Substitute for form 1449/PTO

INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(Use as many sheets as necessary)

Sheet | 1 | of | 14

Complete if Known	
Application Number	17151938
Filing Date	01-19-2021
First Named Inventor	MARK; E. Deem
Art Unit	1645
Examiner Name	-
Attorney Docket Number	5187.01US03

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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
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Substitute for form 1449/PTO

INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(Use as many sheets as necessary)

Sheet | 2 | of | 14

Complete if Known	
Application Number	17151938
Filing Date	01-19-2021
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Art Unit	1645
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Substitute for form 1449/PTO

INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(Use as many sheets as necessary)

Sheet | 3 | of | 14

Complete if Known	
Application Number	17151938
Filing Date	01-19-2021
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Art Unit	1645
Examiner Name	-
Attorney Docket Number	5187.01US03

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Substitute for form 1449/PTO

INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(Use as many sheets as necessary)

Sheet | 4 | of | 14

Complete if Known	
Application Number	17151938
Filing Date	01-19-2021
First Named Inventor	MARK; E. Deem
Art Unit	1645
Examiner Name	-
Attorney Docket Number	5187.01US03

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Substitute for form 1449/PTO

INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(Use as many sheets as necessary)

Sheet | 5 | of | 14

Complete if Known	
Application Number	17151938
Filing Date	01-19-2021
First Named Inventor	MARK; E. Deem
Art Unit	1645
Examiner Name	-
Attorney Docket Number	5187.01US03

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INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(Use as many sheets as necessary)

Sheet 6 of 14

Complete if Known	
Application Number	17151938
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Examiner Name	-
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INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(Use as many sheets as necessary)

Sheet 7 of 14

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(Use as many sheets as necessary)

Sheet 8 of 14

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		US-20120016364	01-19-2012	MAYSE; Martin L. et al.
		US-20120029261	02-02-2012	DEEM; Mark E. et al.

Examiner Signature		Date Considered	

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INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(Use as many sheets as necessary)

Sheet | 9 | of | 14

Complete if Known	
Application Number	17151938
Filing Date	01-19-2021
First Named Inventor	MARK; E. Deem
Art Unit	1645
Examiner Name	-
Attorney Docket Number	5187.01US03

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
		US-20120158101	06-21-2012	STONE; Corbett W. et al.
		US-20120203216	08-09-2012	MAYSE; Martin L. et al.
		US-20120203222	08-09-2012	MAYSE; Martin L. et al.
		US-20120209261	08-16-2012	MAYSE; Martin L. et al.
		US-20120209296	08-16-2012	MAYSE; Martin L. et al.
		US-20120302909	11-29-2012	MARTIN; L. Mayse et al.
		US-20120310233	12-06-2012	DIMMER; Steven C. et al.
		US-20120316552	12-13-2012	MAYSE; Martin L. et al.
		US-20120316559	12-13-2012	MAYSE; Martin L. et al.
		US-20130123751	05-16-2013	DEEM; Mark E. et al.
		US-20130289555	10-31-2013	MAYSE; Martin L. et al.
		US-20130289556	10-31-2013	MAYSE; Martin L. et al.
		US-20130303948	11-14-2013	DEEM; Mark E. et al.
		US-20130310822	11-21-2013	MAYSE; Martin L. et al.
		US-20140186341	07-03-2014	MAYSE; Martin L.
		US-20140257271	09-11-2014	MAYSE; Martin L. et al.
		US-20140276792	09-18-2014	KAVECKIS; Ryan et al.
		US-20150051597	02-19-2015	MAYSE; Martin L. et al.
		US-20150141985	05-21-2015	MAYSE; Martin L. et al.
		US-20150190193	07-09-2015	MAYSE; Martin L. et al.
		US-20150366603	12-24-2015	HLAVKA; Edwin J. et al.
		US-20160022351	01-28-2016	KAVECKIS; Ryan et al.
		US-20160038725	02-11-2016	MARTIN; L. Mayse et al.
		US-20190083768	03-21-2019	DEEM; Mark E. et al.
		US-20200360677	11-19-2020	MARK; E. Deem et al.

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Sheet | 10 | of | 14

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Attorney Docket Number	5187.01US03

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]
	001	CA-2152002-A1	12-18-1995	TRUDELL MEDICAL LTD [CA]		☐
	002	EP-3248612-A1	11-29-2017	THE FOUNDRY LLC [US]		☐
	003	JP-2002145784-A	05-22-2002	MORISHITA RYUICHI.		☒
	004	WO-0062699-A2	10-26-2000	BRONCUS TECH INC [US], et al.		☐
	005	WO-2004006954-A2	01-22-2004	ALLERGAN INC [US], et al.		☐
	006	WO-2004048519-A2	06-10-2004	SANDERS IRA [US]		☐
	007	WO-2004077987-A1	09-16-2004	LALINE INTERNAT SARL [TN], et al.		☐
	008	WO-2004101028-A2	11-25-2004	THE FOUNDRY INC [US], et al.		☐
	009	WO-2004101028-A3	12-14-2006	THE FOUNDRY INC [US], et al.		☐
	010	WO-2005032646-A2	04-14-2005	EASTERN VIRGINIA MED SCHOOL [US], et al.		☐
	011	WO-2005048988-A1	06-02-2005	SCOTT NEAL [US], et al.		☐
	012	WO-2007014003-A2	02-01-2007	THE FOUNDRY INC [US], et al.		☐

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	013	WO-9119529-A1	12-26-1991	CORTRAK MEDICAL INC [US]		☐
	014	WO-9519805-A1	07-27-1995	GENETRONICS INC [US], et al.		☐
	015	WO-9934831-A1	07-15-1999	UNIV WASHINGTON [US], et al.		☐

Examiner Signature		Date Considered	

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Sheet | 12 | of | 14

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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]
		AHNERT-HILGER., et al., "Introduction of Macromolecules into Bovine Adrenal-Medullary Chromaffin Cells and Rat Pheochromocytoma Cells (PC12) by Permeabilization with Streptolysin O: Inhibitory Effect of Teanus Toxin on Catecholamine Secretion," J. Neurochem, June 1989, Vol. 52 (6), pp. 1751-1758.	☐
		"Anonymous: Neurotoxin (from Wikipedia)," Retrieved from http://en.wikipedia.org/w/index.php?title=Neurotoxin&printable=yes, 2 April 2015, 23 pages.	☐
		Application and File History for U.S. Patent Application No. 16/659,893, filed 22 October 2019, Inventors: Deem et al. as available on PAIR at http://www.uspto.gov.	☐
		Application and File History for U.S. Patent Application No. 16/842,209, filed 07 April 2020, Inventors: Deem et al. as available on PAIR at http://www.uspto.gov.	☐
		BIGALKE., et al., "Clostridial Neurotoxins," Handbook of Experimental Pharmacology (Aktories, K., and Just, I., eds), 2000, Vol. 145, pp. 407-443.	☐
		BITTNER., et al., "Isolated Light Chains of Botulinum Neurotoxins Inhibit Exocytosis," The Journal of Biological Chemistry, 1989, Vol. 264(18), pp. 10354-10360.	☐
		BLINDT., et al., "Development of a New Biodegradable Intravascular Polymer Stent with Simultaneous Incorporation of Bioactive Substances," The International Journal of Artificial Organs, 1999, Vol. 22 (12), pp. 843-853.	☐
		BUZZI., "Diphtheria Toxin Treatment of Human Advanced Cancer," Cancer Research, 1982, Vol. 42, pp. 2054-2058.	☐
		CHADDOCK., et al., "Expression and Purification of Catalytically Active, Non-Toxic Endopeptidase Derivatives of Clostridium Botulinum Toxin Type A," Protein Expression and Purification, July 2002, Vol. 25 (2), pp. 219-228.	☐
		CHANG., "Cell Poration and Cell Fusion Using an Oscillating Electric Field," Biophys. J, 1989, Vol. 56 (4), pp. 641-652.	☐

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Sheet 13 of 14

Complete if Known	
Application Number	17151938
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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]
		DE PAIVA., et al., "Light Chain of Botulinum Neurotoxin is Active in Mammalian Motor Nerve Terminals When Delivered Via Liposomes," FEBS Lett, December 1990, Vol. 17:277(1-2), pp. 171-174.	☐
		GUZMAN., et al., "Bioeffects Caused by Changes in Acoustic Cavitation Bubble Density and Cell Concentration: A Unified Explanation Based on Cell-to-Bubble Ratio and Blast Radius," Ultrasound in medicine & biology, 2003, Vol. 29 (8), pp. 1211-1222.	☐
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		KREITMAN., "Taming Ricin Toxin," Nature Biotechnology, 2003, Vol. 21, pp. 372-374.	☐
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		SCHMITT G.S., et al., "Indwelling Transbronchial Catheter Drainage of Pulmonary Abscess," Ann Thorac Surg, January 1988, Vol. 45 (1), pp. 43-47.	☐
		SHAARI., et al., "Rhinorrhea is Decreased in Dogs After Nasal Application of Botulinum Toxin," Otolaryngol Head Neck Surgery, April 1995, Vol. 112 (4), pp. 566-571.	☐
		SIMPSON., et al., "Isolation and Characterization of the botulinum Neurotoxins," Methods Enzymol, 1988, Vol. 165, pp. 76-85.	☐
		SIMPSON L.L., "The Origin, Structure, and Pharmacological Activity of Botulinum Toxin," Pharmacol Reviews, September 1981, Vol. 33 (3), pp. 155-188.	☐

Examiner Signature		Date Considered	

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Sheet 14 of 14

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Application Number	17151938
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		SUNDARAM, et al., "An Experimental and Theoretical Analysis of Ultrasound-Induced Permeabilization of Cell Membranes," Biophysical Journal, May 2003, Vol. 84 (5), pp. 3087-3101.	☐
		TSUJI., et al., "Biodegradable Stents as a Platform to Drug Loading," International Journal of Cardiovascular Interventions, 2003, Vol. 5(1), pp. 13-16.	☐
		UNAL., et al., "Effect of Botulinum Toxin Type A on Nasal Symptoms in Patients with Allergic Rhinitis: A Double-blind, Placebo-controlled Clinical Trial," Acta Oto-Laryngologica, December 2003, Vol. 123 (9), pp. 1060-1063.	☐
		WEAVER, "Electroporation: A General Phenomenon for Manipulating Cells and Tissues," Journal of Cellular Biochemistry, Apr. 1993, Vol. 51(4), pp.426-435.	☐

Examiner Signature	/ALBERT M NAVARRO/	Date Considered	04/05/2022

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PTO/SB/06 (09-11)
Approved for use through 1/31/2014. OMB 0651-0032
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
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PATENT APPLICATION FEE DETERMINATION RECORD Substitute for Form PTO-875	Application or Docket Number 17/151,938	Filing Date 01/19/2021	☐ To be Mailed

ENTITY: ☐ LARGE ☑ SMALL ☐ MICRO

APPLICATION AS FILED - PART I

FOR	(Column 1) NUMBER FILED	(Column 2) NUMBER EXTRA		RATE ($)	FEE ($)
☐ BASIC FEE (37 CFR 1.16(a), (b), or (c))	N/A	N/A		N/A	
☐ SEARCH FEE (37 CFR 1.16(k), (i), or (m))	N/A	N/A		N/A	
☐ EXAMINATION FEE (37 CFR 1.16(o), (p), or (q))	N/A	N/A		N/A	
TOTAL CLAIMS (37 CFR 1.16(i))	minus 20 =	*		x $50 =	
INDEPENDENT CLAIMS (37 CFR 1.16(h))	minus 3 =	*		x $240 =	
☐ APPLICATION SIZE FEE (37 CFR 1.16(s))	If the specification and drawings exceed 100 sheets of paper, the application size fee due is $310 ($155 for small entity) for each additional 50 sheets or fraction thereof. See 35 U.S.C. 41(a)(1)(G) and 37 CFR 1.16(s).				
☐ MULTIPLE DEPENDENT CLAIM PRESENT (37 CFR 1.16(j))					
* If the difference in column 1 is less than zero, enter "0" in column 2.				TOTAL	

APPLICATION AS AMENDED - PART II

		(Column 1)		(Column 2)	(Column 3)			
AMENDMENT	08/29/2022	CLAIMS REMAINING AFTER AMENDMENT		HIGHEST NUMBER PREVIOUSLY PAID FOR	PRESENT EXTRA		RATE ($)	ADDITIONAL FEE ($)
	Total (37 CFR 1.16(i))	* 8	Minus	** 20	= 0		x $50 =	0
	Independent (37 CFR 1.16(h))	* 1	Minus	*** 3	= 0		x $240 =	0
	☐ Application Size Fee (37 CFR 1.16(s))							
	☐ FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))							
							TOTAL ADD'L FEE	0

		(Column 1)		(Column 2)	(Column 3)			
AMENDMENT		CLAIMS REMAINING AFTER AMENDMENT		HIGHEST NUMBER PREVIOUSLY PAID FOR	PRESENT EXTRA		RATE ($)	ADDITIONAL FEE ($)
	Total (37 CFR 1.16(i))	*	Minus	**	=		x $0 =	
	Independent (37 CFR 1.16(h))	*	Minus	***	=		x $0 =	
	☐ Application Size Fee (37 CFR 1.16(s))							
	☐ FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))							
							TOTAL ADD'L FEE	

* If the entry in column 1 is less than the entry in column 2, write "0" in column 3.	SLIE
** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 20, enter "20".	/DEIDRE C KING-WOODWARD/
*** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 3, enter "3".	
The "Highest Number Previously Paid For" (Total or Independent) is the highest number found in the appropriate box in column 1.	

This collection of information is required by 37 CFR 1.16. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 12 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

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

PATENT APPLICATION

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re the application of:	Attorney Docket No.: 5187.01US03
Deem et al.	Confirmation No.: 1034
Application No.: 17/151,938	Examiner: Albert Mark Navarro
Filed: January 19, 2021	Group Art Unit: 1645

For: SYSTEMS AND METHODS FOR DELIVERY OF A THERAPEUTIC AGENT

AMENDMENT

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

Commissioner:

INTRODUCTORY COMMENTS

In response to the Office Action of April 8, 2022, and in accordance with the automatic extension of time for response provided by 37 CFR § 1.136(a), amendment to the above-identified patent application is requested.

The present amendment comprises the following sections:

A. Amendments to the Claims

B. Remarks

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

AMENDMENTS TO THE CLAIMS

A detailed listing of all claims that are, or were, in the present application, irrespective of whether the claim(s) remain(s) under examination in the application is presented below. The claims are presented in ascending order and each includes one status identifier. Those claims not cancelled or withdrawn but amended by the current amendment utilize the following notations for amendment: 1. deleted matter is shown by strikethrough for six or more characters and double brackets for five or fewer characters; and 2. added matter is shown by underlining.

1.-20. (Cancelled)

Please add new claims 21-28 as follows:

21. (New) A method of treating a nasal condition of a patient, the method comprising:

advancing a shaft of a nasal treatment device into a nostril of the patient, wherein a distal portion of the shaft comprises a treatment element;

positioning the treatment element proximate to target tissue in a nasopharyngeal passage of a patient; and

activating multiple radiofrequency electrodes on the treatment element to alter the target tissue and thus alter autonomic nerve function in the nasopharyngeal passage so that mucus secretion is reduced in the nasopharyngeal passage.

