

Application Data Sheet

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Applicant Information

Applicant Authority Type::	Inventor
Primary Citizenship Country::	US
Status::	Full Capacity
Given Name::	MARK
Middle Name::	E.
Family Name::	DEEM
City of Residence::	Mountain View
State or Province of Residence::	CA
Country of Residence::	US
Street of Mailing Address::	685 Sierra Avenue
City of Mailing Address::	Mountain View
State or Province of mailing address::	CA
Country of mailing address::	US

Postal or Zip Code of mailing address:: 94041

Applicant Authority Type:: Inventor
Primary Citizenship Country:: US
Status:: Full Capacity
Given Name:: HANSON
Family Name:: GIFFORD
City of Residence:: Woodside
State or Province of Residence:: CA
Country of Residence:: US
Street of Mailing Address:: 3180 Woodside Road
City of Mailing Address:: Woodside
State or Province of mailing address:: CA
Country of mailing address:: US
Postal or Zip Code of mailing address:: 94062

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Assignee Information

Assignee Name:: The Foundry Inc.
Street of mailing address:: 199 Jefferson Drive

City of mailing address:: Menlo Park

State or Province of mailing address:: CA

Country of mailing address:: US

Postal or Zip Code of mailing address:: 94025

PATENT APPLICATION

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

Inventors: MARK E. DEEM, a citizen of The United States
residing at 685 Sierra Avenue
Mountain View, California 94041; and

HANSON GIFFORD, a citizen of The United States
residing at 3180 Woodside Road
Woodside, California 94062.

Assignee: The Foundry Inc.
199 Jefferson Drive
Menlo Park, CA 94025

Status: Small Entity

61054629 v1

TOWNSEND and TOWNSEND and CREW LLP
Two Embarcadero Center, Eighth Floor
San Francisco, California 94111-3834
Tel: 650-326-2400

METHODS AND SYSTEMS FOR TOXIN DELIVERY TO THE NASAL CAVITY

CROSS-REFERENCES TO RELATED APPLICATIONS

5 [0001] The present application 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
10 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
15 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
20 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.
25 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,
30 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.

5 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
10 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
15 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
20 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*
25 *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
30 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.
- 5 [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
10 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.
- 15 [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.
- 20 [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
25 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 portation energy to the nasal cavity.
- [0041] Figures 24 and 25 - depict an alternate occlusion catheter system for targeted toxin delivery to the nasopharynx.
- 5 [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 olfactory 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 through an ostium open to the sinus.
- [0044] Figure 29 - depicts toxin delivery using a nasal spray and energy delivery using a face
10 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.
- 15 [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.
- 20 [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.
- 25 [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.

5 [0057] Figure 44 – 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.

[0058] Figure 45 - depicts an embodiment of the present invention utilizing an inhaler with an in vivo energy delivery source.

10 [0059] Figure 46 - depicts an interstitial method of use of the present invention.

[0060] Figure 47 – depicts a fully implantable pulse generator, lead and agent delivery pump of the present invention.

[0061] Figure 48 – 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.

15 [0062] Figure 49 – depicts an embodiment of the present invention wherein the energy and therapeutic agent are delivered transdermally.

DETAILED DESCRIPTION OF THE INVENTION

[0063] 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.

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[0064] 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

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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.

[0065] 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.

[0066] 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.

[0067] 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.

[0068] 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.

[0069] 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.

[0070] 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.

[0071] 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).

[0072] 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.

[0073] 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.

[0074] 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.

[0075] 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.

[0076] 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.

[0077] 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.

[0078] 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.

[0079] 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.

[0080] 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.

[0081] 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.

[0082] Systems for permeabilization of target tissue cell membranes may employ either high acoustic pressure or low acoustic pressure ultrasound. Some embodiments may preferably
5 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
10 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
15 systems may also be employed.

[0083] 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
20 deliver microwave energy using one or more microwave antennas.

[0084] 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
25 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
30 discontinued, the pores in the cell membrane recover or close as depicted in Figure 4.

[0085] The terms "poration" and "permeablization" will also cover forms of cellular sonoporation. Just as pulses of high voltage electricity can open transient pores in the cell

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

[0086] 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.

[0087] 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.

[0088] Referring to Figure 5, electroporation catheter system 20 comprises a pulse generator 24 such as those generators available from Cytopulse Sciences, Inc. (Columbia, MD) or the Gene Pulser Xcell (Bio-Rad, Inc.), or IGEA (Carpi, Italy), electrically connected to a catheter 22 having a proximal end and a distal region 26 adapted for minimally invasive insertion into the desired region of the body as described herein. The catheter further comprises an electroporation element 28 at the distal region thereof. The electroporation element consists for example of a first electrode 30 and a second electrode 32 operatively connected to the pulse generator for delivering the desired number, duration, amplitude and frequency of pulses to affect the targeted cells. These parameters can be modified either by the

system or the user, depending on the location of the catheter within the body (intervening tissues or structures), and the timing and duration of reversible cell poration desired.

[0089] 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.

[0090] 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.

[0091] 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.

[0092] 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.

[0093] 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.

[0094] 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.

[0095] 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
5 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.

[0096] While the toxins and porating energy of the present invention may be delivered to the
10 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
15 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
20 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
25 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.

[0097] In all the above cases, the ultrasonic transducers can be configured in order to
30 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.

[0098] 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.

[0099] The balloon catheters can be introduced by any conventional technique, for example, in some instances, it may be desirable to use a guidewire to place the catheter into a desired sinus or other location, optionally using fluoroscopic, MRI or ultrasound imaging.

[0100] 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.

[0101] 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.

[0102] 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).

5 **[0103]** 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
10 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.

15 **[0104]** 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.
20 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.

25 **[0105]** 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.

30 **[0106]** 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.

5 **[0107]** 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
10 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.

[0108] 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
15 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
20 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.

[0109] As shown in Figures 22 and 23, specially designed nose plugs 105 can be provided
25 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
30 external transducer as described previously.

[0110] 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
5 through or reside in the nostrils or the catheter which occludes the posterior nasopharynx.

[0111] 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

[0112] 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),
10 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.

[0113] Referring to Figure 29, the toxin may be delivered as a conventional nasal
20 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
25 relatively short distance into the nose. Thus the entire therapy might comprise the specialized delivery of two mists.

[0114] 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
30 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.

[0115] 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.

[0116] 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.

[0117] 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.

[0118] 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.

[0119] 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

5 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
10 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.

[0120] 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
15 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
20 lateral pressure to the first and second members of the handle body.

[0121] 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
25 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.

[0122] In the embodiment illustrated in Figures 39A and 39B, the dry sponge applicator
30 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.

5 **[0123]** 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
10 wet/dry sponge embodiment discussed above.

[0124] 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
15 illustrated in Figure 41.

[0125] 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
20 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.

[0126] 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
25 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.

[0127] The device may optionally comprise an engagement element 127 for engaging and
30 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.

[0128] 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.

[0129] Although toxins can be administered to the body to achieve a therapeutic benefit, the same toxins can cause local and systematic damage to non-targeted body tissues. Accordingly, it would also be desirable for the apparatus to be configured such that only the amount of toxin necessary to treat the nasal cavity is loaded on the applicator tip and applied to the nasal wall.

It this embodiment, it would be desirable for the applicator to carry a predetermined quantity of toxin, wherein the predetermined quantity is the amount necessary to provide a therapeutic effect. It would also be desirable for the applicator to be configured such that most, if not all, of the toxin carried on the applicator is delivered to the nasal wall, wherein little to no toxin runs, escapes or migrates to non-target portions of body tissue.

[0130] 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.

[0131] 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.

[0132] In one embodiment, both the inner and outer members may comprise balloons, wherein the BoNT is carried in the space between the inner and outer balloons. The outer balloon can be a perforated polymer (e.g., polyethylene terephthalate or expanded polytetrafluoroethylene) for releasing BoNT in a controlled and uniform matter. The inner member can be a compliant balloon, wherein the volume occupied by the inner balloon can be adjusted by injecting a fluid (e.g., air or saline) into the inner balloon. In this configuration, the impermeable lining is comprised of the wall of the inner balloon and the applicator's BoNT carrying capacity is based on the volume of the outer balloon relative to that of the inner balloon. For example, an applicator could be configured to carry less BoNT by increasing the inner balloon's volume relative to the the outer balloon's volume.

[0133] 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.

[0134] 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.

[0135] 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.

[0136] 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.

[0137] 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.

[0138] 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.

[0139] The lyophilized powder could also be formed into sheets, ribbons, pellets microspheres, or any other desirable form, and introduced to the target tissues.

5 **[0140]** 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.

10 **[0141]** 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.

15 **[0142]** In addition to BTX-LC, it may be desirable to deliver additional agents to the nasal passages and sinuses prior to, coincident with, or after deliver of the LC. Adjunctive therapies may include agents designed to slow down or halt the motion of the cilia, in order to aid in delivery of the LC to the target tissues by prevention of their mobilization by the cilia. Agents known to slow or halt the motion of cilia include but are not limited to epinephrine dilutions of 1:1000 (which causes ciliary death), 1:10,000 (which causes reversible paralysis), 10% cocaine (induces paralysis) or 2.5% cocaine (slows or stops cilia).

20 **[0143]** 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.

[0144] 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.

[0145] 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.

[0146] 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.

WHAT IS CLAIMED IS:

- 1 1. A method for delivering toxins to target cells in a nasal membrane of a
2 patient, said method comprising:
3 introducing a toxin to a region proximate the target cells; and
4 applying energy to the target cells to enhance delivery of the toxin to the cells.
- 1 2. A method as in claim 1, wherein the region comprises at least one
2 paranasal sinus, a main nasal passage or a nasal turbinate.
- 1 3. A method as in claim 1, wherein the region comprises substantially the
2 entire nasal cavity.
- 1 4. A method as in claim 1, wherein the region comprises the
2 nasopharynx.
- 1 5. A method as in claim 1, wherein the target cells comprise epithelial or
2 goblet cells.
- 1 6. A method as in claim 1, wherein the energy is selectively applied to
2 target cells within the region where toxin has been introduced.
- 1 7. A method as in claim 1, wherein the energy is applied non-selectively
2 within the region where toxin has been introduced.
- 1 8. A method as in claim 1, wherein the patient suffers from or is at risk of
2 suffering from rhinorrea.
- 1 9. A method as in claim 1, wherein the patient suffers from or is at risk of
2 suffering from sinus headaches.
- 1 10. A method as in claim 1, wherein the patient suffers from or is at risk of
2 suffering from migraine headaches.
- 1 11. A method as in claim 1, wherein the toxin comprises botulinum toxin.
- 1 12. A method as in claim 11, wherein the toxin is a fragment of botulinum
2 toxin.

- 1 13. A method as in claim 12, wherein the fragment is a light chain
2 fragment of botulinum toxin.
- 1 14. A method as in claim 13, wherein the light chain fragment is derived
2 from at least one of botulinum toxins A, B, C, D, E, F, and G.
- 1 15. A method as in claim 1, wherein the energy applied to the targeted
2 region is an electric pulse.
- 1 16. A method as in claim 15, wherein the electric pulse is applied from
2 between 1V to 500V.
- 1 17. A method as in claim 15, wherein the electric pulse is an RF signal.
- 1 18. A method of claim 15, wherein the electric pulse is pulsed for
2 durations between 5 microseconds to 100 milliseconds.
- 1 19. A method as in claim 15, wherein the electric pulse is produced by a
2 DC power source.
- 1 20. A method as in claim 15, wherein the electric pulse is produced by an
2 AC power source.
- 1 21. A method as in claim 1, wherein the energy applied to the target region
2 is ultrasonic.
- 1 22. A method as in claim 1, wherein the energy applied to the targeted
2 region is an x-ray beam.
- 1 23. A method as in claim 1, wherein the energy applied to the targeted
2 region is focused ultrasound.
- 1 24. A method as in claim 1, wherein the energy applied to the targeted
2 region is microwave.
- 1 25. A method as in claim 1, wherein the toxin is introduced to the target
2 region through a catheter.

1 26. A method as in claim 25, wherein the toxin is introduced through a
2 balloon on the catheter.

1 27. A method as in claim 26, wherein the balloon is porous and the toxin is
2 introduced through the balloon.

1 28. A method as in claim 25, wherein the toxin is introduced through a
2 needle on the catheter.

1 29. A method as in claim 25, wherein the toxin is aerosolized from the
2 catheter.

1 30. A method as in claim 25, wherein energy is applied from a source on
2 the catheter.

1 31. A method as in claim 30, wherein acoustic energy is applied from a
2 transducer on the catheter.

1 32. A method as in claim 30, wherein electrical energy is applied from an
2 electrode on the catheter.

1 33. A method as in claim 1, wherein the energy is delivered from a source
2 external to the patient.

1 34. A method as in claim 33, wherein the source is an acoustic energy
2 transducer.

1 35. A method as in claim 34, wherein the acoustic energy transducer is a
2 focused ultrasound transducer.

1 36. A system for delivering toxins to target cells in a nasal membrane, said
2 system comprising:

3 a catheter adapted to introduce a toxin to a region proximate the target cells;
4 an energy applicator configured for applying energy to the target cells under
5 conditions which cause poration of the cell membranes to enhance delivery of the toxin; and
6 a source of toxin suitable for introduction from the catheter.

- 1 37. A system as in claim 36, wherein the energy applicator is adapted to
2 selectively apply energy to target cells within the region where toxin has been introduced.
- 1 38. A system as in claim 36, wherein the energy applicator is adapted to
2 apply energy non-selectively within the region where toxin has been introduced.
- 1 39. A system as in claim 36, wherein the toxin comprises botulinum toxin.
- 1 40. A system as in claim 39, wherein the toxin is a fragment of botulinum
2 toxin.
- 1 41. A system as in claim 40, wherein the fragment is a light chain fragment
2 of botulinum toxin.
- 1 42. A system as in claim 41, wherein the light chain fragment is derived
2 from at least one of botulinum toxins A, B, C, D, E, F, and G.
- 1 43. A system as in claim 1, wherein the energy applicator is adapted to
2 apply an electric pulse of between 1v and 500V to the targeted region.
- 1 44. A system as in claim 43, wherein the electric pulse is an RF signal.
- 1 45. A system as in claim 43, wherein the electric pulse is pulsed for
2 durations between 5 microseconds to 100 milliseconds.
- 1 46. A system as in claim 43, wherein the electric pulse is produced by a
2 DC power source.
- 1 47. A system as in claim 43, wherein the electric pulse is produced by an
2 AC power source.
- 1 48. A system as in claim 1, wherein the energy applicator is adapted to
2 apply ultrasonic energy to the targeted region.
- 1 49. A system as in claim 36, wherein the energy applicator is adapted to
2 apply an x-ray beam to the targeted region.

- 1 50. A system as in claim 36, wherein the energy applicator is adapted to
2 apply focused ultrasound to the targeted region.
- 1 51. A system as in claim 36, wherein the energy applicator is adapted to
2 apply microwave to the targeted region.
- 1 52. A system as in claim 36, wherein the toxin is introduced by a balloon
2 on the catheter.
- 1 53. A system as in claim 52, wherein the balloon comprises one or more
2 pores and the toxin is introduced through the pores of the balloon.
- 1 54. A system as in claim 52, wherein the toxin is introduced through a
2 needle on the catheter.
- 1 55. A system as in claim 52, wherein the toxin is aerosolized from the
2 catheter.
- 1 56. A system as in claim 36, wherein energy applicator is on the catheter.
- 1 57. A system as in claim 56, wherein energy applicator applies acoustic
2 energy from a transducer on the catheter.
- 1 58. A system as in claim 56, wherein energy applicator applies electrical
2 energy from an electrode on the catheter.
- 1 59. A system as in claim 36, wherein the applicator applies energy from a
2 source external to the patient.
- 1 60. A system as in claim 59, wherein the source further comprises an
2 acoustic energy transducer.
- 1 61. A system as in claim 60, wherein the acoustic energy transducer
2 further comprises a focused ultrasound transducer.
- 1 62. A system as in claim 36, wherein the toxin is introduced through a
2 membrane supported on a scaffold on the catheter.

1 63. A system as in claim 36, wherein the toxin is introduced by a needless
2 injector.

1 64. A system as in claim 36, wherein the energy applicator comprises a
2 wave guide configured to be positioned within a nasal passageway.

1 65. A system as in claim 52, wherein the balloon is configured to be
2 positioned within a nasal passageway.

1 66. A system as in claim 52, wherein the balloon is configured to be
2 positioned outside of a sinus cavity.

1 67. A method as in claim 1, wherein applying energy to the target cells
2 further comprises applying energy to the target cells under conditions which cause poration
3 of the cell membranes.

1 68. A system as in claim 59, wherein the source further comprises a
2 microwave antenna.

1 69. A method as in claim 30, wherein microwave energy is applied from
2 an antenna on the catheter

ABSTRACT OF THE DISCLOSURE

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.

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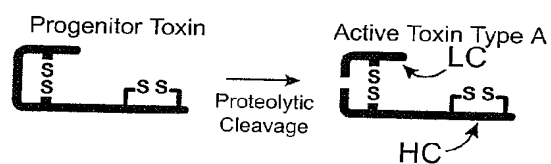


FIG. 1

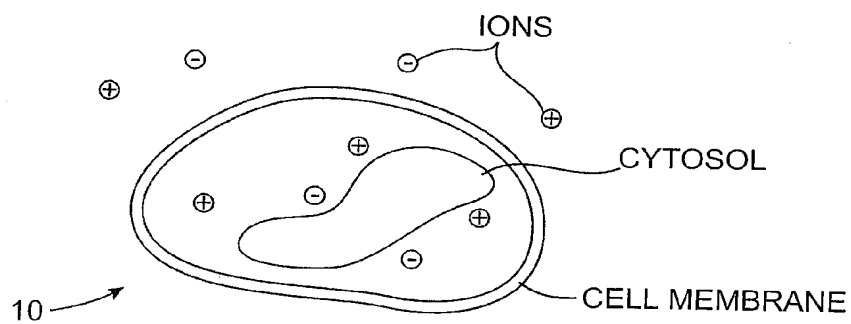


FIG. 2A

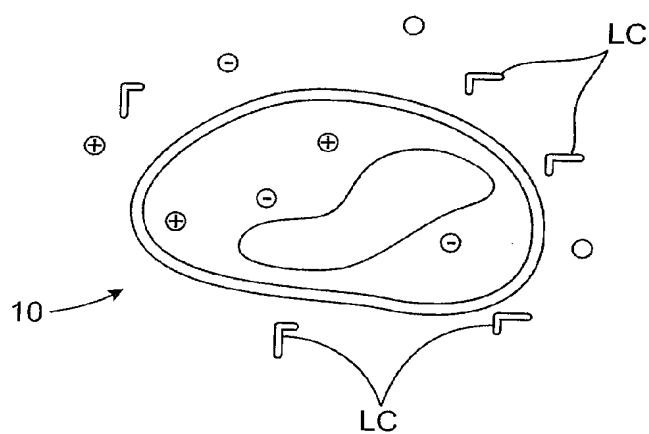


FIG. 2B

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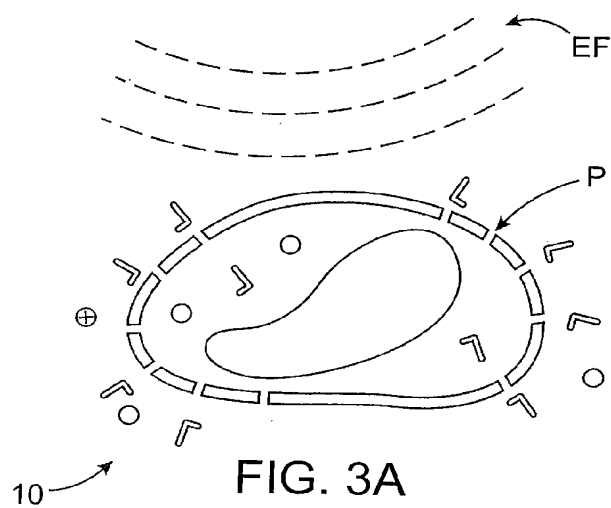


FIG. 3A

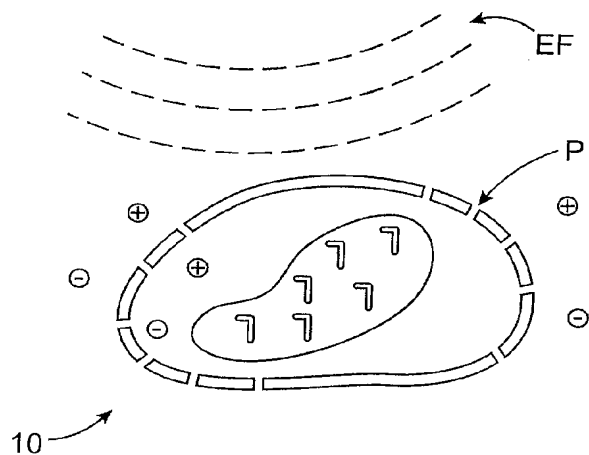


FIG. 3B

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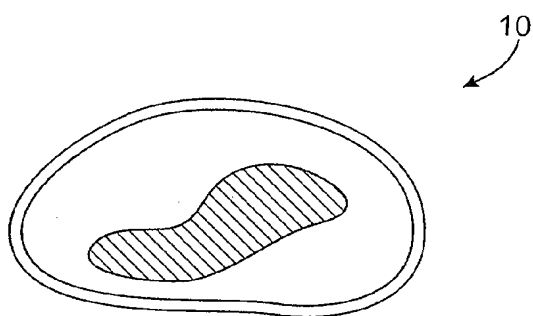


FIG. 4

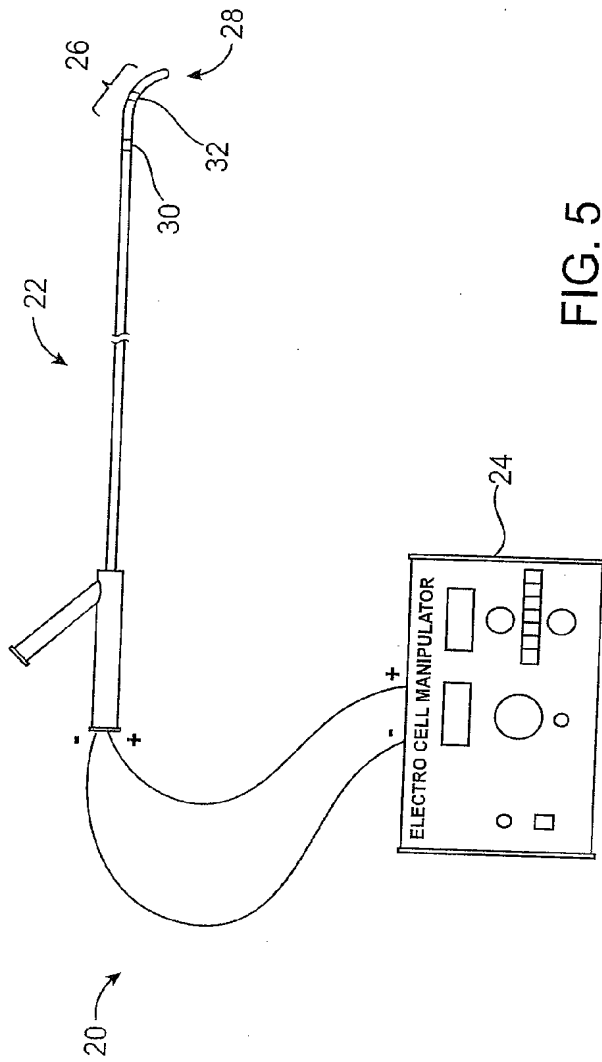


FIG. 5

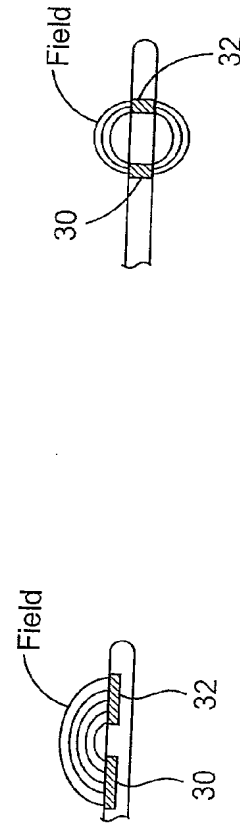


FIG. 5A

FIG. 5B

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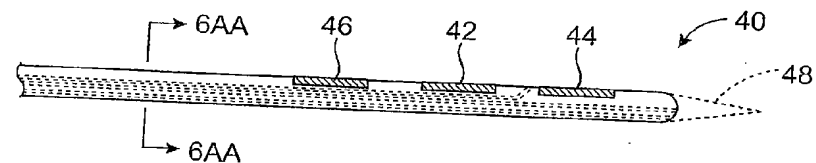


FIG. 6A



FIG. 6AA

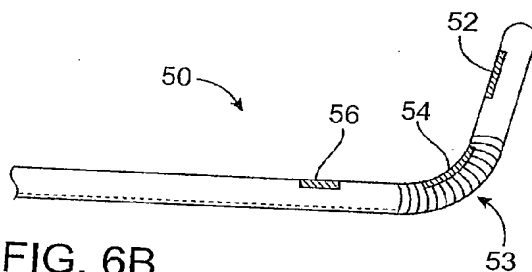


FIG. 6B

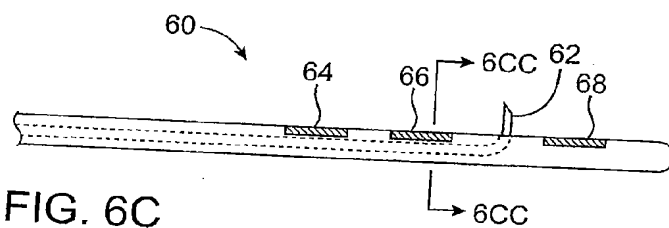


FIG. 6C



FIG. 6CC

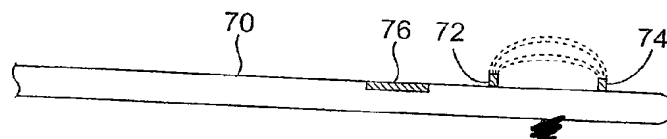


FIG. 6D

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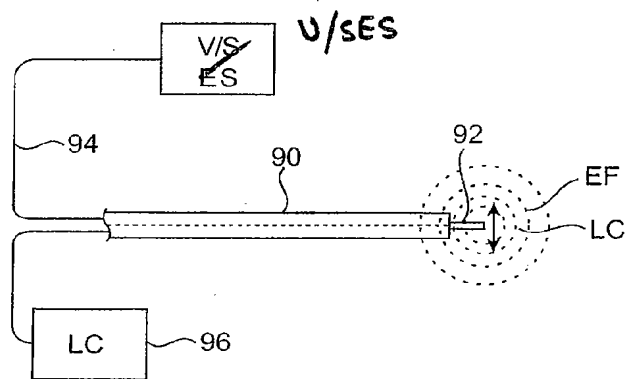
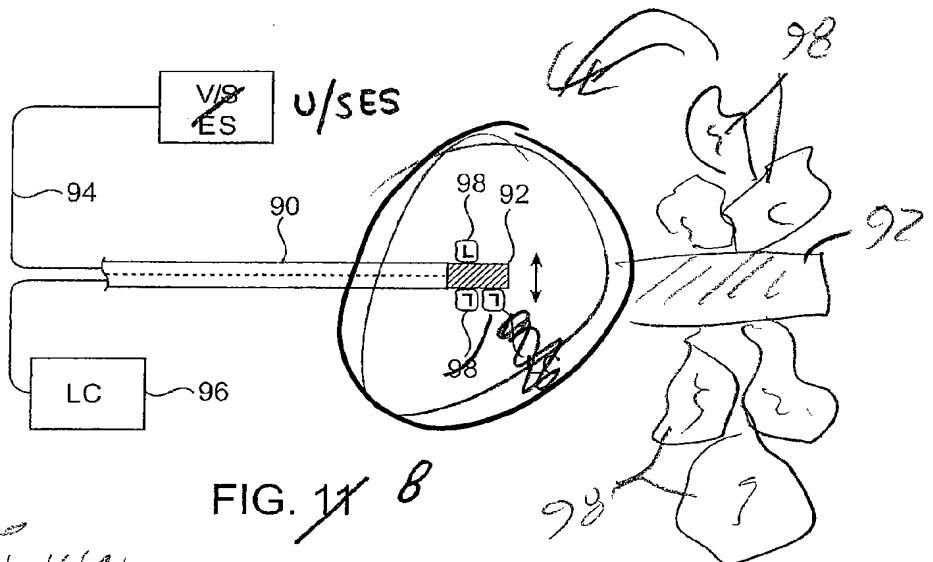


