22, wherein the toxin comprises botulinum toxin (col 10, ln 18). Muni, Kahl and Sanders fail to expressly disclose wherein the toxin is a fragment of botulinum toxin. However, Voet discloses wherein the toxin is a fragment of botulinum toxin (para [0065]). It would have been obvious to one of ordinary skill in the art to combine the disclosure of Voet with the combination of Muni, Kahl and Sanders because Voet expressly references Sanders (para [0043]).

Regarding claim 25, Voet discloses the apparatus of claim 24, wherein the fragment is a light chain fragment of botulinum toxin (para [0065] and [0013]-[0014]).

Claims 26-28 and 30 lack an inventive step under PCT Article 33(3) as being obvious over Muni in view of Sanders and in view of Kahl and in view of Voet and further in view of Donovan.

Regarding claim 26, Kahl discloses the apparatus of claim 25, further comprising an energy delivery applicator configured for delivering energy to the region of nasal tissue (col 1, ln 22-35). Kahl does not expressly disclose wherein the delivery of energy enhances delivery of the toxin. However, Donovan discloses wherein the delivery of energy enhances delivery of the toxin (para [0081]-[0083]). It would have been obvious to one of ordinary skill in the art to combine the disclosure of Donovan with the combination of Muni, Kahl, Sanders and Voet because Kahl discloses delivery of energy to nasal tissues (col 1, ln 22-35) and Donovan discloses an advantage of that energy delivery (para [0081]-[0083]).

Regarding claim 27, Donovan discloses the apparatus of claim 27, wherein the energy delivery applicator is adapted to deliver energy under conditions which cause poration of at least one cell in the region of nasal tissue (para [0081] - 'permeabilizes the skin').

Regarding claim 28, Donovan discloses the apparatus of claim 26, wherein the energy delivery applicator is adapted to deliver an electric pulse (para [0083]).

Regarding claim 30, Donovan discloses the apparatus of claim 26, wherein the energy delivery is adapted to deliver ultrasound energy (para [0081]-[0082]).

Claim 29 lacks an inventive step under PCT Article 33(3) as being obvious over Muni in view of Sanders and in view of Kahl and in view of Voet and in view of Donovan and further in view of Krespi.

Regarding claim 29, Donovan discloses the apparatus of claim 28, wherein the energy delivery applicator is adapted to deliver an electric pulse (para [0083]). Donovan does not expressly disclose wherein the pulse is an RF signal. However, Krespi discloses wherein the pulse is an RF signal (para [0115]). It would have been obvious to one of ordinary skill in the art to combine the disclosure of Krespi with the combination of Kahl, Sanders, Voet and Donovan because Sanders suggests delivering botulinum toxin to the nasal passages (col 2, ln 34-36), Donovan describes an improved method for delivering botulinum toxin that uses application of energy (para [0083]), and Krespi discloses application of energy to the nasal passages (para [0037]).

Claims 1-78 have industrial applicability as defined by PCT Article 33(4) because the subject matter can be made or used in industry.

Electronic Acknowledgement Receipt

EFS ID:	11894390
Application Number:	13328203
International Application Number:	
Confirmation Number:	9512
Title of Invention:	METHODS AND SYSTEMS FOR TOXIN DELIVERY TO THE NASAL CAVITY
First Named Inventor/Applicant Name:	Mark E. Deem
Customer Number:	21971
Filer:	Douglas Portnow/Steven Dieu (DPOR)
Filer Authorized By:	Douglas Portnow
Attorney Docket Number:	38077-714.301
Receipt Date:	23-JAN-2012
Filing Date:	16-DEC-2011
Time Stamp:	13:22:35
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	no
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File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1		IDS38077-714-301-01-23-12.pdf	222810 88444c6ec4d193daa6f31879295281e70643f47d	yes	10

	Multipart Description/PDF files in .zip description				
	Document Description		Start	End	
	Transmittal Letter		1	4	
	Information Disclosure Statement (IDS) Form (SB08)		5	10	
Warnings:					
Information:					
2	Foreign Reference	WO2004048519A2.pdf	1367509	no	28
			9e846aea27d5b39e7fc701ba9c08eacbe026e577		
Warnings:					
Information:					
3	Foreign Reference	WO2004048519A3.pdf	193968	no	4
			d15b9405ddc87d1e05b1fec957ed1157c30a8b11		
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5	Foreign Reference	WO2004101028A3.pdf	185404	no	4
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6	Foreign Reference	WO2007014003A2.pdf	1801065	no	42
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7	Foreign Reference	WO2007014003A3.pdf	134321	no	2
			8cab6b2f179e3cf08838755a5e2e5b206dd2442		
Warnings:					
Information:					
8	Non Patent Literature	Z-ISR-WO-03-03-08-PCT-US07-069391.pdf	773132	no	12
			31270870b502097f327589079a0f878963d009db		
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9	Non Patent Literature	Z-ESR-SO-06-18-10-EP-07784000-7.pdf	284121 c861c0a63ae74dc0d2dcae0e530374ab5c3b0b4b	no	8
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Total Files Size (in bytes):				6942638	
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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Inventor: Mark E. DEEM, et al.

Serial Number: 13/328,203

Filing Date: December 16, 2011

Title: METHODS AND SYSTEMS FOR TOXIN
DELIVERY TO THE NASAL CAVITY

Group Art Unit: 1645

Examiner: Albert Mark Navarro

CONFIRMATION NO: 9512

FILED ELECTRONICALLY ON: January 23, 2012

Commissioner for Patents
P.O. Box 1450
Alexandria VA 22313-1450

INFORMATION DISCLOSURE STATEMENT
UNDER 37 CFR §1.97

Sir:

An Information Disclosure Statement along with attached PTO/SB/08 is hereby submitted. A copy of each listed publication is submitted, if required, pursuant to 37 CFR §§1.97-1.98, as indicated below.

The Examiner is requested to review the information provided and to make the information of record in the above-identified application. The Examiner is further requested to initial and return the attached PTO/SB/08 in accordance with MPEP §609.

The right to establish the patentability of the claimed invention over any of the information provided herewith, and/or to prove that this information may not be prior art, and/or to prove that this information may not be enabling for the teachings purportedly offered, is hereby reserved.

This statement is not intended to represent that a search has been made or that the information cited in the statement is, or is considered to be, prior art or material to patentability as defined in §1.56.

- A. ☒ 37 CFR §1.97(b). This Information Disclosure Statement should be considered by the Office because:
- ☐ (1) It is being filed within 3 months of the filing date of a national application and is other than a continued prosecution application under §1.53(d);
-- OR --
 - ☐ (2) It is being filed within 3 months of entry of the national stage as set forth in §1.491 in an international application;
-- OR --
 - ☒ (3) It is being filed before the mailing of a first Office action on the merits;
-- OR --
 - ☐ (4) It is being filed before the mailing of a first Office action after the filing of a request for continued examination under §1.114.
- B. ☐ 37 CFR §1.97(c). Although this Information Disclosure Statement is being filed after the period specified in 37 CFR §1.97(b), above, it is filed before the mailing date of the earlier of (1) a final office action under §1.113, (2) a notice of allowance under §1.311, or (3) an action that otherwise closes prosecution on the merits, this Information Disclosure Statement should be considered because it is accompanied by one of:
- ☐ a statement as specified in §1.97(e) provided concurrently herewith;
-- OR --
 - ☐ a fee of \$180.00 as set forth in §1.17(p) authorized below, enclosed, or included with the payment of other papers filed together with this statement.
- C. ☐ 37 CFR §1.97(d). Although this Information Disclosure Statement is being filed after the mailing date of the earlier of (1) a final office action under §1.113 or (2) a notice of allowance under §1.311, it is being filed before payment of the issue fee and should be considered because it is accompanied by:
- i. a statement as specified in §1.97(e);
-- AND --
 - ii. a fee of \$180.00 as set forth in §1.17(p) is authorized below, enclosed, or included with the payment of other papers filed together with this Statement.
- D. ☐ 37 CFR §1.97(e). Statement.
- ☐ A statement is provided herewith to satisfy the requirement under 37 CFR §§1.97(c);
-- AND/OR --
 - ☐ A statement is provided herewith to satisfy the requirement under 37 CFR §§1.97(d);
-- AND/OR --
 - ☐ A copy of a dated communication from a foreign patent office clearly showing that the information disclosure statement is being submitted within 3 months of the filing date on the communication is provided in lieu of a statement under 37 C.F.R. § 1.97(e)(1) as provided for under MPEP 609.04(b) V.
- E. ☐ Statement Under 37 C.F.R. §1.704(d). Each item of information contained in the information disclosure statement was first cited in a communication from a foreign patent office in a counterpart application that was received by an individual designated in § 1.56(c) not more than thirty (30) days prior to the filing of this information disclosure statement. This statement is made pursuant to the

requirements of 37 C.F.R. §1.704(d) to avoid reduction of the period of adjustment of the patent term for Applicant(s) delay.

