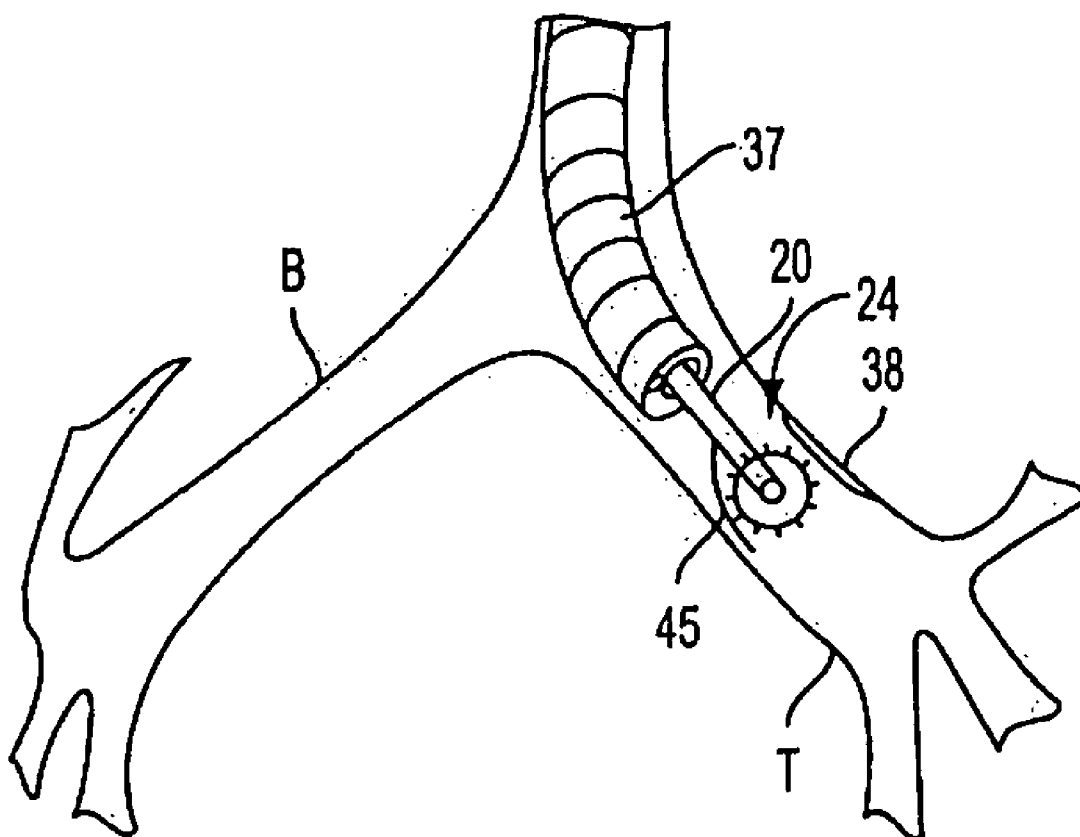


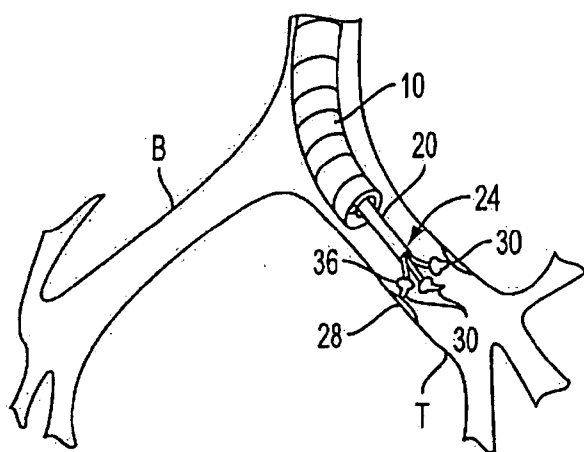
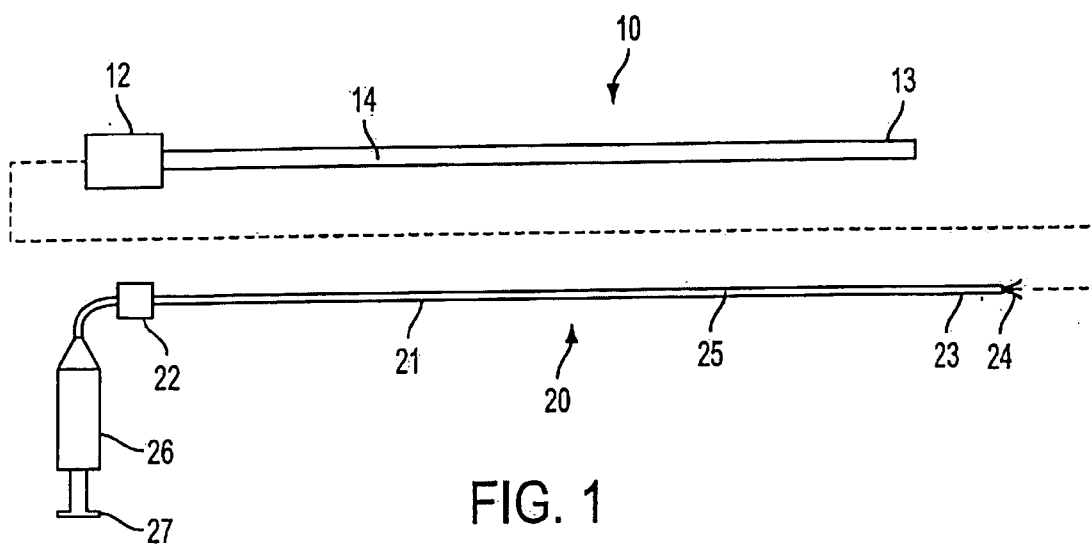