FIG. 8 7



98 refers to
small most bubbles
being released from
the catheter

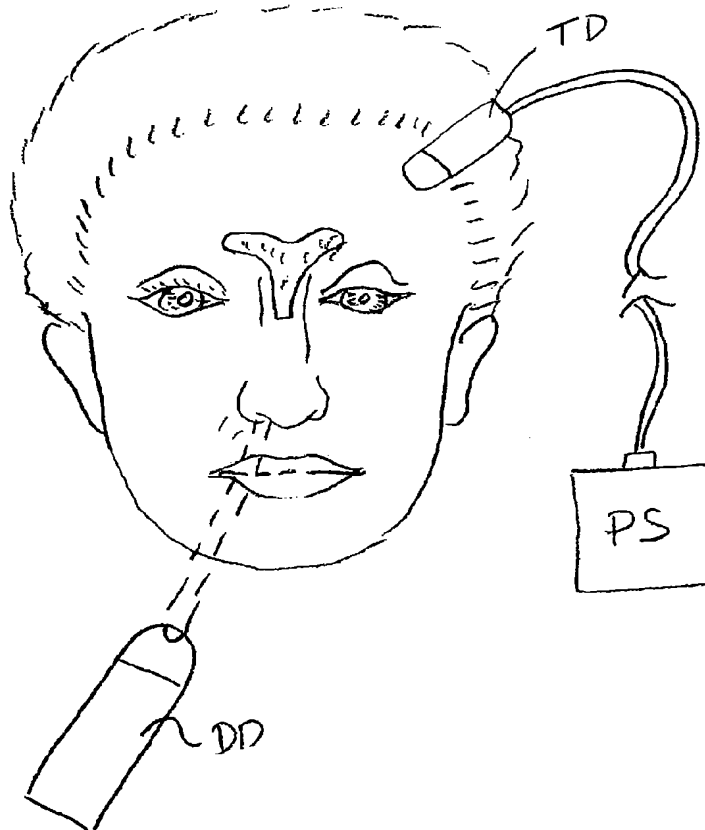
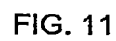
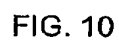
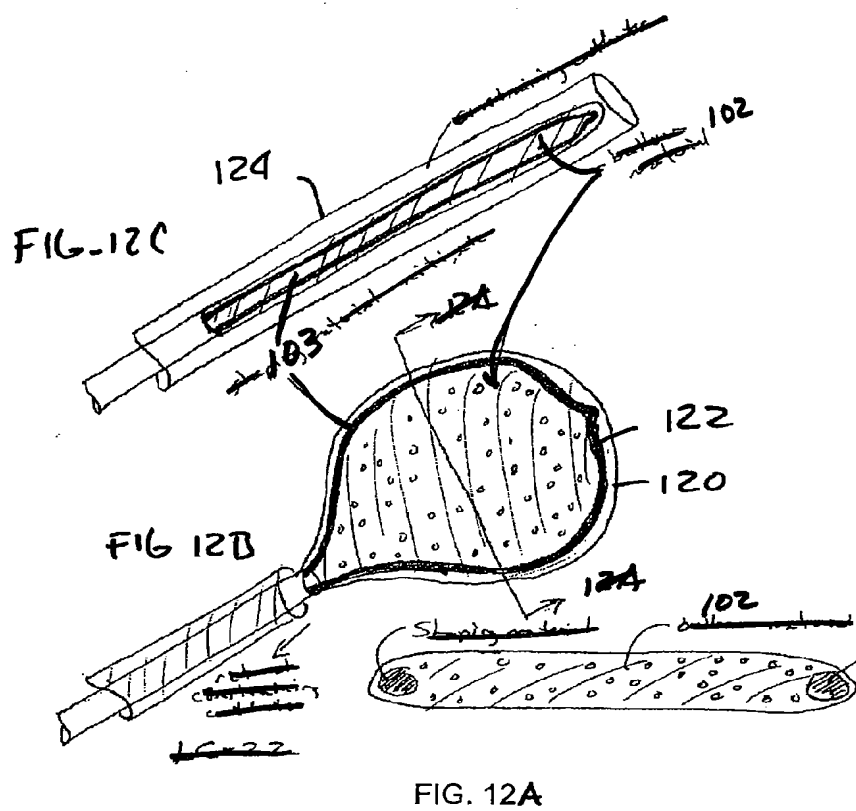


FIG-9





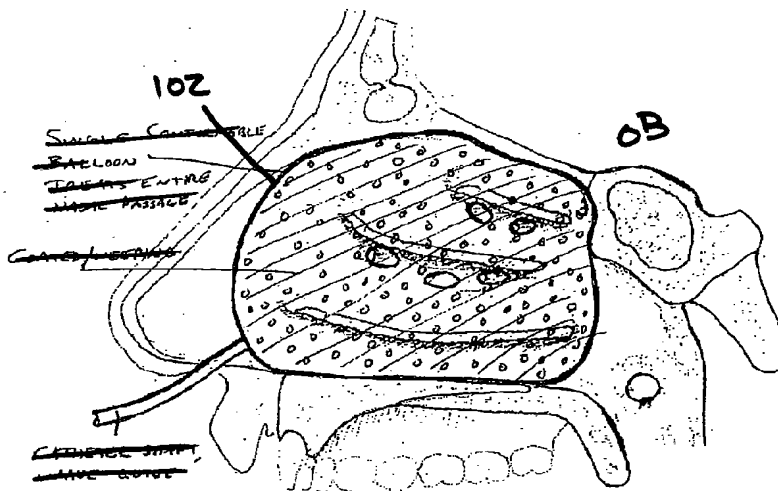


FIG. 13

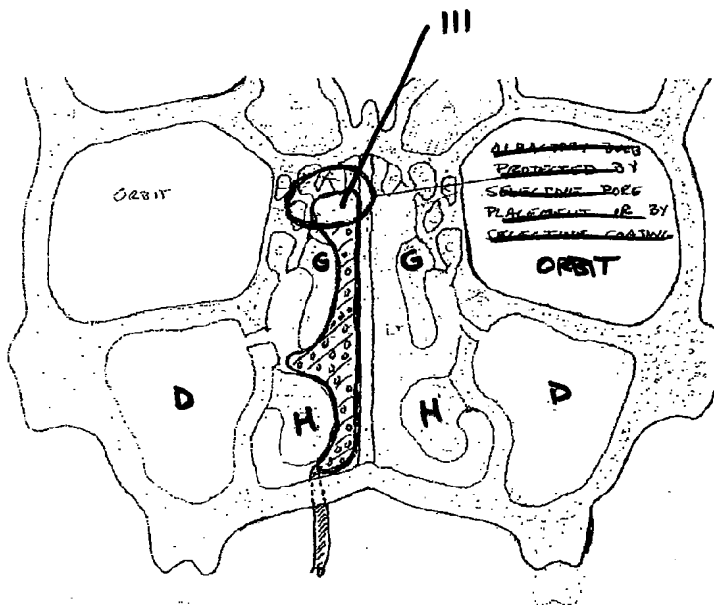


FIG. 14

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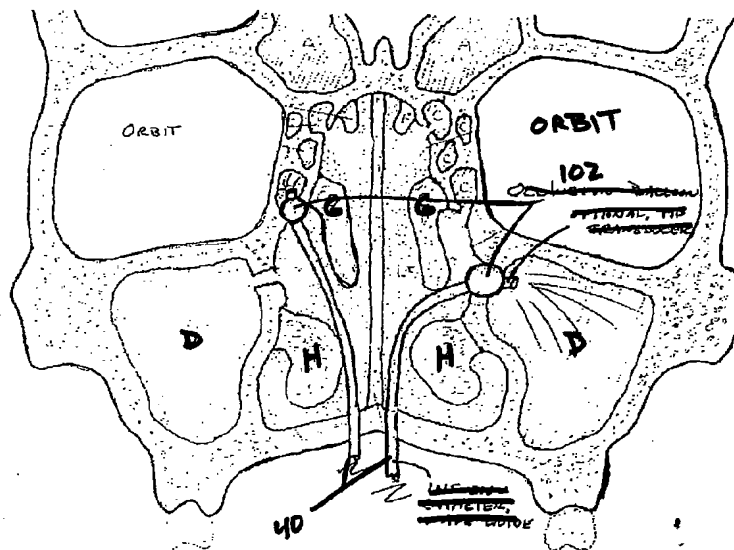