F. ☒ 37 CFR §1.98(a)(2). The content of the Information Disclosure Statement is as follows:

☐ Copies of each of the references listed on the attached Form PTO/SB/08 are enclosed herewith.

-- OR --

☒ Copies of U.S. Patent Documents (issued patents and patent publications) listed on the attached Form PTO/SB/08 are NOT enclosed.

-- AND/OR --

☒ Copies of Foreign Patent Documents and/or Non Patent Literature Documents listed on the attached Form PTO/SB/08 as **items no. 89 to 94 and 114 to 115** are enclosed in accordance with 37 CFR §1.98 (a)(2).

-- AND/OR --

☐ Copies of pending unpublished U.S. patent applications are enclosed in accordance with 37 CFR §1.98(a)(2)(iii).

G. ☐ 37 CFR §1.98(a)(3). The Information Disclosure Statement includes non-English patents and/or references.

☐ Pursuant to 37 CFR §1.98(a)(3)(i), a concise explanation of the relevance of each patent, publication or other information provided that is not in English is provided herewith.

☐ Pursuant to MPEP 609(B), an English language copy of a foreign search report is submitted herewith to satisfy the requirement for a concise explanation where non-English language information is cited in the search report.

-- OR --

☐ A concise explanation of the relevance of each patent, publication or other information provided that is not in English is as follows: _____

☐ Pursuant to 37 CFR §1.98(a)(3)(ii), a copy of a translation, or a portion thereof, of the non-English language reference(s) is provided herewith.

H. ☒ 37 CFR §1.98(d). Copies of patents, publications and pending U.S. patent applications, or other information specified in 37 C.F.R. § 1.98(a) are not provided herewith because:

☒ Pursuant to 37 CFR §1.98(d)(1) the information listed on the attached Form PTO/SB/08 as **items no. 95 to 113** was previously submitted in an Information Disclosure Statement, or cited by examiner for another application under which this application claims priority for an earlier effective filing date under 35 U.S.C. 120.

Application in which the information was submitted: Serial No. 12/636,477

Information Disclosure Statement(s) filed on: 05/06/2010 and 07/14/2012

AND

☒ The information disclosure statement submitted in the earlier application complied with paragraphs (a) through (c) of 37 CFR §1.98.

- I. ☒ *Fee Authorization.* The Commissioner is hereby authorized to charge the above-referenced fees of \$0.00 and charge any additional fees or credit any overpayment associated with this communication to Deposit Account No. 23-2415 (Docket No. 38077-714.301).

Respectfully submitted,

WILSON SONSINI GOODRICH & ROSATI

Dated: January 23, 2012

By: /Douglas Portnow/
Douglas Portnow
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(650) 493-9300
Customer No. 021971



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APPLICATION NUMBER	FILING OR 371(C) DATE	FIRST NAMED APPLICANT	ATTY. DOCKET NO./TITLE
13/328,203	12/16/2011	Mark E. Deem	38077-714.301

CONFIRMATION NO. 9512

PUBLICATION NOTICE



OC000000053687122

21971
WILSON, SONSINI, GOODRICH & ROSATI
650 PAGE MILL ROAD
PALO ALTO, CA 94304-1050

Title:METHODS AND SYSTEMS FOR TOXIN DELIVERY TO THE NASAL CAVITY

Publication No.US-2012-0089078-A1

Publication Date:04/12/2012

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 Office of Public Records. The Office of Public Records can be reached by telephone at (703) 308-9726 or (800) 972-6382, by facsimile at (703) 305-8759, by mail addressed to the United States Patent and Trademark Office, Office of Public Records, 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 <http://pair.uspto.gov/>. Prior to publication, such status information is confidential and may only be obtained by applicant using the private side of PAIR.

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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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13/328,203

12/16/2011

Mark E. Deem

38077-714.301

9512

21971

7590

04/24/2013

WILSON, SONSINI, GOODRICH & ROSATI

650 PAGE MILL ROAD

PALO ALTO, CA 94304-1050

EXAMINER

NAVARRO, ALBERT MARK

ART UNIT

PAPER NUMBER

1645

MAIL DATE

DELIVERY MODE

04/24/2013

PAPER

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.

Office Action Summary	Application No. 13/328,203	Applicant(s) DEEM ET AL.	
	Examiner Mark Navarro	Art Unit 1645	AIA (First Inventor to File) 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 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, 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) 2-68 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) 2-68 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.

Interim copies:

- a) ☐ All b) ☐ Some c) ☐ None of the: Interim copies of the priority documents have been received.

Attachment(s)

- | | |
|--|---|
| 1) ☒ Notice of References Cited (PTO-892) | 3) ☐ Interview Summary (PTO-413)
Paper No(s)/Mail Date. _____ |
| 2) ☒ Information Disclosure Statement(s) (PTO/SB/08)
Paper No(s)/Mail Date <u>1/23/12</u> | 4) ☐ Other: _____ |

DETAILED ACTION

Applicants preliminary amendment filed January 12, 2012 has been received and entered. Claim 1 has been cancelled, and new claims 2-68 have been added. Consequently, claims 2-68 are pending in the instant application.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

1. Claim 2 is rejected under 35 U.S.C. 102(b) as being anticipated by Rohrbach et al.

The claim is directed to 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.

Rohrbach et al (Ann Oto Rhinol Laryngol Vol. 110, pp 1045-1050, 2001) disclose of the local treatment (sponge soaked with botulinum toxin A) of the nasal mucosal tissue. (See abstract and page 1046).

Given that a sponge against an air nasal cavity will prevent the toxin from entering the remaining portion of the nasal cavity, it is deemed to meet the instant limitation of an occlusion device. Accordingly, Rohrbach et al disclose of each and every limitation of the instantly filed claims.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

2. Claims 2, 34 and 38-68 are rejected under 35 U.S.C. 103(a) as being unpatentable over Rohrbach et al in view of Coleman et al and Donovan et al.

The claims are directed to a method of treating a nasal condition in a patient, said method comprising:

introducing a gel of 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 as to inhibit mucous secretion in the target cells.

The teachings of Rohrbach et al are set forth above.

Rohrbach et al do not teach of a gel or foam carrier comprising a toxin.

Coleman et al (US Publication 2003/0113349) teach that it was routine to combine botulinum toxin with a gel for topical administration.

Donovan et al (US Publication 2004/0009180) teach that transdermal administration of medication (specifically botulinum toxins) have included the use of ultrasound or iontophoresis to facilitate the permeation of pharmaceuticals through the skin. (See paragraphs 41, and 81-83).

Accordingly, it would have been prima facie obvious to have incorporated botulinum toxin in a gel as taught by Coleman et al in the method as taught by Rohrbach et al, as both methods involve the administration of botulinum toxin through the skin. It would have been further obvious to apply energy at the site of administration based on the demonstration by Donovan et al that ultrasound energy increases permeation of pharmaceuticals through the skin.

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 obviousness-type 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); and *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 a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Art Unit: 1645

3. Claims 2-68 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-35 of U.S. Patent No. 7,608,275.

Although the conflicting claims are not identical, they are not patentably distinct from each other because each set of claims encompasses the administration of an active neurotoxin light chain substantially free of heavy chain fragments in combination with focusing energy on membranes of cells.

4. Claims 2-68 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-35 of U.S. Patent No. 7,655,243.

Although the conflicting claims are not identical, they are not patentably distinct from each other because each set of claims encompasses the administration of an active neurotoxin light chain substantially free of heavy chain fragments in combination with applying energy to target cells.