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(19) **United States**(12) **Patent Application Publication****Deem et al.**(10) **Pub. No.: US 2006/0225742 A1**(43) **Pub. Date: Oct. 12, 2006**(54) **APPARATUS FOR TREATING ASTHMA  
USING NEUROTOXIN**(75) Inventors: **Mark E. Deem**, Mountain View, CA  
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May 13, 2003.**Publication Classification**(51) **Int. Cl.**  
**A62B 9/06** (2006.01)(52) **U.S. Cl.** ..... **128/207.14**(57) **ABSTRACT**

Apparatus for providing intrabronchial delivery of neurotoxins to control the effects of asthma comprises a shaft having proximal and distal ends and a neurotoxin applicator assembly disposed on the distal end. The neurotoxin applicator assembly comprises a deployable needle assembly, a rotating needle assembly, and a needle-less injection assembly or a nebulizer assembly.





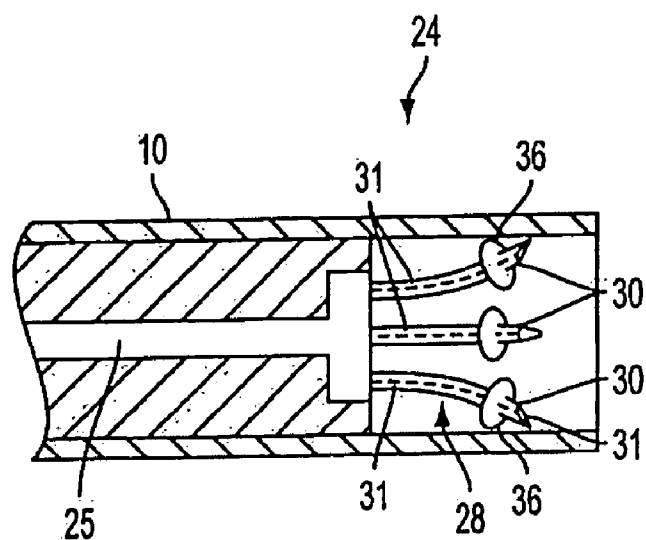


FIG. 3A

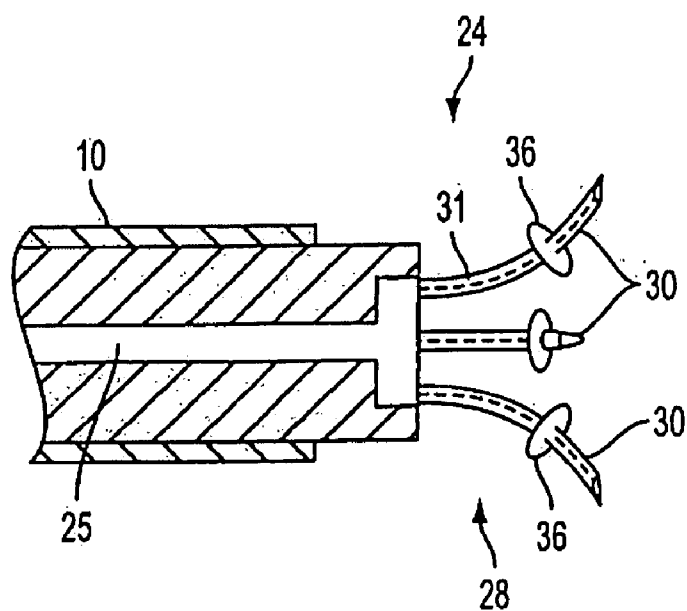


FIG. 3B

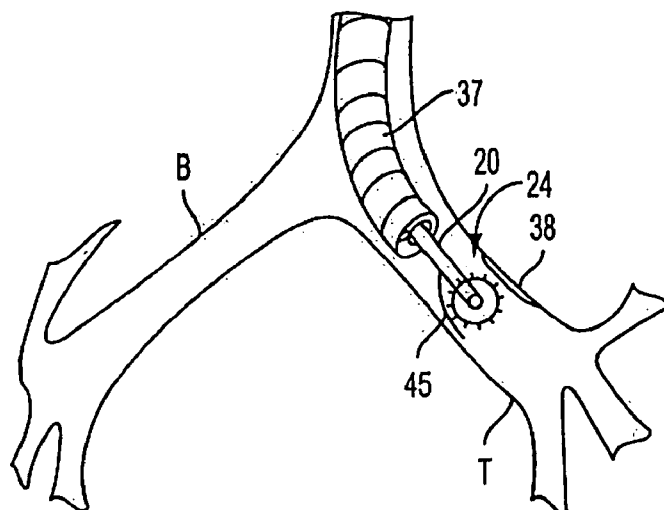


FIG. 4

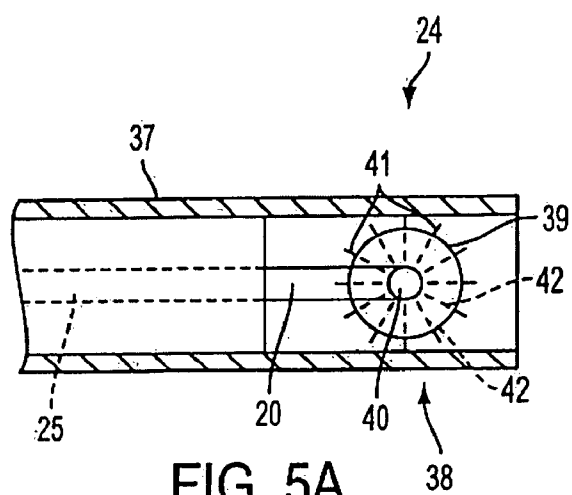


FIG. 5A

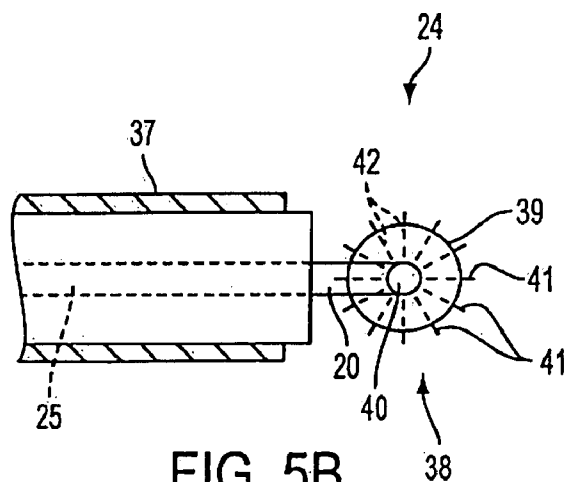


FIG. 5B

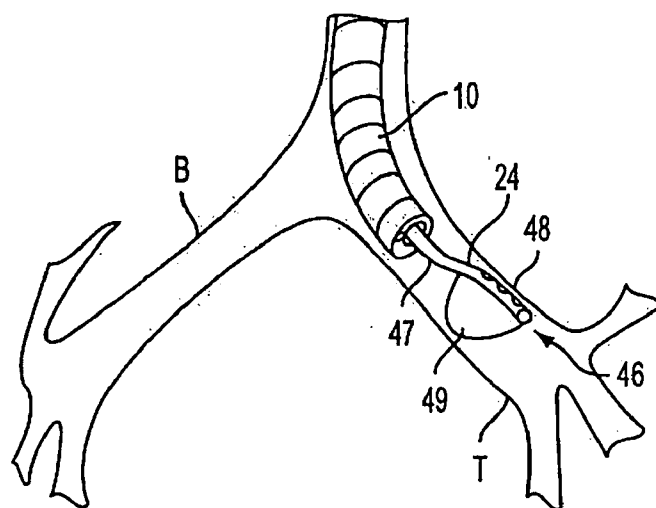


FIG. 6

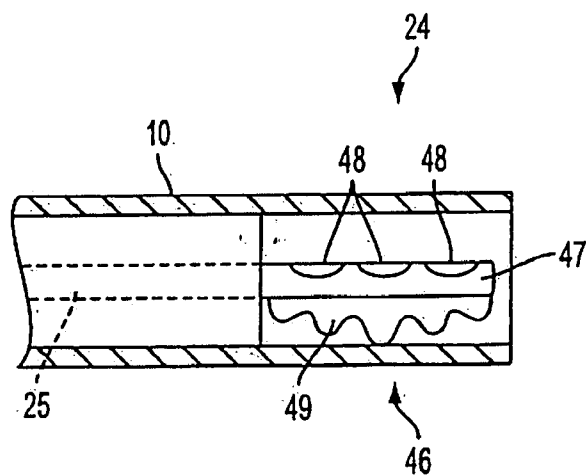


FIG. 7A

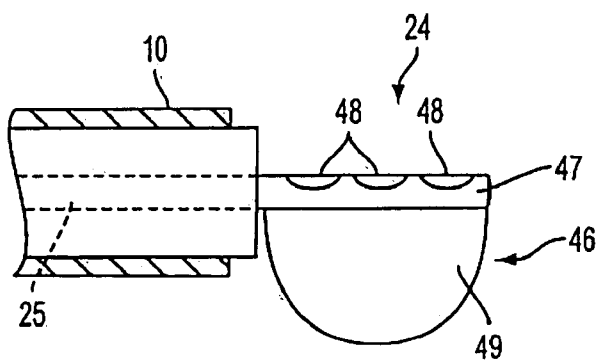


FIG. 7B

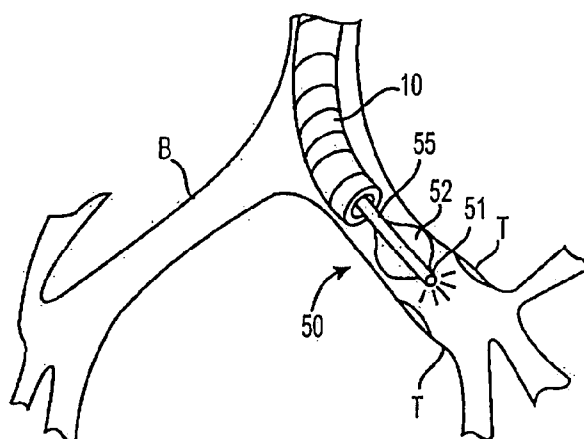


FIG. 8