FIG. 17

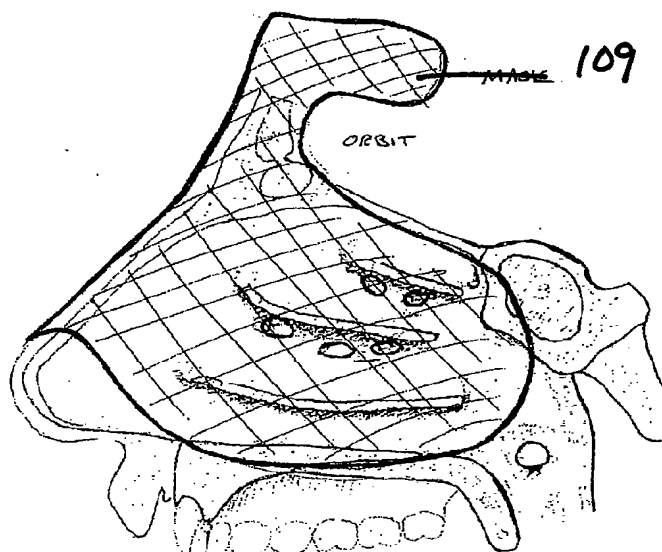


FIG. 18



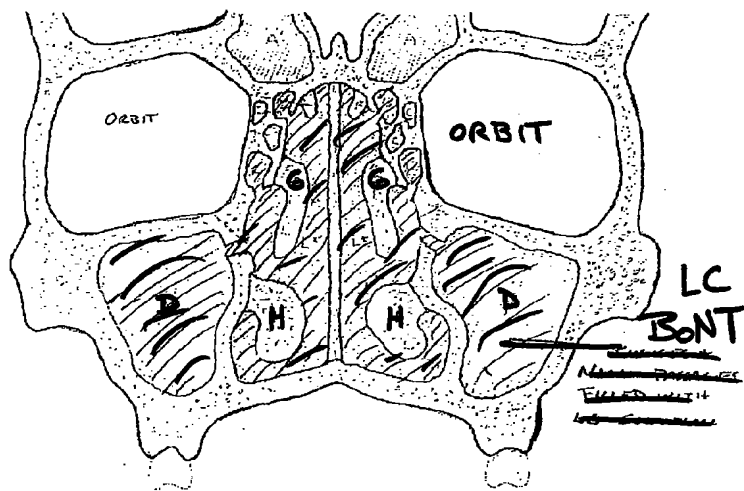


FIG. 21

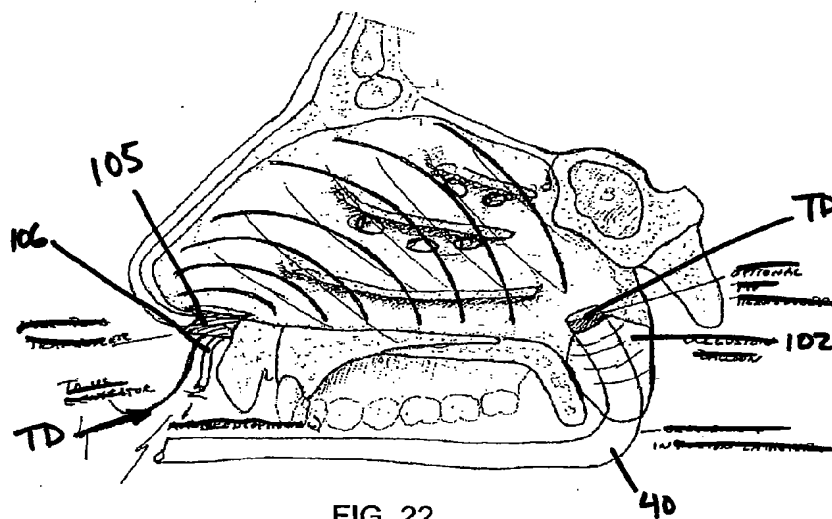


FIG. 22

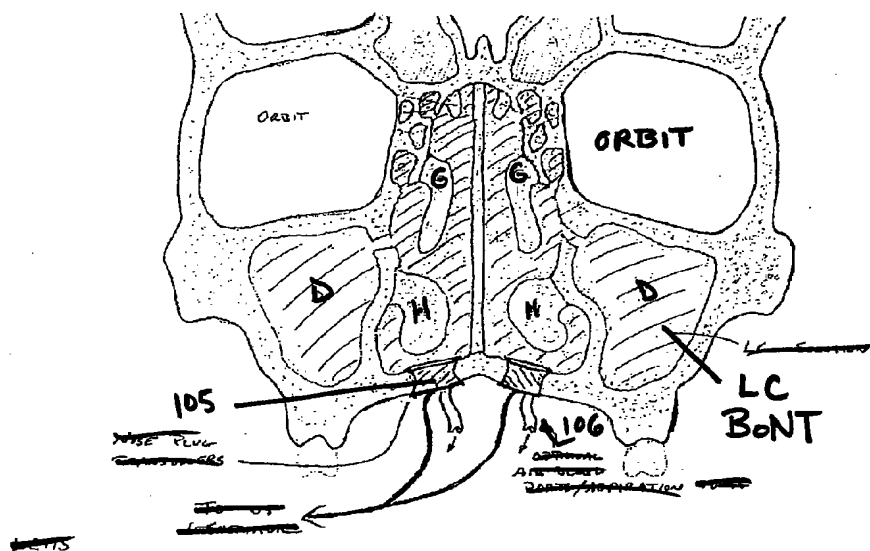


FIG. 23

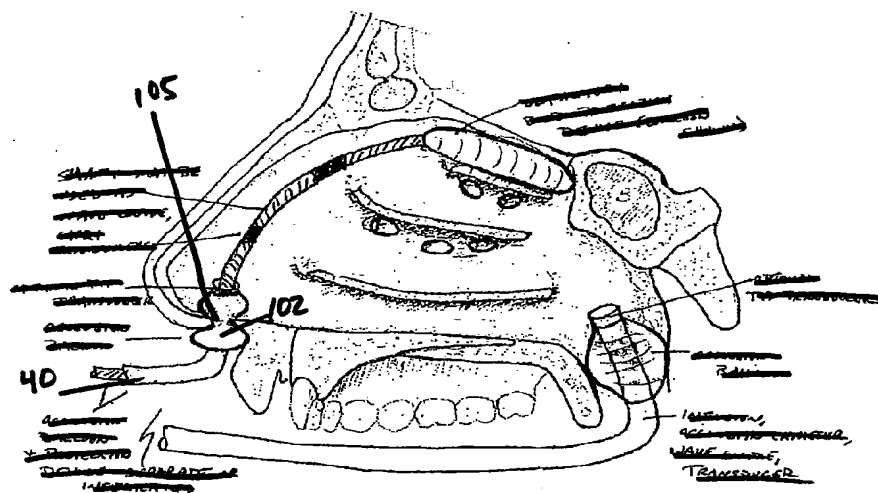


FIG. 24

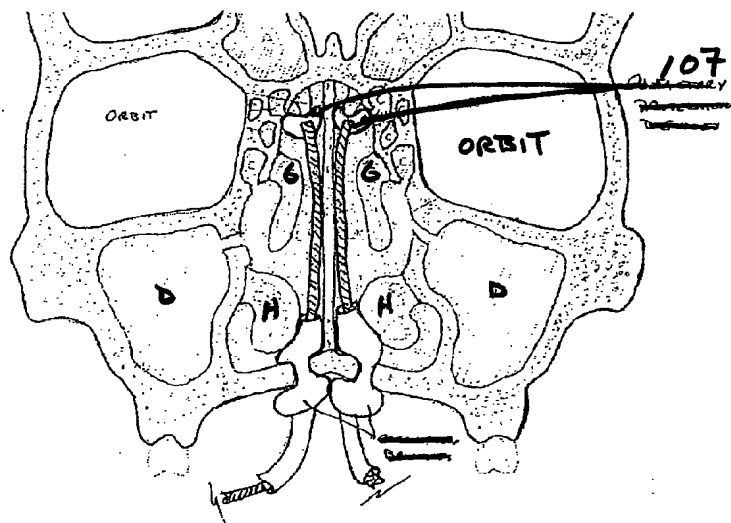


FIG. 25

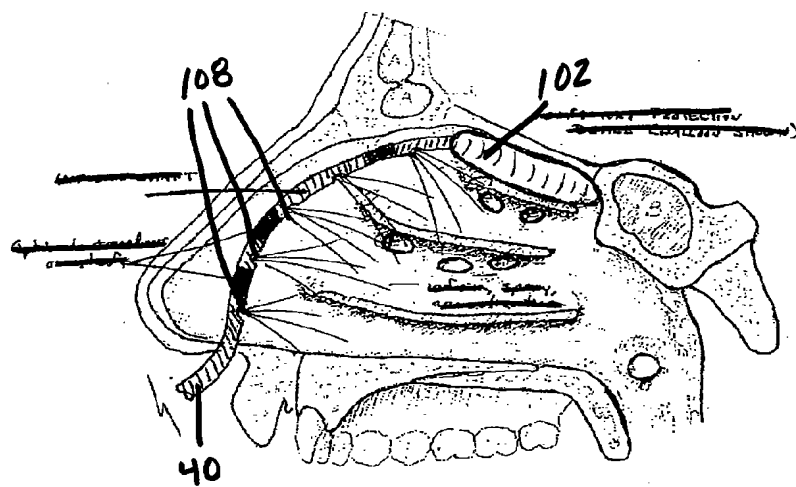


FIG. 26

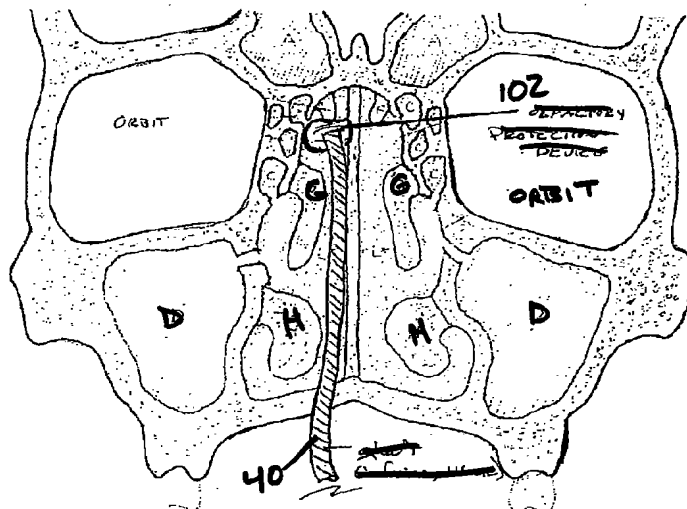


FIG. 27

FIG. 27

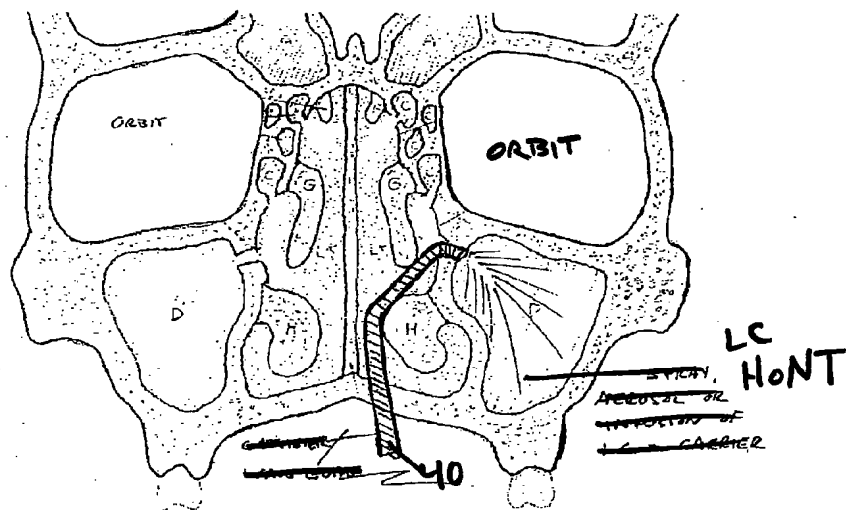


FIG. 28

FIG. 28

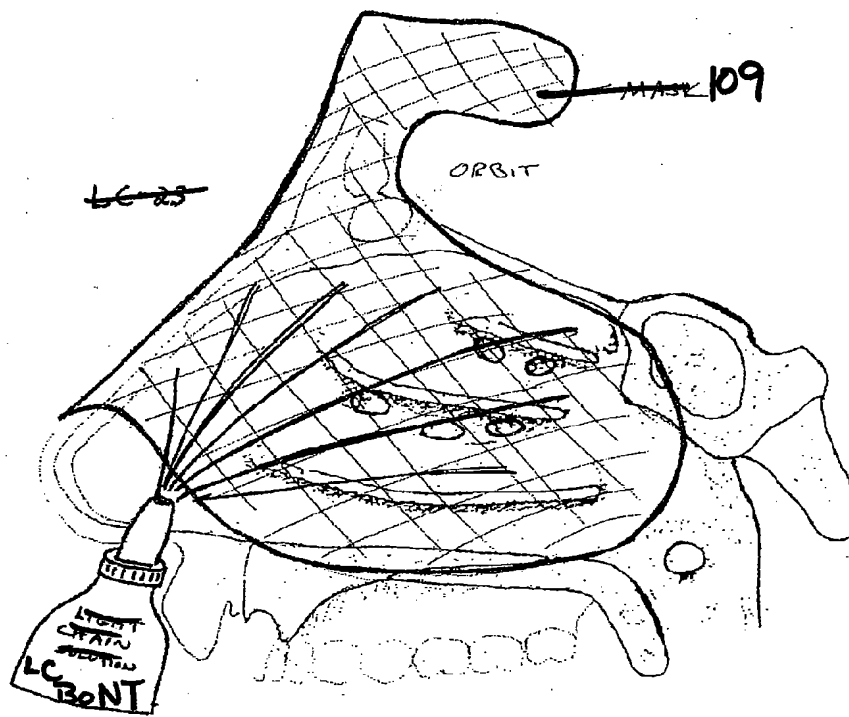


FIG. 29

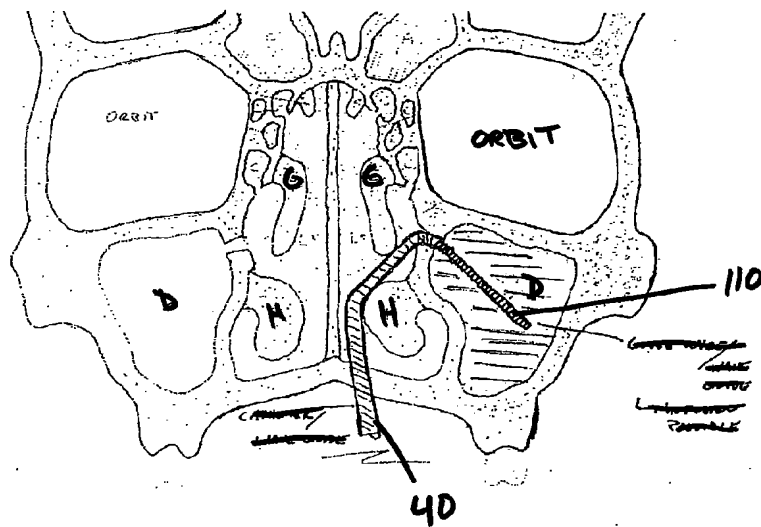


FIG. 30

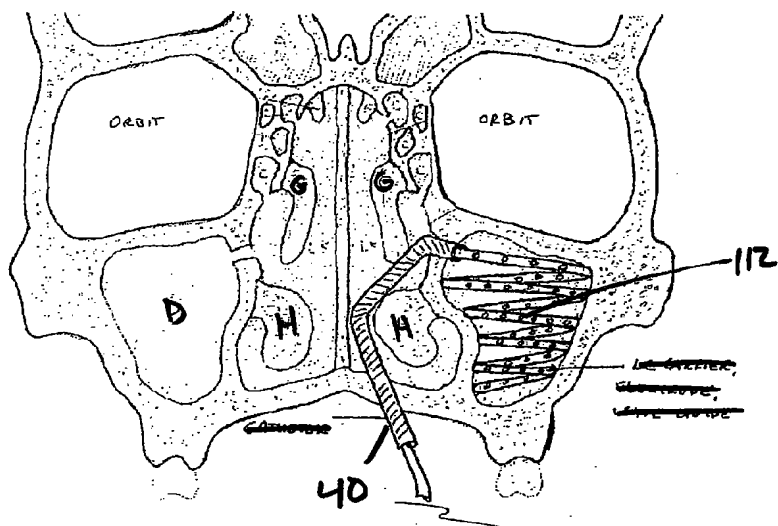


FIG. 31

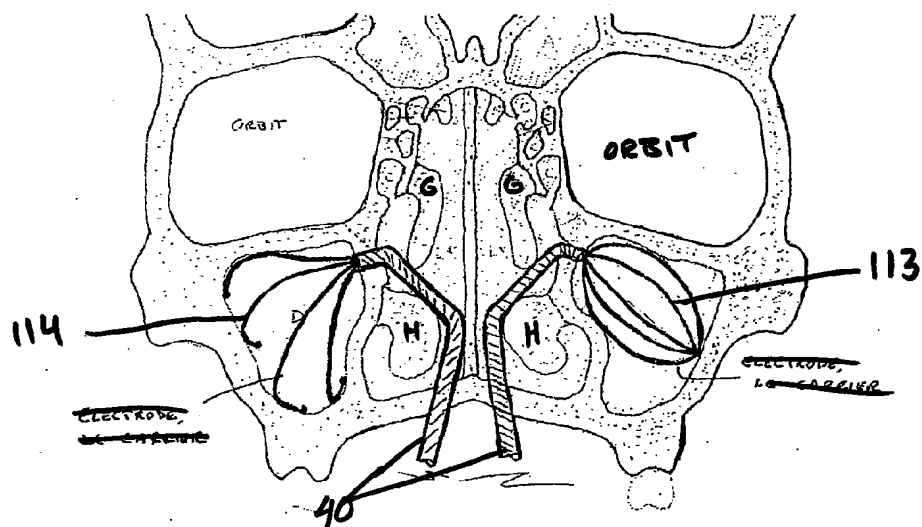
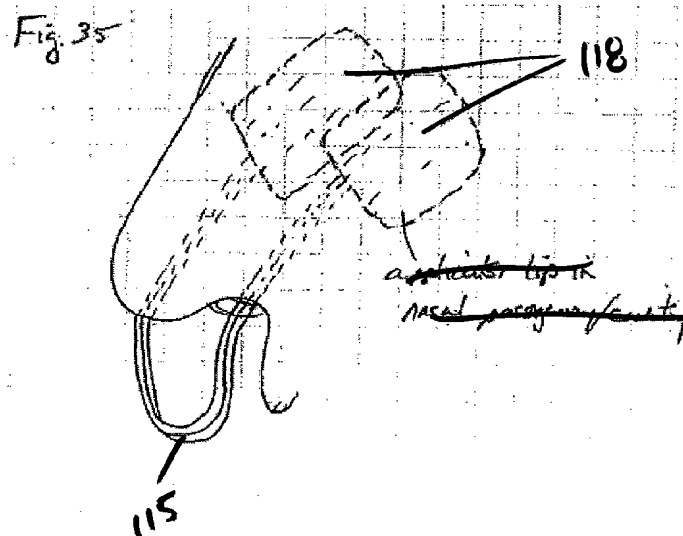
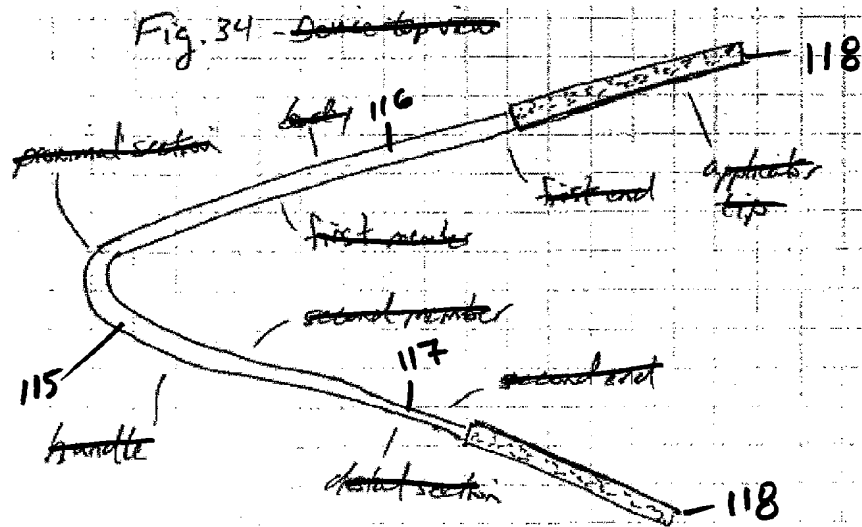
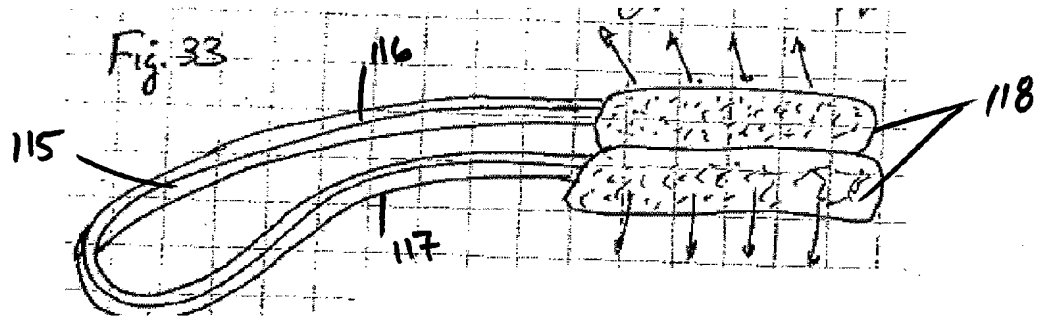
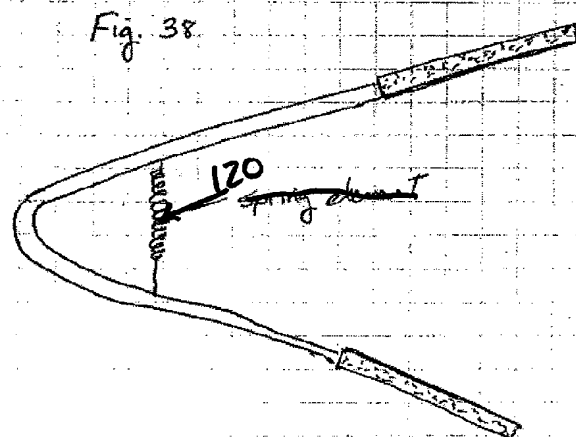
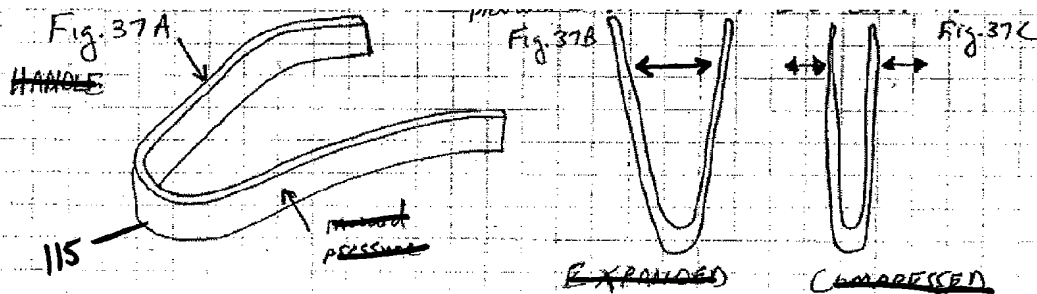
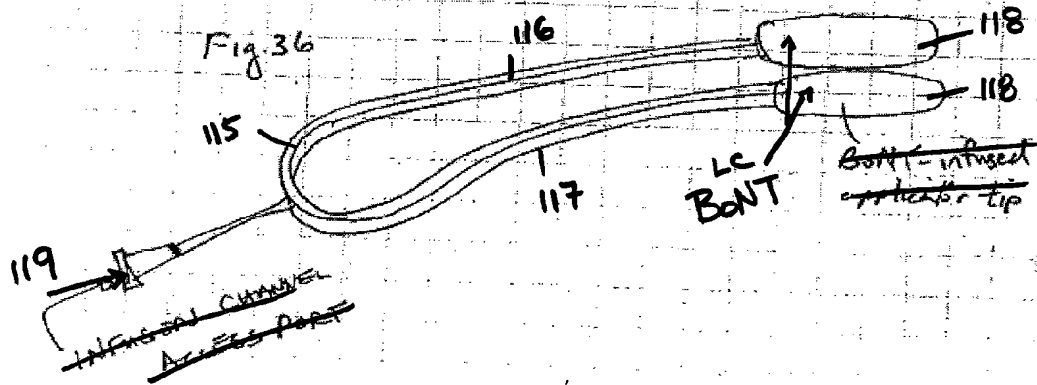
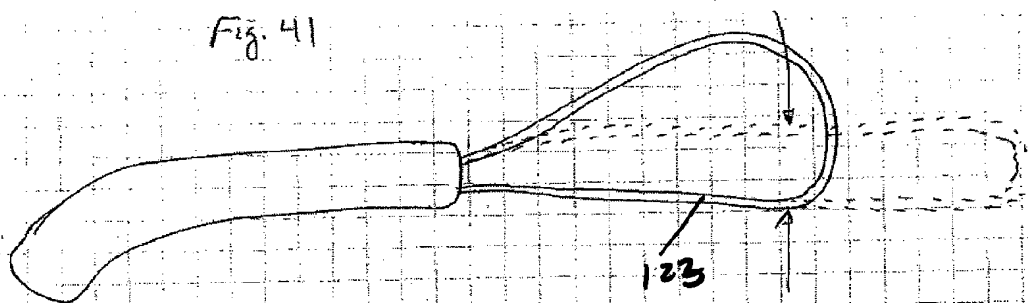
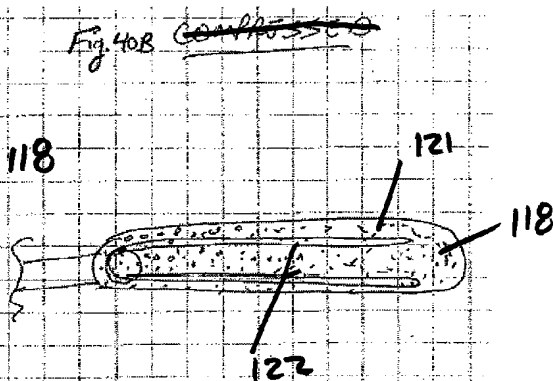
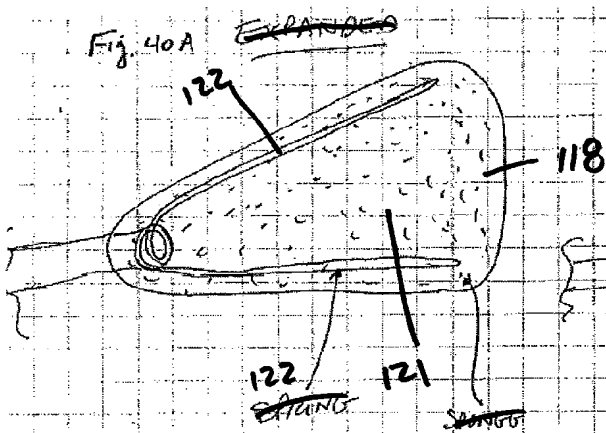
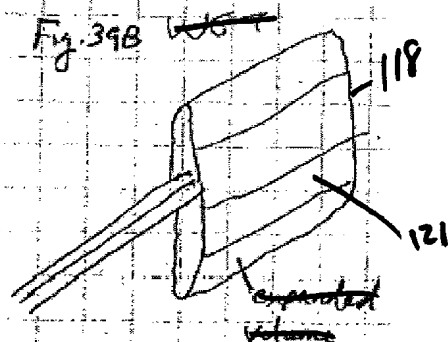
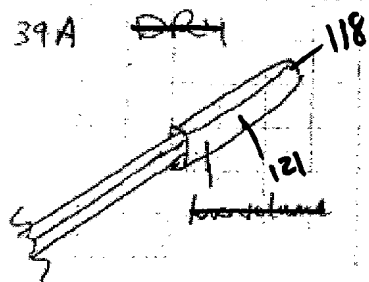
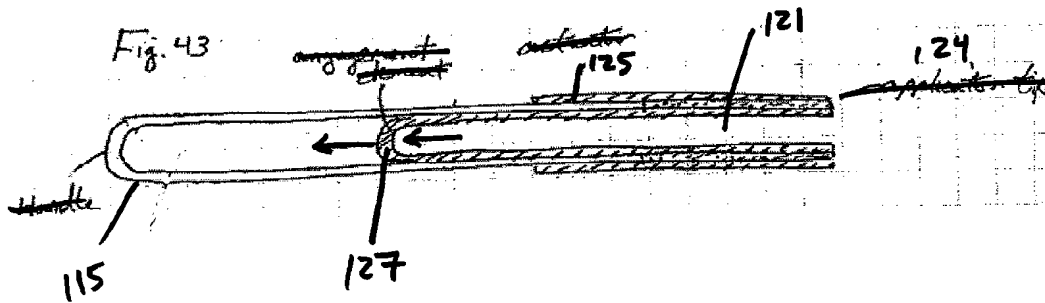
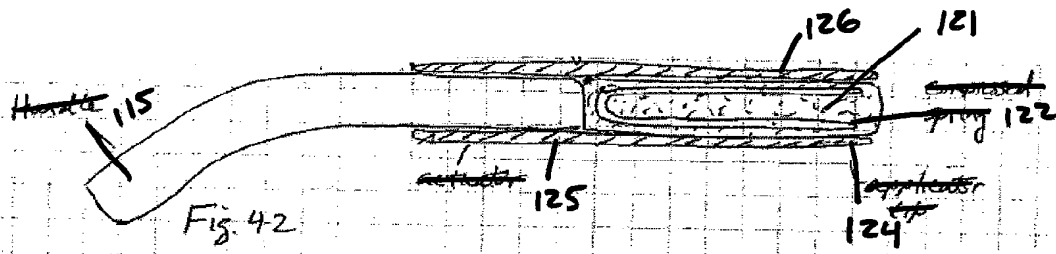


FIG. 32









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/JoAnn Evangelista			
Attorney Docket Number:	020979-003710US			
Filed as Small Entity				
Utility Filing Fees				
Description	Fee Code	Quantity	Amount	Sub-Total in USD(\$)
Basic Filing:				
Utility filing Fee (Electronic filing)	4011	1	75	75
Utility Search Fee	2111	1	250	250
Utility Examination Fee	2311	1	100	100
Pages:				
Claims:				
Claims in excess of 20	2202	49	25	1225
Miscellaneous-Filing:				
Petition:				

Description	Fee Code	Quantity	Amount	Sub-Total in USD(\$)
Patent-Appeals-and-Interference:				
Post-Allowance-and-Post-Issuance:				
Extension-of-Time:				
Miscellaneous:				
Total in USD (\$)				1650

Electronic Acknowledgement Receipt

EFS ID:	1792088
Application Number:	11750963
International Application Number:	
Confirmation Number:	1089
Title of Invention:	METHODS AND SYSTEMS FOR TOXIN DELIVERY TO THE NASAL CAVITY
First Named Inventor/Applicant Name:	Mark E. Deem
Customer Number:	20350
Filer:	James Mitchell Heslin/JoAnn Evangelista
Filer Authorized By:	James Mitchell Heslin
Attorney Docket Number:	020979-003710US
Receipt Date:	18-MAY-2007
Filing Date:	
Time Stamp:	20:13:44
Application Type:	Utility

Payment information:

Submitted with Payment	yes
Payment was successfully received in RAM	\$ 1650
RAM confirmation Number	1348
Deposit Account	201430
The Director of the USPTO is hereby authorized to charge indicated fees and credit any overpayment as follows: Charge any Additional Fees required under 37 C.F.R. Section 1.16 and 1.17	

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)	Multi Part /.zip	Pages (if appl.)
1	Application Data Sheet	ads.pdf	65823	no	3
Warnings:					
Information:					
This is not an USPTO supplied ADS fillable form					
2		CIPpatapp.pdf	217362	yes	38
	Multipart Description/PDF files in .zip description				
	Document Description		Start	End	
	Specification		1	31	
	Claims		32	37	
	Abstract		38	38	
Warnings:					
Information:					
3	Drawings	drawings3710.pdf	578868	no	24
Warnings:					
Information:					
4	Fee Worksheet (PTO-06)	fee-info.pdf	8528	no	2
Warnings:					
Information:					
Total Files Size (in bytes):			870581		

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

New Applications Under 35 U.S.C. 111

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

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

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

New International Application Filed with the USPTO as a Receiving Office

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

Electronic Acknowledgement Receipt

EFS ID:	1792088
Application Number:	11750963
International Application Number:	
Confirmation Number:	1089
Title of Invention:	METHODS AND SYSTEMS FOR TOXIN DELIVERY TO THE NASAL CAVITY
First Named Inventor/Applicant Name:	Mark E. Deem
Customer Number:	20350
Filer:	James Mitchell Heslin/JoAnn Evangelista
Filer Authorized By:	James Mitchell Heslin
Attorney Docket Number:	020979-003710US
Receipt Date:	18-MAY-2007
Filing Date:	
Time Stamp:	20:13:44
Application Type:	Utility

Payment information:

Submitted with Payment	yes
Payment was successfully received in RAM	\$ 1650
RAM confirmation Number	1348
Deposit Account	201430
The Director of the USPTO is hereby authorized to charge indicated fees and credit any overpayment as follows: Charge any Additional Fees required under 37 C.F.R. Section 1.16 and 1.17	

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)	Multi Part /.zip	Pages (if appl.)
1	Application Data Sheet	ads.pdf	65823	no	3
Warnings:					
Information:					
This is not an USPTO supplied ADS fillable form					
2		CIPpatapp.pdf	217362	yes	38
	Multipart Description/PDF files in .zip description				
	Document Description		Start	End	
	Specification		1	31	
	Claims		32	37	
	Abstract		38	38	
Warnings:					
Information:					
3	Drawings	drawings3710.pdf	578868	no	24
Warnings:					
Information:					
4	Fee Worksheet (PTO-06)	fee-info.pdf	8528	no	2
Warnings:					
Information:					
Total Files Size (in bytes):			870581		

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

New Applications Under 35 U.S.C. 111

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518107

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PATENT APPLICATION FEE DETERMINATION RECORD

Substitute for Form PTO-875

11/750,963**APPLICATION AS FILED – PART I**

(Column 1)

(Column 2)

SMALL ENTITY

OR

**OTHER THAN
SMALL ENTITY**

FOR	NUMBER FILED	NUMBER EXTRA
BASIC FEE (37 CFR 1.16(a), (b), or (c))		
SEARCH FEE (37 CFR 1.16(k), (l), or (m))		
EXAMINATION FEE (37 CFR 1.16(o), (p), or (q))		
TOTAL CLAIMS (37 CFR 1.16(j))	69 minus 20 =	* 49
INDEPENDENT CLAIMS (37 CFR 1.16(h))	2 minus 3 =	*
APPLICATION SIZE FEE (37 CFR 1.16(s))	If the specification and drawings exceed 100 sheets of paper, the application size fee due is \$250 (\$125 for small entity) for each additional 50 sheets or fraction thereof. See 35 U.S.C. 41(a)(1)(G) and 37 CFR	
MULTIPLE DEPENDENT CLAIM PRESENT (37 CFR 1.16(j))		

RATE (\$)	FEE (\$)
	75
	250
	100
X\$ 25=	1225
X\$100=	
N/A	
TOTAL	1650

RATE (\$)	FEE (\$)
X\$50=	
X\$200=	
N/A	
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
Total (37 CFR 1.16(i))	*	Minus **	=
Independent (37 CFR 1.16(h))	*	Minus ***	=
Application Size Fee (37 CFR 1.16(s))			
FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))			

RATE (\$)	ADDITIONAL FEE (\$)
X =	
X =	
N/A	
TOTAL ADD'T FEE	

RATE (\$)	ADDITIONAL FEE (\$)
X =	
X =	
N/A	
TOTAL ADD'T FEE	

(Column 1)

(Column 2)

(Column 3)

AMENDMENT B	CLAIMS REMAINING AFTER AMENDMENT	HIGHEST NUMBER PREVIOUSLY PAID FOR	PRESENT EXTRA
Total (37 CFR 1.16(i))	*	Minus **	=
Independent (37 CFR 1.16(h))	*	Minus ***	=
Application Size Fee (37 CFR 1.16(s))			
FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))			

RATE (\$)	ADDITIONAL FEE (\$)
X =	
X =	
N/A	
TOTAL ADD'T FEE	

OR

RATE (\$)	ADDITIONAL FEE (\$)
X =	
X =	
N/A	
TOTAL ADD'T 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.

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.

I hereby certify that this correspondence is being filed via
EFS-Web with the United States Patent and Trademark Office
on June 4, 2007.

PATENT
Attorney Docket No.: 020979-003710US

TOWNSEND and TOWNSEND and CREW LLP

By: *JoAnn Evangelista*
JoAnn Evangelista

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of:

MARK E. DEEM et al.

Application No.: 11/750,963

Filed: May 18, 2007

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

Customer No.: 20350

Confirmation No. 1089

Examiner: Unassigned

Technology Center/Art Unit: Unassigned

PRELIMINARY AMENDMENT

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

Sir:

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

Amendments to the Specification begin on page 2 of this paper.

Remarks/Arguments begin on page 3 of this paper.

Amendments to the Specification:

Please delete the paragraphs [0057] through [0062] from the BRIEF DESCRIPTION OF THE DRAWINGS as follows:

~~[0057]—Figure 44—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.~~

~~[0058]—Figure 45—depicts an embodiment of the present invention utilizing an inhaler with an in vivo energy delivery source.~~

~~[0059]—Figure 46—depicts an interstitial method of use of the present invention.~~

~~[0060]—Figure 47—depicts a fully implantable pulse generator, lead and agent delivery pump of the present invention.~~

~~[0061]—Figure 48—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.~~

~~[0062]—Figure 49—depicts an embodiment of the present invention wherein the energy and therapeutic agent are delivered transdermally.~~

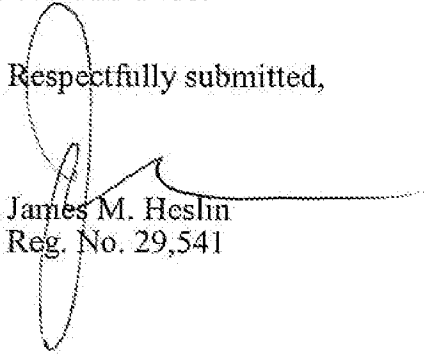
REMARKS/ARGUMENTS

Figures 44-49 were erroneously added to the Brief Description of the Drawings in the Specification. Figures 44-49 were not included in the Drawings on the initial filing date of May 18, 2007. Applicants have deleted the description Figures 44-49 to correct the inconsistency. No new matter has been added.

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.

If the Examiner believes a telephone conference would expedite prosecution of this application, please telephone the undersigned at 650-326-2400.

Respectfully submitted,


James M. Heslin
Reg. No. 29,541

TOWNSEND and TOWNSEND and CREW LLP
Two Embarcadero Center, Eighth Floor
San Francisco, California 94111-3834
Tel: 650-326-2400
Fax: 415-576-0300
Attachments
JMH:jke
61067178 v1

Electronic Acknowledgement Receipt

EFS ID:	1837406
Application Number:	11750963
International Application Number:	
Confirmation Number:	1089
Title of Invention:	METHODS AND SYSTEMS FOR TOXIN DELIVERY TO THE NASAL CAVITY
First Named Inventor/Applicant Name:	Mark E. Deem
Customer Number:	20350
Filer:	James Mitchell Heslin/JoAnn Evangelista
Filer Authorized By:	James Mitchell Heslin
Attorney Docket Number:	020979-003710US
Receipt Date:	04-JUN-2007
Filing Date:	
Time Stamp:	18:18:08
Application Type:	Utility

Payment information:

Submitted with Payment	no
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File Listing:

Document Number	Document Description	File Name	File Size(Bytes)	Multi Part /.zip	Pages (if appl.)
1		prelimamend.pdf	345530	yes	3

Multipart Description/PDF files in .zip description			
Document Description	Start	End	
Preliminary Amendment	1	1	
Specification	2	2	
Applicant Arguments/Remarks Made in an Amendment	3	3	

Warnings:

Information:

Total Files Size (in bytes):	345530
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New Applications Under 35 U.S.C. 111
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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.

PATENT APPLICATION FEE DETERMINATION RECORD Substitute for Form PTO-875					Application or Docket Number 11/750,963		Filing Date 05/18/2007		☐ To be Mailed	
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	75	N/A					
☒ SEARCH FEE (37 CFR 1.16(k), (l), or (m))	N/A	N/A	N/A	250	N/A					
☒ EXAMINATION FEE (37 CFR 1.16(o), (p), or (q))	N/A	N/A	N/A	100	N/A					
TOTAL CLAIMS (37 CFR 1.16(i))	69 minus 20 =	* 49	X \$25 =	1225	OR	X \$ =				
INDEPENDENT CLAIMS (37 CFR 1.16(h))	2 minus 3 =	* 0	X \$100 =	0	OR	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 \$250 (\$125 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	1650	TOTAL					
APPLICATION AS AMENDED – PART II										
(Column 1)			(Column 2)		SMALL ENTITY OR			OTHER THAN SMALL ENTITY		
AMENDMENT	06/04/2007	CLAIMS REMAINING AFTER AMENDMENT	HIGHEST NUMBER PREVIOUSLY PAID FOR	PRESENT EXTRA	RATE (\$)	ADDITIONAL FEE (\$)	RATE (\$)	ADDITIONAL FEE (\$)		
Total (37 CFR 1.16(i))	* 69	Minus	** 69	= 0	X \$25 =	0	OR	X \$ =		
Independent (37 CFR 1.16(h))	* 2	Minus	*** 3	= 0	X \$100 =	0	OR	X \$ =		
☐ Application Size Fee (37 CFR 1.16(s))										
☐ FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))							OR			
					TOTAL ADD'L FEE	0	OR	TOTAL ADD'L FEE		
(Column 1)			(Column 2)		SMALL ENTITY OR			OTHER THAN SMALL ENTITY		
AMENDMENT		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))										
☐ 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 number found in the appropriate box in column 1.										

Legal Instrument Examiner:
Marcus Monroe

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.



UNITED STATES PATENT AND TRADEMARK OFFICE

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

APPLICATION NUMBER	FILING or 371(c) DATE	GRP ART UNIT	FIL FEE REC'D	ATTY. DOCKET NO	TOT CLAIMS	IND CLAIMS
11/750,963	05/18/2007	1645	1650	020979-003710US	69	2

CONFIRMATION NO. 1089

20350
TOWNSEND AND TOWNSEND AND CREW, LLP
TWO EMBARCADERO CENTER
EIGHTH FLOOR
SAN FRANCISCO, CA 94111-3834

FILING RECEIPT

Date Mailed: 06/22/2007

Receipt is acknowledged of this regular Patent Application. It will be considered in its order and you will be notified as to the results of the examination. Be sure to provide the U.S. APPLICATION NUMBER, FILING DATE, NAME OF APPLICANT, and TITLE OF INVENTION when inquiring about this application. 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 mail to the Commissioner for Patents P.O. Box 1450 Alexandria Va 22313-1450. 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 (if appropriate).**

Applicant(s)

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

Assignment For Published Patent Application

The Foundry Inc., Menlo Park, CA

Power of Attorney: None

Domestic Priority data as claimed by applicant

This application is a CIP of 11/459,090 07/21/2006
which claims benefit of 60/747,771 05/19/2006
and claims benefit of 60/702,077 07/22/2005

Foreign Applications

If Required, Foreign Filing License Granted: 06/22/2007

The country code and number of your priority application, to be used for filing abroad under the Paris Convention, is
US11/750,963

Projected Publication Date: To Be Determined - pending completion of Missing Parts

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).

LICENSE FOR FOREIGN FILING UNDER**Title 35, United States Code, Section 184****Title 37, Code of Federal Regulations, 5.11 & 5.15****GRANTED**

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

This license is to be retained by the licensee and may be used at any time on or after the effective date thereof unless it is revoked. This license is automatically transferred to any related applications(s) filed under

37 CFR 1.53(d). This license is not retroactive.

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

NOT GRANTED

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UNITED STATES PATENT AND TRADEMARK OFFICE

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

APPLICATION NUMBER	FILING OR 371 (c) DATE	FIRST NAMED APPLICANT	ATTORNEY DOCKET NUMBER
11/750,963	05/18/2007	Mark E. Deem	020979-003710US

CONFIRMATION NO. 1089

FORMALITIES
 LETTER

20350
 TOWNSEND AND TOWNSEND AND CREW, LLP
 TWO EMBARCADERO CENTER
 EIGHTH FLOOR
 SAN FRANCISCO, CA 94111-3834

Date Mailed: 06/22/2007

NOTICE TO FILE MISSING PARTS OF NONPROVISIONAL APPLICATION

FILED UNDER 37 CFR 1.53(b)

*Filing Date Granted*Items Required To Avoid Abandonment:

An application number and filing date have been accorded to this application. The item(s) indicated below, however, are missing. Applicant is given **TWO MONTHS** from the date of this Notice within which to file all required items and pay any fees required below to avoid abandonment. Extensions of time may be obtained by filing a petition accompanied by the extension fee under the provisions of 37 CFR 1.136(a).

- The oath or declaration is missing. *A properly signed oath or declaration in compliance with 37 CFR 1.63, identifying the application by the above Application Number and Filing Date, is required.*
Note: If a petition under 37 CFR 1.47 is being filed, an oath or declaration in compliance with 37 CFR 1.63 signed by all available joint inventors, or if no inventor is available by a party with sufficient proprietary interest, is required.

The application is informal since it does not comply with the regulations for the reason(s) indicated below.

The required item(s) identified below must be timely submitted to avoid abandonment:

- Replacement drawings in compliance with 37 CFR 1.84 and 37 CFR 1.121(d) are required. The drawings submitted are not acceptable because:
 - The drawings must be reasonably free from erasures and must be free from alterations, overwriting, interlineations, folds, and copy marks. See Figure(s) 7,8,10-12c,13-43.
 - The drawings submitted to the Office are not electronically reproducible. Drawing sheets must be submitted on paper, which is flexible, strong, white, smooth, non-shiny, and durable (see 37 CFR 1.84(e)). See Figure(s) 10-12c,13-43.

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

The applicant needs to satisfy supplemental fees problems indicated below.

The required item(s) identified below must be timely submitted to avoid abandonment:

- To avoid abandonment, a surcharge (for late submission of filing fee, search fee, examination fee or oath or declaration) as set forth in 37 CFR 1.16(f) of \$65 for a small entity in compliance with 37 CFR 1.27, must be submitted with the missing items identified in this letter.

SUMMARY OF FEES DUE:

Total additional fee(s) required for this application is **\$65** for a small entity

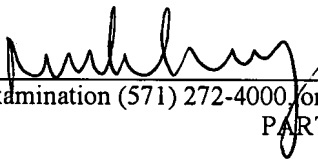
- **\$65 Surcharge.**

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Commissioner for Patents
P.O. Box 1450
Alexandria VA 22313-1450

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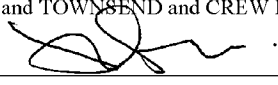


Office of Initial Patent Examination (571) 272-4000, or 1-800-PTO-9199
PART 3 - OFFICE COPY

I hereby certify that this correspondence is being filed via
EFS-Web with the United States Patent and Trademark Office
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PATENT
Attorney Docket No.: 020979-003710US

TOWNSEND and TOWNSEND and CREW LLP

By: 
Tiffany Wu

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of:

MARK E. DEEM et al.

Application No.: 11/750,963

Filed: May 18, 2007

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

Confirmation No.: 1089

Examiner: Unassigned

Art Unit: 1645

INFORMATION DISCLOSURE
STATEMENT UNDER 37 CFR §1.97 and
§1.98

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

Sir:

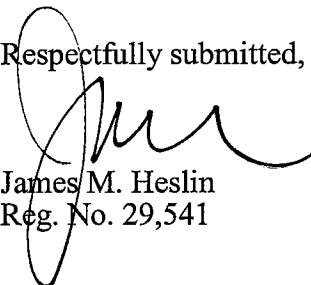
The references cited on attached form PTO/SB/08A and PTO/SB/08B are being called to the attention of the Examiner. In accordance with 37 CFR §1.98(d), copies of the references can be found in Application No. 11/459,090, filed July 21, 2006 (Attorney Docket No. 020979-003410US), except for Cite Nos. 57 and 62. Copies of Cite Nos. 57 and 62 are enclosed herewith.

It is respectfully requested that the cited references be expressly considered during the prosecution of this application, and the references be made of record therein and appear among the "references cited" on any patent to issue therefrom.

As provided for by 37 CFR §1.97(g) and (h), no inference should be made that the information and references cited are prior art merely because they are in this statement and no representation is being made that a search has been conducted or that this statement encompasses all the possible relevant information.

Applicant believes that no fee is required for submission of this statement. However, if a fee is required, the Commissioner is authorized to deduct such fee from the undersigned's Deposit Account No. 20-1430. Please deduct any additional fees from, or credit any overpayment to, the above-noted Deposit Account.