3. Claims 2-68 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-30 of U.S. Patent No. 8,105,817.

Although the conflicting claims are not identical, they are not patentably distinct from each other because the instantly claimed method of administration of an active neurotoxin light chain substantially free of heavy chain fragments in combination with focusing energy on membranes of cells is accomplished with the system disclosed in '817.

Pfizer Inc. v Teva pharmaceuticals USA Inc., 86 USPQ2d 1001 (CAFC 2008) sets forth that there is no patentable distinction between claims to a product and method of using that product disclosed in the specification of the application and that the preclusion of such a double patenting rejection under 35 USC 121 does not apply where the present application is other than a divisional application of the patent application containing such patentably indistinct claims. This application is a continuation of 12/636,477 (US Patent 8,105,817). It is because this application is a continuation (as opposed to a divisional) of the parent that this rejection is applied.

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

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.

Art Unit: 1645

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

/Mark Navarro/
Primary Examiner, Art Unit 1645
April 22, 2013

Notice of References Cited	Application/Control No. 13/328,203		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	Classification
*	A	US-8,105,817	01-2012	Deem et al.	435/283.1
*	B	US-2003/0113349	06-2003	Coleman, William P. III	424/239.1
	C	US-			
	D	US-			
	E	US-			
	F	US-			
	G	US-			
	H	US-			
	I	US-			
	J	US-			
	K	US-			
	L	US-			
	M	US-			

FOREIGN PATENT DOCUMENTS

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

NON-PATENT DOCUMENTS

*		Include as applicable: Author, Title Date, Publisher, Edition or Volume, Pertinent Pages)
	U	Rohrbach et al (Ann Otol Rhinol Laryngol Vol. 110, pp 1045-1050, 2001)
	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.

Substitute for form 1449/PTO INFORMATION DISCLOSURE STATEMENT BY APPLICANT <i>(Use as many sheets as necessary)</i>				Complete if Known	
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				Filing Date	December 16, 2011
				First Named Inventor	Mark E. Deem
				Art Unit	1645
				Examiner Name	Albert Mark Navarro
Sheet	1	of	6	Attorney Docket Number	38077-714.301

U.S. PATENT DOCUMENTS					
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	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear
	1.	US 1,695,107	12/11/1928	Kahl	
	2.	US 2,566,806	09/04/1951	Miller	
	3.	US 2001/0044596 A1	11/22/2001	Jaafar	
	4.	US 2002/0082197 A1	06/27/2002	Aoki et al.	
	5.	US 2002/0111620 A1	08/15/2002	Cooper et al.	
	6.	US 2002/0198512 A1	12/26/2002	Seward	
	7.	US 2003/0018344 A1	01/23/2003	Kaji et al.	
	8.	US 2003/0050591 A1	03/13/2003	McHale	
	9.	US 2003/0153881 A1	08/14/2003	Roche et al.	
	10.	US 2003/0202990 A1	10/30/2003	Donovan et al.	
	11.	US 2003/0211121 A1	11/13/2003	Donovan	
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	13.	US 2004/0010290 A1	01/15/2004	Schroeppe et al.	
	14.	US 2004/0086531 A1	05/06/2004	Barron	
	15.	US 2004/0091880 A1	05/13/2004	Wiebusch et al.	
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	20.	US 2004/0213813 A1	10/28/2004	Ackerman	
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	27.	US 2005/0152924 A1	07/14/2005	Voet	
	28.	US 2005/0281751 A1	12/22/2005	Levin	
	29.	US 2006/0008462 A1	01/12/2006	Sanders	

Examiner Signature	Date Considered
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*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 802. Draw line through citation if not in conformance and not considered. Include copy of the form with next communication to applicant. ¹ Applicant's unique citation designation number (optional). ² See Kind Codes of USPTO Patent Documents at www.uspto.gov or MPEP 901.04. ³ Enter Office that issued the document, by the two-letter code (WIPO Standard ST.1). ⁴ For Japanese patent documents, the indication of the year of the reign of the Emperor must precede the serial number of the patent document. ⁵ Kind of document by the appropriate symbol as indicated on the document under WIPO Standard ST.16 if possible. ⁶ Applicant is to place a check mark here if English language translation is attached.

This collection of information is required by 37 CFR 1.97 and 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 as 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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				Art Unit	1645
				Examiner Name	Albert Mark Navarro
Sheet	2	of	6	Attorney Docket Number	38077-714.301

U.S. PATENT DOCUMENTS					
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		Number-Kind Code ² (if known)			
	30.	US 2006/0106361 A1	05/18/2006	Muni et al.	
	31.	US 2006/0222667 A1	10/05/2006	Deem et al.	
	32.	US 2006/0225742 A1	10/12/2006	Deem et al.	
	33.	US 2007/0021803 A1	01/25/2007	Deem et al.	
	34.	US 2007/0267011 A1	11/22/2007	Deem et al.	
	35.	US 2010/0003282 A1	01/07/2010	Deem et al.	
	36.	US 2010/0087775 A1	04/08/2010	Deem et al.	
	37.	US 3,469,139	09/23/1969	Colvin	
	38.	US 3,788,296	01/29/1974	Klatt et al.	
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	40.	US 4,767,402	08/30/1988	Kost et al.	
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	57.	US 6,432,092	08/13/2002	Miller	
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		Number-Kind Code ² (if known)			
	59.	US 6,448,231	09/10/2002	Graham	
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	61.	US 6,475,160	11/05/2002	Sher	
	62.	US 6,488,673	12/03/2002	Laufer et al.	
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	75.	US 6,767,544	07/27/2004	Brooks et al.	
	76.	US 6,773,711	08/10/2004	Voet et al.	
	77.	US 6,776,991	08/17/2004	Naimann	
	78.	US 6,827,931	12/07/2004	Donovan	
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	80.	US 6,841,156	01/11/2005	Aoki et al.	
	81.	US 6,843,998	01/18/2005	Steward et al.	
	82.	US 6,847,849	01/25/2005	Mamo et al.	
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	85.	US 6,974,578	12/13/2005	Aoki et al.	
	86.	US 7,238,357	07/03/2007	Barron	
	87.	US 7,608,275	10/27/2009	Deem et al.	

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Sheet	4	of	6	Attorney Docket Number		38077-714.301

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	88.	US 7,655,243	02/02/2010	Deem et al.	

FOREIGN PATENT DOCUMENTS						
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		Country Code ⁴ - Number ⁵ - Kind Code ⁶ (if known)				
	89.	WO 2004/048519 A2	06/10/2004	Sanders		
	90.	WO 2004/048519 A3	07/01/2004	Sanders		
	91.	WO 2004/101028 A2	11/25/2004	Deem et al.		
	92.	WO 2004/101028 A3	12/14/2006	Deem et al.		
	93.	WO 2007/014003 A2	02/01/2007	Deem et al.		
	94.	WO 2007/014003 A3	10/04/2007	Deem et al.		

Continued on the next page with more references.

Examiner Signature	Date Considered
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This collection of information is required by 37 CFR 1.97 and 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 as 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 22315-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22315-1450.