22. (New) The method of claim 21, further comprising activating at least one monitoring electrode on the distal portion of the shaft of the treatment device to localize a treatment area in the nasopharyngeal passage.

23. (New) The method of claim 22, wherein the at least one monitoring electrode is selected from the group consisting of a thermocouple, an ultrasound transducer, and a fiberoptic.

24. (New) The method of claim 21, wherein the multiple radiofrequency electrodes comprise bipolar radiofrequency electrodes.

25. (New) The method of claim 21, wherein activating the multiple radiofrequency electrodes causes electroporation of cells in the target tissue.

26. (New) The method of claim 25, further comprising delivering an agent to the electroporated cells in the target tissue.

27. (New) The method of claim 26, wherein the agent comprises a neurotoxin.

28. (New) The method of claim 21, further comprising activating at least two of the multiple radiofrequency electrodes to localize a treatment area in the nasopharyngeal passage.

REMARKS

Claims 1-20 are pending. By this Amendment, claims 1-20 are cancelled, no claims are amended, and new claims 21-28 are added.

Double Patenting

Claims 1-20 stand rejected under 35 U.S.C. § 101 as claiming the same invention as that of claims 1-20 of U.S. Pat. No. 10,894,011, and claims 1-20 stand rejected on the ground of nonstatutory double patenting as being unpatentable over claims 1-20 of U.S. Pat. No. 10,894,011. Solely to advance prosecution, claims 1-20 have been cancelled, and new claims 21-28 have been added, rendering the rejections moot.

In view of the foregoing, it is submitted that this application is in condition for allowance. Favorable consideration and prompt allowance of the application are respectfully requested.

The Examiner is invited to telephone the undersigned if the Examiner believes it would be useful to advance prosecution.

Respectfully submitted,

/Daidre L. Burgess/

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UNITED STATES
PATENT AND TRADEMARK OFFICE

P.O. Box 1450
Alexandria, VA 22313 - 1450
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ELECTRONIC ACKNOWLEDGEMENT RECEIPT

APPLICATION #	RECEIPT DATE / TIME	ATTORNEY DOCKET #
17/151,938	**08/29/2022 06:15:46 PM ET**	**5187.01US03**

Title of Invention

SYSTEMS AND METHODS FOR DELIVERY OF A THERAPEUTIC AGENT

Application Information

APPLICATION TYPE	Utility - Nonprovisional Application under 35 USC 111(a)	PATENT #	-
CONFIRMATION #	1034	FILED BY	Margaret Rausch
PATENT CENTER #	60916935	FILING DATE	01/19/2021
CUSTOMER #	24113	FIRST NAMED INVENTOR	Mark E. Deem
CORRESPONDENCE ADDRESS	-	AUTHORIZED BY	Daidre Burgess

Documents

TOTAL DOCUMENTS: 4

DOCUMENT		PAGES	DESCRIPTION	SIZE (KB)
EOT.pdf		1	Extension of Time	81 KB
Amendment.pdf		5	-	125 KB
Amendment-A....pdf	(1-1)	1	Amendment/Request for Reconsideration-After Non-Final Rejection	89 KB
Amendment-CLM.pdf	(2-4)	3	Claims	52 KB
Amendment-REM.pdf	(5-5)	1	Applicant Arguments/Remarks Made in an Amendment	72 KB

Digest

DOCUMENT	MESSAGE DIGEST(SHA-512)
EOT.pdf	2FE9F0A2D629F6231FDEF0C628750074840 4CF9FC1EF432B96A312483527F1FE5DEBD4CF53B5BF7B91747695F94164E34ECB67F8EEF529C37098FDC35A84D4BC
Amendment.pdf	77EA6506AE1EF0BB7F7B99E455D1D53DBCB4F2FDCE3AB86A5DC220E8D2F55CE9C5E1263503BCC848EAC4B2718F5028B2456B633D98E75B11207D654F866AD158
Amendment-A....pdf	3BCE45D697294AB91DCBDC1F128A1EF8FD16C629DAE5A020643E9F2035F33448C60970BC27F574291A59089E2241223C6AB16955C32FC7A6F7895FDD31799531
Amendment-CLM.pdf	C4440B47ADEE3ECEC2AD42B79BD5F7AA03B4FD913F09D55D50D6A58019ABC6DD0601D4E2968E43F91EA3054493251B63AEDA664496F416A34087FC40EDC41347
Amendment-REM.pdf	104B312C23ABC9067F68CF5E2A198F11D27C8E4CC9C9C4F24ECE9680F6F78C2909317E171A7077E5E73FE8E30B3E05A60F3B55970BF39878D2D814BDB2534F97

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New Applications Under 35 U.S.C. 111

If a new application is being filed and the application includes the necessary components for 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

P.O. Box 1450
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ELECTRONIC PAYMENT RECEIPT

APPLICATION #	RECEIPT DATE / TIME	ATTORNEY DOCKET #
17/151,938	08/29/2022 06:15:46 PM ET	5187.01US03

Title of Invention

SYSTEMS AND METHODS FOR DELIVERY OF A THERAPEUTIC AGENT

Application Information

APPLICATION TYPE	Utility - Nonprovisional Application under 35 USC 111(a)	PATENT #	-
CONFIRMATION #	1034	FILED BY	Margaret Rausch
PATENT CENTER #	60916935	AUTHORIZED BY	Daidre Burgess
CUSTOMER #	24113	FILING DATE	01/19/2021
CORRESPONDENCE ADDRESS	-	FIRST NAMED INVENTOR	Mark E. Deem

Payment Information

PAYMENT METHOD	PAYMENT TRANSACTION ID	PAYMENT AUTHORIZED BY
CARD / 1214	E20228SI17070992	Margaret Rausch

PRE-AUTHORIZED ACCOUNT	PRE-AUTHORIZED CATEGORY
160631	37 CFR 1.16 (National application filing, search, and examination fees); 37 CFR 1.17 (Patent application and reexamination processing fees); 37 CFR 1.19 (Document supply fees); 37 CFR 1.20 (Post Issuance fees); 37 CFR 1.21 (Miscellaneous fees and charges)

FEE CODE	DESCRIPTION	ITEM PRICE($)	QUANTITY	ITEM TOTAL($)
2252	EXTENSION FOR RESPONSE WITHIN SECOND MONTH -	320.00	1	320.00
			TOTAL AMOUNT:	$320.00

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New Applications Under 35 U.S.C. 111

If a new application is being filed and the application includes the necessary components for 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.

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

PATENT APPLICATION

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re the application of:	Attorney Docket No.: 5187.01US03
Deem et al.	Confirmation No.: 1034
Application No.: 17/151,938	Examiner: Albert Mark Navarro
Filed: January 19, 2021	Group Art Unit: 1645

For: SYSTEMS AND METHODS FOR DELIVERY OF A THERAPEUTIC AGENT

PETITION FOR EXTENSION OF PERIOD FOR RESPONSE
UNDER 37 CFR 1.136(a)

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

Commissioner:

Pursuant to 37 CFR § 1.136(a), an extension of time of two (2) month (from July 8, 2022 to September 8, 2022) within which to respond to the Office Action dated April 8, 2022 is requested. Electronic payment is submitted by credit card to cover the extension fee. Applicant is entitled to small entity status in accordance with 37 CFR 1.27. The Commissioner is authorized to charge to Deposit Account No. 16-0631 any underpayments, overpayments or additionally required fees.

Respectfully submitted,

/Daidre L. Burgess/

Daidre L. Burgess
Registration No. 60389

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

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

UNITED STATES PATENT AND TRADEMARK OFFICE

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

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
17/151,938	01/19/2021	Mark E. Deem	5187.01US03	1034

24113 7590 09/19/2022

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

EXAMINER	
NAVARRO, ALBERT MARK	

ART UNIT	PAPER NUMBER
1645	

NOTIFICATION DATE	DELIVERY MODE
09/19/2022	ELECTRONIC

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

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

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

efsuspto@ptslaw.com

Notice of Pre-AIA or AIA Status

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

NON-RESPONSIVE AMENDMENT

The reply filed August 29, 2022 is not fully responsive to the prior Office action because of the following omission(s) or matter(s):

Newly added claims 21-28 are directed to an invention that is independent or distinct from the originally claimed for the following reasons:

Claims 1-20 were drawn to apparatuses. New claims 21-28 are drawn to methods of treatment. Applicants will hopefully appreciate that parent application 11/459,090 contained a restriction requirement between apparatus and methods. Furthermore 11/459,090 was a divisional. See 37 CFR 1.111.

Since Applicant has received an action on the merits for the originally presented invention, this invention has been constructively elected by original presentation for prosecution on the merits. Accordingly, claims 21-28 are withdrawn from consideration as being directed to a non-elected invention. See 37 CFR 1.142(b) and MPEP § 821.03.

Since the above-mentioned reply appears to be bona fide, applicant is given a shortened statutory period of **TWO (2) MONTHS** from the mailing date of this notice within which to supply the omission or correction in order to avoid abandonment. EXTENSIONS OF THIS TIME PERIOD MAY BE GRANTED UNDER 37 CFR 1.136(a),

but in no case can any extension carry the date for reply to this letter beyond the maximum period of SIX MONTHS set by statute (35 U.S.C. 133).

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

Examiner interviews are available via telephone, in-person, and video conferencing using a USPTO supplied web-based collaboration tool. To schedule an interview, applicant is encouraged to use the USPTO Automated Interview Request (AIR) at http://www.uspto.gov/interviewpractice.

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

Information regarding the status of published or unpublished applications may be obtained from Patent Center. Unpublished application information in Patent Center is available to registered users. To file and manage patent submissions in Patent Center, visit: https://patentcenter.uspto.gov. Visit https://www.uspto.gov/patents/apply/patent-center for more information about Patent Center and https://www.uspto.gov/patents/docx for information about filing in DOCX format. For

additional questions, contact the Electronic Business Center (EBC) at 866-217-9197

(toll-free). If you would like assistance from a USPTO Customer Service

Representative, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/ALBERT M NAVARRO/
Primary Examiner, Art Unit 1645
September 12, 2022

PTO/SB/06 (09-11)
Approved for use through 1/31/2014. OMB 0651-0032
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
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PATENT APPLICATION FEE DETERMINATION RECORD Substitute for Form PTO-875	Application or Docket Number 17/151,938	Filing Date 01/19/2021	☐ To be Mailed

ENTITY: ☐ LARGE ☑ SMALL ☐ MICRO

APPLICATION AS FILED - PART I

FOR	(Column 1) NUMBER FILED	(Column 2) NUMBER EXTRA		RATE ($)	FEE ($)
☐ BASIC FEE (37 CFR 1.16(a), (b), or (c))	N/A	N/A		N/A	
☐ SEARCH FEE (37 CFR 1.16(k), (i), or (m))	N/A	N/A		N/A	
☐ EXAMINATION FEE (37 CFR 1.16(o), (p), or (q))	N/A	N/A		N/A	
TOTAL CLAIMS (37 CFR 1.16(i))	minus 20 =	*		x $50 =	
INDEPENDENT CLAIMS (37 CFR 1.16(h))	minus 3 =	*		x $240 =	
☐ APPLICATION SIZE FEE (37 CFR 1.16(s))	If the specification and drawings exceed 100 sheets of paper, the application size fee due is $310 ($155 for small entity) for each additional 50 sheets or fraction thereof. See 35 U.S.C. 41(a)(1)(G) and 37 CFR 1.16(s).				
☐ MULTIPLE DEPENDENT CLAIM PRESENT (37 CFR 1.16(j))					
* If the difference in column 1 is less than zero, enter "0" in column 2.				TOTAL	

APPLICATION AS AMENDED - PART II

		(Column 1)		(Column 2)	(Column 3)			
AMENDMENT	10/24/2022	CLAIMS REMAINING AFTER AMENDMENT		HIGHEST NUMBER PREVIOUSLY PAID FOR	PRESENT EXTRA		RATE ($)	ADDITIONAL FEE ($)
	Total (37 CFR 1.16(i))	* 8	Minus	** 20	= 0		x $50 =	0
	Independent (37 CFR 1.16(h))	* 1	Minus	*** 3	= 0		x $240 =	0
	☐ Application Size Fee (37 CFR 1.16(s))							
	☐ FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))							
							TOTAL ADD'L FEE	0

		(Column 1)		(Column 2)	(Column 3)			
AMENDMENT		CLAIMS REMAINING AFTER AMENDMENT		HIGHEST NUMBER PREVIOUSLY PAID FOR	PRESENT EXTRA		RATE ($)	ADDITIONAL FEE ($)
	Total (37 CFR 1.16(i))	*	Minus	**	=		x $0 =	
	Independent (37 CFR 1.16(h))	*	Minus	***	=		x $0 =	
	☐ Application Size Fee (37 CFR 1.16(s))							
	☐ FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))							
							TOTAL ADD'L FEE	

* If the entry in column 1 is less than the entry in column 2, write "0" in column 3.	LIE
** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 20, enter "20".	/VICTOR BARLOW/
*** 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.

Document Description: Power of Attorney

PTO/AIA/82B (07-13)
Approved for use through 03/31/2021. OMB 0651-0035
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
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POWER OF ATTORNEY BY APPLICANT

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

Application Number	Filing Date
17/151938	01/19/2021

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

☑ I hereby appoint the Patent Practitioner(s) associated with the following Customer Number as my/our attorney(s) or agent(s), and to transact all business in the United States Patent and Trademark Office connected therewith for the application referenced in the attached transmittal letter (form PTO/AIA/82A) or identified above: 23552

OR

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

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

☑ The address associated with the above-mentioned Customer Number

OR

☐ The address associated with Customer Number:

OR

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

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

The Foundry, LLC

☐ Inventor or Joint Inventor (title not required below)

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

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

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

SIGNATURE of Applicant for Patent

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

Signature	DocuSigned by: Karen D. Naga B218E9F9A01D444...	Date (Optional)	
Name	Karen D. Naga		
Title	Partner, The Foundry, LLC		

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

☐ Total of forms are submitted.

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

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UNITED STATES
PATENT AND TRADEMARK OFFICE

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ELECTRONIC ACKNOWLEDGEMENT RECEIPT

APPLICATION #	RECEIPT DATE / TIME	ATTORNEY DOCKET #
17/151,938	**10/24/2022 11:08:28 AM ET**	**5187.01US03**

Title of Invention

SYSTEMS AND METHODS FOR DELIVERY OF A THERAPEUTIC AGENT

Application Information

APPLICATION TYPE	Utility - Nonprovisional Application under 35 USC 111(a)	PATENT #	-
CONFIRMATION #	1034	FILED BY	Theresa Powless
PATENT CENTER #	61097100	FILING DATE	01/19/2021
CUSTOMER #	24113	FIRST NAMED INVENTOR	Mark E. Deem
CORRESPONDENCE ADDRESS	-	AUTHORIZED BY	Robert Kalinsky

Documents

TOTAL DOCUMENTS: 2

DOCUMENT	PAGES	DESCRIPTION	SIZE (KB)
2022-10-24--POA for US 17151938--19264.0001USC8.PDF	1	Power of Attorney	359 KB
Warning: The PDF file has been signed with a digital signature and the legal effect of the document will be based on the contents of the file not the digital signature.			
2022-10-14--Response--19264.0001USC8.PDF	5	Amendment/Request for Reconsideration-After Non-Final Rejection	93 KB

Digest

DOCUMENT	MESSAGE DIGEST(SHA-512)
2022-10-24--POA for US 17151938--19264.0001USC8.PDF	3B15F69D29C2A3519C19F574141FBF9180FF15BEB5806CE3F3F5D8AAB8FC348FAE663CB0A649B2F8EBDFAED872344792770C8F43A0C5A5EF7168B3396935D2A6
2022-10-14--Response--19264.0001USC8.PDF	A9F50184CE2B1FB8661C435E6FBB7A9C540E9F5731ADDACA53F7AC13F8D73B5788823860C550D192093BDA4E5B1444E903C9259540F3EB254BF16E14F4304109

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If a new application is being filed and the application includes the necessary components for 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

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PATENT APPLICATION

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re the application of:	Attorney Docket No.: 19264.0001USC8
Deem et al.	Confirmation No.: 1034
Application No.: 17/151,938	Examiner: Albert Mark Navarro
Filed: January 19, 2021	Group Art Unit: 1645

For: SYSTEMS AND METHODS FOR DELIVERY OF A THERAPEUTIC AGENT

AMENDMENT

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

Commissioner:

INTRODUCTORY COMMENTS

In response to the Notice of September 19, 2022, and in accordance with the automatic extension of time for response provided by 37 CFR § 1.136(a), amendment to the above-identified patent application is requested.