Respectfully submitted,



James M. Heslin
Reg. No. 29,541

TOWNSEND and TOWNSEND and CREW LLP
Two Embarcadero Center, Eighth Floor
San Francisco, California 94111-3834
Tel: 650-326-2400
Fax: 650-326-2422
JMH:tfw
61143664 v1

Substitute for form 1449A/PTO INFORMATION DISCLOSURE STATEMENT BY APPLICANT <i>(Use as many sheets as necessary)</i>			Complete if Known		
			Application Number	11/750,963	
			Filing Date	May 18, 2007	
			First Named Inventor	DEEM, MARK E.	
			Art Unit	1645	
			Examiner Name	Unassigned	
Sheet	1	of	4	Attorney Docket Number	020979-003710US

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	4,767,402	08-30-1988	Kost et al.	
	2	5,286,254	02-15-1994	Shapland et al.	
	3	5,766,605	06-16-1998	Sanders et al.	
	4	5,820,589	10-13-1998	Torgerson et al.	
	5	5,964,223	10-12-1999	Baran	
	6	6,063,768	05-16-2000	First	
	7	6,139,845	10-31-2000	Donovan	
	8	6,265,379	07-24-2001	Donovan	
	9	6,358,926	03-19-2002	Donovan	
	10	6,361,554	03-26-2002	Briskin	
	11	6,447,785	09-10-2002	Donovan	
	12	6,448,231	09-10-2002	Graham	
	13	6,464,680	10-15-2002	Briskin et al.	
	14	6,526,976	03-04-2003	Baran	
	15	6,601,581	08-05-2003	Babaev	
	16	6,620,415	09-16-2003	Donovan	
	17	6,623,742	09-23-2003	Voet	
	18	6,626,855	09-30-2003	Weng et al.	
	19	6,632,440	10-14-2003	Quinn et al.	
	20	6,645,496	11-11-2003	Aoki et al.	
	21	6,649,161	11-18-2003	Donovan	
	22	6,719,694	04-13-2004	Weng et al.	
	23	6,740,321	05-25-2004	Donovan	
	24	6,767,544	07-27-2004	Brooks et al.	
	25	6,773,711	08-10-2004	Voet et al.	
	26	6,776,991	08-17-2004	Naumann	
	27	6,827,931	12-07-2004	Donovan	
	28	6,838,434	01-04-2005	Voet	
	29	6,841,156	01-11-2005	Aoki et al.	
	30	6,843,998	01-18-2005	Steward et al.	
	31	6,847,849	01-25-2005	Mamo et al.	
	32	6,861,058	03-01-2005	Aoki et al.	
	33	6,872,397	03-29-2005	Aoki et al.	
	34	6,974,578	12-13-2005	Aoki et al.	
	35	2001/0044596	11-22-2001	Jaafar	

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				Application Number	11/750,963
				Filing Date	May 18, 2007
				First Named Inventor	DEEM, MARK E.
				Art Unit	1645
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Sheet	2	of	4	Attorney Docket Number	020979-003710US

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)			
	36	2002/0198512	12-26-2002	Seward	
	37	2003/0050591	03-13-2003	McHale	
	38	2003/0202990	10-30-2003	Donovan et al.	
	39	2003/0211121	11-13-2003	Donovan	
	40	2004/0009180	01-15-2004	Donovan	
	41	2004/0010290	01-15-2004	Schroeppel et al.	
	42	2004/0091880	05-13-2004	Wiebusch et al.	
	43	2004/0142005	07-22-2004	Brooks et al.	
	44	2004/0151741	08-05-2004	Borodic	
	45	2004/0175399	09-09-2004	Schiffman	
	46	2004/0213813	10-28-2004	Ackerman	
	47	2004/0213814	10-28-2004	Ackerman	
	48	2004/0226556	11-18-2004	Deem et al.	
	49	2004/0253274	12-16-2004	Voet	
	50	2005/0019346	01-27-2005	Boulis	
	51	2005/0074461	04-07-2005	Donovan	
	52	2007/0021803	01-25-2007	Deem et al.	

FOREIGN PATENT DOCUMENTS								
Examiner Initials*	Cite No. ¹	Foreign Patent Document			Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear	T ⁶
		Country Code ³	Number ⁴	Kind Code ⁵ (if known)				
	53	WO	2004/101028	A2	11-25-2004	The Foundry, Inc.		☐
								☐

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				Application Number	11/750,963
				Filing Date	May 18, 2007
				First Named Inventor	DEEM, MARK E.
				Art Unit	1645
				Examiner Name	Unassigned
Sheet	3	of	4	Attorney Docket Number	020979-003710US

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	
	54	AHNERT-HILGER et al., "Introduction of Macromolecules into Bovine Adrenal-Medullary Chromaffin Cells and Rat Pheochromocytoma Cells (PC12) by Permeabilization with Streptolysin-Oinhibitory Effect of Tetanus Toxin on Catecholamine Secretion," <i>J. Neurochem.</i> 1989 Jun; 52(6):1751-1758.	☐	
	55	BIGALKE et al., "Clostridial Toxins", <i>Handbook of Experimental Pharmacology</i> (Aktories, K., and Just, I., eds) 2000, 145:407-443, Springer Verlag, Berlin, Heidelberg	☐	
	56	BITTNER et al., "Isolated Light Chains of Botulinum Neurotoxins Inhibit Exocytosis. Studies in Digitonin-Permeabilized Chromaffin Cells." <i>J Biol Chem</i> 1989 Jun 25; 264(18):10354-10360	☐	
	57	BUZZI, "Diphtheria Toxin Treatment of Human Advanced Cancer," <i>Cancer Research</i> , 1982, 42:2054-2058.	☐	
	58	CHADDOCK et al "Expression and Purification of Catalytically Active, Non-Toxic Endopeptidase Derivatives of Clostridium Botulinum Toxin Type A," <i>Protein Expression and Purification</i> , July 2002, 25(2): 219-228	☐	
	59	CHANG, "Cell Poration and Cell Fusion Using an Oscillating Electric Field," <i>Biophys J.</i> 1989 October; 56(4): 641-652.	☐	
	60	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," <i>Ultrasound in Med. & Biol.</i> , 2003, 29(8): 1211-1222.	☐	
	61	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," <i>Naunyn Schmiedebergs Arch Pharmacol.</i> 1992 Feb; 345(2):227-34.	☐	
	62	KREITMAN, "Taming Ricin," <i>Nature Biotechnology</i> , 2003, 21:372-374.	☐	
	63	RAJ, Editorial, <i>Pain Practice</i> , 4(1S):S1-S3.	☐	

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¹ Applicant's unique citation designation number (optional). ² Applicant is to place a check mark here if English language Translation is attached.

Substitute for form 1449B/PTO INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Use as many sheets as necessary)				Complete if Known	
				Application Number	11/750,963
				Filing Date	May 18, 2007
				First Named Inventor	DEEM, MARK E.
				Art Unit	1645
				Examiner Name	Unassigned
Sheet	4	of	4	Attorney Docket Number	020979-003710US

NON PATENT LITERATURE DOCUMENTS			
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	64	SHAARI et al., "Rhinorrhea is Decreased in Dogs After Nasal Application of Botulinum Toxin," <i>Otolaryngol Head Neck Surg</i> 1995;112:566-571.	☐
	65	SIMPSON et al., "Isolation and Characterization of the Botulinum Neurotoxins," <i>Methods Enzymol.</i> 1988; 165:76-85.	☐
	66	UNAL et al, "Effect of Botulinum Toxin Type A on Nasal Symptoms in Patients with Allergic Rhinitis: A Double-blind, Placebo-controlled Clinical Trial," <i>Acta Oto-Laryngologica</i> , 2003 Dec, 123(9):1060-0163	☐
	67	WEAVER, "Electroporation: A General Phenomenon for Manipulating Cells and Tissues," <i>Cell Biochem.</i> 1993 Apr; 51(4):426-35.	☐

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*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

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Electronic Acknowledgement Receipt

EFS ID:	2178985
Application Number:	11750963
International Application Number:	
Confirmation Number:	1089
Title of Invention:	METHODS AND SYSTEMS FOR TOXIN DELIVERY TO THE NASAL CAVITY
First Named Inventor/Applicant Name:	Mark E. Deem
Customer Number:	20350
Filer:	James Mitchell Heslin/Tiffany Wu
Filer Authorized By:	James Mitchell Heslin
Attorney Docket Number:	020979-003710US
Receipt Date:	10-SEP-2007
Filing Date:	18-MAY-2007
Time Stamp:	18:57:40
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	Information Disclosure Statement (IDS) Filed	020979-003710US.pdf	252411 13ce07fadb715c1c9e459ee68d530b971657549e	no	6

Warnings:

Information:					
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2	NPL Documents	BUZZI.pdf	396494 fa5d60b28b8820afe1efc7f396d48ca5b03bec7c	no	5
Warnings:					
Information:					
3	NPL Documents	KREITMAN.pdf	346657 2838377dccc5c2057468394e089b4bceb96396	no	3
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Electronic Acknowledgement Receipt

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Application Number:	11750963
International Application Number:	
Confirmation Number:	1089
Title of Invention:	METHODS AND SYSTEMS FOR TOXIN DELIVERY TO THE NASAL CAVITY
First Named Inventor/Applicant Name:	Mark E. Deem
Customer Number:	20350
Filer:	James Mitchell Heslin/Tiffany Wu
Filer Authorized By:	James Mitchell Heslin
Attorney Docket Number:	020979-003710US
Receipt Date:	10-SEP-2007
Filing Date:	18-MAY-2007
Time Stamp:	19:32:17
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	no
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Warnings:

Information:					
2	NPL Documents	Unal.pdf	332108	no	4
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Warnings:					
Information:					
Total Files Size (in bytes):				893351	
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1 / 24

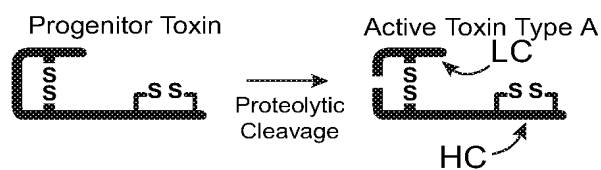


FIG. 1

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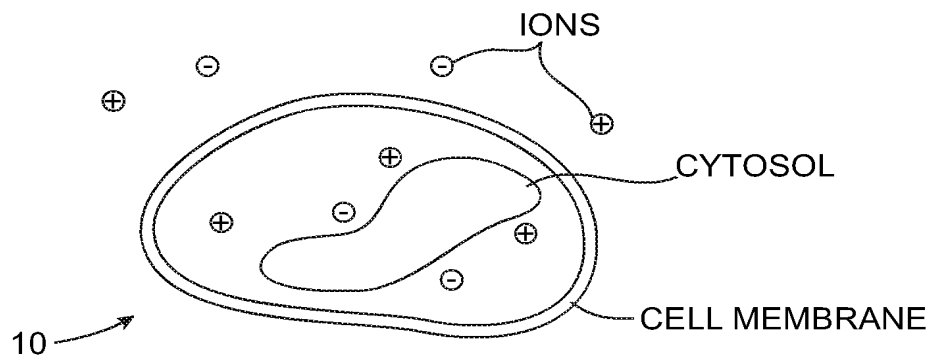


FIG. 2A

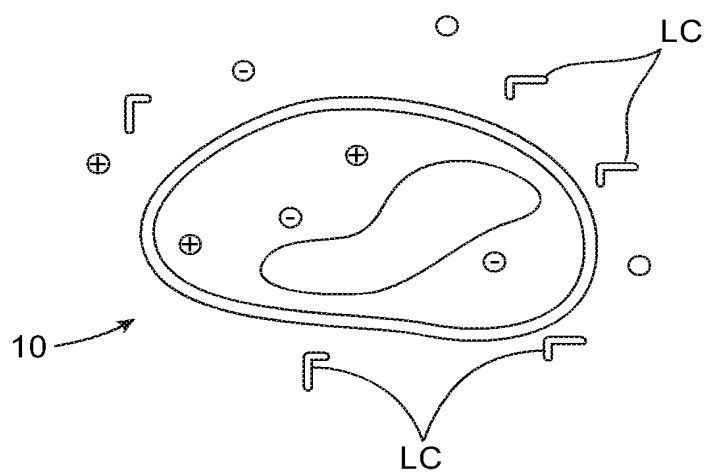
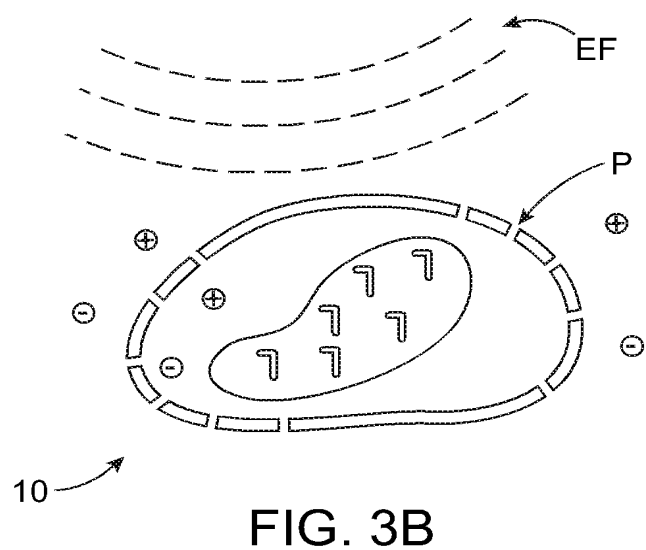
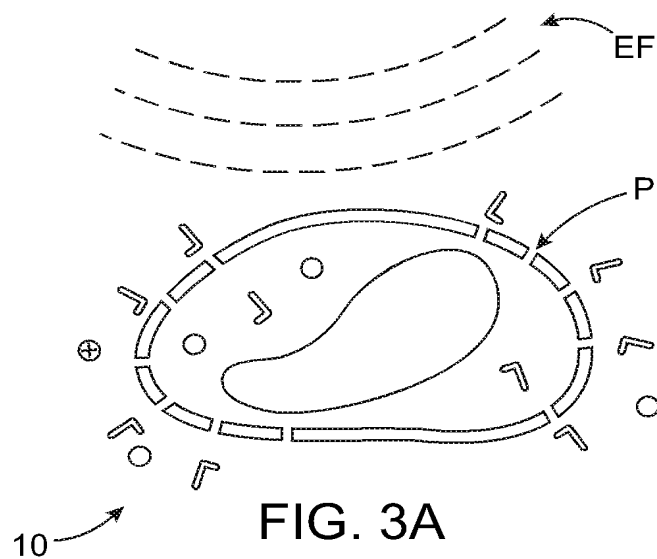


FIG. 2B

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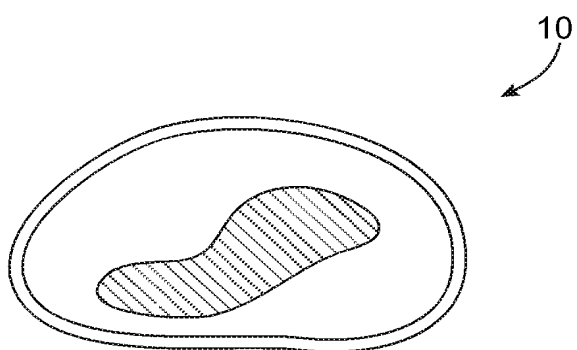


FIG. 4

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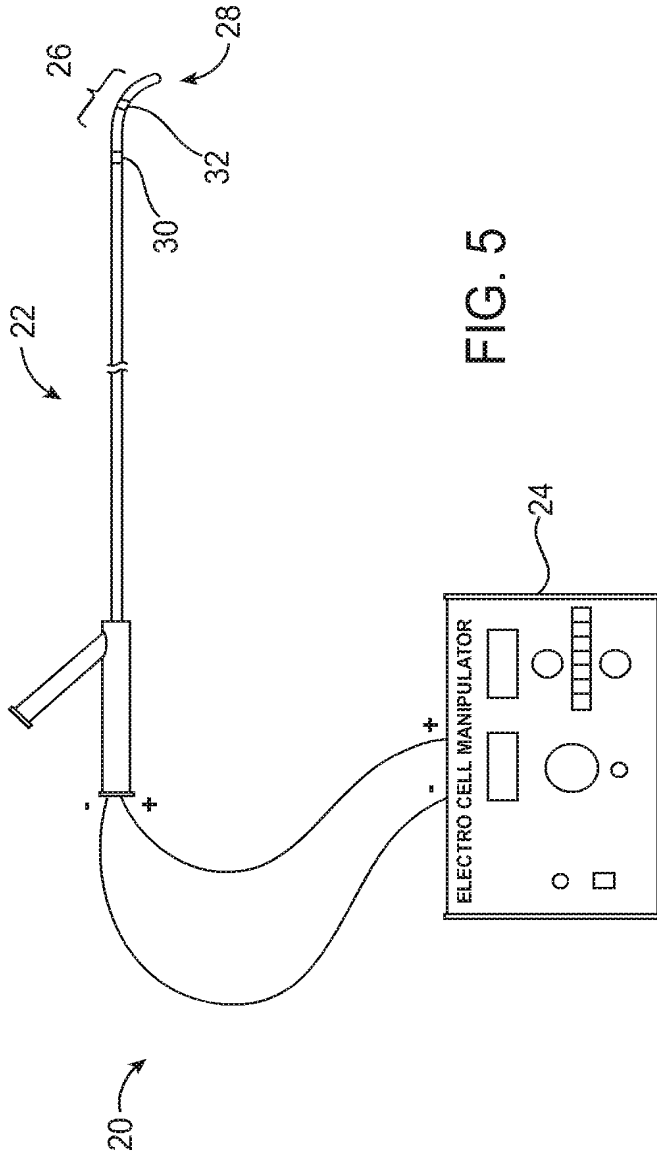


FIG. 5

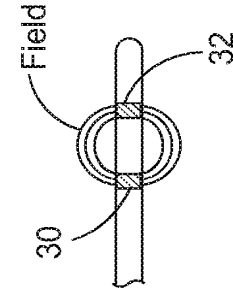


FIG. 5B

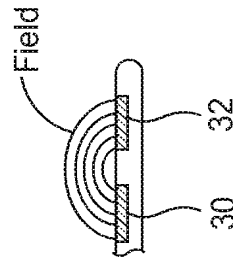


FIG. 5A

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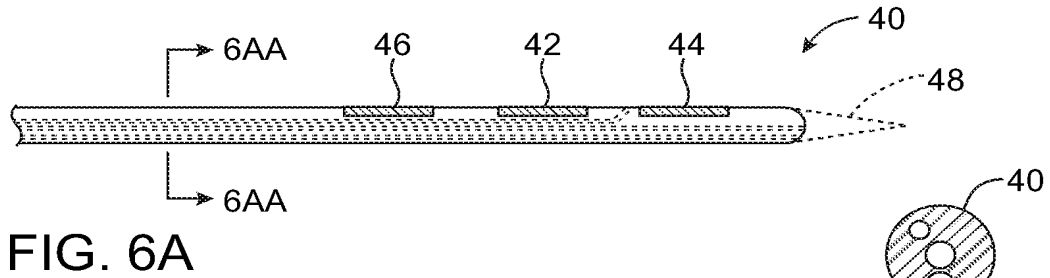


FIG. 6A

FIG. 6AA

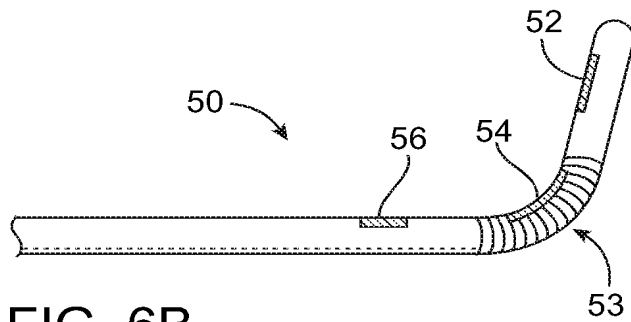


FIG. 6B

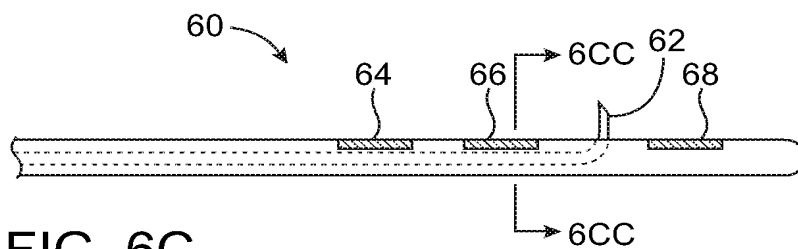


FIG. 6C

FIG. 6CC

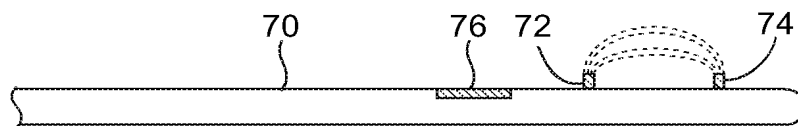


FIG. 6D

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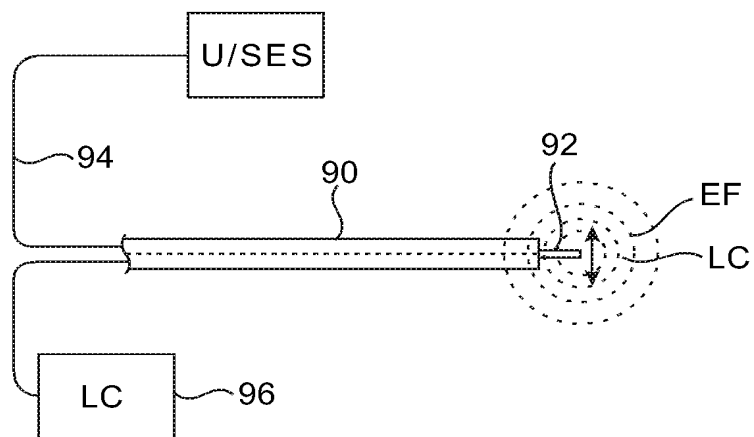


FIG. 7

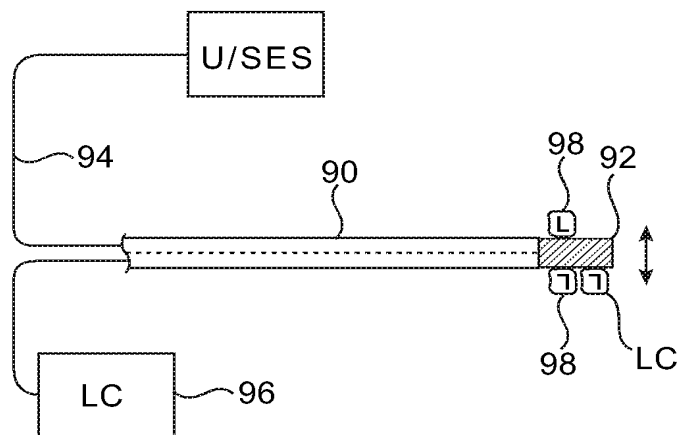


FIG. 8

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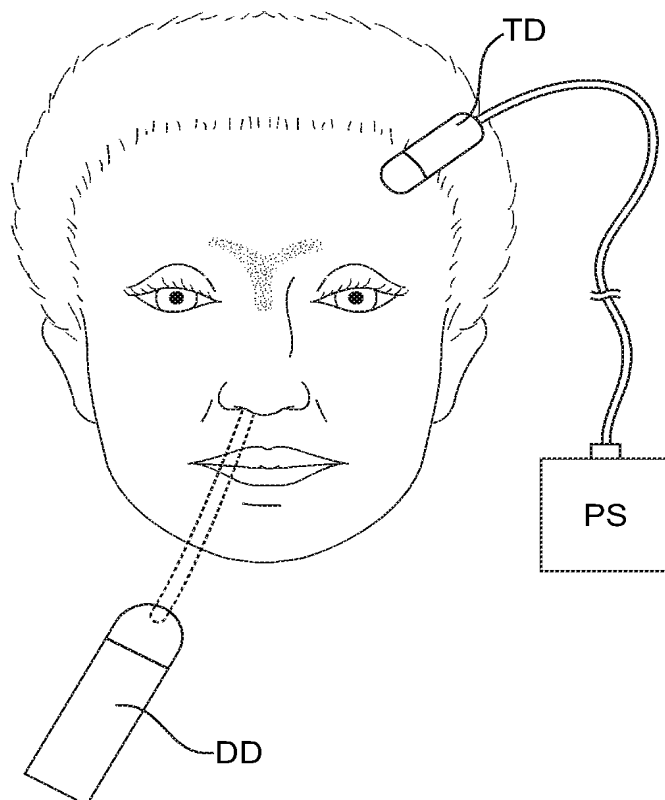


FIG. 9

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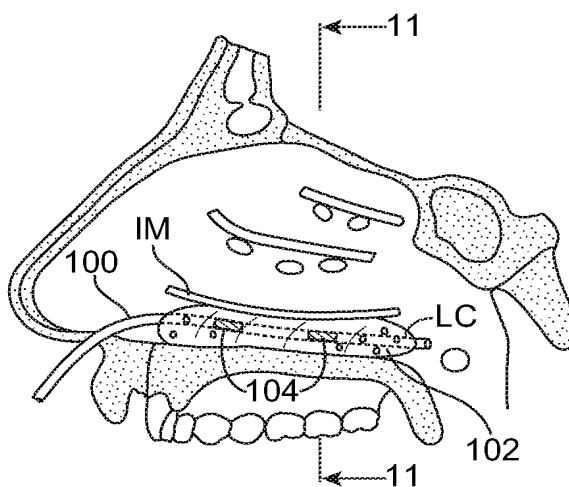


FIG. 10

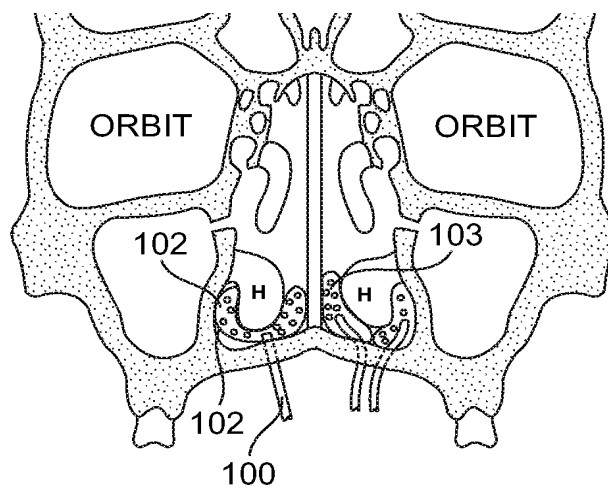


FIG. 11

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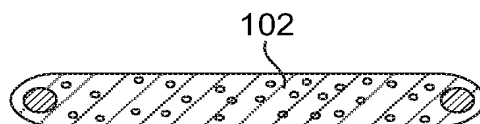


FIG. 12A

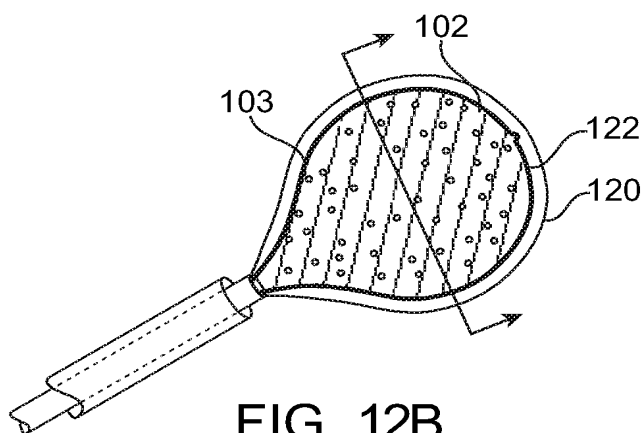


FIG. 12B

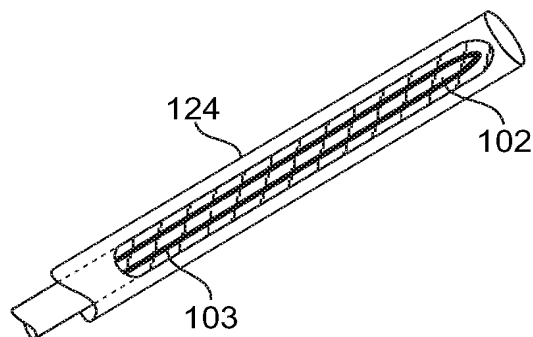


FIG. 12C

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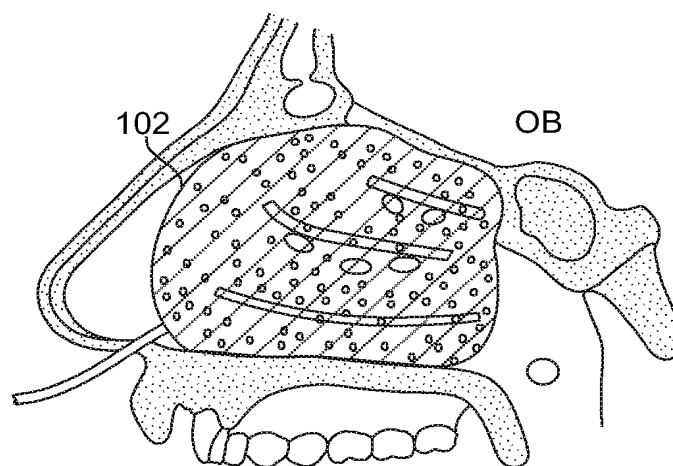