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Substitute for form 1449/PTO INFORMATION DISCLOSURE STATEMENT BY APPLICANT <i>(Use as many sheets as necessary)</i>				Complete if Known	
				Application Number	13/328,203
				Filing Date	December 16, 2011
				First Named Inventor	Mark E. Deem
				Art Unit	1645
				Examiner Name	Albert Mark Navarro
Sheet	5	of	6	Attorney Docket Number	38077-714.301

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
	95.	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 tetanus toxin on catecholamine secretion. J Neurochem. 1989 Jun;52(6):1751-8.	
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	99.	BUZZI. Diphtheria toxin treatment of human advanced cancer. Cancer Res. 1982 May;42(5):2054-8.	
	100.	CHADDOCK, et al. Expression and purification of catalytically active, non-toxic endopeptidase derivatives of Clostridium botulinum toxin type A. Protein Expr Purif. 2002 Jul;25(2):219-28.	
	101.	CHANG. Cell poration and cell fusion using an oscillating electric field. Biophys J. 1989 Oct;56(4):641-52.	
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	103.	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 Med Biol. 2003 Aug;29(8):1211-22.	
	104.	KISTNER, et al. Reductive cleavage of tetanus toxin and botulinum neurotoxin A by the thioredoxin system from brain. Evidence for two redox isomers of tetanus toxin. Naunyn-Schmiedeberg's Arch Pharmacol. 1992 Feb;345(2):227-34.	
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Substitute for form 1449/PTO INFORMATION DISCLOSURE STATEMENT BY APPLICANT <i>(Use as many sheets as necessary)</i>				Complete if Known	
				Application Number	13/328,203
				Filing Date	December 16, 2011
				First Named Inventor	Mark E. Deem
				Art Unit	1645
				Examiner Name	Albert Mark Navarro
Sheet	6	of	6	Attorney Docket Number	38077-714.301

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
	105.	KORPELA, et al. Comparison of tissue reactions in the tracheal mucosa surrounding a bioabsorbable and silicone airway stents. Ann Thorac Surg. 1998 Nov;66(5):1772-6.	
	106.	KREITMAN. Taming ricin toxin. Nat Biotechnol. 2003 Apr;21(4):372-4.	
	107.	RAJ. Editorial, Pain Practice. 2004; 4(1S):S1-S3.	
	108.	SHAARI, et al. Rhinorrhea is decreased in dogs after nasal application of botulinum toxin. Otolaryngol Head Neck Surg. 1995 Apr;112(4):566-71.	
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	110.	SUNDARAM, et al. An experimental and theoretical analysis of ultrasound-induced permeabilization of cell membranes. Biophys J. 2003 May;84(5):3087-101.	
	111.	TSUJI, et al. Biodegradable stents as a platform to drug loading. Int J Cardiovasc Intervent. 2003;5(1):13-6.	
	112.	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 Otolaryngol. 2003 Dec;123(9):1060-3.	
	113.	WEAVER, et al. Electroporation: a general phenomenon for manipulating cells and tissues. J Cell Biochem. 1993 Apr;51(4):426-35.	

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
	114.	International search report and written opinion dated 03/03/2008 for PCT/US2007/069391.	
	115.	European search report and opinion dated 06/18/2010 for EP Application No. 07784000.7.	

Examiner Signature	/Albert M Navarro/	Date Considered	04/22/2013
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¹ Applicant's unique citation designation number (optional). ² Applicant is to place a checkmark here if English language Translation is attached.

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BIB DATA SHEET

CONFIRMATION NO. 9512

SERIAL NUMBER 13/328,203	FILING or 371(c) DATE 12/16/2011 RULE	CLASS 604	GROUP ART UNIT 3767	ATTORNEY DOCKET NO. 38077-714.301	
APPLICANTS Mark E. Deem, Mountain View, CA; Hanson Gifford, Woodside, CA; ** CONTINUING DATA ***** This application is a CON of 12/636,477 12/11/2009 PAT 8105817 which is a DIV of 11/750,963 05/18/2007 PAT 7655243 which is a CIP of 11/459,090 07/21/2006 PAT 7608275 which claims benefit of 60/702,077 07/22/2005 and claims benefit of 60/747,771 05/19/2006 ** FOREIGN APPLICATIONS ***** ** IF REQUIRED, FOREIGN FILING LICENSE GRANTED ** ** SMALL ENTITY ** 12/29/2011					
Foreign Priority claimed ☐ Yes ☒ No 35 USC 119(a-d) conditions met ☐ Yes ☒ No Verified and /ALBERT MARK NAVARRO/ Acknowledged Examiner's Signature	☐ Met after Allowance Initials	STATE OR COUNTRY CA	SHEETS DRAWINGS 24	TOTAL CLAIMS 1	INDEPENDENT CLAIMS 1
ADDRESS WILSON, SONSINI, GOODRICH & ROSATI 650 PAGE MILL ROAD PALO ALTO, CA 94304-1050 UNITED STATES					
TITLE METHODS AND SYSTEMS FOR TOXIN DELIVERY TO THE NASAL CAVITY					
FILING FEE RECEIVED 1940	FEES: Authority has been given in Paper No. _____ to charge/credit DEPOSIT ACCOUNT No. _____ for following:		☐ All Fees ☐ 1.16 Fees (Filing) ☐ 1.17 Fees (Processing Ext. of time) ☐ 1.18 Fees (Issue) ☐ Other _____ ☐ Credit		

Search Notes 	Application/Control No. 13328203	Applicant(s)/Patent Under Reexamination DEEM ET AL.
	Examiner ALBERT NAVARRO	Art Unit 1645

CPC- SEARCHED		
Symbol	Date	Examiner

CPC COMBINATION SETS - SEARCHED		
Symbol	Date	Examiner

US CLASSIFICATION SEARCHED			
Class	Subclass	Date	Examiner

SEARCH NOTES		
Search Notes	Date	Examiner
Medline, Biosis, Ca, Caplus, Embase, USPatfull, update search history of 12/636,477, 11/750,963, 11/459,090	4/22/2013	MN

INTERFERENCE SEARCH			
US Class/ CPC Symbol	US Subclass / CPC Group	Date	Examiner

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**TERMINAL DISCLAIMER TO OBVIATE A DOUBLE PATENTING
REJECTION OVER A "PRIOR" PATENT**Docket Number (Optional)
38077-714.301

In re Application of: Mark E. Deem et al.

Application No.: 13/328,203

Filed: December 16, 2011

For: METHODS AND SYSTEMS FOR TOXIN DELIVERY TO THE NASAL CAVITY

The owner*, The Foundry, LLC, of 100 percent interest in the instant application hereby disclaims, except as provided below, the terminal part of the statutory term of any patent granted on the instant application which would extend beyond the expiration date of the full statutory term prior patent No. 7,608,275; 7,655,243; 8,105,817 as the term of said prior patent is defined in 35 U.S.C. 154 and 173, and as the term of said prior patent is presently shortened by any terminal disclaimer. The owner hereby agrees that any patent so granted on the instant application shall be enforceable only for and during such period that it and the prior patent are commonly owned. This agreement runs with any patent granted on the instant application and is binding upon the grantee, its successors or assigns.

In making the above disclaimer, the owner does not disclaim the terminal part of the term of any patent granted on the instant application that would extend to the expiration date of the full statutory term as defined in 35 U.S.C. 154 and 173 of the prior patent, "as the term of said prior patent is presently shortened by any terminal disclaimer," in the event that said prior patent later:

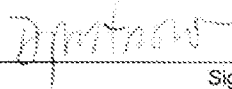
- expires for failure to pay a maintenance fee;
- is held unenforceable;
- is found invalid by a court of competent jurisdiction;
- is statutorily disclaimed in whole or terminally disclaimed under 37 CFR 1.321;
- has all claims canceled by a reexamination certificate;
- is reissued; or
- is in any manner terminated prior to the expiration of its full statutory term as presently shortened by any terminal disclaimer.

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1. ☐ For submissions on behalf of a business/organization (e.g., corporation, partnership, university, government agency, etc.), the undersigned is empowered to act on behalf of the business/organization.

I hereby 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 issued thereon.

2. ☒ The undersigned is an attorney or agent of record. Reg. No. 59,660.



Signature

Sept. 13, 2013

Date

Douglas Portnow

Typed or printed name

650-493-9300

Telephone Number

- ☒ Terminal disclaimer fee under 37 CFR 1.20(d) included.