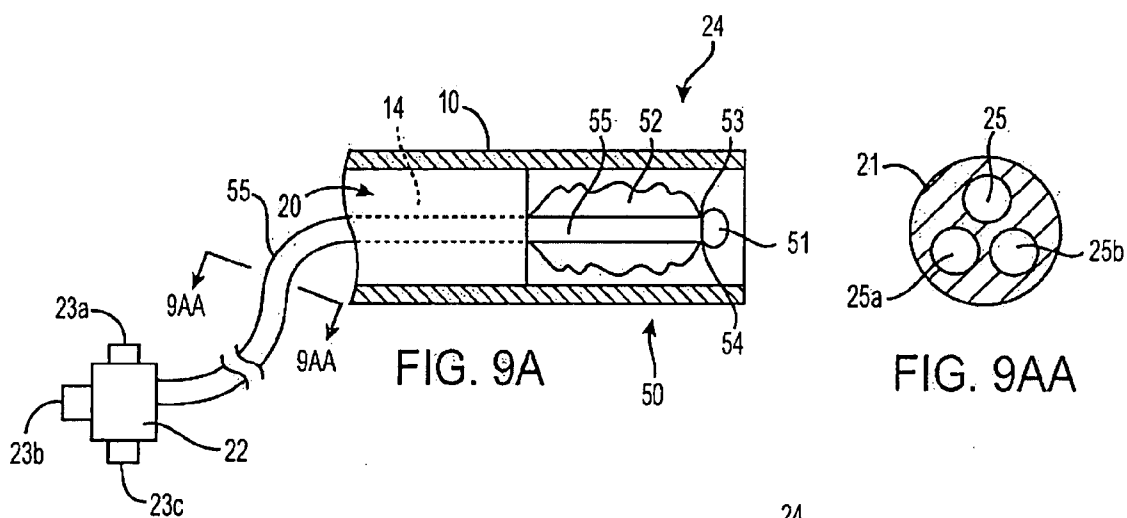


FIG. 9A

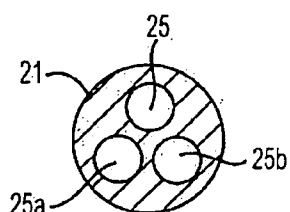


FIG. 9AA

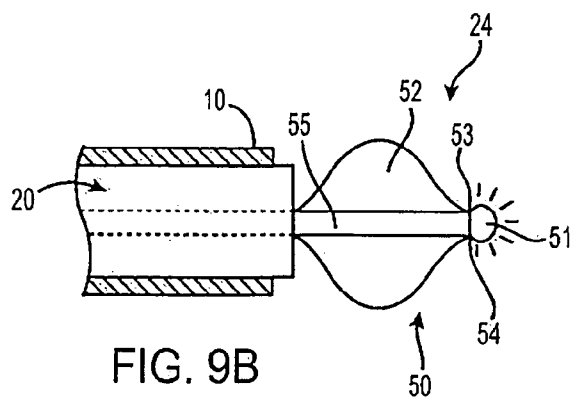


FIG. 9B

## APPARATUS FOR TREATING ASTHMA USING NEUROTOXIN

### CROSS-REFERENCES TO RELATED APPLICATIONS

[0001] The present application is a continuation of U.S. patent application Ser. No. 10/437,882 (Attorney Docket No. 020979-003600US), filed May 13, 2003, the full disclosure of which is incorporated herein by reference.

### BACKGROUND OF THE INVENTION

#### Field of the Invention

[0002] The present invention relates to apparatus for treating asthma by controlled delivery of neurotoxin 5 using a neurotoxin applicator assembly.