FIG. 13

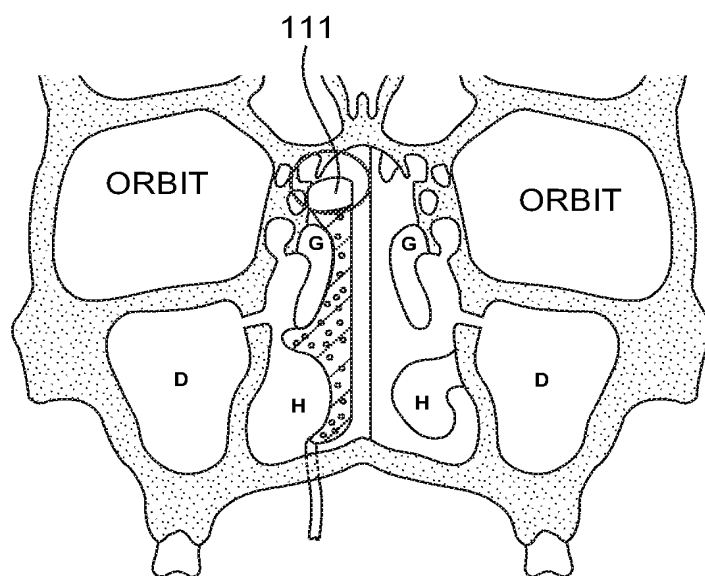


FIG. 14

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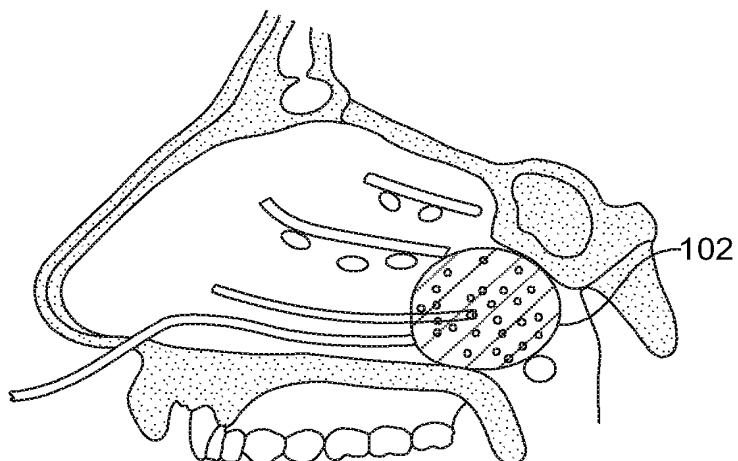


FIG. 15

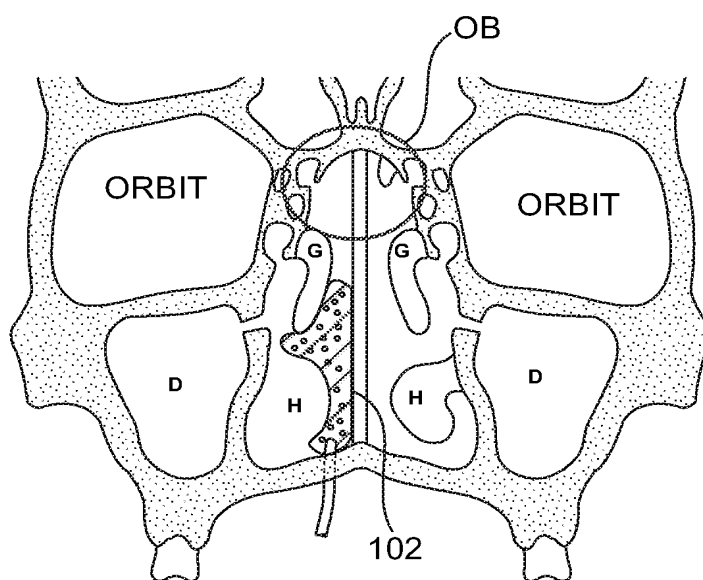


FIG. 16

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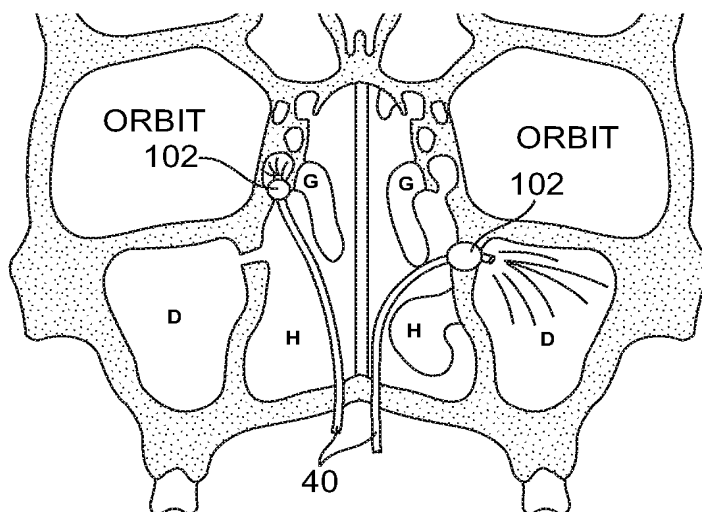


FIG. 17

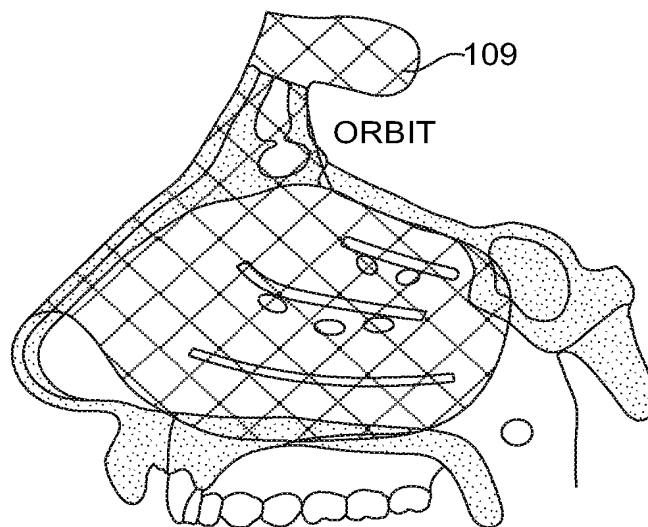


FIG. 18

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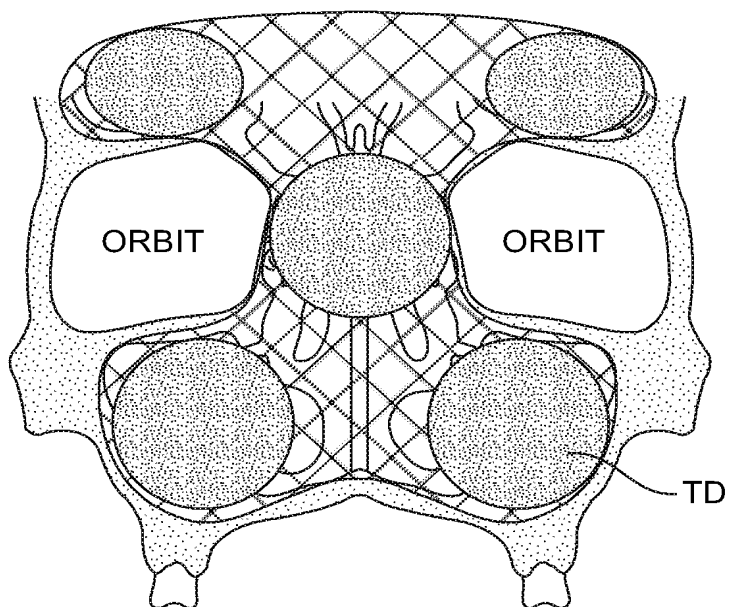


FIG. 19

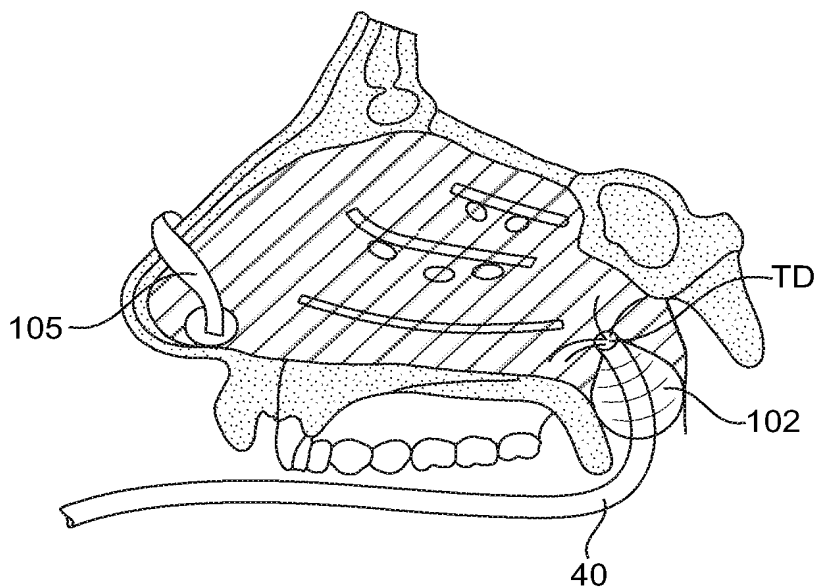


FIG. 20

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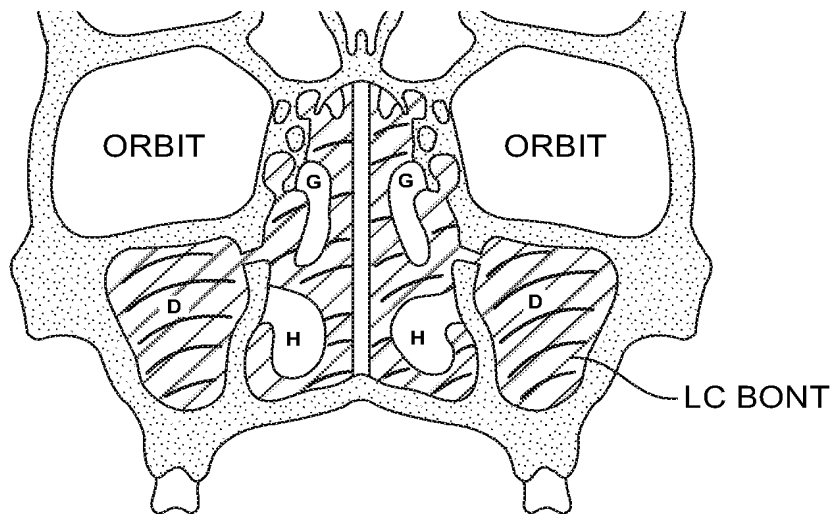


FIG. 21

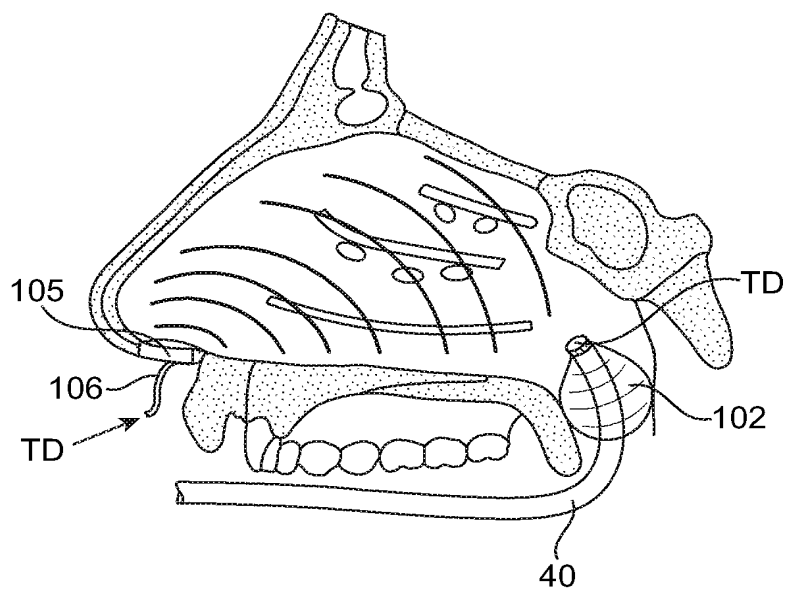


FIG. 22

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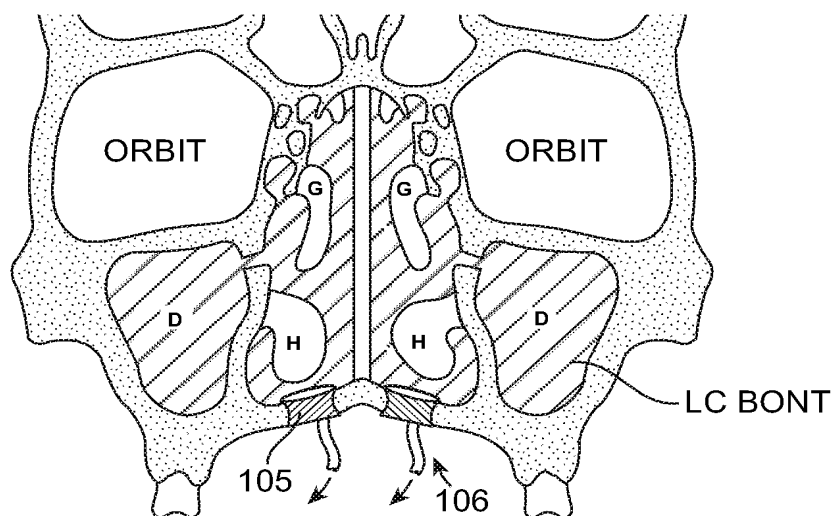


FIG. 23

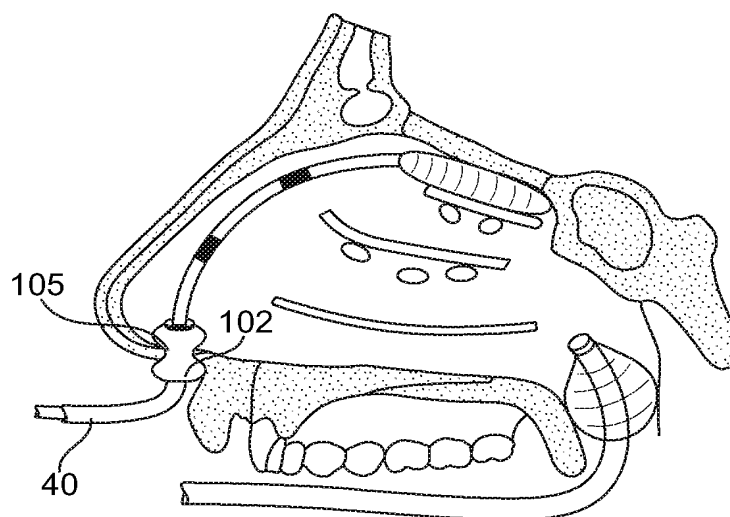


FIG. 24

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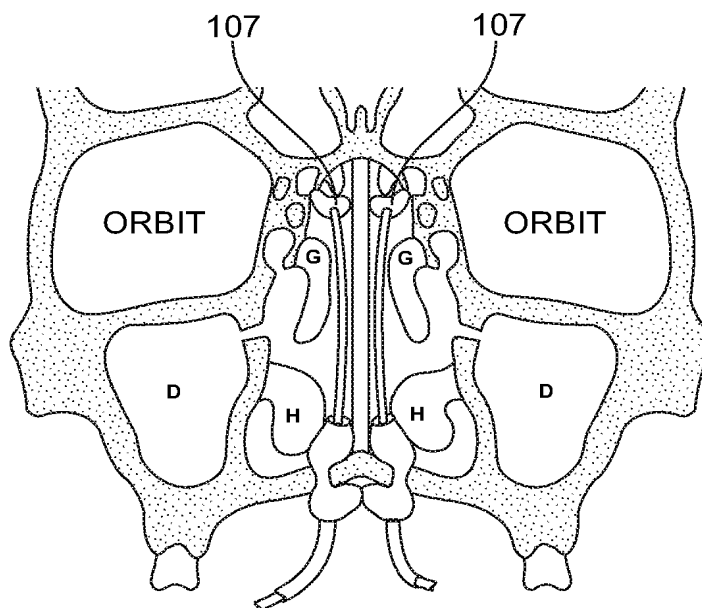


FIG. 25

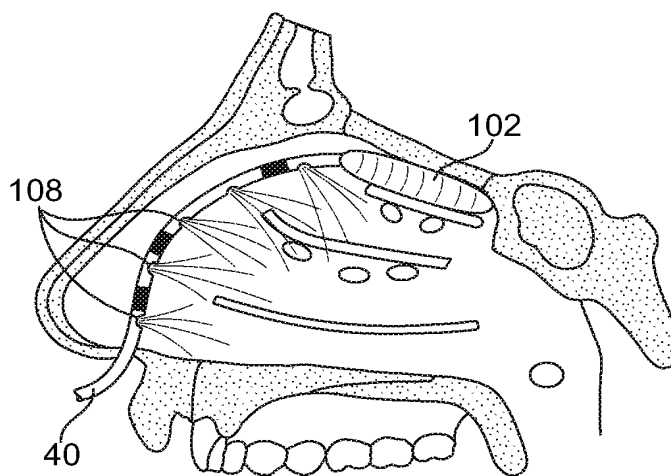


FIG. 26

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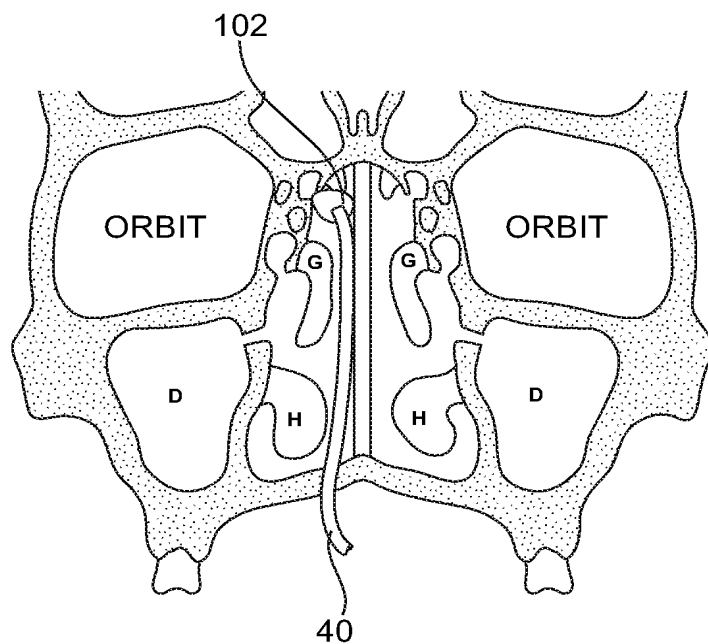


FIG. 27

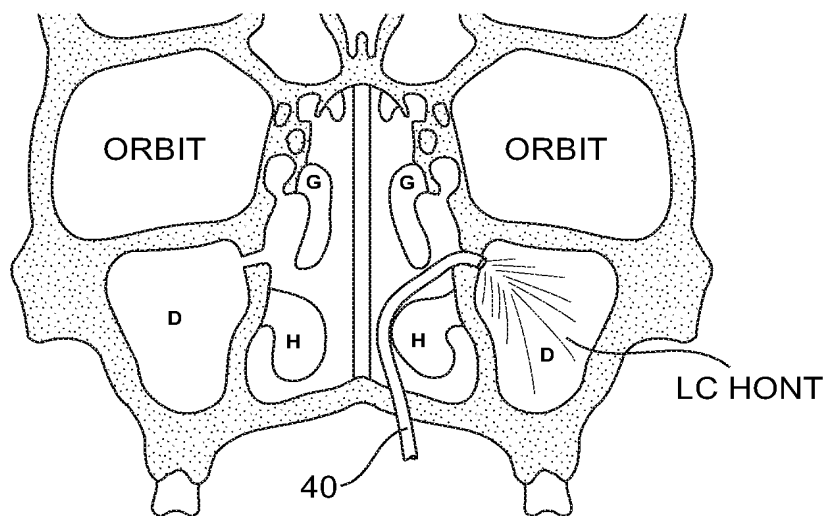


FIG. 28

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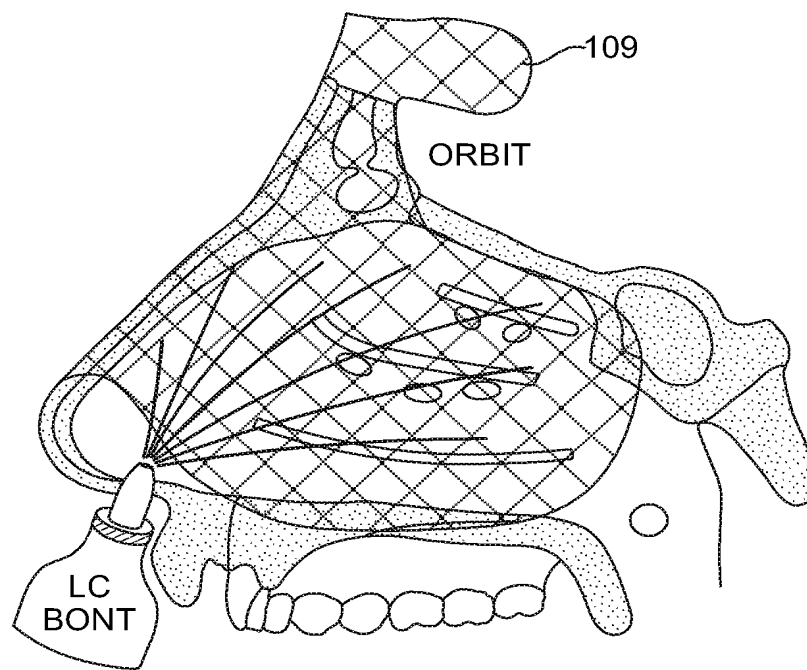


FIG. 29

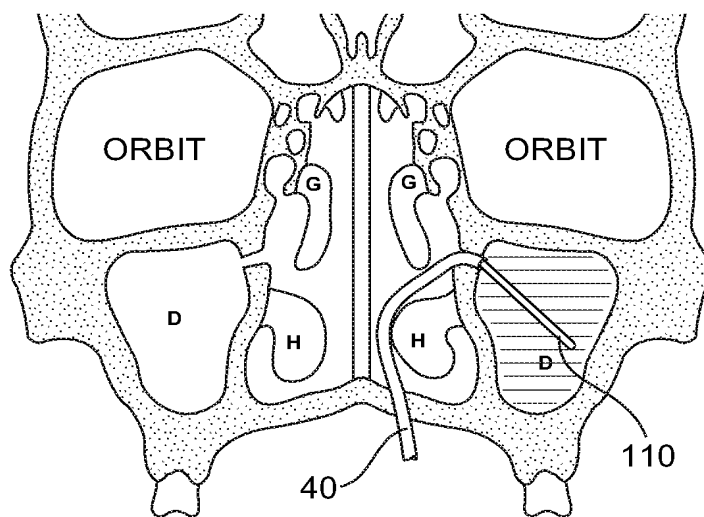


FIG. 30

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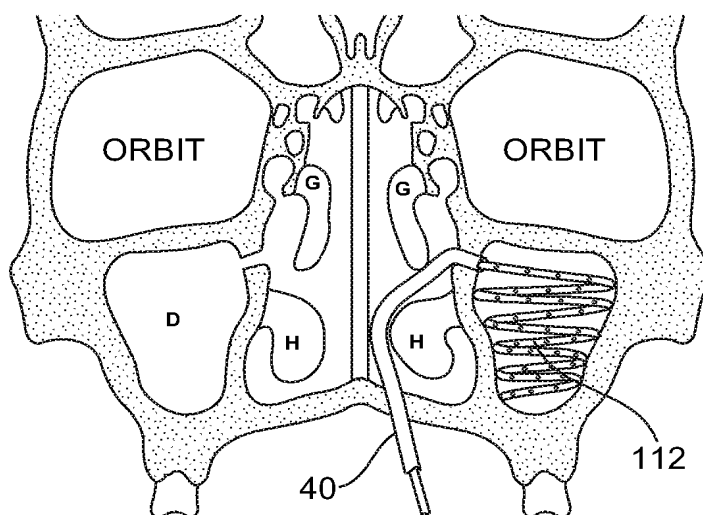


FIG. 31

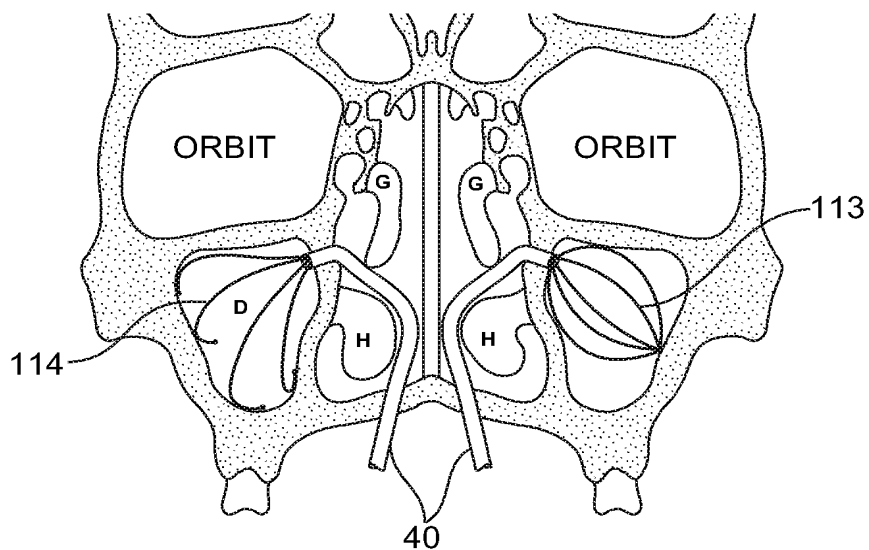


FIG. 32



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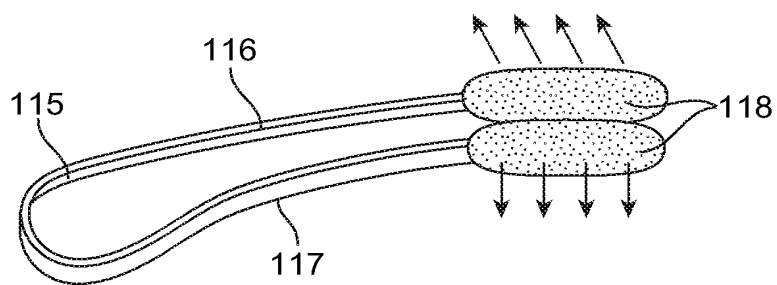


FIG. 33

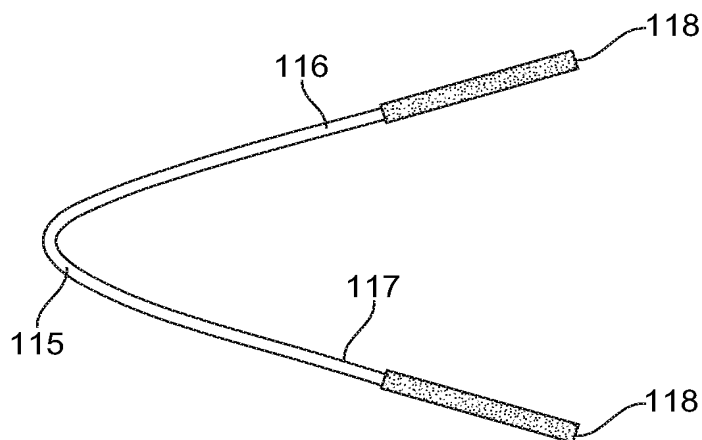


FIG. 34

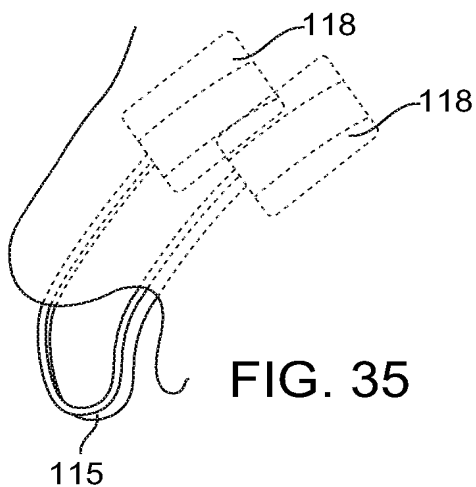


FIG. 35



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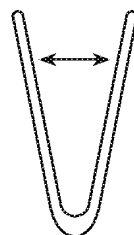
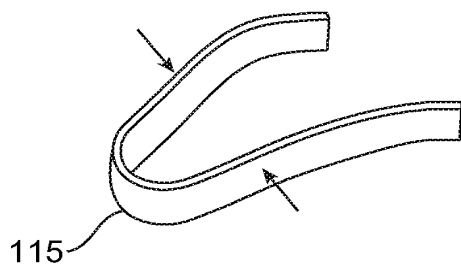
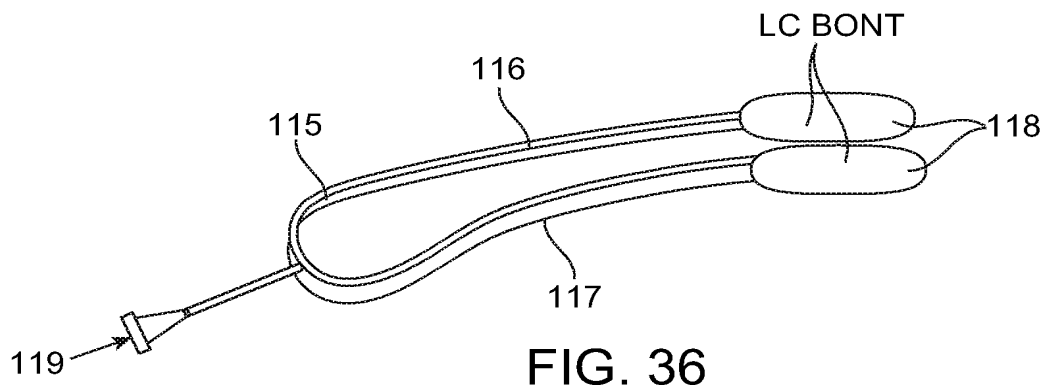