The present amendment comprises the following sections:

A. Amendments to the Claims

B. Remarks

Please grant any extension of time necessary for entry; charge any fee due to Deposit Account No. 15-2725.

AMENDMENTS TO THE CLAIMS

A detailed listing of all claims that are, or were, in the present application, irrespective of whether the claim(s) remain(s) under examination in the application is presented below. The claims are presented in ascending order and each includes one status identifier. Those claims not cancelled or withdrawn but amended by the current amendment utilize the following notations for amendment: 1. deleted matter is shown by strikethrough for six or more characters and double brackets for five or fewer characters; and 2. added matter is shown by underlining.

1.-28. (Cancelled)

Please add new claims 29-43 as follows.

29. (New) An apparatus for treating rhinitis in a nasal cavity, the apparatus comprising:

an elongate body, comprising:

a proximal portion; and

a distal portion configured for positioning in the nasal cavity;

multiple radiofrequency electrodes coupled with the distal portion of the elongate body; and

a radiofrequency generator coupled with the proximal portion of the elongate body for supplying radiofrequency energy to the multiple radiofrequency electrodes to treat a target tissue in the nasal cavity and thus treat rhinitis.

30. (New) The apparatus of claim 29, wherein the multiple radiofrequency electrodes comprise at least two bipolar radiofrequency electrodes.

31. (New) The apparatus of claim 30, further comprising at least one sensing electrode.

32. (New) The apparatus of claim 30, wherein the at least two bipolar radiofrequency electrodes comprise multiple pairs of bipolar radiofrequency electrodes.

33. (New) The apparatus of claim 29, wherein the target tissue comprises nerve tissue.

34. (New) The apparatus of claim 29, wherein at least one of the multiple radiofrequency electrodes is movable relative to the distal portion of the elongate body.

35. (New) The apparatus of claim 29, wherein the multiple radiofrequency electrodes are configured to deliver energy laterally relative to the distal portion of the elongate body.

36. (New) The apparatus of claim 29, wherein at least one of the multiple radiofrequency electrodes is configured to extend laterally from the distal portion of the elongate body.

37. (New) The apparatus of claim 35, wherein the at least one of the multiple radiofrequency electrodes is configured to penetrate nasal mucosa lining the nasal cavity.

38. (New) The apparatus of claim 29, further comprising a thermocouple coupled with the distal portion of the elongate body for sensing temperature of a nasal tissue in the nasal cavity.

39. (New) The apparatus of claim 29, further comprising a monitoring system coupled with the distal portion of the elongate body for monitoring a degree of treatment of the target tissue.

40. (New) The apparatus of claim 29, further comprising an agent delivery element coupled with the distal portion of the elongate body for delivering a therapeutic agent to the target tissue.

41. (New) The apparatus of claim 40, wherein the agent delivery element comprises at least one needle.

42. (New) The apparatus of claim 41, further comprising a source of the therapeutic agent coupled with the proximal portion of the elongate body.

43. (New) The apparatus of claim 42, wherein the therapeutic agent comprises a neurotoxin.

REMARKS

Claims 21-28 are pending. By this Amendment, claims 21-28 are cancelled, no claims are amended, and new claims 29-43 are added.

Claims 29-43 are directed to the same statutory class (apparatus) as original claims 1-20. Consideration and entry of these new claims are requested.

In view of the foregoing, it is submitted that this application is in condition for allowance. Favorable consideration and prompt allowance of the application are respectfully requested.

The Examiner is invited to telephone the undersigned if the Examiner believes it would be useful to advance prosecution.

Respectfully submitted,

MERCHANT & GOULD P.C.
P.O. Box 2903
Minneapolis, Minnesota 55402-0903
(612) 332-5300

Date: October 23, 2022

/Robert A. Kalinsky/
Name: Robert A. Kalinsky
Reg. No.: 50,471

UNITED STATES PATENT AND TRADEMARK OFFICE

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APPLICATION NUMBER	FILING OR 371(C) DATE	FIRST NAMED APPLICANT	ATTY. DOCKET NO./TITLE
17/151,938	01/19/2021	Mark E. Deem	5187.01US03

CONFIRMATION NO. 1034

POWER OF ATTORNEY NOTICE

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

OC000000136687890

Date Mailed: 11/04/2022

NOTICE REGARDING CHANGE OF POWER OF ATTORNEY

This is in response to the Power of Attorney filed 10/24/2022.

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

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

/sstephanos/

UNITED STATES PATENT AND TRADEMARK OFFICE

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Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NUMBER	FILING OR 371(C) DATE	FIRST NAMED APPLICANT	ATTY. DOCKET NO./TITLE
17/151,938	01/19/2021	Mark E. Deem	5187.01US03

CONFIRMATION NO. 1034

23552
MERCHANT & GOULD P.C.
P.O. BOX 2903
MINNEAPOLIS, MN 55402-0903

POA ACCEPTANCE LETTER

OC000000136687894

Date Mailed: 11/04/2022

NOTICE OF ACCEPTANCE OF POWER OF ATTORNEY

This is in response to the Power of Attorney filed 10/24/2022.

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.

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

/sstephanos/

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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
17/151,938	01/19/2021	Mark E. Deem	5187.01US03	1034

23552 7590 12/05/2022

MERCHANT & GOULD P.C.
P.O. BOX 2903
MINNEAPOLIS, MN 55402-0903

EXAMINER	
NAVARRO, ALBERT MARK	

ART UNIT	PAPER NUMBER
1645	

NOTIFICATION DATE	DELIVERY MODE
12/05/2022	ELECTRONIC

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

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

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

USPTO23552@merchantgould.com

Office Action Summary	Application No. 17/151,938	Applicant(s) Deem et al.	
	Examiner Mark NAVARRO	Art Unit 1645	AIA (FITF) Status No

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

Period for Reply

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

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

Status

1)☑ Responsive to communication(s) filed on 24 October 2022.

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

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

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

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

Disposition of Claims*

5) ☑ Claim(s) 29-43 is/are pending in the application.

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

6) ☐ Claim(s) _____ is/are allowed.

7) ☑ Claim(s) 29-43 is/are rejected.

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

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

* If any claims have been determined allowable, you may be eligible to benefit from the **Patent Prosecution Highway** program at a participating intellectual property office for the corresponding application. For more information, please see http://www.uspto.gov/patents/init_events/pph/index.jsp or send an inquiry to **PPHfeedback@uspto.gov.**

Application Papers

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

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

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

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

Priority under 35 U.S.C. § 119

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

Certified copies:

a)☐ All b)☐ Some** c)☐ None of the:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

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

Attachment(s)

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

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

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

4) ☐ Other: _____.

DETAILED ACTION

Notice of Pre-AIA or AIA Status

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

Applicants amendment filed October 24, 2022 has been received and entered. Claims 1-28 have been cancelled and new claims 29-43 have been added. Accordingly, claims 29-43 are pending in the instant application.

Double Patenting

1. The rejection of claims 1-20 under 35 U.S.C. 101 as claiming the same invention as that of claims 1-20 of prior U.S. Patent No. 10,894,011 is withdrawn in view of Applicants amendment.

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46

USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on nonstatutory double patenting provided the reference application or patent either is shown to be commonly owned with the examined application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement. See MPEP § 717.02 for applications subject to examination under the first inventor to file provisions of the AIA as explained in MPEP § 2159. See MPEP § 2146 *et seq.* for applications not subject to examination under the first inventor to file provisions of the AIA. A terminal disclaimer must be signed in compliance with 37 CFR 1.321(b).

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

2. The rejection of claims 1-20 (as applied to new claims 29-43) on the ground of nonstatutory double patenting as being unpatentable over claims 1-20 of U.S. Patent No. 10,894,011 is maintained. Although the claims at issue are not identical, they are not patentably distinct from each other because the instantly recited claims drawn to an apparatus for treatment of rhinitis in a nasal cavity comprising a proximal portion, a distal portion configured for positioning in the nasal cavity, multiple radiofrequency electrodes coupled to the distal portion of the elongate body, and a radiofrequency generator are anticipated by the claims of '011 drawn to an apparatus for treatment of a nasal condition comprising a proximal portion, a distal portion configured for positioning in the nasalpharyngeal passage (extension beyond nasal cavity), electrodes coupled to the distal portion of the elongate body, and a radiofrequency generator. (See claims 1-2 and 5).

Applicants have not provided any argument concerning this rejection. Accordingly, this rejection is maintained for the reasons set forth above.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within

TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

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

Examiner interviews are available via telephone, in-person, and video conferencing using a USPTO supplied web-based collaboration tool. To schedule an interview, applicant is encouraged to use the USPTO Automated Interview Request (AIR) at http://www.uspto.gov/interviewpractice.

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

Information regarding the status of published or unpublished applications may be obtained from Patent Center. Unpublished application information in Patent Center is available to registered users. To file and manage patent submissions in Patent Center, visit: https://patentcenter.uspto.gov. Visit https://www.uspto.gov/patents/apply/patent-center for more information about Patent Center and

https://www.uspto.gov/patents/docx for information about filing in DOCX format. For additional questions, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/ALBERT M NAVARRO/
Primary Examiner, Art Unit 1645
November 30, 2022

Search Notes	Application/Control No.	Applicant(s)/Patent Under Reexamination
	17/151,938	Deem et al.
	Examiner	Art Unit
	Mark NAVARRO	1645

CPC - Searched*		
Symbol	Date	Examiner

CPC Combination Sets - Searched*		
Symbol	Date	Examiner

US Classification - Searched*			
Class	Subclass	Date	Examiner

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

Search Notes		
Search Notes	Date	Examiner
Medline, Biosis, Ca, Caplus, Embase, PCTfull, USPatfull, terms: update search history 16/842,209, 16/659,893, 16/036,381, 15/358,187, 14/601,529, 13/660,629, 13/253,595, 12/559,278, 11/459,090	11/30/2022	MN

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

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* * * * * * * * * *   Welcome to STN International   * * * * * * * * * *

 NEWS  1  OCT  7  New CAS FORMULATIONS TM Database Launched on STNext
 NEWS  2  OCT  8  Third 2019 update to Emtree(TM) now available on STN(R)
 NEWS  3  NOV  8  Derwent Markush Resource (DWPIM) Enhanced to Improve Search
                  and Retrieval Quality
 NEWS  4  NOV 15  INPADOC Enhanced with More Current and Complete Japanese Legal
                  Status Information.
 NEWS  5  NOV 18  German Patent Full-Text Database DEFULL enhanced
 NEWS  6  NOV 25  CAS FORMULATIONS (TM) Enhanced on STNext
 NEWS  7  NOV 25  PatentPak(R) now available in USPATFULL/USPAT2 on STNext(R)
 NEWS  8  DEC 10  CAplus (SM) Now Provides Non-Conventional Patent Families
                  for Chinese Dual Filings
 NEWS  9  DEC 23  Derwent World Patents Index: Manual Code Revision 2020
 NEWS 10  FEB 13  Changes to Derwent WPI Update Numbering and Total
                  Number of Annual DWPI Updates
 NEWS 11  FEB 13  New Legal Event Data from Croatia, Italy, and Poland
                  in INPADOCDB and INPAFAMDB
 NEWS 12  MAR 10  2020 Version of MEDLINE Now Available on STN(R)
 NEWS 13  MAR 11  First 2020 Update to Emtree(TM) Now Available on STN(R)
 NEWS 14  MAR 26  STN Database Updates Continue as Usual
 NEWS 15  APR  6  Advanced German Patent Full-Text Database DEFULL
                  Replaces Patdpafull
 NEWS 16  APR  6  Announcements from Patent Offices Concerning
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=> s (apparatus? or device? or instrument?)

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

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

L2   3010 L1 (300A) (NASOPHARY?)

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

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

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

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

=> dup rem l4

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

=> d ibib kwic 1-44

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

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

headaches or facial pain

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

L5 ANSWER 2 OF 44 USPATFULL on STN
ACCESSION NUMBER: 2020:53186 USPATFULL
TITLE: SYSTEMS AND METHODS FOR DELIVERY OF A THERAPEUTIC AGENT
INVENTOR(S): Deem, Mark E., Mountain View, CA, UNITED STATES
Gifford, Hanson, Woodside, CA, UNITED STATES
APPLICANT(S): The Foundry, LLC, Menlo Park, CA, UNITED STATES

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

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

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

DOCUMENT TYPE: Utility
FILE SEGMENT: APPLICATION
NUMBER OF CLAIMS: 30
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 27 Drawing Page(s)
LINE COUNT: 1712
CAS INDEXING IS AVAILABLE FOR THIS PATENT. Full-text
SUMM . . . also be caused by anatomic pathologies such as blockages (as in the case of sinusitis). Symptoms may include sneezing, itching, nasal congestion, and a runny nose.
SUMM . . . selective and repeatable delivery of the toxins to defined target areas within the nasal cavities, including particular paranasal sinuses, the nasopharynx, and in some cases substantially the entire nasal cavity. The systems and methods should provide for the safe and effective. . . of botulinum light chain are described in US2004/0151741, US2005/0019346, and Chaddock et al. (2002) Protein Expression and Purification 25: 219-228. Energy-mediated transdermal delivery of intact botulinum toxin is suggested in US2005/007441 and 2004/0009180. The use of catheters and other devices for the energy-mediated delivery of botulinum light chain is described in commonly owned co-pending provisional application 60/702,077, filed Jul.

22, 2005, the full. . .
SUMM Allergic rhinitis is an immunologic response modulated by IgE and characterized predominantly by sneezing, rhinorrhea, nasal congestion, and pruritus of the nose. It may be seasonal (a condition commonly referred to as hay fever) or perennial. The. . .
DETD . . . of high goblet cell (G) concentration, for example in the back of the nasal passages in the area of the nasopharynx. By targeting this area of the nasal membrane, a high percentage of mucus-secreting epithelial or goblet cells can be treated with a device which is relatively small and which may carry a relatively low infusion volume and require less energy. Moreover, the olfactory bulb is inherently protected with this technique since the balloon is positioned well away from that area.. . . of course, additional shielding, shaping or other protective balloons could be positioned between the olfactory bulb and the toxin and energy delivering components of the present invention.
CLM What is claimed is:
1. A method of treating a nasal condition of a patient comprising: positioning a distal portion of a treatment device proximate to target tissue in a nasopharyngeal passage of a patient; and administering therapy to the target tissue with the treatment device so as to disrupt neural activity such that mucus secretion is reduced in the nasopharyngeal passage; wherein administering therapy comprises at least one of delivering energy to the target tissue and changing the temperature of the target tissue.