[0003] The lung is made up of progressively smaller bronchial bifurcations stemming downward from the trachea. The trachea and proximal bronchi are lumens consisting of an outer layer of fascia surrounding a U-shaped inner cartilaginous layer, wherein the open portion of the U is spanned by smooth muscle. Inside the cartilaginous layer are a collagenous elastic layer and an innermost epithelial layer. Mucus secreting goblet cells and transport cilia cells are interspersed within these inner layers.

[0004] As the bronchi branch and get smaller, the cartilaginous layer changes from a U-shape to irregular and helical shapes. In addition, the smooth muscle layer becomes helical bands surrounding the entire circumference of the bronchi, the goblet cells gradually decrease in numbers and the ciliated cells get smaller and fewer in number. In the most distal bronchi, the outer cartilaginous layer disappears completely, the smooth muscle layer becomes the outermost layer and goblet cells and ciliated cells disappear completely.

[0005] Asthma is a complex disease of the bronchial tree, characterized by airway hyperresponsiveness to allergens, stress and environmental triggers. Environmental triggers include irritants such as pollutants and non-allergenic triggers such as exposure to cold air. Airway hyperresponsiveness results in acute narrowing of the entire bronchial tree reducing airflow through the lungs, compromising respiration and limiting gas exchange in the alveoli. The narrowing of the bronchial tree is a result of three basic characteristic physiologic responses: (1) smooth muscle contraction; (2) increased mucus production; and (3) edema caused by arterial dilatation and increased arterial permeability. The triggering mechanisms for these physiologic responses are part of the body's inflammatory response system.

[0006] Chronic uncontrolled asthma can result in structural changes to the bronchial wall itself. Smooth muscle hyperplasia results in thickening of the smooth muscle components of the bronchial wall. Thickening of the sub-epithelial collagen layer that lies between the airway epithelium and the smooth muscle layer results in progressive stiffening of the wall of the bronchi. Studies have shown that stiffening of the airway wall results in more profound narrowing of the airway for a given asthma attack. This is due to changes in the ability of the mucosal layer to fold in response to the smooth muscle layer contraction.

[0007] Recently, the controlled injection of neurotoxin has become a common procedure for controlling skeletal muscle

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

[0008] The use of neurotoxin for the control of asthma is described in U.S. Pat. No. 6,063,768 to First, wherein asthma is included in a list of neurogenic inflammatory disorders that may be controlled through the action of neurotoxins such as BOTOX® neurotoxin. That patent also describes that BOTOX® neurotoxin could be aerosolized and introduced into the lungs. An earlier patent, U.S. Pat. No. 5,766,605 to Sanders, et al. describes the use of BOTOX® neurotoxin to treat asthma and COPD, but does not describe the methods or devices used to do so. Further mention of BOTOX® neurotoxin in connection with asthma is provided in a press release dated Feb. 7, 2003 by the University of Alberta in describing the work of Dr. Redwan Moqbel. The release mentions that Dr. Moqbel and others are researching the possible use of neurotoxins such as tetanus and botulinum toxin to prevent eosinophils from activating and starting the inflammatory cascade that results in an asthma attack.

[0009] While it may be possible to simply aerosolize neurotoxins for introduction into the lungs, introducing it into the patient through traditional inhalation means would expose the mouth, tongue, epiglottis, vocal cords, etc. to the actions of the neurotoxin, with obvious deleterious results. Much more controlled and direct application of the neurotoxin to the desired tissue is required for safe and effective therapy.

[0010] Accordingly, it would be desirable to provide apparatus that enables controlled delivery of a neurotoxin to target treatment areas within a patient's bronchial airways.

[0011] It also would be desirable to provide an apparatus permitting the controlled injection of neurotoxin into the bronchial wall of a patient.

[0012] It would further be desirable to provide a needleless injection apparatus to eliminate potential complications related to the presence of needles within a patient's bronchial airways.

[0013] Additionally, it would be desirable to provide an apparatus permitting the application of neurotoxin onto a target treatment area within a patient's bronchial airways.

## BRIEF SUMMARY OF THE INVENTION

[0014] In view of the foregoing, it is an object of the present invention to provide apparatus that enables the controlled delivery of a neurotoxin to target treatment areas within a patient's bronchial airways.

[0015] It is a further object of the present invention to provide an apparatus permitting the controlled injection of neurotoxin into the bronchial wall of a patient.

[0016] It is an additional object of the present invention to provide a needle-less injection apparatus to eliminate potential complications related to the presence of needles within a patient's bronchial airways.

[0017] It is another object of the present invention to provide an apparatus permitting the application of neurotoxin onto a target treatment area within a patient's bronchial airways.

[0018] These and other objects of the present invention are accomplished by providing an intrabronchial neurotoxin delivery system for controlled delivery of neurotoxin to a target treatment area within a patient's bronchial airways to lessen the effects of asthma. The introduction of neurotoxin into the bronchial airways disables the hyperresponsive smooth muscle layer and controls the hypersecretion of mucus.