FIG. 37B

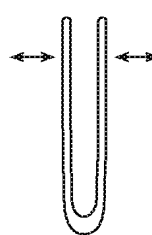
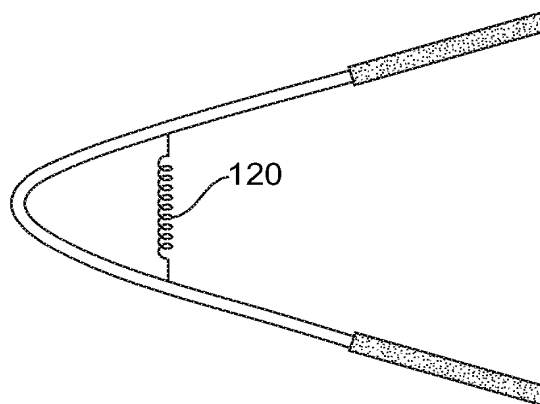


FIG. 37C



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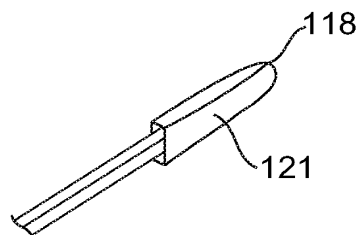


FIG. 39A

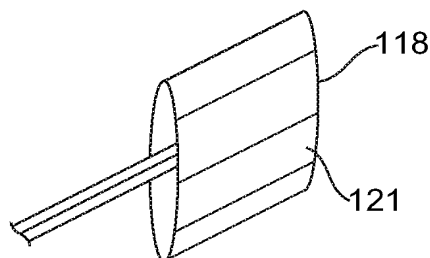


FIG. 39B

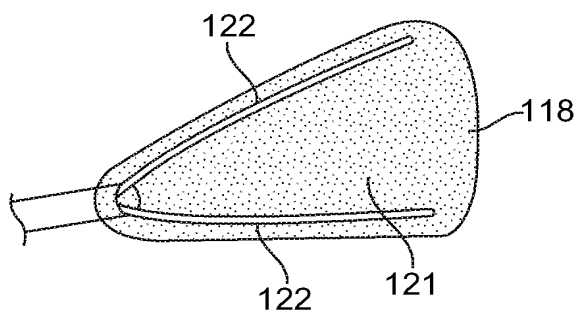


FIG. 40A

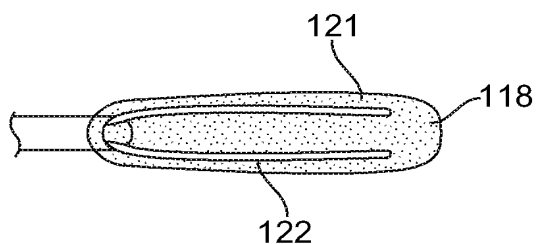


FIG. 40B

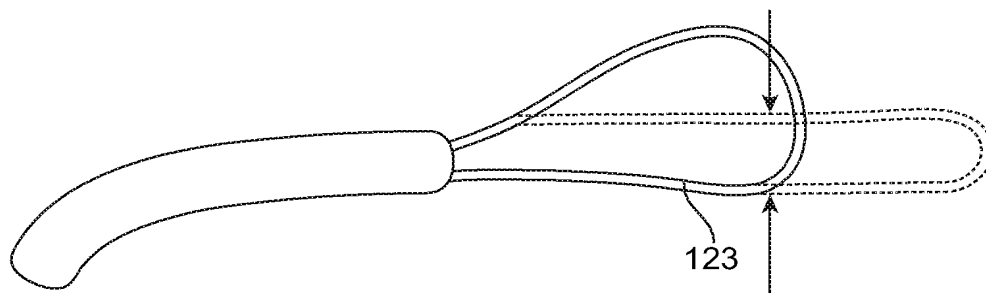


FIG. 41

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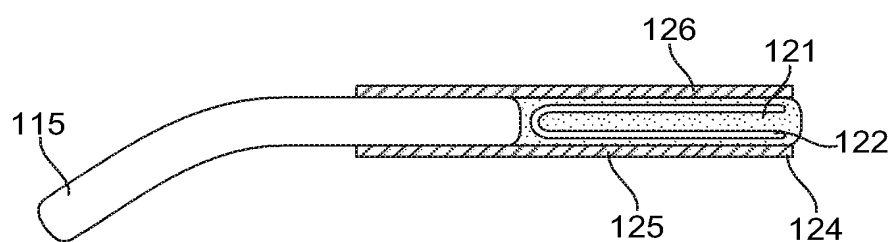


FIG. 42

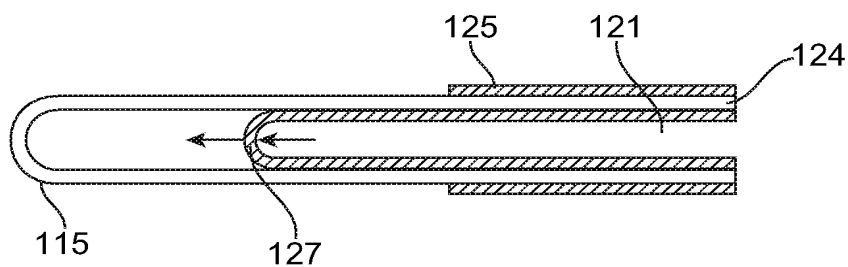


FIG. 43

Electronic Patent Application Fee Transmittal

Application Number:	11750963			
Filing Date:	18-May-2007			
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/JoAnn Evangelista			
Attorney Docket Number:	020979-003710US			
Filed as Small Entity				
Utility Filing Fees				
Description	Fee Code	Quantity	Amount	Sub-Total in USD(\$)
Basic Filing:				
Pages:				
Claims:				
Miscellaneous-Filing:				
Late filing fee for oath or declaration	2051	1	65	65
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	230	230
Miscellaneous:				
Total in USD (\$)				295

Electronic Acknowledgement Receipt

EFS ID:	2287317
Application Number:	11750963
International Application Number:	
Confirmation Number:	1089
Title of Invention:	METHODS AND SYSTEMS FOR TOXIN DELIVERY TO THE NASAL CAVITY
First Named Inventor/Applicant Name:	Mark E. Deem
Customer Number:	20350
Filer:	James Mitchell Heslin/JoAnn Evangelista
Filer Authorized By:	James Mitchell Heslin
Attorney Docket Number:	020979-003710US
Receipt Date:	05-OCT-2007
Filing Date:	18-MAY-2007
Time Stamp:	17:43:50
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	yes
Payment was successfully received in RAM	\$ 295
RAM confirmation Number	2470
Deposit Account	201430
The Director of the USPTO is hereby authorized to charge indicated fees and credit any overpayment as follows: Charge any Additional Fees required under 37 C.F.R. Section 1.16 and 1.17	

File Listing:

Document Number	Document Description	File Name	File Size(Bytes) /Message Digest	Multi Part /.zip	Pages (if appl.)				
1		EOT_RespNOMP.pdf	812256 60a31b46f048470b2b8f4ed9deed75ae1085decb	yes	4				
	Multipart Description/PDF files in .zip description								
	Document Description		Start	End					
	Extension of Time		1	1					
	Oath or Declaration filed		2	2					
	Power of Attorney		3	3					
	Assignee showing of ownership per 37 CFR 3.73(b).		4	4					
Warnings:									
Information:									
2	Drawings-only black and white line drawings	ReplaceformalDraw.pdf	526415 d9ff73762c0544c406c68c851e0e0e37ad7612c5	no	24				
Warnings:									
Information:									
3	Fee Worksheet (PTO-06)	fee-info.pdf	8366 47d4f732719f8bd4c550efe6fb461876b7e40480	no	2				
Warnings:									
Information:									
Total Files Size (in bytes):			1347037						
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.									

POWER OF ATTORNEY TO PROSECUTE APPLICATIONS BEFORE THE USPTO

I hereby appoint:

☒ Practitioners associated with the Customer Number

20350

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

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).

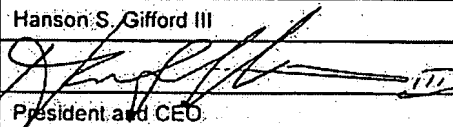
Assignee Name and Address:

The Foundry Inc.
199 Jefferson Drive
Menlo Park, CA 94025

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

Name	Hanson S. Gifford III			
Signature			Date	2/12/04
Title	President and CEO	Telephone	650-298-9500	

60138574 v1

Attorney Docket No. 020979-003710US

STATEMENT UNDER 37 CFR 3.73(b)Applicant/Patent Owner: MARK E. DEEMApplication No./Patent No./Control No.: 11/750,963 Filed/Issue Date: May 18, 2007Entitled: METHODS AND SYSTEMS FOR TOXIN DELIVERY TO THE NASAL CAVITYThe Foundry, Inc.

(Name of Assignee)

, a Corporation

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

states that it is:

1. ☒ the assignee of the entire right, title, and interest; or
2. ☐ an assignee of less than the entire right, title and interest.
(The extent (by percentage) of its ownership interest is _____ %)

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 a true copy of the original assignment 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:

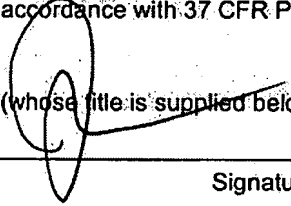
1. From: _____ To: _____
The document was recorded in the United States Patent and Trademark Office at Reel _____, Frame _____, or for which a copy thereof is attached.
2. From: _____ To: _____
The document was recorded in the United States Patent and Trademark Office at Reel _____, Frame _____, or for which a copy thereof is attached.
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.

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:

	<u>October 5, 2007</u>
Signature	Date
<u>James M. Heslin</u>	<u>650.326.2400</u>
Printed or Typed Name	Telephone Number
<u>Attorney of Record</u>	
Title	

PETITION FOR EXTENSION OF TIME UNDER 37 CFR 1.136(a)		Docket Number (Optional) 020979-003710US	
FY 2007 <i>(Fees pursuant to the Consolidated Appropriations Act, 2005 (H.R. 4818).)</i>			
Application Number 11/750,963		Filed May 18, 2007	
For METHODS AND SYSTEMS FOR TOXIN DELIVERY TO THE NASAL CAVITY			
Art Unit 1645		Examiner Unassigned	

This is a request under the provisions of 37 CFR 1.136(a) to extend the period for filing a reply in the above identified application.

The requested extension and fee are as follows (check time period desired and enter the appropriate fee below):

	<u>Fee</u>	<u>Small Entity Fee</u>	
☐ One month (37 CFR 1.17(a)(1))	\$120	\$60	\$ _____
☒ Two months (37 CFR 1.17(a)(2))	\$460	\$230	\$ 230
☐ Three months (37 CFR 1.17(a)(3))	\$1050	\$525	\$ _____
☐ Four months (37 CFR 1.17(a)(4))	\$1640	\$820	\$ _____
☐ Five months (37 CFR 1.17(a)(5))	\$2230	\$1115	\$ _____

☒ Applicant claims small entity status. See 37 CFR 1.27.

☐ A check in the amount of the fee is enclosed.

☐ Payment by credit card. Form PTO-2038 is attached.

☒ The Director has already been authorized to charge fees in this application to a Deposit Account.

☒ The Director is hereby authorized to charge any fees which may be required, or credit any overpayment, to Deposit Account Number 20-1430. I have enclosed a duplicate copy of this sheet.

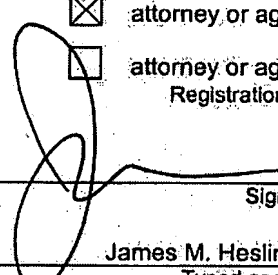
WARNING: Information on this form may become public. Credit card information should not be included on this form. Provide credit card information and authorization on PTO-2038.

I am the ☐ applicant/inventor.

☐ assignee of record of the entire interest. See 37 CFR 3.71.
Statement under 37 CFR 3.73(b) is enclosed (Form PTO/SB/96).

☒ attorney or agent of record. Registration Number 29,541

☐ attorney or agent under 37 CFR 1.34.
Registration number if acting under 37 CFR 1.34 _____



Signature

James M. Heslin, Reg. No. 29,541
Typed or printed name

October 5, 2007
Date

650.326.2400
Telephone Number

NOTE: Signatures of all the inventors or assignees of record of the entire interest or their representative(s) are required. Submit multiple forms if more than one signature is required, see below.

☐ Total of _____ forms are submitted.

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;

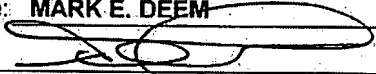
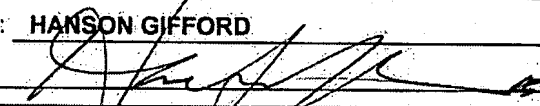
I/we have reviewed and understand the contents of the above-identified application, including the claims, as amended by any amendment specifically referred to above;

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: Date: 9/21/07Inventor two: HANSON GIFFORDCitizen of: United StatesSignature: Date: 9/21/07

Additional inventors or a legal representative are being named on

additional form(s) attached hereto.



UNITED STATES PATENT AND TRADEMARK OFFICE

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

APPLICATION NUMBER	FILING or 371(c) DATE	GRP ART UNIT	FIL FEE REC'D	ATTY. DOCKET NO	TOT CLAIMS	IND CLAIMS
11/750,963	05/18/2007	1645	1715	020979-003710US	69	2

CONFIRMATION NO. 1089

UPDATED FILING RECEIPT

20350
TOWNSEND AND TOWNSEND AND CREW, LLP
TWO EMBARCADERO CENTER
EIGHTH FLOOR
SAN FRANCISCO, CA 94111-3834



Date Mailed: 10/18/2007

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 write to the Office of Initial Patent Examination's Filing Receipt Corrections. 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 Inc., Menlo Park, CA

Power of Attorney: The patent practitioners associated with Customer Number 20350

Domestic Priority data as claimed by applicant

This application is a CIP of 11/459,090 07/21/2006
which claims benefit of 60/747,771 05/19/2006
and claims benefit of 60/702,077 07/22/2005

Foreign Applications

If Required, Foreign Filing License Granted: 06/22/2007

The country code and number of your priority application, to be used for filing abroad under the Paris Convention, is **US 11/750,963**

Projected Publication Date: 01/24/2008

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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The applicant has been granted a license under 35 U.S.C. 184, if the phrase "IF REQUIRED, FOREIGN FILING LICENSE GRANTED" followed by a date appears on this form. Such licenses are issued in all applications where the conditions for issuance of a license have been met, regardless of whether or not a license may be required as

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NOT GRANTED

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



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APPLICATION NUMBER	FILING OR 371(c) DATE	FIRST NAMED APPLICANT	ATTY. DOCKET NO./TITLE
11/750,963	05/18/2007	Mark E. Deem	020979-003710US

CONFIRMATION NO. 1089

20350
TOWNSEND AND TOWNSEND AND CREW, LLP
TWO EMBARCADERO CENTER
EIGHTH FLOOR
SAN FRANCISCO, CA94111-3834

Date Mailed. 10/18/2007

NOTICE OF NEW OR REVISED PROJECTED PUBLICATION DATE

The above-identified application has a new or revised projected publication date. The current projected publication date for this application is 01/24/2008. If this is a new projected publication date (there was no previous projected publication date), the application has been cleared by Licensing & Review or a secrecy order has been rescinded and the application is now in the publication queue.

If this is a revised projected publication date (one that is different from a previously communicated projected publication date), the publication date has been revised due to processing delays in the USPTO or the abandonment and subsequent revival of an application. The application is anticipated to be published on a date that is more than six weeks different from the originally-projected publication date.

More detailed publication information is available through the private side of Patent Application Information Retrieval (PAIR) System. The direct link to access PAIR is currently <http://pair.uspto.gov>. Further assistance in electronically accessing the publication, or about PAIR, is available by calling the Patent Electronic Business Center at 1-866-217-9197.

Questions relating to this Notice should be directed to the Office of Patent Publication at 1-888-786-0101.

PART 1 - ATTORNEY/APPLICANT COPY



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APPLICATION NUMBER	FILING OR 371(c) DATE	FIRST NAMED APPLICANT	ATTY. DOCKET NO./TITLE
11/750,963	05/18/2007	Mark E. Deem	020979-003710US

CONFIRMATION NO. 1089

20350
TOWNSEND AND TOWNSEND AND CREW, LLP
TWO EMBARCADERO CENTER
EIGHTH FLOOR
SAN FRANCISCO, CA94111-3834

Title: METHODS AND SYSTEMS FOR TOXIN DELIVERY TO THE NASAL CAVITY

Publication No. US-2008-0021369-A1

Publication Date: 01/24/2008

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 publicly 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.

Further assistance in electronically accessing the publication, or about PAIR, is available by calling the Patent Electronic Business Center at 1-866-217-9197.

Pre-Grant Publication Division, 703-605-4283

Electronic Acknowledgement Receipt

EFS ID:	3010129
Application Number:	11750963
International Application Number:	
Confirmation Number:	1089
Title of Invention:	METHODS AND SYSTEMS FOR TOXIN DELIVERY TO THE NASAL CAVITY
First Named Inventor/Applicant Name:	Mark E. Deem
Customer Number:	20350
Filer:	James Mitchell Heslin/Tiffany Wu
Filer Authorized By:	James Mitchell Heslin
Attorney Docket Number:	020979-003710US
Receipt Date:	17-MAR-2008
Filing Date:	18-MAY-2007
Time Stamp:	16:16:34
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		020979-003710_SIDS.PDF	99996 c8ceb40b54a20ab7bd043dd816205e7a7e215c2c	yes	3

Multipart Description/PDF files in .zip description							
Document Description			Start	End			
Information Disclosure Statement Letter			1	2			
Information Disclosure Statement (IDS) Filed			3	3			
Warnings:							
Information:							
2	NPL Documents	020979-003730_ISR.PDF	328232	no	7		
			de21f8176eafeb54e77735f0b8e56b30b015941c				
Warnings:							
Information:							
Total Files Size (in bytes):			428228				
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.							

I hereby certify that this correspondence is being filed via
EFS-Web with the United States Patent and Trademark Office
on 3/17/08

PATENT
Attorney Docket No.: 020979-003710US

TOWNSEND and TOWNSEND and CREW LLP

By: 
Tiffany Wu

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of:

MARK E. DEEM et al.

Application No.: 11/750,963

Filed: May 18, 2007

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

Confirmation No.: 1089

Examiner: Unassigned

Art Unit: 3767

SUPPLEMENTAL INFORMATION
DISCLOSURE STATEMENT UNDER
37 CFR §1.97 and §1.98

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

Sir:

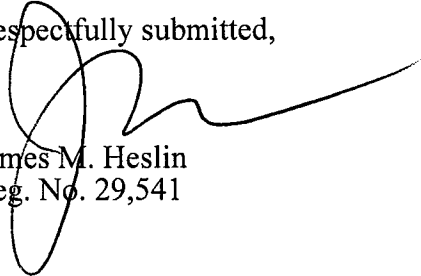
The references cited on attached form PTO/SB/08A and PTO/SB/08B are being called to the attention of the Examiner. Copies of the references are not enclosed. It is respectfully requested that the cited references be expressly considered during the prosecution of this application, and the references be made of record therein and appear among the "references cited" on any patent to issue therefrom.

Enclosed is a copy of the Search/Examination report corresponding to the PCT application.

As provided for by 37 CFR §1.97(g) and (h), no inference should be made that the information and references cited are prior art merely because they are in this statement and no representation is being made that a search has been conducted or that this statement encompasses all the possible relevant information.

Applicant believes that no fee is required for submission of this statement. However, if a fee is required, the Commissioner is authorized to deduct such fee from the undersigned's Deposit Account No. 20-1430. Please deduct any additional fees from, or credit any overpayment to, the above-noted Deposit Account.

Respectfully submitted,


James M. Heslin
Reg. No. 29,541

TOWNSEND and TOWNSEND and CREW LLP
Two Embarcadero Center, Eighth Floor
San Francisco, California 94111-3834
Tel: 650-326-2400
Fax: 650-326-2422
JMH:tfw
61312125 v1

Substitute for form 1449A&B/PTO INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Use as many sheets as necessary)				Complete if Known	
				Application Number	11/750,963
				Filing Date	May 18, 2007
				First Named Inventor	DEEM, MARK E.
				Art Unit	3767
				Examiner Name	Unassigned
Sheet	1	of	1	Attorney Docket Number	020979-003710US

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	1,695,107	12-11-1928	Kahl	
	2	2005/0152924	07-14-2005	Voet	
	3	2005/0107853	05-19-2005	Krespi et al.	
	4	2006/0106361	05-18-2006	Muni et al.	

FOREIGN PATENT DOCUMENTS								
Examiner Initials*	Cite No. ¹	Foreign Patent Document			Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear	T ⁶
		Country Code ³	Number ⁴	Kind Code ⁵ (if known)				
								☐
								☐

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
	5	International Search Report and Written Opinion of PCT/US07/69391, dated March 3, 2008, 7 pages total.	☐

Examiner Signature		Date Considered	
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*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

¹ Applicant's unique citation designation number (optional). ² Applicant is to place a check mark here if English language Translation is attached.

Electronic Acknowledgement Receipt

EFS ID:	3010545
Application Number:	11750963
International Application Number:	
Confirmation Number:	1089
Title of Invention:	METHODS AND SYSTEMS FOR TOXIN DELIVERY TO THE NASAL CAVITY
First Named Inventor/Applicant Name:	Mark E. Deem
Customer Number:	20350
Filer:	James Mitchell Heslin/Tiffany Wu
Filer Authorized By:	James Mitchell Heslin
Attorney Docket Number:	020979-003710US
Receipt Date:	17-MAR-2008
Filing Date:	18-MAY-2007
Time Stamp:	16:41:34
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		020979-003710_SIDS.PDF	102630	yes	3
			a3156da9083db7e65bad5e423f751819 aea68646		

Multipart Description/PDF files in .zip description							
Document Description			Start	End			
Information Disclosure Statement Letter			1	2			
Information Disclosure Statement (IDS) Filed			3	3			
Warnings:							
Information:							
2	NPL Documents	020979-003730_ISR.PDF	328232	no	7		
			de21f8176eafeb54e77735f0b8e56b30b015941c				
Warnings:							
Information:							
Total Files Size (in bytes):			430862				
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.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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11/750,963

05/18/2007

Mark E. Deem

020979-003710US

1089

20350 7590 06/24/2009
TOWNSEND AND TOWNSEND AND CREW, LLP
TWO EMBARCADERO CENTER
EIGHTH FLOOR
SAN FRANCISCO, CA 94111-3834

EXAMINER

NAVARRO, ALBERT MARK

ART UNIT

PAPER NUMBER

1645

MAIL DATE

DELIVERY MODE

06/24/2009

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. 11/750,963	Applicant(s) DEEM ET AL.	
	Examiner Mark Navarro	Art Unit 1645	

-- 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 1 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 ____.
- 2a) ☐ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ 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

- 4) ☒ Claim(s) 1-69 is/are pending in the application.
- 4a) Of the above claim(s) ____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) ____ is/are allowed.
- 6) ☐ Claim(s) ____ is/are rejected.
- 7) ☐ Claim(s) ____ is/are objected to.
- 8) ☒ Claim(s) 1-69 are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ 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).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

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).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. ____.
 3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

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

Attachment(s)

- | | |
|--|---|
| 1) ☐ Notice of References Cited (PTO-892) | 4) ☐ Interview Summary (PTO-413) |
| 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948) | Paper No(s)/Mail Date. ____. |
| 3) ☐ Information Disclosure Statement(s) (PTO/SB/08) | 5) ☐ Notice of Informal Patent Application |
| Paper No(s)/Mail Date ____. | 6) ☐ Other: ____. |

Election/Restrictions

Restriction to one of the following inventions is required under 35 U.S.C. 121:

- I. Claims 1-35, 67, and 69, drawn to methods for delivering toxins, classified in class 424, subclass 184.1.
- II. Claims 36-66 and 68, drawn to a system for delivering toxins, classified in class 206, subclass 571.

The inventions are distinct, each from the other because of the following reasons:

Inventions I and II are related as product and process of use. The inventions can be shown to be distinct if either or both of the following can be shown: (1) the process for using the product as claimed can be practiced with another materially different product or (2) the product as claimed can be used in a materially different process of using that product. See MPEP § 806.05(h). In the instant case the method of delivering toxins to target cells can be practiced as claimed, or alternatively can be applied in the form of nasal drops.

Restriction for examination purposes as indicated is proper because all these inventions listed in this action are independent or distinct for the reasons given above and there would be a serious search and examination burden if restriction were not required because one or more of the following reasons apply:

- (a) the inventions have acquired a separate status in the art in view of their different classification;

- (b) the inventions have acquired a separate status in the art due to their recognized divergent subject matter;
- (c) the inventions require a different field of search (for example, searching different classes/subclasses or electronic resources, or employing different search queries);
- (d) the prior art applicable to one invention would not likely be applicable to another invention;
- (e) the inventions are likely to raise different non-prior art issues under 35 U.S.C. 101 and/or 35 U.S.C. 112, first paragraph.

Applicant is advised that the reply to this requirement to be complete must include (i) an election of a invention to be examined even though the requirement may be traversed (37 CFR 1.143) **and (ii) identification of the claims encompassing the elected invention.**

The election of an invention may be made with or without traverse. To reserve a right to petition, the election must be made with traverse. If the reply does not distinctly and specifically point out supposed errors in the restriction requirement, the election shall be treated as an election without traverse. Traversal must be presented at the time of election in order to be considered timely. Failure to timely traverse the requirement will result in the loss of right to petition under 37 CFR 1.144. If claims are added after the election, applicant must indicate which of these claims are readable on the elected invention.

If claims are added after the election, applicant must indicate which of these claims are readable upon the elected invention.

Should applicant traverse on the ground that the inventions are not patentably distinct, applicant should submit evidence or identify such evidence now of record showing the inventions to be obvious variants or clearly admit on the record that this is the case. In either instance, if the examiner finds one of the inventions unpatentable over the prior art, the evidence or admission may be used in a rejection under 35 U.S.C. 103(a) of the other invention.

Applicant is reminded that upon the cancellation of claims to a non-elected invention, the inventorship must be amended in compliance with 37 CFR 1.48(b) if one or more of the currently named inventors is no longer an inventor of at least one claim remaining in the application. Any amendment of inventorship must be accompanied by a request under 37 CFR 1.48(b) and by the fee required under 37 CFR 1.17(i).

The examiner has required restriction between product and process claims. Where applicant elects claims directed to the product, and the product claims are subsequently found allowable, withdrawn process claims that depend from or otherwise require all the limitations of the allowable product claim will be considered for rejoinder. All claims directed to a nonelected process invention must require all the limitations of an allowable product claim for that process invention to be rejoined.

In the event of rejoinder, the requirement for restriction between the product claims and the rejoined process claims will be withdrawn, and the rejoined process claims will be fully examined for patentability in accordance with 37 CFR 1.104. Thus, to

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be allowable, the rejoined claims must meet all criteria for patentability including the requirements of 35 U.S.C. 101, 102, 103 and 112. Until all claims to the elected product are found allowable, an otherwise proper restriction requirement between product claims and process claims may be maintained. Withdrawn process claims that are not commensurate in scope with an allowable product claim will not be rejoined. See MPEP § 821.04(b). Additionally, in order to retain the right to rejoinder in accordance with the above policy, applicant is advised that the process claims should be amended during prosecution to require the limitations of the product claims. **Failure to do so may result in a loss of the right to rejoinder.** Further, note that the prohibition against double patenting rejections of 35 U.S.C. 121 does not apply where the restriction requirement is withdrawn by the examiner before the patent issues. See MPEP § 804.01.

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, Robert Mondesi can be reached on (571) 272-0956. 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
June 22, 2009

I hereby certify that this correspondence is being filed via
EFS-Web with the United States Patent and Trademark Office
on 7/24/09.

PATENT
Docket No.: 020979-003710US

TOWNSEND and TOWNSEND and CREW LLP

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.: 11/750,963

Filed: May 18, 2007

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

Confirmation No.: 1089

Examiner: Navarro, Albert Mark

Art Unit: 1645

**RESPONSE TO RESTRICTION
REQUIREMENT**

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

Sir:

In response to the Restriction Requirement mailed June 24, 2009, Applicants respectfully elect to initially prosecute claims 1-35, 67 and 69 of Group I without traverse. Group I claims are directed to a method.