CLM What is claimed is:
17. A method of treating a nasal condition of a patient comprising: positioning a distal portion of a treatment device proximate to target tissue in a nasopharyngeal passage of a patient; and administering therapy to the target tissue with the treatment device to alter nasopharyngeal cells such that congestion in the nasopharyngeal passage is reduced; wherein administering therapy comprises delivering energy to the target tissue.

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

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

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

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

SUMM nasal congestion or postnasal drainage

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

L5 ANSWER 4 OF 44 USPATFULL on STN

ACCESSION NUMBER: 2019:449166 USPATFULL

TITLE: DEVICES, SYSTEMS AND METHODS FOR DIAGNOSING AND TREATING SINUSITIS AND OTHER DISORDERS OF THE EARS, NOSE AND/OR THROAT

INVENTOR(S): Chang, John Y., Los Altos, CA, UNITED STATES
Makower, Joshua, Los Altos, CA, UNITED STATES

APPLICANT(S): Acclarent, Inc., Irvine, CA, UNITED STATES

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 20190388113	A1	20191226
APPLICATION INFO.:	US 2019-16424728	A1	20190529 (16)

RELATED APPLN. INFO.: Continuation of Ser. No. US 2017-15443319, filed on 27 Feb 2017, PENDING Continuation of Ser. No. US 2016-15363002, filed on 29 Nov 2016, ABANDONED Continuation of Ser. No. US 2013-13867972, filed on 22 Apr 2013, ABANDONED Continuation of Ser. No. US 2009-649050, filed on 29 Dec 2009, Pat. No. US 8425457 Continuation of Ser. No. US 2004-829917, filed on 21 Apr 2004, Pat. No. US 7654997

DOCUMENT TYPE: Utility

FILE SEGMENT: APPLICATION

NUMBER OF CLAIMS: 21

EXEMPLARY CLAIM: 1-18

NUMBER OF DRAWINGS: 41 Drawing Page(s)

LINE COUNT: 2882

CAS INDEXING IS AVAILABLE FOR THIS PATENT. Full-text

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

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

headaches or facial pain

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

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

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

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

headaches or facial pain

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

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

L5 ANSWER 6 OF 44 USPATFULL on STN

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

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

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

L5 ANSWER 7 OF 44 USPATFULL on STN

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

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

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

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

headaches or facial pain

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

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

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

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

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

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

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

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

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

NUMBER	DATE

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

CAS INDEXING IS AVAILABLE FOR THIS PATENT. Full-text

SUMM . . . also be caused by anatomic pathologies such as blockages (as in the case of sinusitis). Symptoms may include sneezing, itching, nasal congestion, and a runny nose.

SUMM Allergic rhinitis is an immunologic response modulated by IgE and characterized predominantly by sneezing, rhinorrhea, nasal congestion, and pruritus of the nose. It may be seasonal (a condition commonly referred to as hay fever) or perennial. The. . .

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

L5 ANSWER 10 OF 44 USPATFULL on STN

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

CAS INDEXING IS AVAILABLE FOR THIS PATENT. Full-text

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

SUMM nasal congestion or postnasal drainage

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

L5 ANSWER 11 OF 44 USPATFULL on STN
ACCESSION NUMBER: 2017:82561 USPATFULL
TITLE: DEVICES, SYSTEMS AND METHODS FOR DIAGNOSING AND TREATING SINUSITIS AND OTHER DISORDERS OF THE EARS, NOSE AND/OR THROAT
INVENTOR(S): Chang, John Y., Los Altos, CA, UNITED STATES
Makower, Joshua, Los Altos, CA, UNITED STATES
APPLICANT(S): Acclarent, Inc., Irvine, CA, UNITED STATES

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

RELATED APPLN. INFO.: Continuation of Ser. No. US 2013-13867972, filed on 22 Apr 2013, PENDING Continuation of Ser. No. US 2009-649050, filed on 29 Dec 2009, Pat. No. US 8425457 Continuation of Ser. No. US 2004-829917, filed on 21 Apr 2004, Pat. No. US 7654997
DOCUMENT TYPE: Utility
FILE SEGMENT: APPLICATION
NUMBER OF CLAIMS: 18
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 41 Drawing Page(s)
LINE COUNT: 2825 Full-text
AB . . . nose and throat are diagnosed and/or treated using minimally invasive approaches and, in many cases, flexible catheters as opposed to instruments having rigid shafts. Various diagnostic procedures and devices are used to perform imaging studies, mucus flow studies, air/gas flow studies, anatomic dimension studies, endoscopic studies and transillumination studies. Access and occluder devices may be used to establish fluid tight seals in the anterior or posterior nasal cavities/nasopharynx and to facilitate insertion of working devices (e.g., scopes, guidewires, catheters, tissue cutting or remodeling devices, electrosurgical devices, energy emitting devices, devices for injecting diagnostic or therapeutic agents, devices for implanting devices such as stents, substance eluting devices, substance delivery implants, etc.
SUMM Patients who suffer from sinusitis typically experience at least some of the following symptoms:

headaches or facial pain

nasal congestion or postnasal drainage
difficulty breathing through one or both nostrils
bad breath
pain in the upper teeth
DETD . . . 9A-9C show a procedure for installation of a cochlear implant in accordance with the present invention. In this procedure, the

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

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

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

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

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

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

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

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

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

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

headaches or facial pain

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

L5 ANSWER 14 OF 44 USPATFULL on STN

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

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

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

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

DOCUMENT TYPE: Utility
FILE SEGMENT: APPLICATION
NUMBER OF CLAIMS: 24
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 24 Drawing Page(s)
LINE COUNT: 1360
CAS INDEXING IS AVAILABLE FOR THIS PATENT. Full-text
SUMM . . . also be caused by anatomic pathologies such as blockages (as in the case of sinusitis). Symptoms may include sneezing, itching, nasal congestion, and a runny nose.
SUMM Allergic rhinitis is an immunologic response modulated by IgE and characterized predominantly by sneezing, rhinorrhea, nasal congestion, and pruritus of the nose. It may be seasonal (a condition commonly referred to as hay fever) or perennial. The. . .
DETD . . . epithelial or goblet cell (G) concentration, for example in the back of the nasal passages in the area of the nasopharynx. By targeting this area of the nasal membrane, a high percentage of mucus-secreting epithelial or goblet cells can be treated with a device which is relatively small and which may carry a relatively low infusion volume and require less energy. Moreover, the olfactory bulb is inherently protected with this technique since the balloon is positioned well away from that area.. . . of course, additional shielding, shaping or other protective balloons could be positioned between the olfactory bulb and the toxin and energy delivering components of the present invention.

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

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

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

headaches or facial pain

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

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

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

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

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

headaches or facial pain

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

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

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

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

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

headaches or facial pain

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

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

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

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

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

headaches or facial pain

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

L5 ANSWER 19 OF 44 USPATFULL on STN
ACCESSION NUMBER: 2014:127127 USPATFULL
TITLE: METHODS AND SYSTEMS FOR TOXIN DELIVERY TO THE NASAL CAVITY
INVENTOR(S): Deem, Mark E., Mountain View, CA, UNITED STATES
Gifford, Hanson, Woodside, CA, UNITED STATES
PATENT ASSIGNEE(S): The Foundry, LLC, Menlo Park, CA, UNITED STATES (U.S. corporation)

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

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

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

DOCUMENT TYPE: Utility
FILE SEGMENT: APPLICATION
NUMBER OF CLAIMS: 31
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 24 Drawing Page(s)
LINE COUNT: 1374
CAS INDEXING IS AVAILABLE FOR THIS PATENT. Full-text
SUMM . . . also be caused by anatomic pathologies such as blockages (as in the case of sinusitis). Symptoms may include sneezing, itching, nasal congestion, and a runny nose.
SUMM Allergic rhinitis is an immunologic response modulated by IgE and characterized predominantly by sneezing, rhinorrhea, nasal congestion, and pruritus of the nose. It may be seasonal (a condition commonly referred to as hay fever) or perennial. The. . .
DETD . . . epithelial or goblet cell (G) concentration, for example in the back of the nasal passages in the area of the nasopharynx. By targeting this area of the nasal membrane, a high percentage of mucus-secreting epithelial or goblet cells can be treated with a device which is relatively small and which may carry a relatively low infusion volume and require less energy. Moreover, the olfactory bulb

is inherently protected with this technique since the balloon is positioned well away from that area.. . . of course, additional shielding, shaping or other protective balloons could be positioned between the olfactory bulb and the toxin and energy delivering components of the present invention.

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

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

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

headaches or facial pain

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

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

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

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

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

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

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

headaches or facial pain

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

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

corporation)

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

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

headaches or facial pain

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

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

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

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

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

DOCUMENT TYPE: Utility
FILE SEGMENT: APPLICATION
NUMBER OF CLAIMS: 68
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 24 Drawing Page(s)
LINE COUNT: 1435
CAS INDEXING IS AVAILABLE FOR THIS PATENT. Full-text
SUMM . . . also be caused by anatomic pathologies such as blockages (as in the case of sinusitis). Symptoms may include sneezing, itching, nasal congestion, and a runny nose.
SUMM Allergic rhinitis is an immunologic response modulated by IgE and characterized predominantly by sneezing, rhinorrhea, nasal congestion, and pruritus of the nose. It may be seasonal (a condition commonly referred to as hay fever) or perennial. The. . .
DETD . . . epithelial or goblet cell (G) concentration, for example in the back of the nasal passages in the area of the nasopharynx. By targeting this area of the nasal membrane, a high percentage of mucus-secreting epithelial or goblet cells can be treated with a device which is relatively small and which may carry a relatively low infusion volume and require less energy. Moreover, the olfactory bulb is inherently protected with this technique since the balloon is positioned well away from that area.. . . of course, additional shielding, shaping or other protective balloons could be positioned between the olfactory bulb and the toxin and energy delivering components of the present invention.

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

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

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

DOCUMENT TYPE: Utility
FILE SEGMENT: APPLICATION
NUMBER OF CLAIMS: 64
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 26 Drawing Page(s)
LINE COUNT: 1729
CAS INDEXING IS AVAILABLE FOR THIS PATENT. Full-text
DETD While FIGS. 1-4 show the insulating guide sheath 104 and electrode 102 being inserted into the ear via the ear canal 122, these components can be also configured for insertion into. . . of the subject. Various disease processes in the ear canal or upon the tympanic membrane may impair access of medical devices through the ear canal. To overcome limited access through the ear canal 122, an apparatus capable of accessing the middle ear through the Eustachian tube 120 can be employed. The Eustachian tube 120 connects the middle ear 116 with the nasopharynx, allowing for pressure equilibration between the middle ear 116 and the external environment and for drainage from the middle ear 116 to enter the throat. The insulating guide sheath 104 and electrode 102 can be inserted into the Eustachian tube 120 without direct visualization through transnasal positioning, under direct visualization transnasally, or under direct visualization transorally.

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

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

CLM What is claimed is:

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

CLM What is claimed is:

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

L5 ANSWER 26 OF 44 USPATFULL on STN

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

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

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

CAS INDEXING IS AVAILABLE FOR THIS PATENT. Full-text

SUMM nasal congestion or post-nasal drainage

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

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

L5 ANSWER 27 OF 44 USPATFULL on STN

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

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

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

CAS INDEXING IS AVAILABLE FOR THIS PATENT. Full-text

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

SUMM nasal congestion or post-nasal drainage

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

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

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

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

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

headaches or facial pain

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

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

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

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

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

headaches or facial pain

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

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

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

L5 ANSWER 30 OF 44 USPATFULL on STN
ACCESSION NUMBER: 2010:112427 USPATFULL
TITLE: DEVICES, SYSTEMS AND METHODS FOR DIAGNOSING AND TREATING SINUSITUS ANDOTHER DISORDERS OF THE EARS, NOSE AND/OR THROAT
INVENTOR(S): Makower, Joshua, Los Altos, CA, UNITED STATES
Chang, John Y., Mountain View, CA, UNITED STATES
PATENT ASSIGNEE(S): ACCLARENT, INC., Menlo Park, CA, UNITED STATES (U.S. corporation)

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

RELATED APPLN. INFO.: Continuation of Ser. No. US 2004-829917, filed on 21 Apr 2004, Pat. No. US 7654997
DOCUMENT TYPE: Utility
FILE SEGMENT: APPLICATION
LEGAL REPRESENTATIVE: Robert D. Buyan, Stout, Uxa, Buyan & Mullins,, LLP/Acclarent, Inc., 4 Venture, Suite 300, Irvine, CA, 92618, US
NUMBER OF CLAIMS: 10
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 41 Drawing Page(s)
LINE COUNT: 2847
CAS INDEXING IS AVAILABLE FOR THIS PATENT. Full-text
AB . . . nose and throat are diagnosed and/or treated using minimally invasive approaches and, in many cases, flexible catheters as opposed to instruments having rigid shafts. Various diagnostic procedures and devices are used to perform imaging studies, mucus flow studies, air/gas flow studies, anatomic dimension studies, endoscopic studies and transillumination studies. Access and occluder devices may be used to establish fluid tight seals in the anterior or posterior nasal cavities/nasopharynx and to facilitate insertion of working devices (e.g., scopes, guidewires, catheters, tissue cutting or remodeling devices, electrosurgical devices, energy emitting devices, devices for injecting diagnostic or therapeutic agents, devices for implanting devices such as stents, substance eluting devices, substance delivery implants, etc.
SUMM nasal congestion or post-nasal drainage
DETD . . . 9A-9C show a procedure for installation of a cochlear implant in accordance with the present invention. In this procedure, the nasopharyngeal opening into the Eustachian tube ET is located and a guidewire is initially advanced into the Eustachian tube ET. A. . . catheter 900 is in or near the tympanic cavity TC of the middle ear. Thereafter, if deemed necessary, a forceps device 790 and/or other devices are advanced through the catheter 900 and used to remove the small bones of the sear (i.e., the malleus, incus. . . This optional removal of the bones of the middle ear may be done under endoscopic visualization using an endoscope equipped device such as the endoscope equipped forceps device 790 shown in FIG. 5T and described above. As shown in FIG. 9B, a cochlear guide catheter 904 having a. . . tympanic membrane. In other applications, the cochlear guide catheter 904 may be positioned adjacent to the cochlea and a cochleostomy device (e.g., a penetrator such as a drill, needle or cutter) may be advanced through or formed or positioned on the. . . cochleostomy through which the distal end of the guide catheter 904 is advanced into the cochlea C. Thereafter, a cochlear electrode array 906 is advanced through the cochlear guide catheter 904 and into the cochlea, as seen in FIG. 9B. One example of a commercially available cochlear electrode array is the Nucleus 24 Countour device manufactured by Cochlear Corporation.