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Electronic Patent Application Fee Transmittal

Application Number:	13328203			
Filing Date:	16-Dec-2011			
Title of Invention:	METHODS AND SYSTEMS FOR TOXIN DELIVERY TO THE NASAL CAVITY			
First Named Inventor/Applicant Name:	Mark E. Deem			
Filer:	Douglas Portnow/Joy Roeder			
Attorney Docket Number:	38077-714.301			
Filed as Small Entity				
Utility under 35 USC 111(a) Filing Fees				
Description	Fee Code	Quantity	Amount	Sub-Total in USD(\$)
Basic Filing:				
Pages:				
Claims:				
Claims in excess of 20	2202	3	40	120
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 - 2 months with \$0 paid	2252	1	300	300
Miscellaneous:				
Statutory or Terminal Disclaimer	1814	1	160	160
Total in USD (\$)				580

Electronic Acknowledgement Receipt

EFS ID:	16853051
Application Number:	13328203
International Application Number:	
Confirmation Number:	9512
Title of Invention:	METHODS AND SYSTEMS FOR TOXIN DELIVERY TO THE NASAL CAVITY
First Named Inventor/Applicant Name:	Mark E. Deem
Customer Number:	21971
Filer:	Douglas Portnow/Joy Roeder
Filer Authorized By:	Douglas Portnow
Attorney Docket Number:	38077-714.301
Receipt Date:	13-SEP-2013
Filing Date:	16-DEC-2011
Time Stamp:	17:20:11
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	yes
Payment Type	Deposit Account
Payment was successfully received in RAM	\$580
RAM confirmation Number	4914
Deposit Account	232415
Authorized User	

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File Listing:					
Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1		2013_09_13_EOT_AMDT_TD_3 8077_714_301.pdf	3965261 21e7920d3fae1b567cc1f22bcbdacb4ed9b319d9	yes	16
	Multipart Description/PDF files in .zip description				
	Document Description		Start	End	
	Amendment/Req. Reconsideration-After Non-Final Reject		1	1	
	Claims		2	9	
	Applicant Arguments/Remarks Made in an Amendment		10	15	
	Terminal Disclaimer Filed		16	16	
Warnings:					
Information:					
2	Fee Worksheet (SB06)	fee-info.pdf	33800 63976f8ab30359101364b983106d98bcf33acc27	no	2
Warnings:					
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Total Files Size (in bytes):			3999061		
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PATENT
Attorney Docket No.: 38077-714.301

WILSON, SONSINI, GOODRICH & ROSATI

By Joy A. Roeder

Joy A. Roeder

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of:

Mark E. Deem et al.

Application No.: 13/328,203

Filed: December 16, 2011

For: METHODS AND SYSTEMS FOR
TOXIN DELIVERY TO THE NASAL
CANAL

Customer No.: 21971

Confirmation No. 9512

Examiner: NAVARRO, Albert Mark

Technology Center/Art Unit: 1645

AMENDMENT

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

Commissioner:

In response to the Office Action mailed April 24, 2013, please enter the following
amendments and remarks:

Amendments to the Claims are reflected in the listing of claims which begins on page 2 of this
paper.

Remarks begin on page 10 of this paper.

Amendments to the Claims:

This listing of claims will replace all prior versions, and listings of claims in the application:

Listing of Claims:

1. (Canceled)
2. (Currently Amended) 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 by a catheter 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.
3. (Previously Presented) The method of claim 2, wherein the toxin comprises a light chain fragment of a neurotoxin substantially free of heavy chain fragments of the neurotoxin.
4. (Previously Presented) The method of claim 3, wherein the neurotoxin consists of botulinum toxin.
5. (Previously Presented) The method of claim 4, wherein the light chain fragment is derived from at least one of botulinum toxins A, B, C, D, E, F, and G.
6. (Previously Presented) The method of claim 2, wherein the one or more occlusion devices comprise one or more balloons.

7. (Previously Presented) The method of claim 6, further comprising inflating the one or more balloons to isolate the treatment region.
8. (Previously Presented) The 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.
9. (Canceled)
10. (Currently Amended) The method of claim 2 9, wherein the toxin is introduced by a balloon on the catheter.
11. (Previously Presented) The method of claim 10, wherein the balloon comprises one or more pores and the toxin is introduced through the pores of the balloon.
12. (Currently Amended) The method of claim 2 9, wherein the toxin is introduced through a needle on the catheter.
13. (Currently Amended) The method of claim 2 9, wherein the toxin is aerosolized from the catheter.
14. (Previously Presented) The method of claim 2, further comprising applying energy to the target cells under conditions which cause poration of the cell membranes to enhance delivery of the toxin.
15. (Previously Presented) The method of claim 14, wherein applying energy to the target cells comprises applying an electric pulse of between 1 V and 500 V to the target cells.

16. (Previously Presented) The method of claim 15, wherein the electric pulse comprises an RF signal.

17. (Previously Presented) The method of claim 15, wherein the electric pulse is applied for durations between 5 microseconds to 100 milliseconds.

18. (Previously Presented) The method of claim 15, wherein the electric pulse is produced by a DC power source.

19. (Previously Presented) The method of claim 15, wherein the electric pulse is produced by an AC power source.

20. (Previously Presented) The method of claim 14, wherein applying energy to the target cells comprises applying acoustic energy to the target cells.

21. (Previously Presented) The method of claim 20, wherein the acoustic energy comprises ultrasonic energy.

22. (Previously Presented) The method of claim 14, wherein applying energy to the target cells comprises applying electromagnetic energy to the target cells.

23. (Previously Presented) The method of claim 22, wherein the electromagnetic energy comprises microwaves.

24. (Previously Presented) The method of claim 22, wherein the electromagnetic energy comprises X-rays.

25. (Previously Presented) The method of claim 14, wherein energy is selectively applied to the target cells.

26. (Previously Presented) The method of claim 14, wherein energy is non-selectively applied to the target cells.

27. (Previously Presented) The method of claim 2, wherein the treatment region comprises at least one paranasal sinus, a main nasal passage, or a nasal turbinate.

28. (Previously Presented) The method of claim 2, wherein the treatment region comprises substantially the entire nasal cavity.

29. (Previously Presented) The method of claim 2, wherein the treatment region comprises substantially the nasopharynx.

30. (Currently Amended) The method of claim 2, wherein the target cells comprise ~~comprises~~ epithelial or goblet cells.

31. (Currently Amended) The method of claim 2, wherein the patient suffers from or is at risk of suffering from rhinorrhea ~~rhinorreal~~.

32. (Currently Amended) The method of claim 2, wherein the patient suffers from or is at risk of suffering from sinus headaches or migraine headaches.

33. (Canceled)

34. (Currently Amended) 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 as to inhibit mucous secretion in the target cells.

35. (Previously Presented) The method of claim 34, wherein the toxin comprises a light chain fragment of a neurotoxin substantially free of heavy chain fragments of the neurotoxin.

36. (Previously Presented) The method of claim 35, wherein the neurotoxin consists of botulinum toxin.

37. (Previously Presented) The method of claim 36, wherein the light chain fragment is derived from at least one of botulinum toxins A, B, C, D, E, F, and G.

38. (Canceled)

39. (Currently Amended) The method of claim 34, further comprising filling a targeted airway of the nasal cavity of the patient with the ~~gel or~~ foam carrier.

40. (Previously Presented) 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.

41. (Currently Amended) 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.

42. (Currently Amended) The method of claim 34, further comprising applying energy to the ~~gel or~~ foam carrier to enhance delivery of the toxin to the cells.

43. (Currently Amended) The method of claim 42, wherein ultrasonic energy is applied to the ~~gel or~~ foam carrier to enhance delivery of the toxin to the cells.

44. (Currently Amended) The method of claim 34, wherein the ~~gel or~~ foam carrier is introduced by a catheter.

45. (Currently Amended) The method of claim 44, wherein the ~~gel or~~ foam carrier is introduced by a balloon on the catheter.

46. (Currently Amended) The method of claim 45, wherein the balloon comprises one or more pores and the ~~gel or~~ foam carrier is introduced through the pores of the balloon.

47. (Currently Amended) The method of claim 44, wherein the ~~gel or~~ foam carrier is introduced through a needle on the catheter.

48. (Previously Presented) The method of claim 34, further comprising applying energy to the target cells to enhance delivery of the toxin to the cells.

49. (Previously Presented) The method of claim 48, wherein the energy is applied to the target cells under conditions which cause poration of the cell membranes to enhance delivery of the toxin.

50. (Previously Presented) The method of claim 48, wherein applying energy to the target cells comprises applying an electric pulse of between 1 V and 500 V to the target cells.

51. (Previously Presented) The method of claim 50, wherein the electric pulse comprises an RF signal.

52. (Currently Amended) The method of claim ~~50~~ 48, wherein the electric pulse is applied for durations between 5 microseconds to 100 milliseconds.

53. (Currently Amended) The method of claim 50 48, wherein the electric pulse is produced by a DC power source.

54. (Currently Amended) The method of claim 50 48, wherein the electric pulse is produced by an AC power source.

55. (Previously Presented) The method of claim 48, wherein applying energy to the target cells comprises applying acoustic energy to the target cells.