[0019] The intrabronchial neurotoxin delivery system preferably includes a bronchoscope and neurotoxin applicator assembly. The neurotoxin applicator assembly may be a needle assembly, rotating needle assembly, needle-less injection assembly or a nebulizer assembly.

[0020] In a first illustrative embodiment, the neurotoxin applicator assembly comprises a needle assembly including at least one needle having a lumen in fluid communication with a source of liquid neurotoxin. The needles are preformed to contract radially when disposed within a lumen, such as a lumen of the bronchoscope, but may be extended to penetrate and inject small doses of neurotoxin into the bronchial wall of a patient.

[0021] In an alternative embodiment, the neurotoxin applicator assembly comprises a rotating needle assembly including plural needles disposed along the circumference of a wheel. Again, the needles include lumens in fluid communication with a source of liquid neurotoxin. In operation, the wheel is adapted to be rolled across a target treatment area about a central hub. Optionally, the rotating needle assembly may include a fender to protect a portion of the bronchial wall substantially opposite the target treatment area.

[0022] In another alternative embodiment, the neurotoxin applicator assembly comprises a needle-less injection assembly including a shaft having at least one port in fluid communication with a source of liquid neurotoxin. The needle-less injection assembly can be used to inject neurotoxin into the bronchial wall without needle penetration. Optionally, an inflatable balloon may be provided to help position the at least one port adjacent the target treatment area.

[0023] In yet a further alternative embodiment, the neurotoxin applicator assembly comprises a nebulizer assembly including an atomizer in fluid communication with a source of liquid neurotoxin. The atomizer converts the liquid neu-

rotoxin into a fine spray or mist that is directed onto the target treatment area. The particle size of the mix can be controlled using injection pressure or atomizer head design to access specific portions of the lung adjacent to or downstream of the treatment device. An inflatable balloon optionally may be provided to facilitate positioning the atomizer adjacent the target treatment area. The balloon also serves to isolate the lung segment downstream of the device to prevent reflux of the mist into undesired portions of the airway. In addition, lumens optionally may be disposed between the balloon and atomizer to provide a ventilation system that allows pressure control of the treatment area to prevent over-inflation of the lung, mixing of the atomized fluid, and evacuation of remaining mist at termination of therapy, prior to balloon deflation.

## BRIEF DESCRIPTION OF THE DRAWINGS

[0024] The above and other objects and advantages of the present invention will be apparent upon consideration of the following detailed description, taken in conjunction with the accompanying drawings, in which like reference characters refer to like parts throughout, and in which:

[0025] **FIG. 1** is a side view of an intrabronchial neurotoxin delivery system of the present invention;

[0026] **FIG. 2** is a perspective view of an illustrative embodiment of a neurotoxin applicator assembly of the present invention;

[0027] **FIGS. 3A and 3B** are cross-sectional views of the neurotoxin applicator assembly of **FIG. 2** in retracted and extended positions, respectively;

[0028] **FIG. 4** is a perspective view of an alternative embodiment of a neurotoxin applicator assembly of the present invention;

[0029] **FIGS. 5A and 5B** are partial cross-sectional views of the neurotoxin applicator assembly of **FIG. 4** in retracted and extended positions, respectively;

[0030] **FIG. 6** is a perspective view, of another alternative embodiment of a neurotoxin applicator assembly of the present invention;

[0031] **FIGS. 7A and 7B** are partial cross-sectional views of the neurotoxin applicator assembly of **FIG. 6** in retracted and extended positions, respectively;

[0032] **FIG. 8** is a perspective view of a yet further alternative embodiment of a neurotoxin applicator assembly of the present invention;

[0033] **FIGS. 9A and 9B** are partial cross-sectional views of the neurotoxin applicator assembly of **FIG. 8** in retracted and extended positions, respectively. **FIG. 9AA** is a cross-sectional view taken along line 9AA-9AA in **FIG. 9A**.

## DETAILED DESCRIPTION OF THE INVENTION

[0034] Referring to **FIG. 1**, apparatus for controlled delivery of neurotoxin to a target treatment area within a patient's bronchial airways to lessen the effects of asthma is described. Preferably, the apparatus comprises bronchoscope **10** and neurotoxin applicator assembly **20**. Bronchoscope **10** has proximal end **12**, distal end **13**, and lumen **14**. As is conventional, bronchoscope **10** also includes a light

source for illuminating the interior of a patient's lung and optics, such as a miniature camera, that enables the physician to view the interior of the patient's lung. Alternatively, bronchoscope 10 may omit the light source and optics, and instead comprise an outer sheath. In this latter case, device 10 and neurotoxin applicator 20 would be observed using a separate conventional bronchoscope.

[0035] In accordance with the principles of the present invention, neurotoxin applicator assembly 20, of which various illustrative embodiments are described hereinbelow, enables the physician to selectively administer controlled doses of neurotoxin to or within selected treatment sites in the patient's lung. More specifically, neurotoxin applicator assembly 20 may be selectively advanced through lumen 14 of bronchoscope 10 to deliver a neurotoxin, such as botulinum toxin, serotype A, to a target treatment area.