L5 ANSWER 31 OF 44 USPATFULL on STN

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

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

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

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

DOCUMENT TYPE: Utility
FILE SEGMENT: APPLICATION
LEGAL REPRESENTATIVE: TOWNSEND AND TOWNSEND AND CREW, LLP, TWO EMBARCADERO CENTER, EIGHTH FLOOR, SAN FRANCISCO, CA, 94111-3834, US
NUMBER OF CLAIMS: 31
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 24 Drawing Page(s)
LINE COUNT: 1356
CAS INDEXING IS AVAILABLE FOR THIS PATENT. Full-text
SUMM . . . also be caused by anatomic pathologies such as blockages (as in the case of sinusitis). Symptoms may include sneezing, itching, nasal congestion, and a runny nose.
SUMM Allergic rhinitis is an immunologic response modulated by IgE and characterized predominantly by sneezing, rhinorrhea, nasal congestion, and pruritus of the nose. It may be seasonal (a condition commonly referred to as hay fever) or perennial. The. . .
DETD . . . epithelial or goblet cell (G) concentration, for example in the back of the nasal passages in the area of the nasopharynx. By targeting this area of the nasal membrane, a high percentage of mucus-secreting epithelial or goblet cells can be treated with a device which is relatively small and which may carry a relatively low infusion volume and require less energy. Moreover, the olfactory bulb is inherently protected with this technique since the balloon is positioned well away from that area.. . . of course, additional shielding, shaping or other protective balloons could be positioned between the olfactory bulb and the toxin and energy delivering components of the present invention.

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

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

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

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

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 20090187098	A1	20090723
	US 9101384	B2	20150811

APPLICATION INFO.: US 2009-355492 A1 20090116 (12)
RELATED APPLN. INFO.: Continuation-in-part of Ser. No. US 2004-829917, filed on 21 Apr 2004, PENDING Continuation-in-part of Ser. No. US 2006-522497, filed on 15 Sep 2006, PENDING
DOCUMENT TYPE: Utility
FILE SEGMENT: APPLICATION
LEGAL REPRESENTATIVE: Townsend and Townsend and Crew LLP, Acclarent, Inc. (73608), Two Embarcadero Center, San Francisco, CA, 94111-3834, US
NUMBER OF CLAIMS: 27
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 51 Drawing Page(s)
LINE COUNT: 4495

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

headaches or facial pain

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

L5 ANSWER 34 OF 44 USPATFULL on STN

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

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

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

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

headaches or facial pain

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

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

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

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

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

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

headaches or facial pain

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

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

L5 ANSWER 36 OF 44 USPATFULL on STN

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

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

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

CAS INDEXING IS AVAILABLE FOR THIS PATENT. Full-text

SUMM nasal congestion or post-nasal drainage

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

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

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

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

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

headaches or facial pain

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

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

L5 ANSWER 38 OF 44 USPATFULL on STN
ACCESSION NUMBER: 2008:111741 USPATFULL
TITLE: DEVICES, SYSTEMS AND METHODS FOR DIAGNOSING AND TREATING SINUSITIS AND OTHER DISORDERS OF THE EARS, NOSE AND/OR THROAT
INVENTOR(S): Makower, Joshua, Los Altos, CA, UNITED STATES
Chang, John Y., Mountain View, CA, UNITED STATES
PATENT ASSIGNEE(S): Acclarent, Inc., Menlo Park, CA, UNITED STATES, 940025 (U.S. corporation)

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

RELATED APPLN. INFO.: Continuation of Ser. No. US 2004-829917, filed on 21 Apr 2004, PENDING
DOCUMENT TYPE: Utility
FILE SEGMENT: APPLICATION
LEGAL REPRESENTATIVE: STEPTOE & JOHNSON - ACCLARENT, INC., 2121 AVENUE OF THE STARS, SUITE 2800, LOS ANGELES, CA, 90067, US
NUMBER OF CLAIMS: 25
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 41 Drawing Page(s)
LINE COUNT: 2875
CAS INDEXING IS AVAILABLE FOR THIS PATENT. Full-text
AB . . . nose and throat are diagnosed and/or treated using minimally invasive approaches and, in many cases, flexible catheters as opposed to instruments having rigid shafts. Various diagnostic procedures and devices are used to perform imaging studies, mucus flow studies, air/gas flow studies, anatomic dimension studies, endoscopic studies and transillumination studies. Access and occluder devices may be used to establish fluid tight seals in the anterior or posterior nasal cavities/nasopharynx and to facilitate insertion of working devices (e.g., scopes, guidewires, catheters, tissue cutting or remodeling devices, electrosurgical devices, energy emitting devices, devices for injecting diagnostic or therapeutic agents, devices for implanting devices such as stents, substance eluting devices, substance delivery implants, etc.
SUMM nasal congestion or post-nasal drainage
DETD . . . 9A-9C show a procedure for installation of a cochlear implant in accordance with the present invention. In this procedure, the nasopharyngeal opening into the Eustachian tube ET is located and a guidewire is initially advanced into the Eustachian tube ET. A. . . catheter 900 is in or near the tympanic cavity TC of the middle ear. Thereafter, if deemed necessary, a forceps device 790 and/or other devices are advanced through the catheter 900 and used to remove the small bones of the sear (i.e., the malleus, incus. . . This optional removal of the bones of the middle ear may be done under endoscopic visualization using an endoscope equipped device such as the endoscope equipped forceps device 790 shown in FIG. 5T and described above. As shown in FIG. 9B, a cochlear guide catheter 904 having a. . . tympanic membrane. In other applications, the cochlear guide catheter 904 may be positioned adjacent to the cochlea and a cochleostomy device (e.g., a penetrator such as a drill, needle or cutter) may be advanced through or formed or positioned on the. . . cochleostomy through which the distal end of the guide catheter 904 is advanced into the cochlea C. Thereafter, a cochlear electrode array 906 is advanced through the cochlear guide catheter 904 and into the cochlea, as seen in FIG. 9B. One example of a commercially available cochlear electrode

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

L5 ANSWER 39 OF 44 USPATFULL on STN
ACCESSION NUMBER: 2008:24188 USPATFULL
TITLE: METHODS AND SYSTEMS FOR TOXIN DELIVERY TO THE NASAL CAVITY
INVENTOR(S): Deem, Mark E., Mountain View, CA, UNITED STATES
Gifford, Hanson, Woodside, CA, UNITED STATES
PATENT ASSIGNEE(S): The Foundry Inc., Menlo Park, CA, UNITED STATES (U.S. corporation)

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

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

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

DOCUMENT TYPE: Utility
FILE SEGMENT: APPLICATION
LEGAL REPRESENTATIVE: TOWNSEND AND TOWNSEND AND CREW, LLP, TWO EMBARCADERO CENTER, EIGHTH FLOOR, SAN FRANCISCO, CA, 94111-3834, US
NUMBER OF CLAIMS: 69
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 24 Drawing Page(s)
LINE COUNT: 1438
CAS INDEXING IS AVAILABLE FOR THIS PATENT. Full-text
SUMM . . . also be caused by anatomic pathologies such as blockages (as in the case of sinusitis). Symptoms may include sneezing, itching, nasal congestion, and a runny nose.
SUMM Allergic rhinitis is an immunologic response modulated by IgE and characterized predominantly by sneezing, rhinorrhea, nasal congestion, and pruritus of the nose. It may be seasonal (a condition commonly referred to as hay fever) or perennial. The. . .
DETD . . . epithelial or goblet cell (G) concentration, for example in the back of the nasal passages in the area of the nasopharynx. By targeting this area of the nasal membrane, a high percentage of mucus-secreting epithelial or goblet cells can be treated with a device which is relatively small and which may carry a relatively low infusion volume and require less energy. Moreover, the olfactory bulb is inherently protected with this technique since the balloon is positioned well away from that area.. . . of course, additional shielding, shaping or other protective balloons could be positioned between the olfactory bulb and the toxin and energy delivering components of the present invention.

L5 ANSWER 40 OF 44 USPATFULL on STN
ACCESSION NUMBER: 2007:305933 USPATFULL
TITLE: APPARATUS FOR TOXIN DELIVERY TO THE NASAL CAVITY
INVENTOR(S): Deem, Mark E., Mountain View, CA, UNITED STATES
Gifford, Hanson, Woodside, CA, UNITED STATES
Kim, Steven, Los Altos, CA, UNITED STATES
Salamini, Alexey, San Francisco, CA, UNITED STATES
PATENT ASSIGNEE(S): The Foundry Inc., Menlo Park, CA, UNITED STATES (U.S. corporation)

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

	NUMBER	DATE

PRIORITY INFORMATION: US 2006-60747771 20060519 (60)
DOCUMENT TYPE: Utility
FILE SEGMENT: APPLICATION
LEGAL REPRESENTATIVE: TOWNSEND AND TOWNSEND AND CREW, LLP, TWO EMBARCADERO CENTER, EIGHTH FLOOR, SAN FRANCISCO, CA, 94111-3834, US
NUMBER OF CLAIMS: 43
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 24 Drawing Page(s)
LINE COUNT: 1513
CAS INDEXING IS AVAILABLE FOR THIS PATENT. Full-text
DETD . . . also be caused by anatomic pathologies such as blockages (as in the case of sinusitis). Symptoms may include sneezing, itching, nasal congestion, and a runny nose.
DETD Allergic rhinitis is an immunologic response modulated by IgE and characterized predominantly by sneezing, rhinorrhea, nasal congestion, and pruritus of the nose. It may be seasonal (a condition commonly referred to as hay fever) or perennial. The. . .
DETD Allergic rhinitis is an immunologic response modulated by IgE and characterized predominantly by sneezing, rhinorrhea, nasal congestion, and pruritus of the nose. It may be seasonal (a condition commonly referred to as hay fever) or perennial. The. . .
DETD . . . epithelial or goblet cell (G) concentration, for example in the back of the nasal passages in the area of the nasopharynx. By targeting this area of the nasal membrane, a high percentage of mucus-secreting epithelial or goblet cells can be treated with a device which is relatively small and which may carry a relatively low infusion volume and require less energy. Moreover, the olfactory bulb is inherently protected with this technique since the balloon is positioned well away from that area.. . . of course, additional shielding, shaping or other protective balloons could be positioned between the olfactory bulb and the toxin and energy delivering components of the present invention.

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

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

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

of the following symptoms:

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

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

L5 ANSWER 42 OF 44 USPATFULL on STN

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

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

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

CAS INDEXING IS AVAILABLE FOR THIS PATENT. Full-text

SUMM nasal congestion or post-nasal drainage

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

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

L5 ANSWER 43 OF 44 USPATFULL on STN

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

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

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

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

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

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

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

CLM What is claimed is:

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

L5 ANSWER 44 OF 44 USPATFULL on STN

ACCESSION NUMBER: 2005:275582 USPATFULL

TITLE: Devices, systems and methods for diagnosing and treating sinusitus and other disorders of the ears, nose and/or throat

INVENTOR(S): Makower, Joshua, Los Altos, CA, UNITED STATES
Chang, John Y., Mountain View, CA, UNITED STATES

PATENT ASSIGNEE(S): ExploraMed II, Inc., Menlo Park, CA, UNITED STATES (U.S. corporation)

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

DOCUMENT TYPE: Utility

FILE SEGMENT: APPLICATION

LEGAL REPRESENTATIVE: Robert D. Buyan, Stout, Uxa, Buyan & Mullins, LLP, 4 Venture, Suite 300, Irvine, CA, 92618, US

NUMBER OF CLAIMS: 91

EXEMPLARY CLAIM: 1

NUMBER OF DRAWINGS: 41 Drawing Page(s)

LINE COUNT: 3253

CAS INDEXING IS AVAILABLE FOR THIS PATENT. Full-text

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

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

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

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

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

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=> e deem ma?/au

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

=> s e6-7

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

=> s l6 and nasal

L7           36 L6 AND NASAL

=> dup rem L7

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

=> d ibib kwic ab 1-31


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

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

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

CAS INDEXING IS AVAILABLE FOR THIS PATENT. Full-text

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

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

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

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

SUMM . . . toxin is a neurotoxin which could have significant negative effects on a patient if accidentally released outside of the targeted nasal passages. Inadvertent distribution of the toxin to muscles of the oropharynx, mouth, tongue, or elsewhere could result in serious complications to the patient. Additionally, the use of botulinum-soaked gauze pads for delivering the toxin to the nasal cavities, as demonstrated by Dr. Sanders, will have limited ability to uniformly and selectively deliver the botulinum to the regions. . .

SUMM . . . be desirable to provide improved methods and systems for delivering toxins, such as botulinum and active botulinum fragments, to the nasal membrane of a patient, particularly a patient suffering from rhinitis or other conditions associated with nasal inflammation and conditions, such as sinus headaches and migraine headaches. The methods and systems should be capable of providing for selective and repeatable delivery of the toxins to defined target areas within the nasal cavities, including particular paranasal sinuses, the nasopharynx, and in some cases substantially the entire nasal cavity. The systems and methods should provide for the safe and effective delivery of the toxins, and in particular should reduce or eliminate the risk of toxin being delivered to non-targeted tissues outside of the nasal cavity. At least some of these objectives will be met by the inventions described herein below. U.S. Pat. No. 5,766,605,. . .

SUMM Rhinorrhea is the term describing the effluence of mucus from the lining of the nasal passages, nasopharynx, or paranasal sinuses. Rhinorrhea can be a symptom of a number of diseases such as the common cold,. . . paranasal sinuses. Sinusitis may have a number of different causes, and can be the result of chronic inflammation of the nasal passages, for example as a result of chronic rhinitis.

SUMM Allergic rhinitis is an immunologic response modulated by IgE and characterized predominantly by sneezing, rhinorrhea, nasal congestion, and pruritus of the nose. It may be seasonal (a condition commonly referred to as hay fever) or perennial.. . .

SUMM . . . ricin, exotoxin A, diphtheria toxin, cholera toxin, tetanus toxin, other neurotoxins, and active fragments thereof are delivered to a patient's nasal membrane while applying energy to target cells within the membrane under conditions which cause a reversible (or in some instances. . . delivery of the toxin into the cells. The region

where the toxin is introduced may comprise any portion of the nasal cavity, such as a single paranasal sinus or portion thereof, a main nasal passage, two or more paranasal sinuses, or in some cases may comprise substantially the entire nasal cavity of the patient. A particular target region for the toxin may comprise the nasopharynx which is at the back of the nasal passage. The nasopharynx comprises a cluster of goblet cells which are responsible for mucus secretion and which are susceptible to. . .

SUMM . . . no energy applied to untargeted regions. It will be appreciated that the energy may be applied to regions of the nasal membrane which are the same or different from the regions to which the toxin has been introduced. By controlling the. . . cells of interest while minimizing the amount of toxin which enters non-targeted cells. That is, only those cells in the nasal membrane which are exposed to both the toxin and the applied energy will preferentially be permeablized or porated to receive. . .

SUMM . . . to be delivered may comprise any neurotoxin capable of disabling mucus secretion in epithelial or goblet cells and other mucus-producing nasal cells. Preferably, the toxin comprises botulinum toxin, although other toxins such as ricin, exotoxin A, diphtheria toxin, cholera toxin, tetanus. . . use. In preferred aspects of the present invention, only an active fragment of the toxin will be delivered to the nasal cavity. botulinum toxin and the other toxins listed above commonly comprise both a heavy chain and a light chain. The. . .

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

SUMM . . . be introduced to the target region through a catheter. For example, the catheter may carry a balloon which engages the nasal membrane in order to effect delivery of the toxin to the target cells. In a particular example, the balloon is. . . over at least a portion of its area so that the toxin may be released to specific areas of the nasal membrane, typically being incorporated into a suitable liquid, gel, or other fluid or fluidizable carrier. In other embodiments, the toxin. . .