Respectfully submitted,

Douglas Portnow

Douglas Portnow
Reg. No. 59,660

TOWNSEND and TOWNSEND and CREW LLP
Two Embarcadero Center, Eighth Floor
San Francisco, California 94111-3834
Tel: (650) 326-2400 / Fax: (650) 326-2422
D3P:
62136976 v1

Electronic Acknowledgement Receipt

EFS ID:	5766795
Application Number:	11750963
International Application Number:	
Confirmation Number:	1089
Title of Invention:	METHODS AND SYSTEMS FOR TOXIN DELIVERY TO THE NASAL CAVITY
First Named Inventor/Applicant Name:	Mark E. Deem
Customer Number:	20350
Filer:	Douglas Portnow/Joy Roeder
Filer Authorized By:	Douglas Portnow
Attorney Docket Number:	020979-003710US
Receipt Date:	24-JUL-2009
Filing Date:	18-MAY-2007
Time Stamp:	16:15:26
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	Response to Election / Restriction Filed	2009_07_24_RESPPR_020979_003710US.PDF	37111 b6f421ea8c003a72f89c5f13a8948f8eefe786a1	no	1

Warnings:

Information:

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

New Applications Under 35 U.S.C. 111

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

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

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

New International Application Filed with the USPTO as a Receiving Office

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



UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
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www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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11/750,963

05/18/2007

Mark E. Deem

020979-003710US

1089

20350 7590 08/14/2009
TOWNSEND AND TOWNSEND AND CREW, LLP
TWO EMBARCADERO CENTER
EIGHTH FLOOR
SAN FRANCISCO, CA 94111-3834

EXAMINER

NAVARRO, ALBERT MARK

ART UNIT

PAPER NUMBER

1645

MAIL DATE

DELIVERY MODE

08/14/2009

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. 11/750,963	Applicant(s) DEEM ET AL.	
	Examiner Mark Navarro	Art Unit 1645	

-- 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 24 July 2009.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ 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

- 4) ☒ Claim(s) 1-69 is/are pending in the application.
- 4a) Of the above claim(s) 36-66 and 68 is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1-35, 67 and 69 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ 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).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

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).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. _____.
 3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

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

Attachment(s)

- | | |
|--|---|
| 1) ☒ Notice of References Cited (PTO-892) | 4) ☐ Interview Summary (PTO-413) |
| 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948) | Paper No(s)/Mail Date. _____ |
| 3) ☒ Information Disclosure Statement(s) (PTO/SB/08) | 5) ☐ Notice of Informal Patent Application |
| Paper No(s)/Mail Date <u>multiple</u> . | 6) ☐ Other: _____ |

DETAILED ACTION

Election/Restrictions

Applicant's election without traverse of Group I, claims 1-35, 67 & 69 in the reply filed on July 24, 2009 is acknowledged.

Claim Objections

1. Claim 69 is objected to because of the following informalities: Claim 69 fails to end with the punctuation mark of a period. Appropriate correction is required.

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 1-35, 67 and 69 are rejected under 35 U.S.C. 103(a) as being unpatentable over Barron et al in view of Donovan.

The claims are directed to a method for delivering toxins to target cells in a nasal membrane of a patient, said method comprising introducing a toxin to a region proximate the target cells and applying energy to the target cells to enhance delivery of the toxin to the cells.

Barron et al (US Publication 2004/0086531) teach that nasal hypersecretion has been treated via application of botulinum toxin type A to mammalian nasal mucosal tissue. (See paragraph 79).

Barron et al do not teach of applying energy to the target cells to enhance delivery of the toxin to the cells.

Donovan (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).

Given that 1) Barron et al have taught of administering botulinum toxin type A to nasal tissue for treatment, and that 2) Donovan has taught that applying energy (ultrasound, electric current, etc.) to the site of delivery of botulinum toxins facilitates greater permeation of pharmaceuticals through the skin, it would have been prima facie obvious to have followed the method of administering botulinum toxin type A to nasal mucosa as taught by Barron et al and combined the teaching of Donovan which shows

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that botulinum toxins have greater permeation through the skin when combined with ultrasound or electric current treatment.

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).

3. Claims 1-35, 67 and 69 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-35 of copending Application No. 11/459,090 (allowed but not yet issued). Although the conflicting claims are not identical, they are not patentably distinct from each other because each set of claims encompasses methods of delivering toxins to a targeted region, followed by the application of energy to enhance delivery of the toxin to cells in the targeted region.

Art Unit: 1645

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

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

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Robert Mondesi can be reached on (571) 272-0956. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

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

/Mark Navarro/
Primary Examiner, Art Unit 1645
August 10, 2009

Notice of References Cited	Application/Control No. 11/750,963	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-2004/0086531	05-2004	Barron, Richard L.	424/239.1
	B	US-			
	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	
	V	
	W	
	X	

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

Search Notes 	Application/Control No. 11750963	Applicant(s)/Patent Under Reexamination DEEM ET AL.
	Examiner Mark Navarro	Art Unit 1645

SEARCHED			
Class	Subclass	Date	Examiner

SEARCH NOTES		
Search Notes	Date	Examiner
Medline, Biosis, Ca, Caplus, Embase, USpatfull , terms: toxin, botulinum, energy, ultrasound, microwave, xray, enhance, delivery, treat, administer	8/10/09	MN

INTERFERENCE SEARCH			
Class	Subclass	Date	Examiner

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Substitute for form 1449A&B/PTO INFORMATION DISCLOSURE STATEMENT BY APPLICANT <i>(Use as many sheets as necessary)</i>				Complete if Known	
				Application Number	11/750,963
				Filing Date	May 18, 2007
				First Named Inventor	DEEM, MARK E.
				Art Unit	3767
				Examiner Name	Unassigned
Sheet	1	of	1	Attorney Docket Number	020979-003710US

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	1,695,107	12-11-1928	Kahl	
	2	2005/0152924	07-14-2005	Voet	
	3	2005/0107853	05-19-2005	Krespi et al.	
	4	2006/0106361	05-18-2006	Muni et al.	

FOREIGN PATENT DOCUMENTS								
Examiner Initials*	Cite No. ¹	Foreign Patent Document			Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear	T ⁶
		Country Code ³	Number ⁴	Kind Code ⁵ (if known)				
								☐
								☐

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
	5	International Search Report and Written Opinion of PCT/US07/69391, dated March 3, 2008, 7 pages total.	☐

Examiner Signature	/Albert M Navarro/	Date Considered	08/13/2009
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*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

¹ Applicant's unique citation designation number (optional). ² Applicant is to place a check mark here if English language Translation is attached.

FILE 'MEDLINE, BIOSIS, CA, CAPLUS, EMBASE, USPATFULL' ENTERED AT 12:41:04
ON 10 AUG 2009

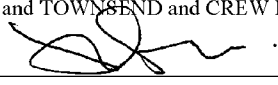
L1 40451 S BOTULINUM (5A) TOXIN#
L2 179 S L1 (300A) NASAL?
L3 83 S L2 AND (X#### OR IONTOPHOR? OR ULTRASOU? OR MICROWAV? OR ELE
L4 81 DUP REM L3 (2 DUPLICATES REMOVED)
L5 31 S L2 AND ((X (1A) RAY) OR IONTOPHOR? OR ULTRASOU? OR MICROWAV?
L6 29 DUP REM L5 (2 DUPLICATES REMOVED)
L7 1593 S TOXIN (50A) NASAL?
L8 1900 S TOXIN? (50A) NASAL?
L9 111 S L8 AND ((X (1A) RAY) OR IONTOPHOR? OR ULTRASOU? OR MICROWAV?
L10 106 DUP REM L9 (5 DUPLICATES REMOVED)

=>

I hereby certify that this correspondence is being filed via
EFS-Web with the United States Patent and Trademark Office
on 09/10/07.

PATENT
Attorney Docket No.: 020979-003710US

TOWNSEND and TOWNSEND and CREW LLP

By: 
Tiffany Wu

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of:

MARK E. DEEM et al.

Application No.: 11/750,963

Filed: May 18, 2007

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

Confirmation No.: 1089

Examiner: Unassigned

Art Unit: 1645

INFORMATION DISCLOSURE
STATEMENT UNDER 37 CFR §1.97 and
§1.98

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

Sir:

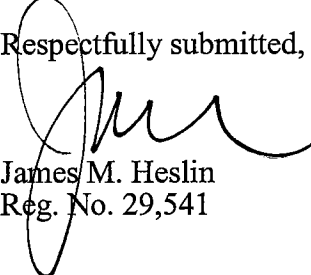
The references cited on attached form PTO/SB/08A and PTO/SB/08B are being called to the attention of the Examiner. In accordance with 37 CFR §1.98(d), copies of the references can be found in Application No. 11/459,090, filed July 21, 2006 (Attorney Docket No. 020979-003410US), except for Cite Nos. 57 and 62. Copies of Cite Nos. 57 and 62 are enclosed herewith.

It is respectfully requested that the cited references be expressly considered during the prosecution of this application, and the references be made of record therein and appear among the "references cited" on any patent to issue therefrom.

As provided for by 37 CFR §1.97(g) and (h), no inference should be made that the information and references cited are prior art merely because they are in this statement and no representation is being made that a search has been conducted or that this statement encompasses all the possible relevant information.

Applicant believes that no fee is required for submission of this statement. However, if a fee is required, the Commissioner is authorized to deduct such fee from the undersigned's Deposit Account No. 20-1430. Please deduct any additional fees from, or credit any overpayment to, the above-noted Deposit Account.

Respectfully submitted,



James M. Heslin
Reg. No. 29,541

TOWNSEND and TOWNSEND and CREW LLP
Two Embarcadero Center, Eighth Floor
San Francisco, California 94111-3834
Tel: 650-326-2400
Fax: 650-326-2422
JMH:tfw
61143664 v1

Substitute for form 1449A/PTO INFORMATION DISCLOSURE STATEMENT BY APPLICANT <i>(Use as many sheets as necessary)</i>				Complete if Known	
				Application Number	11/750,963
				Filing Date	May 18, 2007
				First Named Inventor	DEEM, MARK E.
				Art Unit	1645
				Examiner Name	Unassigned
Sheet	1	of	4	Attorney Docket Number	020979-003710US

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	4,767,402	08-30-1988	Kost et al.	
	2	5,286,254	02-15-1994	Shapland et al.	
	3	5,766,605	06-16-1998	Sanders et al.	
	4	5,820,589	10-13-1998	Torgerson et al.	
	5	5,964,223	10-12-1999	Baran	
	6	6,063,768	05-16-2000	First	
	7	6,139,845	10-31-2000	Donovan	
	8	6,265,379	07-24-2001	Donovan	
	9	6,358,926	03-19-2002	Donovan	
	10	6,361,554	03-26-2002	Briskin	
	11	6,447,785	09-10-2002	Donovan	
	12	6,448,231	09-10-2002	Graham	
	13	6,464,680	10-15-2002	Briskin et al.	
	14	6,526,976	03-04-2003	Baran	
	15	6,601,581	08-05-2003	Babaev	
	16	6,620,415	09-16-2003	Donovan	
	17	6,623,742	09-23-2003	Voet	
	18	6,626,855	09-30-2003	Weng et al.	
	19	6,632,440	10-14-2003	Quinn et al.	
	20	6,645,496	11-11-2003	Aoki et al.	
	21	6,649,161	11-18-2003	Donovan	
	22	6,719,694	04-13-2004	Weng et al.	
	23	6,740,321	05-25-2004	Donovan	
	24	6,767,544	07-27-2004	Brooks et al.	
	25	6,773,711	08-10-2004	Voet et al.	
	26	6,776,991	08-17-2004	Naumann	
	27	6,827,931	12-07-2004	Donovan	
	28	6,838,434	01-04-2005	Voet	
	29	6,841,156	01-11-2005	Aoki et al.	
	30	6,843,998	01-18-2005	Steward et al.	
	31	6,847,849	01-25-2005	Mamo et al.	
	32	6,861,058	03-01-2005	Aoki et al.	
	33	6,872,397	03-29-2005	Aoki et al.	
	34	6,974,578	12-13-2005	Aoki et al.	
	35	2001/0044596	11-22-2001	Jaafar	

Examiner Signature	Date Considered
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*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant. ¹ Applicant's unique citation designation number (optional). ² Kind Codes of U.S. 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.3). 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 symbols 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.

Substitute for form 1449A/PTO INFORMATION DISCLOSURE STATEMENT BY APPLICANT <i>(Use as many sheets as necessary)</i>		Complete if Known			
		Application Number	11/750,963		
		Filing Date	May 18, 2007		
		First Named Inventor	DEEM, MARK E.		
		Art Unit	1645		
		Examiner Name	Unassigned		
Sheet	2	of	4	Attorney Docket Number	020979-003710US

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)			
	36	2002/0198512	12-26-2002	Seward	
	37	2003/0050591	03-13-2003	McHale	
	38	2003/0202990	10-30-2003	Donovan et al.	
	39	2003/0211121	11-13-2003	Donovan	
	40	2004/0009180	01-15-2004	Donovan	
	41	2004/0010290	01-15-2004	Schroeppel et al.	
	42	2004/0091880	05-13-2004	Wiebusch et al.	
	43	2004/0142005	07-22-2004	Brooks et al.	
	44	2004/0151741	08-05-2004	Borodic	
	45	2004/0175399	09-09-2004	Schiffman	
	46	2004/0213813	10-28-2004	Ackerman	
	47	2004/0213814	10-28-2004	Ackerman	
	48	2004/0226556	11-18-2004	Deem et al.	
	49	2004/0253274	12-16-2004	Voet	
	50	2005/0019346	01-27-2005	Boulis	
	51	2005/0074461	04-07-2005	Donovan	
	52	2007/0021803	01-25-2007	Deem et al.	

FOREIGN PATENT DOCUMENTS								
Examiner Initials*	Cite No. ¹	Foreign Patent Document			Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear	T ⁶
		Country Code ³	Number ⁴	Kind Code ⁵ (if known)				
	53	WO	2004/101028	A2	11-25-2004	The Foundry, Inc.		☐
								☐

Examiner Signature		Date Considered	
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*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant. ¹ Applicant's unique citation designation number (optional). ² Kind Codes of U.S. 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.3). 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 symbols 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.

Substitute for form 1449B/PTO INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Use as many sheets as necessary)				Complete if Known	
				Application Number	11/750,963
				Filing Date	May 18, 2007
				First Named Inventor	DEEM, MARK E.
				Art Unit	1645
				Examiner Name	Unassigned
Sheet	3	of	4	Attorney Docket Number	020979-003710US

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	
	54	AHNERT-HILGER et al., "Introduction of Macromolecules into Bovine Adrenal-Medullary Chromaffin Cells and Rat Pheochromocytoma Cells (PC12) by Permeabilization with Streptolysin-Oinhibitory Effect of Tetanus Toxin on Catecholamine Secretion," <i>J. Neurochem.</i> 1989 Jun; 52(6):1751-1758.	☐	
	55	BIGALKE et al., "Clostridial Toxins", <i>Handbook of Experimental Pharmacology</i> (Aktories, K., and Just, I., eds) 2000, 145:407-443, Springer Verlag, Berlin, Heidelberg	☐	
	56	BITTNER et al., "Isolated Light Chains of Botulinum Neurotoxins Inhibit Exocytosis. Studies in Digitonin-Permeabilized Chromaffin Cells." <i>J Biol Chem</i> 1989 Jun 25; 264(18):10354-10360	☐	
	57	BUZZI, "Diphtheria Toxin Treatment of Human Advanced Cancer," <i>Cancer Research</i> , 1982, 42:2054-2058.	☐	
	58	CHADDOCK et al "Expression and Purification of Catalytically Active, Non-Toxic Endopeptidase Derivatives of Clostridium Botulinum Toxin Type A," <i>Protein Expression and Purification</i> , July 2002, 25(2): 219-228	☐	
	59	CHANG, "Cell Poration and Cell Fusion Using an Oscillating Electric Field," <i>Biophys J.</i> 1989 October; 56(4): 641-652.	☐	
	60	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," <i>Ultrasound in Med. & Biol.</i> , 2003, 29(8): 1211-1222.	☐	
	61	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," <i>Naunyn Schmiedebergs Arch Pharmacol.</i> 1992 Feb; 345(2):227-34.	☐	
	62	KREITMAN, "Taming Ricin," <i>Nature Biotechnology</i> , 2003, 21:372-374.	☐	
	63	RAJ, Editorial, <i>Pain Practice</i> , 4(1S):S1-S3.	☐	NO PUB DATE

Examiner Signature		Date Considered	
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* EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

¹ Applicant's unique citation designation number (optional). ² Applicant is to place a check mark here if English language Translation is attached.

Substitute for form 1449B/PTO INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Use as many sheets as necessary)				Complete if Known	
				Application Number	11/750,963
				Filing Date	May 18, 2007
				First Named Inventor	DEEM, MARK E.
				Art Unit	1645
				Examiner Name	Unassigned
Sheet	4	of	4	Attorney Docket Number	020979-003710US

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
	64	SHAARI et al., "Rhinorrhea is Decreased in Dogs After Nasal Application of Botulinum Toxin," <i>Otolaryngol Head Neck Surg</i> 1995;112:566-571.	☐
	65	SIMPSON et al., "Isolation and Characterization of the Botulinum Neurotoxins," <i>Methods Enzymol.</i> 1988; 165:76-85.	☐
	66	UNAL et al, "Effect of Botulinum Toxin Type A on Nasal Symptoms in Patients with Allergic Rhinitis: A Double-blind, Placebo-controlled Clinical Trial," <i>Acta Oto-Laryngologica</i> , 2003 Dec, 123(9):1060-0163	☐
	67	WEAVER, "Electroporation: A General Phenomenon for Manipulating Cells and Tissues," <i>Cell Biochem.</i> 1993 Apr; 51(4):426-35.	☐

Examiner Signature	/Albert M Navarro/	Date Considered	08/10/2009
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¹ Applicant's unique citation designation number (optional). ² Applicant is to place a check mark here if English language Translation is attached.



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BIB DATA SHEET

CONFIRMATION NO. 1089

SERIAL NUMBER 11/750,963	FILING or 371(c) DATE 05/18/2007 RULE	CLASS 424	GROUP ART UNIT 1645	ATTORNEY DOCKET NO. 020979-003710US	
APPLICANTS Mark E. Deem, Mountain View, CA; Hanson Gifford, Woodside, CA; ** CONTINUING DATA ***** This application is a CIP of 11/459,090 07/21/2006 which claims benefit of 60/747,771 05/19/2006 and claims benefit of 60/702,077 07/22/2005 ** FOREIGN APPLICATIONS ***** ** IF REQUIRED, FOREIGN FILING LICENSE GRANTED ** ** SMALL ENTITY ** 06/22/2007					
Foreign Priority claimed ☐ Yes ☒ No 35 USC 119(a-d) conditions met ☐ Yes ☒ No Verified and <u>/ALBERT MARK NAVARRO/</u> Acknowledged <u>Examiner's Signature</u>	☐ Met after Allowance <u>Initials</u>	STATE OR COUNTRY CA	SHEETS DRAWINGS 24	TOTAL CLAIMS 69	INDEPENDENT CLAIMS 2
ADDRESS TOWNSEND AND TOWNSEND AND CREW, LLP TWO EMBARCADERO CENTER EIGHTH FLOOR SAN FRANCISCO, CA 94111-3834 UNITED STATES					
TITLE METHODS AND SYSTEMS FOR TOXIN DELIVERY TO THE NASAL CAVITY					
FILING FEE RECEIVED 1715	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		

Substitute for form 1449/PTO INFORMATION DISCLOSURE STATEMENT BY APPLICANT <i>(Use as many sheets as necessary)</i>				Complete if Known	
				Application Number	11/750,963
				Filing Date	May 18, 2007
				First Named Inventor	DEEM, MARK E.
				Art Unit	1645
				Examiner Name	NAVARRO, Albert Mark
Sheet	1	of	1	Attorney Docket Number	020979-003710US

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

FOREIGN PATENT DOCUMENTS								
Examiner Initials*	Cite No. ¹	Foreign Patent Document Country Code ³ Number ⁴ Kind Code ⁵ (if known)			Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear	T ⁶
								☐

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
	1	DE PAIVA et al., "Light chain of botulinum neurotoxin is active in mammalian motor nerve terminals when delivered via liposomes," <i>FEBS Lett.</i> 1990 Dec 17;277(1-2):171-174.	☐
	2	RAJ, Editorial, <i>Pain Practice</i> , 2004; 4(1S): S1-S3.	☐
	3	SUNDARAM et al., "An Experimental and Theoretical Analysis of Ultrasound-Induced Permeabilization of Cell Membranes," <i>Biophysical Journal</i> , 2003 May 1; 84(5): 3087-3101.	☐

Examiner Signature		Date Considered	
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¹ Applicant's unique citation designation number (optional). ² Applicant is to place a check mark here if English language Translation is attached.

Electronic Patent Application Fee Transmittal				
Application Number:		11750963		
Filing Date:		18-May-2007		
Title of Invention:		METHODS AND SYSTEMS FOR TOXIN DELIVERY TO THE NASAL CAVITY		
First Named Inventor/Applicant Name:		Mark E. Deem		
Filer:		Douglas Portnow/Tiffany Wu		
Attorney Docket Number:		020979-003710US		
Filed as Large 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:				
Extension-of-Time:				

Description	Fee Code	Quantity	Amount	Sub-Total in USD(\$)
Miscellaneous:				
Submission- Information Disclosure Stmt	1806	1	180	180
Total in USD (\$)				180

Electronic Acknowledgement Receipt

EFS ID:	6161842
Application Number:	11750963
International Application Number:	
Confirmation Number:	1089
Title of Invention:	METHODS AND SYSTEMS FOR TOXIN DELIVERY TO THE NASAL CAVITY
First Named Inventor/Applicant Name:	Mark E. Deem
Customer Number:	20350
Filer:	Douglas Portnow/Tiffany Wu
Filer Authorized By:	Douglas Portnow
Attorney Docket Number:	020979-003710US
Receipt Date:	28-SEP-2009
Filing Date:	18-MAY-2007
Time Stamp:	21:27:18
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	yes
Payment Type	Deposit Account
Payment was successfully received in RAM	\$ 180
RAM confirmation Number	5861
Deposit Account	201430
Authorized User	

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
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1		020979-003710_IDS.pdf	150217	yes	3
			7ed3f6b7fa7ff7a2cf7192b7044d1c9b849a70ab		
	Multipart Description/PDF files in .zip description				
	Document Description		Start	End	
	Transmittal Letter		1	2	
	Information Disclosure Statement (IDS) Filed (SB/08)		3	3	
Warnings:					
Information:					
2	NPL Documents	de_PAIVA.pdf	322124	no	4
			184ff71b3433417d8f8d66938942a238026b07d9		
Warnings:					
Information:					
3	NPL Documents	RAJ.pdf	209691	no	3
			a9ca57a7676d691aa8ebe339da4af7b821871817		
Warnings:					
Information:					
4	NPL Documents	SUNDARAM.pdf	265883	no	15
			a1f22c650da88ea9344bcb74c1fceed598619be4		
Warnings:					
Information:					
5	Fee Worksheet (PTO-875)	fee-info.pdf	30522	no	2
			10a4ae8e6056c8d1970bfd9c0f299611860de171		
Warnings:					
Information:					
Total Files Size (in bytes):			978437		

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

New Applications Under 35 U.S.C. 111

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

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

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

New International Application Filed with the USPTO as a Receiving Office

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

I hereby certify that this correspondence is being filed via
EFS-Web with the United States Patent and Trademark Office
on September 28, 2009.

PATENT
Attorney Docket No.: 020979-003710US

TOWNSEND and TOWNSEND and CREW LLP

By: /Tiffany Wu/
Tiffany Wu

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of:

MARK E. DEEM et al.

Application No.: 11/750,963

Filed: May 18, 2007

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

Customer No.: 20350

Confirmation No.: 1089

Examiner: NAVARRO, Albert Mark

Art Unit: 1645

SUPPLEMENTAL INFORMATION
DISCLOSURE STATEMENT UNDER
37 CFR §1.97 and §1.98

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

Commissioner:

The references cited on attached form PTO/SB/08A and PTO/SB/08B are being called to the attention of the Examiner. Copies of the references [in compliance with the requirements of 37 CFR §1.98(a)(2)] are enclosed.

It is respectfully requested that the cited references be expressly considered during the prosecution of this application, and the references be made of record therein and appear among the “references cited” on any patent to issue therefrom.

Cite Nos. 1 and 3 cited in this IDS were cited in an Office Action mailed on November 19, 2007 in related U.S. Patent Application No. 11/459,090. Copies of the Office

Actions in 11/459,090 are available on PAIR and are believed to be readily accessible to the Examiner.

As provided for by 37 CFR §1.97(g) and (h), no inference should be made that the information and references cited are prior art merely because they are in this statement and no representation is being made that a search has been conducted or that this statement encompasses all the possible relevant information.

This IDS is being filed before the mailing date of the final Office Action or Notice of Allowance.

Please charge the IDS fee of \$180 to Deposit Account No. 20-1430. Please deduct any additional fees from, or credit any overpayment to, the above-noted Deposit Account.

Respectfully submitted,

/Douglas Portnow/

Douglas Portnow
Reg. No. 59,660

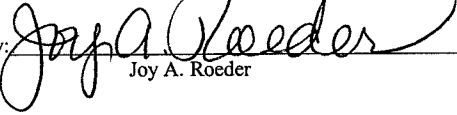
TOWNSEND and TOWNSEND and CREW LLP
Two Embarcadero Center, Eighth Floor
San Francisco, California 94111-3834
Tel: 650-326-2400
Fax: 650-326-2422
D3P:tfw

62237431 v1

I hereby certify that this correspondence is being filed via
EFS-Web with the United States Patent and Trademark Office
on October 1, 2009.

PATENT
Attorney Docket No.: 020979-003710US

TOWNSEND and TOWNSEND and CREW LLP

By: 
Joy A. Roeder

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of:

MARK E. DEEM et al.

Application No.: 11/750,963

Filed: May 18, 2007

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

Customer No.: 20350

Confirmation No. 1089

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 August 14, 2009, 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/Arguments begin on page 6 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. (Currently Amended) A method for delivering toxins to target cells in a nasal membrane of a patient, said method comprising:
introducing a toxin to a region proximate the target cells, said toxin comprising a light chain fragment of a neurotoxin and being substantially free of heavy chain fragments of the neurotoxin; and
applying energy to the target cells to enhance delivery of the toxin to the cells.
2. (Original) A method as in claim 1, wherein the region comprises at least one paranasal sinus, a main nasal passage or a nasal turbinate.
3. (Original) A method as in claim 1, wherein the region comprises substantially the entire nasal cavity.
4. (Original) A method as in claim 1, wherein the region comprises the nasopharynx.
5. (Original) A method as in claim 1, wherein the target cells comprise epithelial or goblet cells.
6. (Currently Amended) A method as in claim 1, wherein the energy is selectively applied to target cells within the region where the toxin has been introduced.
7. (Currently Amended) A method as in claim 1, wherein the energy is applied non-selectively within the region where the toxin has been introduced.
8. (Original) A method as in claim 1, wherein the patient suffers from or is at risk of suffering from rhinorrhea.

9. (Original) A method as in claim 1, wherein the patient suffers from or is at risk of suffering from sinus headaches.

10. (Original) A method as in claim 1, wherein the patient suffers from or is at risk of suffering from migraine headaches.

11. (Currently Amended) A method as in claim 1, wherein the ~~toxin~~ comprises neurotoxin consists of botulinum toxin.

12. – 13. (Cancelled)

14. (Currently Amended) A method as in claim ~~13~~ 11, wherein the light chain fragment is derived from at least one of botulinum toxins A, B, C, D, E, F, and G.

15. (Original) A method as in claim 1, wherein the energy applied to the targeted region is an electric pulse.

16. (Original) A method as in claim 15, wherein the electric pulse is applied from between 1V to 500V.

17. (Original) A method as in claim 15, wherein the electric pulse is an RF signal.

18. (Original) A method of claim 15, wherein the electric pulse is pulsed for durations between 5 microseconds to 100 milliseconds.

19. (Original) A method as in claim 15, wherein the electric pulse is produced by a DC power source.

20. (Original) A method as in claim 15, wherein the electric pulse is produced by an AC power source.

21. (Original) A method as in claim 1, wherein the energy applied to the target region is ultrasonic.

22. (Original) A method as in claim 1, wherein the energy applied to the targeted region is an x-ray beam.

23. (Original) A method as in claim 1, wherein the energy applied to the targeted region is focused ultrasound.

24. (Original) A method as in claim 1, wherein the energy applied to the targeted region is microwave.

25. (Original) A method as in claim 1, wherein the toxin is introduced to the target region through a catheter.

26. (Original) A method as in claim 25, wherein the toxin is introduced through a balloon on the catheter.

27. (Original) A method as in claim 26, wherein the balloon is porous and the toxin is introduced through the balloon.

28. (Original) A method as in claim 25, wherein the toxin is introduced through a needle on the catheter.

29. (Original) A method as in claim 25, wherein the toxin is aerosolized from the catheter.

30. (Original) A method as in claim 25, wherein energy is applied from a source on the catheter.

31. (Original) A method as in claim 30, wherein acoustic energy is applied from a transducer on the catheter.

32. (Original) A method as in claim 30, wherein electrical energy is applied from an electrode on the catheter.

33. (Original) A method as in claim 1, wherein the energy is delivered from a source external to the patient.

34. (Original) A method as in claim 33, wherein the source is an acoustic energy transducer.

35. (Original) A method as in claim 34, wherein the acoustic energy transducer is a focused ultrasound transducer.

36. – 66. (Cancelled)

67. (Original) A method as in claim 1, wherein applying energy to the target cells further comprises applying energy to the target cells under conditions which cause poration of the cell membranes.

68. (Cancelled)

69. (Currently Amended) A method as in claim 30, wherein microwave energy is applied from an antenna on the catheter.