56. (Previously Presented) The method of claim 55, wherein the acoustic energy comprises ultrasonic energy.

57. (Previously Presented) The method of claim 48, wherein applying energy to the target cells comprises applying electromagnetic energy to the target cells.

58. (Previously Presented) The method of claim 57, wherein the electromagnetic energy comprises microwaves.

59. (Previously Presented) The method of claim 57, wherein the electromagnetic energy comprises X-rays.

60. (Previously Presented) The method of claim 48, wherein energy is selectively applied to the target cells.

61. (Previously Presented) The method of claim 48, wherein energy is non-selectively applied to the target cells.

62. (Previously Presented) The method of claim 34, wherein the treatment region comprises at least one paranasal sinus, a main nasal passage, or a nasal turbinate.

63. (Previously Presented) The method of claim 34, wherein the treatment region comprises substantially the entire nasal cavity.

64. (Previously Presented) The method of claim 34, wherein the treatment region comprises substantially the nasopharynx.

65. (Currently Amended) The method of claim 34, wherein the target cells comprise ~~comprises~~ epithelial or goblet cells.

66. (Currently Amended) The method of claim 34, wherein the patient suffers from or is at risk of suffering from rhinorrhea ~~rhinorrea~~.

67. (Currently Amended) The method of claim 34, wherein the patient suffers from or is at risk of suffering from sinus headaches or migraine headaches.

68. (Canceled)

69. (New) The method of claim 40, wherein fluidly isolating a treatment region of the nasal cavity comprises positioning one or more occlusion devices in the nasal cavity.

70. (New) 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 comprising at least one paranasal sinus; 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.

71. (New) The method of claim 70, wherein the toxin comprises a light chain fragment of a neurotoxin substantially free of heavy chain fragments of the neurotoxin.

72. (New) The method of claim 71, wherein the neurotoxin consists of botulinum toxin.

73. (New) The method of claim 70, wherein the one or more occlusion devices comprise one or more balloons.

74. (New) The method of claim 70, wherein the toxin is introduced by a catheter.

75. (New) The method of claim 70, further comprising applying energy to the target cells under conditions which cause poration of the cell membranes to enhance delivery of the toxin.

76. (New) The method of claim 70, wherein the target cells comprise epithelial or goblet cells.

77. (New) The method of claim 70, wherein the patient suffers from or is at risk of suffering from rhinorrhea, sinus headache or migraine headaches.

REMARKS/ARGUMENTS

Claims 2-68 were pending in the present application. In the Office Action, claims 2-68 were rejected. In response to the Office Action, claims 2, 10, 12, 13, 30-32, 34, 39, 41-47, 52-54, and 65-67 have been amended. Claims 9, 33, 38, and 68 have been canceled. Claims 69-77 have been added. Support for these claims can be found in the application as filed therefore no new matter has been added. Reexamination and reconsideration of the pending claims as amended is respectfully requested.

Claim Rejections – 35 USC § 102

Claim 2 was rejected under 35 USC § 102(b) as being anticipated by Ann Oto Rhinol Laryngol Vol. 110, pp 1045-1050, 2001 to Rohrbach et al. (hereinafter referred to as Rohrbach). Such rejections are overcome for at least the following reasons.

Independent claim 2 has been amended to include the features recited in dependent claim 9, thus claim 2 now recites in part introducing a toxin by a catheter to the treatment region while the one or more occlusion devices block the toxin from entering the remaining portion of the nasal cavity. Support for this amendment may be found in claim 9, which has now been canceled. No new matter has been added. Dependent claims 10, 12, and 13 have been amended to be consistent with amended claim 2 and the cancellation of claim 9. Dependent claim 32 has been amended to include the features recited in dependent claim 33, which has now been canceled. Rohrbach fails to anticipate the claimed method.

Rohrbach discloses introducing a sponge soaked in botulinum toxin to the nasal mucosal tissue (Abstract, p. 1046). Nowhere does Rohrbach teach or suggest anything about introducing a toxin by a catheter to the treatment region, as now claimed. Thus, Rohrbach fails to teach or suggest this feature of the claimed invention.

Because the cited reference fails to teach or suggest each and every element of the claimed invention, anticipation cannot be established under 35 USC § 102(b). Applicants respectfully request withdrawal of the § 102(b) rejection and allowance of claim 2.

Claim Rejections -- 35 USC § 103

Claims 2, 34, and 38-68 were rejected under 35 USC § 103(a) as being unpatentable over Rohrbach in view of US Patent Publication No. 2004/0009180 to Donovan et al. (hereinafter Donovan) and US Patent Publication No. 2003/0113349 to Coleman et al. (hereinafter Coleman). Such rejections are overcome for at least the following reasons.

Claim 2 has been amended and distinguished from Rohrbach as described above. Donovan and Coleman fail to provide the missing elements. Donovan discloses pharmaceutical compositions for transdermal administration of neurotoxins (Abstract). However, Donovan fails to teach or suggest anything about introducing a toxin by a catheter to the treatment region, as now recited by amended claim 2.

Coleman discloses applying botulinum toxin compositions to the skin (Abstract). Nowhere does Coleman teach or suggest anything about introducing a toxin by a catheter to the treatment region, as now recited by amended claim 2. Therefore, the cited references alone or in combination fail to teach or suggest each and every element of the claimed invention. Thus, claim 2 is patently distinguished from the cited references.

Independent claim 34 has been amended to remove the element reciting a gel carrier, thus claim 34 now recites in part introducing a foam carrier comprising a toxin to a treatment region in a nasal cavity containing target cells, wherein the toxin is delivered from the foam carrier to the target cells so as to inhibit mucous secretion in the target cells. Support for this amendment can be found in the original claim 34 therefore no new matter has been added. Dependent claim 38 has been canceled. Dependent claims 39 and 41-47 have been amended to be consistent with amended claim 34. Dependent claim 67 has been amended to include the features recited in dependent claim 68, which has now been canceled. The combination of Rohrbach, Donovan, and Coleman fails to teach or suggest each and every element of the claimed method.

Rohrbach discloses introducing a sponge soaked in botulinum toxin A to the nasal mucosal tissue (Abstract, p. 1046). Nowhere does Rohrbach teach or suggest anything about introducing a foam carrier comprising a toxin to a treatment region in a nasal cavity wherein the toxin is delivered from the foam carrier to the target cells, as now recited by amended claim 34.

Donovan fails to provide the elements missing from Rohrbach. Donovan discloses pharmaceutical compositions for transdermal administration of neurotoxins (Abstract). However, Donovan fails to teach or suggest anything about introducing a foam carrier comprising a toxin to a treatment region in a nasal cavity wherein the toxin is delivered from the foam carrier to the target cells, as now recited by amended claim 34.

Coleman also fails to provide the missing elements. Coleman discloses applying botulinum toxin compositions to the skin (Abstract). Nowhere does Coleman teach or suggest anything about introducing a foam carrier comprising a toxin to a treatment region in a nasal cavity wherein the toxin is delivered from the foam carrier to the target cells, as now recited by amended claim 34. Therefore, because the cited references alone or in combination fail to teach or suggest each and every element of the claimed invention, claim 34 is patently distinguished from the cited references.

With respect to dependent claims 39-67, these claims are allowable for at least depending from allowable claim 34, as well as on their own merits.

Therefore, because the cited references alone or in combination, fail to teach or suggest each and every element of the claimed invention, *prima facie* obviousness cannot be established under USC § 103(a). Applicants respectfully request withdrawal of the § 103(a) rejection and allowance of independent claims 2 and 34 and the claims depending therefrom.

Double Patenting

In the Office Action, claims 2-68 of the present application were rejected on the grounds of non-statutory obviousness-type double patenting as being unpatentable over: claims 1-35 of US Patent No. 7,608,275; claims 1-35 of US Patent No. 7,655,243; and claims 1-30 of US Patent No. 8,105,817. Such rejections are overcome for at least the following reasons.

Without conceding the issue of patentability, and in order to expedite prosecution of the present application, a Terminal Disclaimer is being filed herewith thereby obviating the rejection. Applicants respectfully request withdrawal of the double patenting rejection and allowance of the rejected claims.