SUMM . . . that the transducer may be located within or beneath the porous balloon which is used to deliver toxin to the nasal membrane. When electrical energy is used for poration, the electrodes may be on the catheter within or surrounding the region which delivers the energy to the nasal membrane. In other instances, the energy may be applied from a separate catheter or other device adapted for intranasal introduction.. . .

SUMM . . . the present invention further provides systems for delivering toxins to goblet and other target cells as defined above in a nasal membrane. The systems may typically comprise a catheter adapted to introduce a toxin to a region adjacent to the target. . .

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

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

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

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

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

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

DETD . . . in a simplified single cell model. A targeted cell 10, e.g. a goblet cell of the type which line the nasal cavity membrane, is shown in FIG. 2A. Fragmented neurotoxin such as BoNT-LC (LC) is introduced into the vicinity of the. . .

DETD . . . present invention may be adapted to introduce a BoNT-LC solution to a target region, such as the lung or the nasal passage and then effect selective membrane transport of the BoNT-LC into the cell using sonoporation.

DETD . . . utilizing an ultrasonic element 92 that may be particularly useful in delivery of the BoNT-LC to bronchial tissue (lung) and/or

nasal tissue that provides a broad but targeted transport of the LC across the target cell walls, for example, epithelial and. . .

DETD Delivery to Nasal Cavity

DETD . . . other embodiments, the present invention is directed to methods and systems for delivering toxins to target cells within a patient's nasal cavity. The toxins may be intact toxins, such as botulinum toxin, ricin, exotoxin A, diphtheria toxin, cholera toxin, tetanus toxin,. . .

DETD Botulinum toxin blocks acetylcholine release from cells, such as the epithelial or goblet cells in the nasal membranes responsible for mucus hypersecretion, and can thus be effective even without energy-mediated delivery in accordance with the principles of. . . energy to permeablize or porate the cell membranes of the epithelial or goblet cells or other mucus-secreting cells of the nasal lining, in accordance with the present invention, allows botulinum and other toxins to be preferentially delivered to the targeted epithelial. . . the toxin light chains may be locally and specifically introduced into the target cells located within defined regions of the nasal membrane. Thus, even if the toxin fragments are accidentally dispersed beyond the desired target regions, the fragments will not generally. . .

DETD . . . the energy, or both, non-invasively. For example, as illustrated in FIG. 17, the patient may draw the toxin into the nasal cavity from a hand-held dispersion device DD. After a sufficient amount of the toxin has been infused into the nasal cavity, a separate hand-held transducer TD connected to an appropriate power supply PS will be energized and applied to the nasal cavities by passing the transducer over the appropriate regions of the forehead and nose. Optionally, the transducer can have a. . .

DETD While the toxins and porating energy of the present invention may be delivered to the nasal cavity in a variety of ways, the following provides a number of specific examples of catheters and other structures for delivering toxins to preselected portions of the nasal cavity. For example, as shown in FIG. 18, a balloon catheter 1000 may be provided with a porous balloon 1002. . . transducers 1004 within the balloon, optionally mounted on the catheter body, ultrasonic poration energy can be delivered to the adjacent nasal membranes which are receiving the toxin solution. As illustrated in FIG. 18, the toxin is being delivered to a lower. . .

DETD . . . sized and positioned to target an area of high goblet cell (G) concentration, for example in the back of the nasal passages in the area of the nasopharynx. By targeting this area of the nasal membrane, a high percentage of mucus-secreting epithelial or goblet cells can be treated with a device which is relatively small. . .

DETD . . . effect of such externally applied ultrasonic energy can be enhanced by introducing microbubbles (free air) into the isolated sinuses and/or nasal passages which have been filled with toxin solution. For example, encapsulated microbubbles, which are generally useful as echocardiographic contrast agents,. . .

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

DETD . . . air bleed valves 1006 which are used to occlude the nostrils in order to evacuate or bleed air from the nasal passages while filling the passages with the toxin solution. The nose plugs 1005 could optionally include ultrasonic transducers in order to deliver ultrasonic or other acoustic energy into the solutions entrapped within the nasal cavities using the nostril plugs. Alternatively, of course, the ultrasound or other acoustic energy could be delivered from an external. . .

DETD . . . can deliver toxin incorporated into vesicles which may be configured as “resonance” bodies, which reduce the need to fill the nasal cavities with a liquid or other form of toxin. For

example, lipid microspheres which incorporate the toxin may be sprayed or aerosolized onto target surfaces of the nasal epithelium. After the lipid or other resonance bodies are attached to the targeted epithelium membrane surface(s), the ultrasound energy can. . .

DETD Referring to FIG. 37, the toxin may be delivered as a conventional nasal spray (BoNT), as mentioned hereinbefore, and the poration energy can be delivered through a face mask. The poration energy might. . .

DETD In addition to BTX-LC, it may be desirable to deliver additional agents to the nasal passages and sinuses prior to, coincident with, or after delivery of the LC. Adjunctive therapies may include agents designed to. . .

DETD Decongestants such as epinephrine also cause constriction of the vasculature in the nasal passages, which in addition to temporarily reducing swelling of the target tissues, may decrease the risks of LC entering the. . .

CLM What is claimed is:
1. A method of treating a nasal condition of a patient comprising: positioning a distal portion of a treatment device proximate to target tissue in a nasopharyngeal. . .

CLM What is claimed is:
17. A method of treating a nasal condition of a patient comprising: positioning a distal portion of a treatment device proximate to target tissue in a nasopharyngeal. . .

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

L8 ANSWER 2 OF 31 USPATFULL on STN

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

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 20200000715	A1	20200102
APPLICATION INFO.:	US 2019-16544884	A1	20190819 (16)
RELATED APPLN. INFO.:	Continuation of Ser. No. US 2017-15852619, filed on 22 Dec 2017, Pat. No. US 10383817 Continuation of Ser. No. US 2017-15405991, filed on 13 Jan 2017, Pat. No. US 9849082 Continuation of Ser. No. US 2015-14858555, filed on 18 Sep 2015, Pat. No. US 9549852 Continuation of Ser. No. US 2014-14265071, filed on 29 Apr 2014, Pat. No. US 9168222 Continuation of Ser. No. US 2011-13184690, filed on 18 Jul 2011, Pat. No. US 8747884 Continuation of Ser. No. US 2007-695545, filed on 2 Apr 2007, Pat. No. US 7998497		

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

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

CAS INDEXING IS AVAILABLE FOR THIS PATENT. Full-text

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

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

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

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

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

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

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

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

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

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

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

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

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

patient's nasal cavity provide for both release of the toxin and delivery of energy which selectively porates target cells to enhance uptake. . .

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

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

IT Chemicals & Biochemicals
toxins: toxin

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

L8 ANSWER 6 OF 31 USPATFULL on STN

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

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

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

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

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

L8 ANSWER 7 OF 31 BIOSIS COPYRIGHT (c) 2020 Clarivate Analytics on STN

ACCESSION NUMBER: 2017:585488 BIOSIS
DOCUMENT NUMBER: PREV201700585488

TITLE: Methods and systems for toxin delivery to the nasal cavity.
AUTHOR(S): Deem, Mark E. [Inventor]; Anonymous; Gifford, Hanson [Inventor]
CORPORATE SOURCE: Mountain View, CA USA
ASSIGNEE: The Foundry LLC
PATENT INFORMATION: US 09700707 20170711
SOURCE: Official Gazette of the United States Patent and Trademark Office Patents, (JUL 11 2017)
CODEN: OGUPE7. ISSN: 0098-1133.
DOCUMENT TYPE: Patent
LANGUAGE: English
ENTRY DATE: Entered STN: 2 Aug 2017
Last Updated on STN: 2 Aug 2017 Full-text
TI Methods and systems for toxin delivery to the nasal cavity.
AU Deem, Mark E. [Inventor]; Anonymous; Gifford, Hanson [Inventor]
AB Methods and systems for delivering toxin and toxin fragments to a patient's nasal cavity provide for both release of the toxin and delivery of energy which selectively porates target cells to enhance uptake. . .
AB Methods and systems for delivering toxin and toxin fragments to a patient's nasal cavity provide for both release of the toxin and delivery of energy which selectively porates target cells to enhance uptake of the toxin. The use of energy-mediated delivery is particularly advantageous with light chain fragment toxins which lack cell binding capacity.

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

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

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

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

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

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

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

SUMM . . . toxin is a neurotoxin which could have significant negative effects on a patient if accidentally released outside of the targeted nasal passages. Inadvertent distribution of the toxin to muscles of the oropharynx, mouth, tongue, or elsewhere could result in serious complications to the patient. Additionally, the use of botulinum-soaked gauze pads for delivering the toxin to the nasal cavities, as demonstrated by Dr. Sanders, will have limited ability to uniformly and selectively deliver the botulinum to the regions. . .

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

SUMM Rhinorrhea is the term describing the effluence of mucus from the lining of the nasal passages, nasopharynx, or paranasal sinuses. Rhinorrhea can be a symptom of a number of diseases such as the common cold,. . . paranasal sinuses. Sinusitis may have a number of different causes, and can be the result of chronic inflammation of the nasal passages, for example as a result of chronic rhinitis.

SUMM Allergic rhinitis is an immunologic response modulated by IgE and characterized predominantly by sneezing, rhinorrhea, nasal congestion, and pruritus of the nose. It may be seasonal (a condition commonly referred to as hay fever) or perennial.. . .

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

SUMM . . . no energy applied to untargeted regions. It will be appreciated that the energy may be applied to regions of the nasal membrane which are the same or different from the regions to which the toxin has been introduced. By controlling the. . . cells of interest while minimizing the amount of toxin which enters non-targeted cells. That is, only those cells in the nasal membrane which are exposed to both the toxin and the applied energy will preferentially be permeablized or porated to receive. . .

SUMM . . . to be delivered may comprise any neurotoxin capable of disabling mucus secretion in epithelial or goblet cells and other mucus-producing nasal cells. Preferably, the toxin comprises botulinum toxin, although other toxins such as ricin, exotoxin A, diphtheria

toxin, cholera toxin, tetanus. . . use. In preferred aspects of the present invention, only an active fragment of the toxin will be delivered to the nasal cavity. Botulinum toxin and the other toxins listed above commonly comprise both a heavy chain and a light chain. The. . .

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

SUMM . . . be introduced to the target region through a catheter. For example, the catheter may carry a balloon which engages the nasal membrane in order to effect delivery of the toxin to the target cells. In a particular example, the balloon is. . . over at least a portion of its area so that the toxin may be released to specific areas of the nasal membrane, typically being incorporated into a suitable liquid, gel, or other fluid or fluidizable carrier. In other embodiments, the toxin. . .

SUMM . . . that the transducer may be located within or beneath the porous balloon which is used to deliver toxin to the nasal membrane. When electrical energy is used for poration, the electrodes may be on the catheter within or surrounding the region which delivers the energy to the nasal membrane. In other instances, the energy may be applied from a separate catheter or other device adapted for intranasal introduction.. . .

SUMM . . . invention further provides systems for delivering toxins to epithelial or goblet and other target cells as defined above in a nasal membrane. The systems may typically comprise a catheter adapted to introduce a toxin to a region adjacent to the target. . .

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

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

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

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

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

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

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

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

DETD The present invention is directed to methods and systems for delivering toxins to target cells within a patient's nasal cavity. The toxins may be intact toxins, such as botulinum toxin, ricin, exotoxin A, diphtheria toxin, cholera toxin, tetanus toxin,. . .

DETD Botulinum toxin blocks acetylcholine release from cells, such as the epithelial or goblet cells in the nasal membranes responsible for mucus hypersecretion, and can thus be effective even without energy-mediated delivery in accordance with the principles of. . . energy to permeablize or porate the cell membranes of the epithelial or goblet cells or other mucus-secreting cells of the nasal lining, in accordance with the present invention, allows botulinum and other toxins to be preferentially delivered to the targeted epithelial. . . the toxin light chains may be locally and specifically introduced into the target cells located within defined regions of the nasal membrane. Thus, even if the toxin fragments are accidentally dispersed beyond the desired target regions, the fragments will not generally. . .

DETD . . . a simplified single cell model. A targeted cell, e.g., an epithelial or goblet cell of the type which line the nasal cavity membrane, is shown in FIG. 2A. Fragmented neurotoxin such as BoNT-LC (LC) is introduced into the vicinity of the. . .

DETD . . . devices of the present invention may be adapted to introduce a BoNT-LC solution to a target region, such as the nasal passages and then effect selective membrane transport of the BoNT-LC into the cell using sonoporation.

DETD . . . embodiment of the present invention utilizing an ultrasonic element that may be particularly useful in delivery of the BoNT-LC to

nasal tissue that provides a broad but targeted transport of the LC across the epithelial and goblet cell walls. In this. . .

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

DETD . . . the energy, or both, non-invasively. For example, as illustrated in FIG. 9, the patient may draw the toxin into the nasal cavity from a hand-held dispersion device DD. After a sufficient amount of the toxin has been infused into the nasal cavity, a separate hand-held transducer TD connected to an appropriate power supply PS will be energized and applied to the nasal cavities by passing the transducer over the appropriate regions of the forehead and nose. Optionally, the transducer can have a. . .

DETD While the toxins and porating energy of the present invention may be delivered to the nasal cavity in a variety of ways, the following provides a number of specific examples of catheters and other structures for delivering toxins to preselected portions of the nasal cavity. For example, as shown in FIG. 10, a balloon catheter 100 may be provided with a porous balloon 102. . . transducers 104 within the balloon, optionally mounted on the catheter body, ultrasonic poration energy can be delivered to the adjacent nasal membranes which are receiving the toxin solution. As illustrated in FIG. 10, the toxin is being delivered to a lower. . .

DETD . . . positioned to target an area of high epithelial or goblet cell (G) concentration, for example in the back of the nasal passages in the area of the nasopharynx. By targeting this area of the nasal membrane, a high percentage of mucus-secreting epithelial or goblet cells can be treated with a device which is relatively small. . .

DETD . . . effect of such externally applied ultrasonic energy can be enhanced by introducing microbubbles (free air) into the isolated sinuses and/or nasal passages which have been filled with toxin solution. For example, encapsulated microbubbles, which are generally useful as echocardiographic contrast agents,. . .

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

DETD . . . air bleed valves 106 which are used to occlude the nostrils in order to evacuate or bleed air from the nasal passages while filling the passages with the toxin solution. The nose plugs 105 could optionally include ultrasonic transducers in order to deliver ultrasonic or other acoustic energy into the solutions entrapped within the nasal cavities using the nostril plugs. Alternatively, of course, the ultrasound or other acoustic energy could be delivered from an external. . .

DETD . . . can deliver toxin incorporated into vesicles which may be configured as "resonance" bodies, which reduce the need to fill the nasal cavities with a liquid or other form of toxin. For example, lipid microspheres which incorporate the toxin may be sprayed or aerosolized onto target surfaces of the nasal epithelium. After the lipid or other resonance bodies are attached to the targeted epithelium membrane surface(s), the ultrasound energy can. . .

DETD Referring to FIG. 29, the toxin may be delivered as a conventional nasal spray (BoNT), as mentioned hereinbefore, and the poration energy can be delivered through a face mask. The poration energy might. . .

DETD FIGS. 33 and 34 illustrate a device for applying BoNT to the treatment area within the nasal cavity. This device comprises a handle 115 having a proximal section, a body and a distal section. The body of. . . 118 connected to each of the first end and second, wherein the applicator tips are configured for insertion into the nasal passageway, as shown in FIG. 35.