REMARKS/ARGUMENTS

Claims 1-69 were pending in the present application. In the Office Action, claims 1-35, 67 and 69 were rejected and claims 36-66, and 68 were withdrawn. In response to the Office Action, claims 1, 6, 7, 11, and 14 have been amended and claims 12-13, 36-66, and 68 have been cancelled. No new subject matter has been added. Reexamination and reconsideration of the pending claims as amended are respectfully requested.

Claim Objections

Claim 69 was objected to for failing to end with a period. Applicants apologize for this typographical error and have amended claim 69 to end with a period thereby obviating the objection. Applicants respectfully request withdrawal of the objection.

Claim Rejections – 35 U.S.C. § 103

Claims 1-35, 67, and 69 were rejected under 35 U.S.C. § 103(a) as being unpatentable over U.S. Patent Publication No. 2004/0086531 to Barron et al. (hereinafter referred to as Barron) in view of U.S. Patent Publication No. 2004/0009180 to Donovan (hereinafter referred to as Donovan). Such rejections are overcome for at least the following reasons.

Independent claim 1 has been amended to recite in part the step of introducing a toxin to a region proximate the target cells, said toxin comprising a light chain fragment of a neurotoxin and being substantially free of heavy chain fragments of the neurotoxin. Support for this amendment may be found in paragraphs 0015, 0064, and 0067 of the application as filed, as well as in originally filed claims 11-13. Therefore, no new subject matter has been added.

The cited references alone or in combination fail to teach or suggest introducing a toxin to a region proximate the target cells, said toxin comprising a light chain fragment of a neurotoxin and being substantially free of heavy chain fragments of the neurotoxin, as now recited by claim 1.

Barron discloses methods for treating peptic ulcers and gastroesophageal reflux disease by oral administration of a botulinum toxin (Abstract). While Barron does disclose that the toxin may take various forms including recombinant produced toxins, derivates and fragments thereof (paragraphs 0047, 0048, 0087, and 0107), nowhere does Barron ever teach or suggest that the toxin comprises a light chain fragment of a neurotoxin and being substantially free of heavy chain fragments of the neurotoxin. In fact, in order for Barron's oral administration of toxin to be successful, once the toxin containing tablet has been swallowed it must include the heavy chain in order to pass through a cell membrane (paragraphs 0046 and 0104), contrary to amended claim 1 which recites that the toxin is substantially free of heavy chain fragments of the neurotoxin. Moreover, even assuming *arguendo* that Barron does teach the use of a light chain fragment of a neurotoxin and being substantially free of heavy chain fragments of the neurotoxin, Barron fails to enable its use as the light chain cannot pass through a cell membrane alone. The light chain must be accompanied by the heavy chain or additional measures are required to facilitate passage of the light chain into the target cells and Barron fails to disclose any of these additional measures.

Donovan fails to provide the elements missing from Barron. Donovan discloses the transdermal delivery of intact neurotoxins, such as the botulinum toxin, for the treatment of various conditions. In particular, Donovan teaches transdermal delivery of the toxin to subdermal muscle or other structures in order to treat various neuromuscular disorders, as set forth in paragraph 0044. While the publication does teach that the neurotoxin can take various forms, including genetically modified forms, complexes, and fragments (paragraphs 0052 and 0068), nowhere does Donovan ever teach or suggest that the toxin comprises a light chain fragment of a neurotoxin and being substantially free of heavy chain fragments of the neurotoxin. Indeed, as set forth in paragraphs 0007 and 0008 of the publication, Donovan assumes that the toxin will pass through the cell membrane via the natural endocytosis process where the heavy chain binds to the cell and mediates passage of the intact molecule into the cytosol. Therefore Donovan's toxin must include the heavy chain as it is required for binding of the toxin with the cell membrane and this is contrary to amended claim 1 which recites that the toxin is substantially free of heavy chain fragments of the neurotoxin.

In addition to the cited references failing to teach or suggest each and every element of the claimed invention, one of skill in the art would not combine Barron and Donovan. Barron discloses the use of a toxin formed into a tablet that may be taken orally to dissolve in the stomach (paragraph 0099) and teaches away from intramuscular or subcutaneous injection of a botulinum toxin to treat an ulcer or gastroesophageal reflux because they are invasive and inconvenient for patients (paragraph 0098). Donovan discloses the use of transdermal administration of a neurotoxin along with an enhancing agent to facilitate absorption (Abstract). Donovan discloses various enhancing agents such as needles, other drugs or stimulation (e.g. ultrasound or electricity) to open skin pores. Such enhancing agents would be invasive and/or inconvenient for the patient and thus contrary to the teachings of Barron which only requires a tablet to be taken orally. Furthermore, Donovan teaches "local administration" which is defined in Donovan's specification as excluding "systemic routes of administration, such as intravenous, or oral administration" (paragraph 0047). Barron's tablet is clearly systemic (paragraph 0128) and thus contrary to Donovan's teachings. Additionally, there is no need to combine the two cited references as the botulinum toxin in Barron can pass unattenuated through the lining of the gut thus there is no need to use an enhancing agent as disclosed in Donovan.

Because the cited references alone or in combination fail to teach or suggest each and every element of the claimed invention, and because of one skill in the art would not combine them, *prima facie* obviousness cannot be established under 35 U.S.C. § 103(a). Applicants respectfully request withdrawal of the § 103(a) rejection and allowance of independent claim 1 along with the claims depending therefrom.

Claims 6, 7, 11, and 14 have been amended to be consistent with amended claim 1. Claims 12-13 have been cancelled as these features are now included in base claim 1, and withdrawn claims 36-66 and 68 have also been cancelled.

Double Patenting

Claims 1-35, 67, and 69 were provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-35 of copending Application No. 11/459,090. Without conceding the issue of patentability and in order to

Appl. No. 11/750,963
Amdt. dated October 1, 2009
Reply to Office Action of August 14, 2009

PATENT

expedite prosecution of the present application, a Terminal Disclaimer is filed herewith, thereby obviating the rejection.

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.

If the Examiner believes a telephone conference would expedite prosecution of this application, please telephone the undersigned at 650-326-2400.

Respectfully submitted,



Douglas Portnow
Reg. No. 59,660

TOWNSEND and TOWNSEND and CREW LLP
Two Embarcadero Center, Eighth Floor
San Francisco, California 94111-3834
Tel: 650-326-2400
Fax: 415-576-0300
Attachments
D3P:jar
62193346 v1

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**TERMINAL DISCLAIMER TO OBVIATE A PROVISIONAL DOUBLE PATENTING
REJECTION OVER A PENDING "REFERENCE" APPLICATION**

Docket Number (Optional)
020979-003710US

In re Application of: Mark E. Deem et al.

Application No. 11/750,963

Filed: May 18, 2007

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 of any patent granted on pending **reference** Application Number 11/459,090, filed on 07/21/2006, as such term is defined in 35 U.S.C. 154 and 173, and as the term of any patent granted on said **reference** application may be shortened by any terminal disclaimer filed prior to the grant of any patent on the pending **reference** application. 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 any patent granted on the **reference** application are commonly owned. This agreement runs with any patent granted on the instant application and is binding upon the grantee, its successors or assigns.

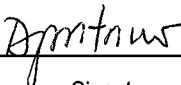
In making the above disclaimer, the owner does not disclaim the terminal part of any patent granted on the instant application that would extend to the expiration date of the full statutory term as defined in 35 U.S.C. 154 and 173 of any patent granted on said **reference** application, "as the term of any patent granted on said **reference** application may be shortened by any terminal disclaimer filed prior to the grant of any patent on the pending **reference** application," in the event that: any such patent: granted on the pending **reference** application: 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 shortened by any terminal disclaimer filed prior to its grant.

Check either box 1 or 2 below, if appropriate.

1. ☐ For submissions on behalf of an organization (e.g., corporation, partnership, university, government agency, etc.), the undersigned is empowered to act on behalf of the 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 of record. Reg. No. 59,660



Signature

October 1, 2009

Date

Douglas Portnow

Typed or printed name

- ☒ Terminal disclaimer fee under 37 CFR §1.20(d) is included.

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*Statement under 37 CFR 3.73(b) is required if terminal disclaimer is signed by the assignee (owner).

Form PTO/SB/96 may be used for making this certification. See MPEP § 324.

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62237301 v1

Electronic Patent Application Fee Transmittal

Application Number:	11750963			
Filing Date:	18-May-2007			
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:	020979-003710US			
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:				
Extension-of-Time:				

Description	Fee Code	Quantity	Amount	Sub-Total in USD(\$)
Miscellaneous:				
Statutory disclaimer	2814	1	70	70
Total in USD (\$)				70

Electronic Acknowledgement Receipt

EFS ID:	6188354
Application Number:	11750963
International Application Number:	
Confirmation Number:	1089
Title of Invention:	METHODS AND SYSTEMS FOR TOXIN DELIVERY TO THE NASAL CAVITY
First Named Inventor/Applicant Name:	Mark E. Deem
Customer Number:	20350
Filer:	Douglas Portnow/Joy Roeder
Filer Authorized By:	Douglas Portnow
Attorney Docket Number:	020979-003710US
Receipt Date:	01-OCT-2009
Filing Date:	18-MAY-2007
Time Stamp:	17:21:17
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	yes
Payment Type	Deposit Account
Payment was successfully received in RAM	\$70
RAM confirmation Number	3575
Deposit Account	201430
Authorized User	

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

Charge any Additional Fees required under 37 C.F.R. Section 1.21 (Miscellaneous fees and charges)

File Listing:					
Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1		2009_10_01_AMDT_TD_020979_003710US.PDF	510544 1f78302f13a3af7b6f25e88ff8f9850c03d34d90	yes	10
	Multipart Description/PDF files in .zip description				
	Document Description	Start	End		
	Amendment/Req. Reconsideration-After Non-Final Reject	1	1		
	Claims	2	5		
	Applicant Arguments/Remarks Made in an Amendment	6	9		
	Terminal Disclaimer Filed	10	10		
Warnings:					
Information:					
2	Fee Worksheet (PTO-875)	fee-info.pdf	30250 d89e0be0210358d7f0d8acf288068a55443522db	no	2
Warnings:					
Information:					
Total Files Size (in bytes):			540794		
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PATENT APPLICATION FEE DETERMINATION RECORD Substitute for Form PTO-875					Application or Docket Number 11/750,963		Filing Date 05/18/2007		☐ To be Mailed	
APPLICATION AS FILED – PART I										
(Column 1)			(Column 2)		SMALL ENTITY ☒ OR			OTHER THAN SMALL ENTITY		
FOR	NUMBER FILED	NUMBER EXTRA	RATE (\$)	FEE (\$)	OR	RATE (\$)	FEE (\$)			
☐ BASIC FEE (37 CFR 1.16(a), (b), or (c))	N/A	N/A	N/A			N/A				
☐ SEARCH FEE (37 CFR 1.16(k), (l), or (m))	N/A	N/A	N/A			N/A				
☐ EXAMINATION FEE (37 CFR 1.16(o), (p), or (q))	N/A	N/A	N/A			N/A				
TOTAL CLAIMS (37 CFR 1.16(i))	minus 20 =	*	X \$	=		X \$	=			
INDEPENDENT CLAIMS (37 CFR 1.16(h))	minus 3 =	*	X \$	=		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 \$250 (\$125 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			TOTAL				
APPLICATION AS AMENDED – PART II										
(Column 1)			(Column 2)		SMALL ENTITY OR			OTHER THAN SMALL ENTITY		
AMENDMENT	10/01/2009	CLAIMS REMAINING AFTER AMENDMENT	HIGHEST NUMBER PREVIOUSLY PAID FOR	PRESENT EXTRA	RATE (\$)	ADDITIONAL FEE (\$)	OR	RATE (\$)	ADDITIONAL FEE (\$)	
	Total (37 CFR 1.16(i))	* 35	Minus	** 69	=	0		X \$	=	
	Independent (37 CFR 1.16(h))	* 1	Minus	*** 3	=	0		X \$	=	
☐ Application Size Fee (37 CFR 1.16(s))										
☐ FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))										
					TOTAL ADD'L FEE	0		TOTAL ADD'L FEE		
(Column 1)			(Column 2)		SMALL ENTITY OR			OTHER THAN SMALL ENTITY		
AMENDMENT		CLAIMS REMAINING AFTER AMENDMENT	HIGHEST NUMBER PREVIOUSLY PAID FOR	PRESENT EXTRA	RATE (\$)	ADDITIONAL FEE (\$)	OR	RATE (\$)	ADDITIONAL FEE (\$)	
	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			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.										

Legal Instrument Examiner:
/KELLY D. HARRIS/

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.**

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Application Number 	Application/Control No. 11/750,963	Applicant(s)/Patent under Reexamination DEEM ET AL.	
Document Code - DISQ		Internal Document – DO NOT MAIL	

TERMINAL DISCLAIMER	☒ APPROVED	☐ DISAPPROVED
Date Filed : 10/01/09	This patent is subject to a Terminal Disclaimer	

Approved/Disapproved by:
j.proctor

U.S. Patent and Trademark Office



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NOTICE OF ALLOWANCE AND FEE(S) DUE

20350 7590 11/17/2009

TOWNSEND AND TOWNSEND AND CREW, LLP
TWO EMBARCADERO CENTER
EIGHTH FLOOR
SAN FRANCISCO, CA 94111-3834

EXAMINER

NAVARRO, ALBERT MARK

ART UNIT

PAPER NUMBER

1645

DATE MAILED: 11/17/2009

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
-----------------	-------------	----------------------	---------------------	------------------

11/750,963

05/18/2007

Mark E. Deem

020979-003710US

1089

TITLE OF INVENTION: METHODS AND SYSTEMS FOR TOXIN DELIVERY TO THE NASAL CAVITY

APPLN. TYPE	SMALL ENTITY	ISSUE FEE DUE	PUBLICATION FEE DUE	PREV. PAID ISSUE FEE	TOTAL FEE(S) DUE	DATE DUE
nonprovisional	YES	\$755	\$300	\$0	\$1055	02/17/2010

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 SMALL ENTITY status shown above.

If the SMALL ENTITY is shown as YES, verify your current SMALL ENTITY status:

A. If the status is the same, pay the TOTAL FEE(S) DUE shown above.

B. If the status above is to be removed, check box 5b on Part B - Fee(s) Transmittal and pay the PUBLICATION FEE (if required) and twice the amount of the ISSUE FEE shown above, or

If the SMALL ENTITY is shown as NO:

A. Pay TOTAL FEE(S) DUE shown above, or

B. If applicant claimed SMALL ENTITY status before, or is now claiming SMALL ENTITY status, check box 5a on Part B - Fee(s) Transmittal and pay the PUBLICATION FEE (if required) and 1/2 the ISSUE FEE shown above.

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PART B - FEE(S) TRANSMITTAL

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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)

20350 7590 11/17/2009

**TOWNSEND AND TOWNSEND AND CREW, LLP
TWO EMBARCADERO CENTER
EIGHTH FLOOR
SAN FRANCISCO, CA 94111-3834**

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

Certificate of Mailing or Transmission

I hereby certify that this Fee(s) Transmittal is being deposited with the United States Postal Service with sufficient postage for first class mail in an envelope addressed to the Mail Stop ISSUE FEE address above, or being 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.
-----------------	-------------	----------------------	---------------------	------------------

11/750,963 05/18/2007 Mark E. Deem 020979-003710US 1089

TITLE OF INVENTION: METHODS AND SYSTEMS FOR TOXIN DELIVERY TO THE NASAL CAVITY

APPLN. TYPE	SMALL ENTITY	ISSUE FEE DUE	PUBLICATION FEE DUE	PREV. PAID ISSUE FEE	TOTAL FEE(S) DUE	DATE DUE
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nonprovisional YES \$755 \$300 \$0 \$1055 02/17/2010

EXAMINER	ART UNIT	CLASS-SUBCLASS
----------	----------	----------------

NAVARRO, ALBERT MARK 1645 424-236100

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, 1 _____
- (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. 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 _____

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- ☐ 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)

- ☐ a. Applicant claims SMALL ENTITY status. See 37 CFR 1.27. ☐ b. Applicant is no longer claiming SMALL ENTITY status. See 37 CFR 1.27(g)(2).

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. _____

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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
11/750,963	05/18/2007	Mark E. Deem	020979-003710US	1089
20350	7590	11/17/2009	EXAMINER	
TOWNSEND AND TOWNSEND AND CREW, LLP TWO EMBARCADERO CENTER EIGHTH FLOOR SAN FRANCISCO, CA 94111-3834			NAVARRO, ALBERT MARK	
			ART UNIT	PAPER NUMBER
			1645	
DATE MAILED: 11/17/2009				

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 341 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 341 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.

Notice of Allowability	Application No.	Applicant(s)	
	11/750,963	DEEM ET AL.	
	Examiner	Art Unit	
	Mark Navarro	1645	

-- 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 October 1, 2009.
2. ☒ The allowed claim(s) is/are 1-11, 14-35, 67, and 69, renumbered as 1-35, respectively.
3. ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
 - 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.

4. ☐ A SUBSTITUTE OATH OR DECLARATION must be submitted. Note the attached EXAMINER'S AMENDMENT or NOTICE OF INFORMAL PATENT APPLICATION (PTO-152) which gives reason(s) why the oath or declaration is deficient.
5. ☐ CORRECTED DRAWINGS (as "replacement sheets") must be submitted.
 - (a) ☐ including changes required by the Notice of Draftsperson's Patent Drawing Review (PTO-948) attached
 - 1) ☐ hereto or 2) ☐ to Paper No./Mail Date ____.
 - (b) ☐ 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. ☐ Notice of Informal Patent Application |
| 2. ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948) | 6. ☐ Interview Summary (PTO-413),
Paper No./Mail Date ____. |
| 3. ☒ Information Disclosure Statements (PTO/SB/08),
Paper No./Mail Date <u>9/28/09</u> | 7. ☐ Examiner's Amendment/Comment |
| 4. ☐ Examiner's Comment Regarding Requirement for Deposit
of Biological Material | 8. ☐ Examiner's Statement of Reasons for Allowance |
| | 9. ☐ Other ____. |

/Mark Navarro/
Primary Examiner, Art Unit 1645

Search Notes 	Application/Control No. 11750963	Applicant(s)/Patent Under Reexamination DEEM ET AL.
	Examiner Mark Navarro	Art Unit 1645

SEARCHED			
Class	Subclass	Date	Examiner

SEARCH NOTES		
Search Notes	Date	Examiner
Medline, Biosis, Ca, Caplus, Embase, USpatfull , terms: toxin, botulinum, energy, ultrasound, microwave, xray, enhance, delivery, treat, administer	11/13/09	MN

INTERFERENCE SEARCH			
Class	Subclass	Date	Examiner
PALM Inventor Search		11/13/09	MN

--	--

Substitute for form 1449/PTO INFORMATION DISCLOSURE STATEMENT BY APPLICANT <i>(Use as many sheets as necessary)</i>				Complete if Known	
				Application Number	11/750,963
				Filing Date	May 18, 2007
				First Named Inventor	DEEM, MARK E.
				Art Unit	1645
Examiner Name	NAVARRO, Albert Mark				
Attorney Docket Number	020979-003710US				
Sheet	1	of	1		

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

FOREIGN PATENT DOCUMENTS								
Examiner Initials*	Cite No. ¹	Foreign Patent Document			Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear	T ⁶
		Country Code ³	Number ⁴	Kind Code ⁵ (if known)				☐

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
	1	DE PAIVA et al., "Light chain of botulinum neurotoxin is active in mammalian motor nerve terminals when delivered via liposomes," <i>FEBS Lett.</i> 1990 Dec 17;277(1-2):171-174.	☐
	2	RAJ, Editorial, <i>Pain Practice</i> , 2004; 4(1S): S1-S3.	☐
	3	SUNDARAM et al., "An Experimental and Theoretical Analysis of Ultrasound-Induced Permeabilization of Cell Membranes," <i>Biophysical Journal</i> , 2003 May 1; 84(5): 3087-3101.	☐

Examiner Signature	/Albert M Navarro/	Date Considered	11/13/2009
-----------------------	--------------------	--------------------	------------

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

¹ Applicant's unique citation designation number (optional). ² Applicant is to place a check mark here if English language Translation is attached.

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)

20350 7590 11/17/2009

TOWNSEND AND TOWNSEND AND CREW, LLP
 TWO EMBARCADERO CENTER
 EIGHTH FLOOR
 SAN FRANCISCO, CA 94111-3834

I hereby certify that this Fee(s) Transmittal is being filed via EFS-Web with the United States Patent and Trademark Office on December 11, 2009.

By:

Joy A. Roeder

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
11/750,963	05/18/2007	Mark E. Deem	020979-003710US	1089

TITLE OF INVENTION: METHODS AND SYSTEMS FOR TOXIN DELIVERY TO THE NASAL CAVITY

APPLN. TYPE	SMALL ENTITY	ISSUE FEE DUE	PUBLICATION FEE DUE	PREV. PAID ISSUE FEE	TOTAL FEE(S) DUE	DATE DUE
nonprovisional	YES	\$755	\$300	\$0	\$1055	02/17/2010

EXAMINER	ART UNIT	CLASS-SUBCLASS
NAVARRO, ALBERT MARK	1645	424-236100

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 **TOWNSEND and TOWNSEND and CREW LLP**

2

3 **Jeffrey Grainger, Esq.**

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)

THE FOUNDRY, LLC

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 **20-1430** (enclose an extra copy of this form).

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

☐ a. Applicant claims SMALL ENTITY status. See 37 CFR 1.27.

☐ b. Applicant is no longer claiming SMALL ENTITY status. See 37 CFR 1.27(g)(2).

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

Douglas Portnow

Date **December 10, 2009**

Typed or printed name

Douglas Portnow

Registration No. **59660**

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:	11750963			
Filing Date:	18-May-2007			
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:	020979-003710US			
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	755	755
Publ. Fee- early, voluntary, or normal	1504	1	300	300

Description	Fee Code	Quantity	Amount	Sub-Total in USD(\$)
Extension-of-Time:				
Miscellaneous:				
Total in USD (\$)				1055

Electronic Acknowledgement Receipt

EFS ID:	6622829
Application Number:	11750963
International Application Number:	
Confirmation Number:	1089
Title of Invention:	METHODS AND SYSTEMS FOR TOXIN DELIVERY TO THE NASAL CAVITY
First Named Inventor/Applicant Name:	Mark E. Deem
Customer Number:	20350
Filer:	Douglas Portnow/Joy Roeder
Filer Authorized By:	Douglas Portnow
Attorney Docket Number:	020979-003710US
Receipt Date:	11-DEC-2009
Filing Date:	18-MAY-2007
Time Stamp:	17:32:57
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	yes
Payment Type	Deposit Account
Payment was successfully received in RAM	\$ 1055
RAM confirmation Number	3844
Deposit Account	201430
Authorized User	
The Director of the USPTO is hereby authorized to charge indicated fees and credit any overpayment as follows: Charge any Additional Fees required under 37 C.F.R. Section 1.21 (Miscellaneous fees and charges)	

File Listing:					
Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	Issue Fee Payment (PTO-85B)	2009_12_11_IFXMTL_020979_003710US.PDF	116251 8bfe1b0f037043e027f13501f36b2cf63f2a6f c5	no	1
Warnings:					
Information:					
2	Fee Worksheet (PTO-875)	fee-info.pdf	31962 988bbcddecd3c6e58a49db2d2d5e24dc12 05f63e	no	2
Warnings:					
Information:					
Total Files Size (in bytes):			148213		
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.					

Substitute for form 1449A/PTO INFORMATION DISCLOSURE STATEMENT BY APPLICANT <i>(Use as many sheets as necessary)</i>			Complete if Known		
			Application Number	11/750,963	
			Filing Date	May 18, 2007	
			First Named Inventor	DEEM, MARK E.	
			Art Unit	1645	
			Examiner Name	Unassigned	
Sheet	2	of	4	Attorney Docket Number	020979-003710US

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)			
	36	2002/0198512	12-26-2002	Seward	
	37	2003/0050591	03-13-2003	Pat rick McHale	
	38	2003/0202990	10-30-2003	Donovan et al.	
	39	2003/0211121	11-13-2003	Donovan	
	40	2004/0009180	01-15-2004	Donovan	
	41	2004/0010290	01-15-2004	Schroeppe et al.	
	42	2004/0091880	05-13-2004	Wiebusch et al.	
	43	2004/0142005	07-22-2004	Brooks et al.	
	44	2004/0151741	08-05-2004	Borodic	
	45	2004/0175399	09-09-2004	Schiffman	
	46	2004/0213813	10-28-2004	Ackerman	
	47	2004/0213814	10-28-2004	Ackerman	
	48	2004/0226556	11-18-2004	Deem et al.	
	49	2004/0253274	12-16-2004	Voet	
	50	2005/0019346	01-27-2005	Boulis	
	51	2005/0074461	04-07-2005	Donovan	
	52	2007/0021803	01-25-2007	Deem et al.	

FOREIGN PATENT DOCUMENTS						
Examiner Initials*	Cite No. ¹	Foreign Patent Document		Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear
		Country Code ³	Number ⁴ Kind Code ⁵ (if known)			
	53	WO	2004/101028 A2	11-25-2004	The Foundry, Inc.	

Examiner Signature	Date Considered
-----------------------	--------------------

* EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant. ¹ Applicant's unique citation designation number (optional). ² Kind Codes of U.S. 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.3). 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 symbols 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.

ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /MN/



UNITED STATES PATENT AND TRADEMARK OFFICE

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

APPLICATION NO.	ISSUE DATE	PATENT NO.	ATTORNEY DOCKET NO.	CONFIRMATION NO.
11/750,963	02/02/2010	7655243	020979-003710US	1089

20350 7590 01/13/2010

TOWNSEND AND TOWNSEND AND CREW, LLP
TWO EMBARCADERO CENTER
EIGHTH FLOOR
SAN FRANCISCO, CA 94111-3834

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 341 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;

POWER OF ATTORNEY TO PROSECUTE APPLICATIONS BEFORE THE USPTO

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

I hereby appoint:

☒ 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:

☒ The address associated with Customer Number:

021971

OR

☐ Firm or Individual Name			
Address			
City	State	Zip	
Country			
Telephone			Email

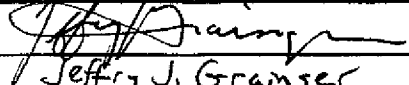
Assignee Name and Address:

**THE FOUNDRY, LLC
199 Jefferson Drive
Menlo Park, CA 94025**

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

Signature		Date	5/6/11
Name	Jeffrey J. Granger	Telephone	650-400-2646
Title	Managing Partner		

STATEMENT UNDER 37 CFR 3.73(b)

Applicant/Patent Owner: The Foundry, LLC

Application No./Patent No.: 11/750,963 Filed/Issue Date: May 18, 2007

Entitled: Methods and Systems for Toxin Delivery to the Nasal Cavity

The 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: M. Deem, and H. Gifford 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, LLC

The 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

Douglas Portnow

May 23, 2011

Date

Douglas Portnow; Reg. No. 59,660

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.

Electronic Acknowledgement Receipt

EFS ID:	10155568
Application Number:	11750963
International Application Number:	
Confirmation Number:	1089
Title of Invention:	METHODS AND SYSTEMS FOR TOXIN DELIVERY TO THE NASAL CAVITY
First Named Inventor/Applicant Name:	Mark E. Deem
Customer Number:	20350
Filer:	Douglas Portnow/Jennifer Altman(DP/ja)
Filer Authorized By:	Douglas Portnow
Attorney Docket Number:	020979-003710US
Receipt Date:	24-MAY-2011
Filing Date:	18-MAY-2007
Time Stamp:	12:19:28
Application Type:	Utility under 35 USC 111(a)

Payment information:

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

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	Power of Attorney	29028-719-501POA.pdf	86265 dae6745918ed7a32f659c94f2c497dd6d0a50d38	no	2

Warnings:

Information:

Total Files Size (in bytes):

86265

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

New Applications Under 35 U.S.C. 111

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

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

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

New International Application Filed with the USPTO as a Receiving Office

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



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APPLICATION NUMBER	FILING OR 371(C) DATE	FIRST NAMED APPLICANT	ATTY. DOCKET NO./TITLE
11/750,963	05/18/2007	Mark E. Deem	29028-719.501

CONFIRMATION NO. 1089

POWER OF ATTORNEY NOTICE



OC000000047939049

20350
KILPATRICK TOWNSEND & STOCKTON LLP
TWO EMBARCADERO CENTER
EIGHTH FLOOR
SAN FRANCISCO, CA 94111-3834

Date Mailed: 05/31/2011

NOTICE REGARDING CHANGE OF POWER OF ATTORNEY

This is in response to the Power of Attorney filed 05/24/2011.

- The Power of Attorney to you in this application has been revoked by the assignee who has intervened as provided by 37 CFR 3.71. Future correspondence will be mailed to the new address of record(37 CFR 1.33).

/qtran/

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



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11/750,963	05/18/2007	Mark E. Deem	29028-719.501

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

CONFIRMATION NO. 1089
POA ACCEPTANCE LETTER



Date Mailed: 05/31/2011

NOTICE OF ACCEPTANCE OF POWER OF ATTORNEY

This is in response to the Power of Attorney filed 05/24/2011.

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.

/qtran/

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