New Claims

Claim 69 depending from claim 34 has been added. Support for this claim can be found in the application as filed (*e.g.*, paragraphs [0099], [102]-[105], and [135]) therefore no new matter has been added. Claim 34 has been amended and distinguished from the cited references as described above, thus claim 69 is allowable for at least depending from claim 34, as well as on its own merits.

Independent claim 70 and claims 71-77 depending therefrom have been added. Support for these claims can be found in the application as filed (*e.g.*, paragraphs [0007] and [0013]) therefore no new matter has been added. Rohrbach, Coleman, and Donovan fail to teach or suggest anything about introducing a toxin to a treatment region comprising at least one paranasal sinus, thus claim 70 is patently distinguished from the cited references. Claims 71-77 are allowable for at least depending from claim 70, as well as on their own merits.

Typographical Errors

Claims 30, 31, 42, 52-54, 65, and 66 have been amended to correct minor typographical errors.

CONCLUSION

In view of the foregoing, Applicants believe all claims now pending in this Application are in condition for allowance. The issuance of a formal Notice of Allowance at an early date is respectfully requested.

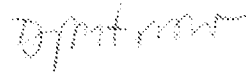
Further, the Commissioner is hereby authorized to charge any additional fees or credit any overpayment in connection with this paper to Deposit Account No. 23-2415.

Appl. No. 13/328,203
Amendment dated September 12, 2013
Reply to OA dated April 24, 2013

PATENT

If the Examiner believes a telephone conference would expedite prosecution of this application, please telephone the undersigned at 650-493-9300.

Respectfully submitted,



Douglas Portnow
Reg. No. 59,660

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Attachments
D3P:jar

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PATENT APPLICATION FEE DETERMINATION RECORD Substitute for Form PTO-875	Application or Docket Number 13/328,203	Filing Date 12/16/2011	☐ To be Mailed
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 ENTITY: ☐ LARGE ☒ SMALL ☐ MICRO

APPLICATION AS FILED – PART I

FOR	NUMBER FILED	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), (l), 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 \$ =	
INDEPENDENT CLAIMS (37 CFR 1.16(h))	minus 3 =	*	X \$ =	
☐ 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

AMENDMENT	(Column 1)	(Column 2)	(Column 3)	HIGHEST NUMBER PREVIOUSLY PAID FOR	PRESENT EXTRA	RATE (\$)	ADDITIONAL FEE (\$)
	09/13/2013	CLAIMS REMAINING AFTER AMENDMENT					
	Total (37 CFR 1.16(i))	* 71	Minus	** 68	= 3	x \$40 =	120
	Independent (37 CFR 1.16(h))	* 3	Minus	***3	= 0	x \$210 =	0
	☐ Application Size Fee (37 CFR 1.16(s))						
	☐ FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))						
TOTAL ADD'L FEE							120

AMENDMENT	(Column 1)	(Column 2)	(Column 3)	HIGHEST NUMBER PREVIOUSLY PAID FOR	PRESENT EXTRA	RATE (\$)	ADDITIONAL FEE (\$)
		CLAIMS REMAINING AFTER AMENDMENT					
	Total (37 CFR 1.16(i))	*	Minus	**	=	X \$ =	
	Independent (37 CFR 1.16(h))	*	Minus	***	=	X \$ =	
	☐ 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.

** 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 number found in the appropriate box in column 1.

 LIE
 /MARQUITA JONES/

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.

Application Number 	Application/Control No. 13/328,203	Applicant(s)/Patent under Reexamination DEEM ET AL.	
Document Code - DISQ		Internal Document – DO NOT MAIL	

TERMINAL DISCLAIMER	☒ APPROVED	☐ DISAPPROVED
Date Filed : 09-13-2013	This patent is subject to a Terminal Disclaimer	

Approved/Disapproved by:

Dorethea Lawrence



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NOTICE OF ALLOWANCE AND FEE(S) DUE

21971 7590 09/20/2013
WILSON, SONSINI, GOODRICH & ROSATI
650 PAGE MILL ROAD
PALO ALTO, CA 94304-1050

EXAMINER

NAVARRO, ALBERT MARK

ART UNIT

PAPER NUMBER

1645

DATE MAILED: 09/20/2013

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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13/328,203

12/16/2011

Mark E. Deem

38077-714.301

9512

TITLE OF INVENTION: METHODS AND SYSTEMS FOR TOXIN DELIVERY TO THE NASAL CAVITY

APPLN. TYPE	ENTITY STATUS	ISSUE FEE DUE	PUBLICATION FEE DUE	PREV. PAID ISSUE FEE	TOTAL FEE(S) DUE	DATE DUE
nonprovisional	SMALL	\$890	\$300	\$0	\$1190	12/20/2013

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: Utility patents issuing on applications filed on or after Dec. 12, 1980 may require payment of maintenance fees. It is patentee's responsibility to ensure timely payment of maintenance fees when due.

PART B - FEE(S) TRANSMITTAL

**Complete and send this form, together with applicable fee(s), to: Mail Mail Stop ISSUE FEE
Commissioner for Patents
P.O. Box 1450
Alexandria, Virginia 22313-1450
or Fax (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)

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.

21971 7590 09/20/2013
WILSON, SONSINI, GOODRICH & ROSATI
650 PAGE MILL ROAD
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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 facsimile transmitted to the USPTO (571) 273-2885, on the date indicated below.

(Depositor's name)
(Signature)
(Date)

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
13/328,203	12/16/2011	Mark E. Deem	38077-714.301	9512

TITLE OF INVENTION: METHODS AND SYSTEMS FOR TOXIN DELIVERY TO THE NASAL CAVITY

APPLN. TYPE	ENTITY STATUS	ISSUE FEE DUE	PUBLICATION FEE DUE	PREV. PAID ISSUE FEE	TOTAL FEE(S) DUE	DATE DUE
nonprovisional	SMALL	\$890	\$300	\$0	\$1190	12/20/2013

EXAMINER	ART UNIT	CLASS-SUBCLASS
NAVARRO, ALBERT MARK	1645	604-019000

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 03-02 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 has been filed for recordation as set forth in 37 CFR 3.11. 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. The following fee(s) are submitted: ☐ Issue Fee ☐ Publication Fee (No small entity discount permitted) ☐ Advance Order - # of Copies _____	4b. Payment of Fee(s): (Please first reapply any previously paid issue fee shown above) ☐ A check is enclosed. ☐ Payment by credit card. Form PTO-2038 is attached. ☐ The Director is hereby authorized to charge the required fee(s), any deficiency, or credit any overpayment, to Deposit Account Number _____ (enclose an extra copy of this form).
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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 form 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: The Issue Fee and Publication Fee (if required) will not be accepted from anyone other than the applicant; a registered attorney or agent; or the assignee or other party in interest as shown by the records of the United States Patent and Trademark Office.

Authorized Signature _____

Date _____

Typed or printed name _____

Registration No. _____

This collection of information 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 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, 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.

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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
13/328,203	12/16/2011	Mark E. Deem	38077-714.301	9512

21971 7590 09/20/2013
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EXAMINER

NAVARRO, ALBERT MARK

ART UNIT	PAPER NUMBER
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1645

DATE MAILED: 09/20/2013

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

The Patent Term Adjustment to date is 16 day(s). If the issue fee is paid on the date that is three months after the mailing date of this notice and the patent issues on the Tuesday before the date that is 28 weeks (six and a half months) after the mailing date of this notice, the Patent Term Adjustment will be 16 day(s).

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 Customer Service Center of the Office of Patent Publication at 1-(888)-786-0101 or (571)-272-4200.