DETD Once within the nasal cavity, the applicator tips 117 and 118 can apply BoNT to the nasal passageway and, specifically, the turbinates

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

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

DETD To facilitate the insertion of the tip applicator through the nostril and into the nasal passageway, it may be desirable for the applicator tip to initially have a low volume configuration. Once properly positioned in the nasal passageway, it would be desirable for the

applicator to have an expanded volume configuration for maximizing contact with the nasal turbinates. In one exemplary embodiment, the tip applicator may comprise a sponge such that the sponge 121 is in a. . . 39A) and an expanded configuration when wet (FIG. 39B), wherein the sponge 121 is configured to fit securely within the nasal passageway.

DETD . . . could be preloaded with lyophilized BoNT and wetted with a liquid (e.g., saline) following placement of the applicator in the nasal passageway. The liquid can be introduced into the nasal passageway using a spray or a catheter, or the BoNT may simply be rewetted by the nasal secretions themselves. Alternatively, as described with respect to FIG. 36, the liquid can be infused into the applicator tip through. . .

DETD To facilitate the expansion of the applicator tip, thereby maximizing the surface contact between the nasal cavity wall and applicator tip, it may be desirable to incorporate a spring element 122 within the applicator tip 118.. . .

DETD . . . it will be necessary to hold the spring 122 in its compressed state until it is properly positioned within the nasal cavity, at which time the spring can be released to allow the applicator to expand into the nasal cavity. In the wet/dry sponge 121 embodiment described with respect to FIGS. 39A and 39B, a sponge and spring can. . .

DETD . . . retractable sheath or collar 126 for holding the spring in its compressed configuration. Once the applicator is positioned within the nasal cavity, the actuator can be retracted to release the spring, thereby expanding the applicator.

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

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

DETD . . . be configured to provide a controlled delivery of toxin to facilitate absorption of the toxin into the walls of the nasal cavity. An applicator providing a controlled delivery of toxin can be configured

such that the rate of toxin delivery is proportionate with the rate of BoNT absorption across the nasal membrane. Such a controlled delivery will ensure that the toxin is absorbed into the nasal tissue and not dispersed elsewhere in the body.

DETD An apparatus for treating a nasal cavity of a patient via a controlled and uniform delivery of BoNT may comprise an applicator having an inner member,. . . open-faced chambers. The outer member may also comprise an array of microneedles to facilitate the passage of BoNT across the nasal membrane. The inner member is configured for occupying space when the applicator is positioned within the nasal cavity such that the outer member is placed in contact with the wall of the nasal cavity. The inner member may be any compliant material such as a sponge, balloon or foam rubber. The impermeable lining. . . outer member to inner member and, accordingly, facilitates the transfer of BoNT from the applicator to the tissue of the nasal wall. As with applicator embodiments that have been previously discussed herein, the outer member can be pre soaked or filled with BoNT solution, infused with BoNT following placement in the nasal passageway, or pre-loaded with freeze-dried BoNT that can be reconstituted with infused saline.

DETD . . . embodiment, the inner member comprises (1) a low volume configuration to facilitate the applicator's insertion into and placement within the nasal passageway and (2) an expanded volume configuration for pressing the outer member against the walls of the nasal cavity. The expansion of the inner member relative to the outer member can also facilitate the controlled release of BoNT. . .

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

DETD . . . carrying BoNT. In this embodiment, the applicator tip may comprise a BoNT-loaded bioresorbable polymer that can be absorbed into the nasal cavity tissue. The tip can be configured such that the BoNT can be delivered to the nasal wall both immediately and as the coating is absorbed into the tissue.

DETD . . . this application, the device described with respect to FIGS. 33 and 34 can be used to deliver BoNT-LC to the nasal cavity instead of the BoNT intact molecule. In cases where this device is used to deliver BoNT-LC to the nasal cavity, any of the previously-described, energy-based delivery systems can be used to cause poration in the nasal tissue to facilitate delivery of the BoNT-LC to the tissue. Additionally or alternatively, this device can be equipped with an. . .

DETD In addition to BTX-LC, it may be desirable to deliver additional agents to the nasal passages and sinuses prior to, coincident with, or after deliver of the LC. Adjunctive therapies may include agents designed to. . .

DETD Decongestants such as epinephrine also cause constriction of the vasculature in the nasal passages, which in addition to temporarily reducing swelling of the target tissues, may decrease the risks of LC entering the. . .

CLM What is claimed is:

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

CLM What is claimed is:

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

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

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

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

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

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

L8 ANSWER 9 OF 31 USPATFULL on STN

ACCESSION NUMBER:	2017:148318 USPATFULL
TITLE:	NASOLACRIMAL DRAINAGE SYSTEM IMPLANTS FOR DRUG THERAPY
INVENTOR(S):	de Juan, Jr., Eugene, San Francisco, CA, UNITED STATES Boyd, Stephen, Murrieta, CA, UNITED STATES Reich, Cary, Los Gatos, CA, UNITED STATES Rapacki, Alan, Redwood, CA, UNITED STATES Gifford, Hanson S, Woodside, CA, UNITED STATES Deem, Mark, Mountain View, CA, UNITED STATES
APPLICANT(S):	Mati Therapeutics Inc., Austin, TX, UNITED STATES

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 20170128361	A1	20170511
	US 9849082	B2	20171226
APPLICATION INFO.:	US 2017-15405991	A1	20170113 (15)

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

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

DOCUMENT TYPE:	Utility
FILE SEGMENT:	APPLICATION
NUMBER OF CLAIMS:	25
EXEMPLARY CLAIM:	1
NUMBER OF DRAWINGS:	30 Drawing Page(s)

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

L8 ANSWER 10 OF 31 BIOSIS COPYRIGHT (c) 2020 Clarivate Analytics on STN
DUPLICATE 1
ACCESSION NUMBER: 2017:53857 BIOSIS
DOCUMENT NUMBER: PREV201700053857
TITLE: Apparatus for toxin delivery to the nasal cavity.
AUTHOR(S): Deem, Mark E. [Inventor]; Anonymous; Gifford, Hanson [Inventor]; Kim, Steven [Inventor]; Salamini, Alexey [Inventor]
CORPORATE SOURCE: Mountain View, CA USA
ASSIGNEE: THE FOUNDRY LLC
PATENT INFORMATION: US 09511210 20161206
SOURCE: Official Gazette of the United States Patent and Trademark Office Patents, (DEC 6 2016)
CODEN: OGUPE7. ISSN: 0098-1133.
DOCUMENT TYPE: Patent
LANGUAGE: English
ENTRY DATE: Entered STN: 28 Dec 2016
Last Updated on STN: 1 Mar 2017 Full-text
TI Apparatus for toxin delivery to the nasal cavity.
AU Deem, Mark E. [Inventor]; Anonymous; Gifford, Hanson [Inventor]; Kim, Steven [Inventor]; Salamini, Alexey [Inventor]
AB Apparatus for delivering toxin and toxin fragments to a patient's nasal cavity provide for both release of the toxin and delivery of energy which selectively porates target cells to enhance uptake. . .
AB Apparatus for delivering toxin and toxin fragments to a patient's nasal cavity provide for both release of the toxin and delivery of energy which selectively porates target cells to enhance uptake of the toxin. The use of energy-mediated delivery is particularly advantageous with light chain fragment toxins which lack cell binding capacity.

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

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

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

NUMBER	DATE

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

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

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

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

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

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EXEMPLARY CLAIM: 1
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SUMM . . . the symptoms of rhinorrhea, is a condition resulting from inflammation and swelling of the patient's mucus membranes which line the nasal cavity. Rhinitis and/or rhinorrea can arise from a number of conditions, most often results from allergies to pollen, dust, seasonal. . . also be caused by anatomic pathologies such as blockages (as in

the case of sinusitis). Symptoms may include sneezing, itching, nasal congestion, and a runny nose.

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

SUMM . . . toxin is a neurotoxin which could have significant negative effects on a patient if accidentally released outside of the targeted nasal passages. Inadvertent distribution of the toxin to muscles of the oropharynx, mouth, tongue, or elsewhere could result in serious complications to the patient. Additionally, the use of botulinum-soaked gauze pads for delivering the toxin to the nasal cavities, as demonstrated by Dr. Sanders, will have limited ability to uniformly and selectively deliver the botulinum to the regions. . .

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

SUMM Rhinorrhea is the term describing the effluence of mucus from the lining of the nasal passages, nasopharynx, or paranasal sinuses. Rhinorrhea can be a symptom of a number of diseases such as the common cold,. . . paranasal sinuses. Sinusitis may have a number of different causes, and can be the result of chronic inflammation of the nasal passages, for example as a result of chronic rhinitis.

SUMM Allergic rhinitis is an immunologic response modulated by IgE and characterized predominantly by sneezing, rhinorrhea, nasal congestion, and pruritus of the nose. It may be seasonal (a condition commonly referred to as hay fever) or perennial.. . .

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

SUMM . . . no energy applied to untargeted regions. It will be appreciated that the energy may be applied to regions of the nasal membrane which are the same or different from the regions to which the toxin has been introduced. By controlling the. . . cells of interest while minimizing the amount of toxin which enters non-targeted cells. That is, only those cells in the nasal membrane which are exposed to both the toxin and the applied energy will preferentially be permeablized or porated to receive. . .

SUMM . . . to be delivered may comprise any neurotoxin capable of disabling mucus secretion in epithelial or goblet cells and other mucus-producing nasal cells. Preferably, the toxin comprises botulinum toxin, although other toxins such as ricin, exotoxin A, diphtheria toxin, cholera toxin, tetanus. . . use. In preferred aspects of the present invention, only an active fragment of the toxin will be delivered to the nasal cavity. Botulinum toxin and the other toxins listed above commonly comprise both a heavy chain and a light chain. The. . .

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

SUMM . . . be introduced to the target region through a catheter. For example, the catheter may carry a balloon which engages the nasal membrane in order to effect delivery of the toxin to the target cells. In a particular example, the balloon is. . . over at least a portion of its area so that the toxin may be released to specific areas of the nasal membrane, typically being incorporated into a suitable liquid, gel, or other fluid or fluidizable carrier. In other embodiments, the toxin. . .

SUMM . . . that the transducer may be located within or beneath the porous balloon which is used to deliver toxin to the nasal membrane. When electrical energy is used for poration, the electrodes may be on the catheter within or surrounding the region which delivers the energy to the nasal membrane. In other instances, the energy may be applied from a separate catheter or other device adapted for intranasal introduction.. . .

SUMM . . . invention further provides systems for delivering toxins to epithelial or goblet and other target cells as defined above in a nasal membrane. The systems may typically comprise a catheter adapted to introduce a toxin to a region adjacent to the target. . .

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

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

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

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

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

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

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

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

DETD The present invention is directed to methods and systems for delivering toxins to target cells within a patient's nasal cavity. The toxins may be intact toxins, such as botulinum toxin, ricin, exotoxin A, diphtheria toxin, cholera toxin, tetanus toxin,. . .

DETD Botulinum toxin blocks acetylcholine release from cells, such as the epithelial or goblet cells in the nasal membranes responsible for mucus hypersecretion, and can thus be effective even without energy-mediated delivery in accordance with the principles of. . . energy to permeablize or porate the cell membranes of the epithelial or goblet cells or other mucus-secreting cells of the nasal lining, in accordance with the present invention, allows botulinum and other toxins to be preferentially delivered to the targeted epithelial. . . the toxin light chains may be locally and specifically introduced into the target cells located within defined regions of the nasal membrane. Thus, even if the toxin fragments are accidentally dispersed beyond the desired target regions, the fragments will not generally. . .

DETD . . . a simplified single cell model. A targeted cell, e.g., an epithelial or goblet cell of the type which line the nasal cavity membrane, is shown in FIG. 2A. Fragmented neurotoxin such as BoNT-LC (LC) is introduced into the vicinity of the. . .

DETD . . . devices of the present invention may be adapted to introduce a BoNT-LC solution to a target region, such as the nasal passages and then effect selective membrane transport of the BoNT-LC into the cell using sonoporation.

DETD . . . embodiment of the present invention utilizing an ultrasonic element that may be particularly useful in delivery of the BoNT-LC to nasal tissue that provides a broad but targeted transport of the LC across the epithelial and goblet cell walls. In this. . .

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

DETD . . . the energy, or both, non-invasively. For example, as illustrated in FIG. 9, the patient may draw the toxin into the nasal cavity from a hand-held dispersion device DD. After a sufficient amount of the toxin has been infused into the nasal cavity, a separate hand-held transducer TD connected to an appropriate power supply PS will be energized and applied to the nasal cavities by passing the transducer over the appropriate regions of the forehead and nose. Optionally, the transducer can have a. . .

DETD While the toxins and porating energy of the present invention may be delivered to the nasal cavity in a variety of ways, the following provides a number of specific examples of catheters and other structures for delivering toxins to preselected portions of the nasal cavity. For example, as shown in FIG. 10, a balloon catheter 100 may be provided with a porous balloon 102. . . transducers 104 within the balloon, optionally mounted on the catheter body, ultrasonic poration energy can be delivered to the adjacent nasal membranes which are receiving the toxin solution. As illustrated in FIG. 10, the toxin is being delivered to a lower. . .

DETD . . . positioned to target an area of high epithelial or goblet cell (G) concentration, for example in the back of the nasal passages in the area of the nasopharynx. By targeting this area of the nasal membrane, a high percentage of mucus-secreting epithelial or goblet cells can be treated with a device which is relatively small. . .

DETD . . . effect of such externally applied ultrasonic energy can be enhanced by introducing microbubbles (free air) into the isolated sinuses and/or nasal passages which have been filled with toxin solution. For example, encapsulated microbubbles, which are generally useful as echocardiographic contrast agents,. . .

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

DETD . . . air bleed valves 106 which are used to occlude the nostrils in order to evacuate or bleed air from the nasal passages while filling the passages with the toxin solution. The nose plugs 105 could optionally include ultrasonic transducers in order to deliver ultrasonic or other acoustic energy into the solutions entrapped within the nasal cavities using the nostril plugs. Alternatively, of course, the ultrasound or other acoustic energy could be delivered from an external. . .

DETD . . . can deliver toxin incorporated into vesicles which may be configured as "resonance" bodies, which reduce the need to fill the nasal cavities with a liquid or other form of toxin. For example, lipid microspheres which incorporate the toxin may be sprayed or aerosolized onto target surfaces of the nasal epithelium. After the lipid or other resonance bodies are attached to the targeted epithelium membrane surface(s), the ultrasound energy can. . .

DETD Referring to FIG. 29, the toxin may be delivered as a conventional nasal spray (BoNT), as mentioned hereinbefore, and the poration energy can be delivered through a face mask. The poration energy might. . .

DETD FIGS. 33 and 34 illustrate a device for applying BoNT to the treatment area within the nasal cavity. This device comprises a handle 115 having a proximal section, a body and a distal section. The body of. . . 118 connected to each of the first end and second, wherein the applicator tips are configured for insertion into the nasal passageway, as shown in FIG. 35.

DETD Once within the nasal cavity, the applicator tips 117 and 118 can apply BoNT to the nasal passageway and, specifically, the turbinates along the nasal wall. The BoNT can be applied or affixed to the applicator tips as a liquid solution, gel, foam, cream, lotion and/or a lyophilized compound prior to being positioned within the nasal passageway. Alternatively, as illustrated in FIG. 36, the handle can be configured with an infusion channel 119 for delivering the BoNT to the

applicator tips following placement in the nasal passageway. In this configuration, the handle may further comprise an access port at its proximal section that is in fluid. . .