[0036] Neurotoxin applicator assembly 20 includes shaft 21 coupled to at its proximal end to handle 22, distal end 23 having neurotoxin applicator 24, and lumen 25. Lumen 25 provides fluid communication between proximal end and handle 22 and applicator 24. Syringe 26 having plunger 27 is coupled to a port on proximal end 22. Syringe 26 is filled with neurotoxin in liquid form, and applies the neurotoxin to applicator 24 via lumen 25 when plunger 27 is actuated.

[0037] Handle 22 enables the physician to extend and retract applicator 24 from within lumen 14 of bronchoscope 10, and to manipulate distal end 23 of neurotoxin applicator assembly 20 under direct visual observation using the optics of bronchoscope 10. The neurotoxin applicator assembly preferably remains retracted within lumen 14 of the bronchoscope during insertion of the catheter into the patient's bronchial airways, and is deployed once the applicator is in a desired position. Alternatively, applicator 20 may be housed inside of a retaining sheath, and both units can be advanced through lumen 14 together.

[0038] Referring now to FIGS. 2-3, a first illustrative embodiment of applicator 24 of neurotoxin applicator assembly 20 constructed in accordance with the principles of the present invention is described. Applicator 24 comprises needle assembly 28 having at least one needle 30 with lumen 31 in fluid communication with lumen 25. The needles are configured to penetrate the airway epithelium and directly inject small amounts of neurotoxin from the syringe into the collagenous and smooth muscle layers of bronchial wall B.

[0039] In FIG. 3A, needle assembly 28 is depicted 10 retracted with lumen 14 of bronchoscope 10. Alternatively, device 10 may comprise an outer sheath that is dimensioned to be slidably accept neurotoxin applicator assembly 20, and which is selectively retractable to expose needle assembly 28. In a further embodiment, a retaining sheath housed within lumen 14 and covering applicator 20 is selectively retractable to expose needle assembly 28. As depicted in FIG. 3B, needles 30 comprise a material capable of retaining a preformed shape, such as nickel-titanium, and are preformed to deflect radially outward when extended beyond distal end 13 of bronchoscope 10 (or the distal end of the outer sheath, if present). Each needle 30 optionally includes hilt 36 disposed a pre-selected distance from the distal end of the needle to control the depth of penetration of the needle tip into the bronchial wall.

[0040] When needle assembly 30 is deployed, as illustrated in FIGS. 2 and 3B, needles 30 penetrate target

treatment area T of bronchial wall B so that neurotoxin may be injected in the bronchial wall. Syringe 26 may include graduations that enable the physician to inject a pre-determined amount of neurotoxin at each target treatment area.

[0041] Referring now to FIGS. 4 and 5, an alternative embodiment of applicator 24 of neurotoxin applicator assembly 20 is described. Applicator 24 in this embodiment comprises rotating needle assembly 38, including wheel 39 mounted to rotate about hub 40. While wheel 39 illustratively is round, it alternatively may comprise an ellipse or hexagon or other polygonal shape. Plurality of needles 41 is disposed around the circumference of the wheel, each needle 41 having lumen 42 in fluid communication with lumen 25 via a passageway in hub 40. Optional fender 45 protects a portion of the bronchial wall substantially opposite the target treatment area.

[0042] In FIG. 5A, rotating needle assembly 38 is shown retracted within outer sheath 37. Outer sheath 37 is dimensioned to fit within lumen 14 of bronchoscope 10, and may be selectively retracted to expose rotating needle assembly 38. Alternatively, rotating needle assembly 38 extends through lumen 14 and past the tip of bronchoscope 10. In this embodiment, the wheel is covered by a retractable protection sheath which covers the wheel during insertion of the system. In FIGS. 4 and 5B, rotating needle assembly 38 is shown in the extended position. When so deployed, wheel 39 may be rolled across target treatment area T, so that as the wheel rotates needles 41 alternately penetrate and inject neurotoxin into bronchial wall B.

[0043] Suitable needles materials for needle assembly 28 of FIGS. 2-3 and rotating needle assembly 38 of FIGS. 4-5 include shape memory alloys such as nickel titanium alloys and spring tempered stainless steel alloys. Advantageously, either needle assembly permits direct injection of neurotoxin into the bronchial wall. This prevents the ciliary transport system from trapping the neurotoxin and transporting it to other regions of the respiratory system, e.g., the oropharynx, where potentially unintended targets may be exposed to the neurotoxin, and prevents accidental exhalation of aerosolized neurotoxin.

[0044] Referring now to FIGS. 6 and 7, another alternative embodiment of applicator 24 of the neurotoxin applicator assembly of the present invention is described. Applicator 24 of FIGS. 6-7 comprises a needle-less injection assembly 46, which uses pressurized injection to deliver neurotoxin from the proximal controller to target treatment area T. Advantageously, the needle-less injection assembly allows controlled introduction of neurotoxin across the airway epithelium without the potential complications of introducing needles proximate to the delicate bronchial tissues, and may allow a lower profile system.