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. 13/328,203	Applicant(s) DEEM ET AL.	
	Examiner Mark Navarro	Art Unit 1645	AIA (First Inventor to File) 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 13, 2013.
☐ 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 2-8, 10-32, 34-37, 39-67, 69-77, renumbered as 1-72, respectively. 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) | 5. ☐ Examiner's Amendment/Comment |
| 2. ☐ Information Disclosure Statements (PTO/SB/08),
Paper No./Mail Date ____ | 6. ☐ Examiner's Statement of Reasons for Allowance |
| 3. ☐ Examiner's Comment Regarding Requirement for Deposit
of Biological Material | 7. ☐ Other ____. |
| 4. ☐ Interview Summary (PTO-413),
Paper No./Mail Date ____. | |

/Mark Navarro/
Primary Examiner, Art Unit 1645

Search Notes 	Application/Control No. 13328203	Applicant(s)/Patent Under Reexamination DEEM ET AL.
	Examiner ALBERT NAVARRO	Art Unit 1645

CPC- SEARCHED		
Symbol	Date	Examiner

CPC COMBINATION SETS - SEARCHED		
Symbol	Date	Examiner

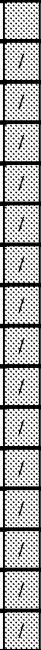
US CLASSIFICATION SEARCHED			
Class	Subclass	Date	Examiner

SEARCH NOTES		
Search Notes	Date	Examiner
Medline, Biosis, Ca, Caplus, Embase, USPatfull, update search history of 12/636,477, 11/750,963, 11/459,090	9/18/2013	MN

INTERFERENCE SEARCH			
US Class/ CPC Symbol	US Subclass / CPC Group	Date	Examiner
PALM Inventor Search		9/18/2013	MN

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Issue Classification 	Application/Control No. 13328203	Applicant(s)/Patent Under Reexamination DEEM ET AL.	
	Examiner ALBERT NAVARRO	Art Unit 1645	

CPC			
Symbol		Type	Version
			

CPC Combination Sets				
Symbol	Type	Set	Ranking	Version
				

NONE		Total Claims Allowed: 72	
(Assistant Examiner)	(Date)		
/ALBERT NAVARRO/ Primary Examiner.Art Unit 1645	9/18/2013	O.G. Print Claim(s)	O.G. Print Figure
(Primary Examiner)	(Date)	1	NONE

Issue Classification 	Application/Control No. 13328203	Applicant(s)/Patent Under Reexamination DEEM ET AL.
	Examiner ALBERT NAVARRO	Art Unit 1645

US ORIGINAL CLASSIFICATION						INTERNATIONAL CLASSIFICATION										
CLASS		SUBCLASS				CLAIMED					NON-CLAIMED					
604		19				A	6	1	K	9 / 22 (2006.01.01)						
CROSS REFERENCE(S)						A	6	1	N	1 / 30 (2006.01.01)						
CLASS	SUBCLASS (ONE SUBCLASS PER BLOCK)															
604	890.1	891.1														

NONE		Total Claims Allowed:	
		72	
(Assistant Examiner)	(Date)		
/ALBERT NAVARRO/ Primary Examiner.Art Unit 1645	9/18/2013	O.G. Print Claim(s)	O.G. Print Figure
(Primary Examiner)	(Date)	1	NONE

PART B - FEE(S) TRANSMITTAL

Complete and send this form, together with applicable fee(s), to: **Mail** **Mail Stop ISSUE FEE**
Commissioner for Patents
P.O. Box 1450
Alexandria, Virginia 22313-1450
or Fax (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)

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.

21971 7590 09/20/2013
WILSON, SONSINI, GOODRICH & ROSATI
650 PAGE MILL ROAD
PALO ALTO, CA 94304-1050

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 facsimile transmitted to the USPTO (571) 273-2885, on the date indicated below.

Joy A. Roeder	(Depositor's name)
<i>Joy A. Roeder</i>	(Signature)
December 20, 2013	(Date)

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
13/328,203	12/16/2011	Mark E. Deem	38077-714.301	9512

TITLE OF INVENTION: METHODS AND SYSTEMS FOR TOXIN DELIVERY TO THE NASAL CAVITY

APPLN. TYPE	ENTITY STATUS	ISSUE FEE DUE	PUBLICATION FEE DUE	PREV. PAID ISSUE FEE	TOTAL FEE(S) DUE	DATE DUE
nonprovisional	SMALL	\$890	\$300	\$0	\$1190	12/20/2013

EXAMINER	ART UNIT	CLASS-SUBCLASS
NAVARRO, ALBERT MARK	1645	604-019000

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 03-02 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 **WILSON, SONSINI, GOODRICH & ROSATI**

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 has been filed for recordation as set forth in 37 CFR 3.11. 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, CA

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

4a. The following fee(s) are submitted:

- ☒ Issue Fee
☒ Publication Fee (No small entity discount permitted)
☐ Advance Order - # of Copies _____

4b. Payment of Fee(s): (Please first reapply any previously paid issue fee shown above)

- ☐ A check is enclosed.
☐ Payment by credit card. Form PTO-2038 is attached.
☒ The Director is hereby authorized to charge the required fee(s), any deficiency, or credit any overpayment, to Deposit Account Number _____ (enclose an extra copy of this form).

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.

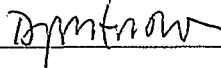
NOTE: Absent a valid certification of Micro Entity Status (see form PTO/SB/15A and 15B), issue fee payment in the micro entity amount will not be accepted at the risk of application abandonment.

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: The Issue Fee and Publication Fee (if required) will not be accepted from anyone other than the applicant; a registered attorney or agent; or the assignee or other party in interest as shown by the records of the United States Patent and Trademark Office.

Authorized Signature



Date December 20, 2013

Typed or printed name Douglas Portnow

Registration No. 59,660

This collection of information 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 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, 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.

Electronic Patent Application Fee Transmittal

Application Number:	13328203			
Filing Date:	16-Dec-2011			
Title of Invention:	METHODS AND SYSTEMS FOR TOXIN DELIVERY TO THE NASAL CAVITY			
First Named Inventor/Applicant Name:	Mark E. Deem			
Filer:	James Mitchell Heslin/Joy Roeder			
Attorney Docket Number:	38077-714.301			
Filed as Small Entity				
Utility under 35 USC 111(a) Filing Fees				
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	890	890
Publ. Fee- Early, Voluntary, or Normal Page 291 of 295	1504	1	300	300

Description	Fee Code	Quantity	Amount	Sub-Total in USD(\$)
Extension-of-Time:				
Miscellaneous:				
Total in USD (\$)				1190

Electronic Acknowledgement Receipt

EFS ID:	17733578
Application Number:	13328203
International Application Number:	
Confirmation Number:	9512
Title of Invention:	METHODS AND SYSTEMS FOR TOXIN DELIVERY TO THE NASAL CAVITY
First Named Inventor/Applicant Name:	Mark E. Deem
Customer Number:	21971
Filer:	James Mitchell Heslin/Joy Roeder
Filer Authorized By:	James Mitchell Heslin
Attorney Docket Number:	38077-714.301
Receipt Date:	20-DEC-2013
Filing Date:	16-DEC-2011
Time Stamp:	19:13:32
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	yes
Payment Type	Deposit Account
Payment was successfully received in RAM	\$ 1190
RAM confirmation Number	10684
Deposit Account	232415
Authorized User	

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
Page 293 of 295					

1	Issue Fee Payment (PTO-85B)	2013_12_20_IFXMTL_38077_7 14_301.pdf	76569 2f73ada321a186ea1c9a32e511b68c4d76e93aef	no	2
Warnings:					
Information:					
2	Fee Worksheet (SB06)	fee-info.pdf	31857 dfc93b4ac70a0d78dec633396b16cd435a3850ca	no	2
Warnings:					
Information:					
Total Files Size (in bytes):			108426		
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. <u>New Applications Under 35 U.S.C. 111</u> 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. <u>National Stage of an International Application under 35 U.S.C. 371</u> 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. <u>New International Application Filed with the USPTO as a Receiving Office</u> 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.	ISSUE DATE	PATENT NO.	ATTORNEY DOCKET NO.	CONFIRMATION NO.
13/328,203	01/28/2014	8636684	38077-714.301	9512

21971 7590 01/08/2014
WILSON, SONSINI, GOODRICH & ROSATI
650 PAGE MILL ROAD
PALO ALTO, CA 94304-1050

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 16 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;
Hanson Gifford, Woodside, CA;

The United States represents the largest, most dynamic marketplace in the world and is an unparalleled location for business investment, innovation, and commercialization of new technologies. The USA offers tremendous resources and advantages for those who invest and manufacture goods here. Through SelectUSA, our nation works to encourage and facilitate business investment. To learn more about why the USA is the best country in the world to develop technology, manufacture products, and grow your business, visit SelectUSA.gov.