[0045] Needle-less injection assembly 46 comprises shaft 47 including at least one port 48 in fluid communication with lumen 25. Inflatable balloon 49 optionally may be coupled to shaft 47, and used to position the shaft adjacent target treatment area T. Balloon 49 is inflated with a fluid introduced through a lumen of shaft 47. When the shaft is aligned with the target treatment area, pulses of pressurized gas may be employed to inject predetermined amounts of neurotoxin across the airway wall and into the collagenous and smooth muscle layers.

[0046] In FIG. 7A, needle-less injection assembly 46, with balloon 49 deflated, is depicted housed within the

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

[0047] With respect to FIGS. 8 and 9, a yet further alternative embodiment of applicator 24 of the neurotoxin applicator assembly constructed in accordance with the present invention is described. Applicator 24 comprises nebulizer assembly 50 having shaft 55 with atomizer 51 disposed at its distal end and in fluid communication with central lumen 25. Atomizer 51 converts the liquid neurotoxin from the syringe into a fine spray or mist. Particle size of the mist can be controlled through nebulizer head design or by varying injection pressure in order to control the depth of penetration of the mist into the target segment.

[0048] Nebulizer assembly 50 may also include optional inflatable balloon 52 disposed on shaft 55 proximal of atomizer 51. Selective inflation of balloon 52 allows positioning of atomizer 51 so that aerosolized neurotoxin may be directly sprayed onto target treatment area T. Balloon 52 also acts to isolate the treatment area from the rest of the lung, preventing reflux of mist into unintended areas. As for the embodiment of FIGS. 6-7, balloon 52' may be inflated using a fluid introduced through an auxiliary lumen in shaft 55.

[0049] In FIG. 9A, the nebulizer assembly, including deflated balloon 52, is disposed within lumen 14 of bronchoscope 10, or alternatively, in an outer sheath (not shown) that is slidably received in lumen 14. Alternatively, the nebulizer assembly 50 may be inserted within a separate delivery sheath (not shown), with the bronchoscope 10 inserted separately. In FIGS. 8 and 9B, nebulizer assembly 50 is depicted deployed from lumen 14 (or the outer sheath, if present), with balloon 52 on shaft 55 inflated. Advantageously, nebulizer assembly 50 can be dimensioned to access very small bronchial passageways, and also may be used to deliver neurotoxin to upstream regions of the lung.

[0050] Still referring to FIGS. 9A and 9B, shaft 55 which carries balloon 52 may optionally also include an additional auxiliary lumen or lumens 25a, 25b (FIG. 9AA) coupled to inlet port 53 and outlet port 54 disposed between the balloon 52 and the atomizer 51. Lumen 25 provides for medicine delivery as in previous embodiments. Inlet port 53 allows the introduction of gas (such as fresh air) near the target treatment area, while outlet port 54 allows air or gas mixed with atomized neurotoxin to be removed. Inlet and outlet

ports 53 and 54 therefore provide a ventilation system that shields tissue adjacent and proximal to target treatment area T from being inadvertently exposed to the atomized neurotoxin. Inlet and outlet ports 53 and 54 further serve to either actively inflate and deflate the isolated segment, or simply to normalize pressure within the lung near the target treatment area. The lumens 25, 25a, and 25b may be connected to the neurotoxin source, gas source, and an aspiration source via ports 23a, 23b, and 23c in handle 22. A control unit may be connected to the proximal outlets of ports 53 and 54 to control the introduction and removal of gases from the lung without allowing escape of atomized neurotoxin to the environment or patient.

[0051] Although preferred illustrative embodiments of the present invention are described above, it will be evident to one skilled in the art that various changes and modifications may be made without departing from the invention. It is intended in the appended claims to cover all such changes and modifications that fall within the true spirit and scope of the invention.

What is claimed is:

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

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

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

2. The apparatus of claim 1, wherein the needle assembly has a retracted delivery position and a deployed position wherein at least one needle extends radially outward from the shaft to penetrate bronchial tissue.

3. The apparatus of claim 1, wherein the needle assembly comprises a wheel having a circumference and a plurality of needles disposed around the circumference, wherein the plurality of needles are in fluid communication with the lumen of the shaft.

4. The apparatus of claim 3, wherein the wheel further comprises a hub that forms an axis of rotation for the wheel.

5. The apparatus of claim 3, wherein the wheel is adapted to be rolled across a target treatment area within a patient's bronchial airways.

6. The apparatus of claim 5, wherein the needle assembly further comprises a fender that protects an area of the patient's bronchial airways opposite the target treatment area.

7. The apparatus of claim 1, further comprising a deflection means disposed on the shaft to position, the port adjacent to the target treatment area.

8. The apparatus of claim 7, wherein the deflection means is an inflatable balloon.

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

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