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

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

tip applicator may comprise a sponge such that the sponge 121 is in a. . . 39A) and an expanded configuration when wet (FIG. 39B), wherein the sponge 121 is configured to fit securely within the nasal passageway.

DETD . . . could be preloaded with lyophilized BoNT and wetted with a liquid (e.g., saline) following placement of the applicator in the nasal passageway. The liquid can be introduced into the nasal passageway using a spray or a catheter, or the BoNT may simply be rewetted by the nasal secretions themselves. Alternatively, as described with respect to FIG. 36, the liquid can be infused into the applicator tip through. . .

DETD To facilitate the expansion of the applicator tip, thereby maximizing the surface contact between the nasal cavity wall and applicator tip, it may be desirable to incorporate a spring element 122 within the applicator tip 118.. . .

DETD . . . it will be necessary to hold the spring 122 in its compressed state until it is properly positioned within the nasal cavity, at which time the spring can be released to allow the applicator to expand into the nasal cavity. In the wet/dry sponge 121 embodiment described with respect to FIGS. 39A and 39B, a sponge and spring can. . .

DETD . . . retractable sheath or collar 126 for holding the spring in its compressed configuration. Once the applicator is positioned within the nasal cavity, the actuator can be retracted to release the spring, thereby expanding the applicator.

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

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

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

DETD An apparatus for treating a nasal cavity of a patient via a controlled

and uniform delivery of BoNT may comprise an applicator having an inner member,. . . open-faced chambers. The outer member may also comprise an array of microneedles to facilitate the passage of BoNT across the nasal membrane. The inner member is configured for occupying space when the applicator is positioned within the nasal cavity such that the outer member is placed in contact with the wall of the nasal cavity. The inner member may be any compliant material such as a sponge, balloon or foam rubber. The impermeable lining. . . outer member to inner member and, accordingly, facilitates the transfer of BoNT from the applicator to the tissue of the nasal wall. As with applicator embodiments that have been previously discussed herein, the outer member can be pre soaked or filled with BoNT solution, infused with BoNT following placement in the nasal passageway, or pre-loaded with freeze-dried BoNT that can be reconstituted with infused saline.

DETD . . . embodiment, the inner member comprises (1) a low volume configuration to facilitate the applicator's insertion into and placement within the nasal passageway and (2) an expanded volume configuration for pressing the outer member against the walls of the nasal cavity. The expansion of the inner member relative to the outer member can also facilitate the controlled release of BoNT. . .

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

DETD . . . carrying BoNT. In this embodiment, the applicator tip may comprise a BoNT-loaded bioresorbable polymer that can be absorbed into the nasal cavity tissue. The tip can be configured such that the BoNT can be delivered to the nasal wall both immediately and as the coating is absorbed into the tissue.

DETD . . . this application, the device described with respect to FIGS. 33 and 34 can be used to deliver BoNT-LC to the nasal cavity instead of the BoNT intact molecule. In cases where this device is used to deliver BoNT-LC to the nasal cavity, any of the previously-described, energy-based delivery systems can be used to cause poration in the nasal tissue to facilitate delivery of the BoNT-LC to the tissue. Additionally or alternatively, this device can be equipped with an. . .

DETD In addition to BTX-LC, it may be desirable to deliver additional agents to the nasal passages and sinuses prior to, coincident with, or after deliver of the LC. Adjunctive therapies may include agents designed to. . .

DETD Decongestants such as epinephrine also cause constriction of the vasculature in the nasal passages, which in addition to temporarily reducing swelling of the target tissues, may decrease the risks of LC entering the. . .

CLM What is claimed is:

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

CLM What is claimed is:

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

CLM What is claimed is:

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

CLM What is claimed is:

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

the nasal cavity with the handle in the compressed configuration.

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

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

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

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

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

L8 ANSWER 13 OF 31 USPATFULL on STN

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

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

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

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

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

CAS INDEXING IS AVAILABLE FOR THIS PATENT. Full-text

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

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

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

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

TI Methods and systems for toxin delivery to the nasal cavity.
AU Deem, Mark E. [Inventor]; Anonymous; Gifford, Hanson [Inventor]
AB Methods and systems for delivering toxin and toxin fragments to a patient's nasal cavity provide for both release of the toxin and delivery of energy which selectively porates target cells to enhance uptake. . .
IT Methods & Equipment
nasal cavity providing toxin delivery system: medical equipment;
nasal cavity providing toxin delivery method: clinical techniques
AB Methods and systems for delivering toxin and toxin fragments to a patient's nasal cavity provide for both release of the toxin and delivery of energy which selectively porates target cells to enhance uptake of the toxin. The use of energy-mediated delivery is particularly advantageous with light chain fragment toxins which lack cell binding capacity.

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

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

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

NUMBER	DATE

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

DOCUMENT TYPE: Utility
FILE SEGMENT: APPLICATION
NUMBER OF CLAIMS: 31
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 24 Drawing Page(s)
LINE COUNT: 1374
CAS INDEXING IS AVAILABLE FOR THIS PATENT. Full-text
TI METHODS AND SYSTEMS FOR TOXIN DELIVERY TO THE NASAL CAVITY
IN Deem, Mark E., Mountain View, CA, UNITED STATES
AB Methods and systems for delivering toxin and toxin fragments to a patient's nasal cavity provide for both release of the toxin and delivery of energy which selectively porates target cells to enhance uptake. . .
SUMM . . . relates to methods and systems for delivering toxins, such as botulinum toxin light chain fragments, to target cells in a nasal cavity.
SUMM . . . the symptoms of rhinorrhea, is a condition resulting from inflammation and swelling of the patient's mucus membranes which line the nasal cavity. Rhinitis and/or rhinorrea can arise from a number of conditions, most often results from allergies to pollen, dust, seasonal. . . also be caused by anatomic pathologies such as blockages (as in the case of sinusitis). Symptoms may include sneezing, itching, nasal congestion, and a runny nose.
SUMM . . . for rhinitis which relies on the use of botulinum toxin ("BoNT") for blocking mucus production by mucus-producing cells in the nasal membrane has been proposed. Botulinum and other neurotoxins are capable of disabling adrenergic cells, including epithelial or goblet cells which are responsible for the majority of mucus production in the nasal cavity membrane. Dr. Ira Sanders has demonstrated that introduction of intact botulinum toxin molecules into the nasal passages of canines can reduce mucus secretion by a significant amount.
SUMM . . . toxin is a neurotoxin which could have significant negative effects on a patient if accidentally released outside of the targeted nasal passages. Inadvertent distribution of the toxin to muscles of the oropharynx, mouth, tongue, or elsewhere could result in serious complications to the patient. Additionally, the use of botulinum-soaked gauze pads for delivering the toxin to the nasal cavities, as demonstrated by Dr. Sanders, will have limited ability to uniformly and selectively deliver the botulinum to the regions. . .
SUMM . . . be desirable to provide improved methods and systems for delivering toxins, such as botulinum and active botulinum fragments, to the nasal membrane of a patient, particularly a patient suffering from rhinitis or other conditions associated with nasal inflammation and conditions, such as sinus headaches and migraine headaches. The methods and systems should be capable of providing for selective and repeatable delivery of the toxins to defined target areas within the nasal cavities, including particular paranasal sinuses, the nasopharynx, and in some cases substantially the entire nasal cavity. The systems and methods should provide for the safe and effective delivery of the toxins, and in particular should reduce or eliminate the risk of toxin being delivered to non-targeted tissues outside of the nasal cavity. At least some of these objectives will be met by the inventions described herein below.
SUMM Rhinorrhea is the term describing the effluence of mucus from the lining of the nasal passages, nasopharynx, or paranasal sinuses. Rhinorrhea can be a symptom of a number of diseases such as the common cold,. . . paranasal sinuses. Sinusitis may have a number of different causes, and can be the result of chronic inflammation of the nasal passages, for example as a result of chronic rhinitis.
SUMM Allergic rhinitis is an immunologic response modulated by IgE and characterized predominantly by sneezing, rhinorrhea, nasal congestion, and pruritus of the nose. It may be seasonal (a condition commonly referred to as hay fever) or perennial.. . .
SUMM . . . ricin, exotoxin A, diphtheria toxin, cholera toxin, tetanus toxin, other neurotoxins, and active fragments thereof are delivered to

a patient's nasal membrane while applying energy to target cells within the membrane under conditions which cause a reversible (or in some instances. . . delivery of the toxin into the cells. The region where the toxin is introduced may comprise any portion of the nasal cavity, such as a single paranasal sinus or portion thereof, a main nasal passage, two or more paranasal sinuses, or in some cases may comprise substantially the entire nasal cavity of the patient. A particular target region for the toxin may comprise the nasopharynx which is at the back of the nasal passage. The nasopharynx comprises a cluster of epithelial or goblet cells which are responsible for mucus secretion and which are. . .

SUMM . . . no energy applied to untargeted regions. It will be appreciated that the energy may be applied to regions of the nasal membrane which are the same or different from the regions to which the toxin has been introduced. By controlling the. . . cells of interest while minimizing the amount of toxin which enters non-targeted cells. That is, only those cells in the nasal membrane which are exposed to both the toxin and the applied energy will preferentially be permeablized or porated to receive. . .

SUMM . . . to be delivered may comprise any neurotoxin capable of disabling mucus secretion in epithelial or goblet cells and other mucus-producing nasal cells. Preferably, the toxin comprises botulinum toxin, although other toxins such as ricin, exotoxin A, diphtheria toxin, cholera toxin, tetanus. . . use. In preferred aspects of the present invention, only an active fragment of the toxin will be delivered to the nasal cavity. Botulinum toxin and the other toxins listed above commonly comprise both a heavy chain and a light chain. The. . .

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

SUMM . . . be introduced to the target region through a catheter. For example, the catheter may carry a balloon which engages the nasal membrane in order to effect delivery of the toxin to the target cells. In a particular example, the balloon is. . . over at least a portion of its area so that the toxin may be released to specific areas of the nasal membrane, typically being incorporated into a suitable liquid, gel, or other fluid or fluidizable carrier. In other embodiments, the toxin. . .

SUMM . . . that the transducer may be located within or beneath the porous balloon which is used to deliver toxin to the nasal membrane. When electrical energy is used for poration, the electrodes may be on the catheter within or surrounding the region which delivers the energy to the nasal membrane. In other instances, the energy may be applied from a separate catheter or other device adapted for intranasal introduction.. . .

SUMM . . . invention further provides systems for delivering toxins to epithelial or goblet and other target cells as defined above in a nasal membrane. The systems may typically comprise a catheter adapted to introduce a toxin to a region adjacent to the target. . .

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

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

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

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

poration energy to the nasal cavity.

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

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

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

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

DETD The present invention is directed to methods and systems for delivering toxins to target cells within a patient's nasal cavity. The toxins may be intact toxins, such as botulinum toxin, ricin, exotoxin A, diphtheria

toxin, cholera toxin, tetanus toxin,. . .

DETD Botulinum toxin blocks acetylcholine release from cells, such as the epithelial or goblet cells in the nasal membranes responsible for mucus hypersecretion, and can thus be effective even without energy-mediated delivery in accordance with the principles of. . . energy to permeablize or porate the cell membranes of the epithelial or goblet cells or other mucus-secreting cells of the nasal lining, in accordance with the present invention, allows botulinum and other toxins to be preferentially delivered to the targeted epithelial. . . the toxin light chains may be locally and specifically introduced into the target cells located within defined regions of the nasal membrane. Thus, even if the toxin fragments are accidentally dispersed beyond the desired target regions, the fragments will not generally. . .

DETD . . . a simplified single cell model. A targeted cell, e.g., an epithelial or goblet cell of the type which line the nasal cavity membrane, is shown in FIG. 2A. Fragmented neurotoxin such as BoNT-LC (LC) is introduced into the vicinity of the. . .

DETD . . . devices of the present invention may be adapted to introduce a BoNT-LC solution to a target region, such as the nasal passages and then effect selective membrane transport of the BoNT-LC into the cell using sonoporation.

DETD . . . embodiment of the present invention utilizing an ultrasonic element that may be particularly useful in delivery of the BoNT-LC to nasal tissue that provides a broad but targeted transport of the LC across the epithelial and goblet cell walls. In this. . .

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

DETD . . . the energy, or both, non-invasively. For example, as illustrated in FIG. 9, the patient may draw the toxin into the nasal cavity from a hand-held dispersion device DD. After a sufficient amount of the toxin has been infused into the nasal cavity, a separate hand-held transducer TD connected to an appropriate power supply PS will be energized and applied to the nasal cavities by passing the transducer over the appropriate regions of the forehead and nose. Optionally, the transducer can have a. . .

DETD While the toxins and porating energy of the present invention may be delivered to the nasal cavity in a variety of ways, the following provides a number of specific examples of catheters and other structures for delivering toxins to preselected portions of the nasal cavity. For example, as shown in FIG. 10, a balloon catheter 100 may be provided with a porous balloon 102. . . transducers 104 within the balloon, optionally mounted on the catheter body, ultrasonic poration energy can be delivered to the adjacent nasal membranes which are receiving the toxin solution. As illustrated in FIG. 10, the toxin is being delivered to a lower. . .

DETD . . . positioned to target an area of high epithelial or goblet cell (G) concentration, for example in the back of the nasal passages in the area of the nasopharynx. By targeting this area of the nasal membrane, a high percentage of mucus-secreting epithelial or goblet cells can be treated with a device which is relatively small. . .

DETD . . . effect of such externally applied ultrasonic energy can be enhanced by introducing microbubbles (free air) into the isolated sinuses and/or nasal passages which have been filled with toxin solution. For example, encapsulated microbubbles, which are generally useful as echocardiographic contrast agents,. . .

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

DETD . . . air bleed valves 106 which are used to occlude the nostrils in order to evacuate or bleed air from the nasal passages while filling the passages with the toxin solution. The nose plugs 105 could

optionally include ultrasonic transducers in order to deliver ultrasonic or other acoustic energy into the solutions entrapped within the nasal cavities using the nostril plugs. Alternatively, of course, the ultrasound or other acoustic energy could be delivered from an external. . .

DETD . . . can deliver toxin incorporated into vesicles which may be configured as "resonance" bodies, which reduce the need to fill the nasal cavities with a liquid or other form of toxin. For example, lipid microspheres which incorporate the toxin may be sprayed or aerosolized onto target surfaces of the nasal epithelium. After the lipid or other resonance bodies are attached to the targeted epithelium membrane surface(s), the ultrasound energy can. . .

DETD Referring to FIG. 29, the toxin may be delivered as a conventional nasal spray (BoNT), as mentioned hereinbefore, and the poration energy can be delivered through a face mask. The poration energy might. . .

DETD FIGS. 33 and 34 illustrate a device for applying BoNT to the treatment area within the nasal cavity. This device comprises a handle 115 having a proximal section, a body and a distal section. The body of. . . 118 connected to each of the first end and second, wherein the applicator tips are configured for insertion into the nasal passageway, as shown in FIG. 35.

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

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

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

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

DETD . . . could be preloaded with lyophilized BoNT and wetted with a liquid (e.g., saline) following placement of the applicator in the nasal passageway. The liquid can be introduced into the nasal passageway using a spray or a catheter, or the BoNT may simply be rewetted by the nasal secretions themselves. Alternatively, as described with respect to FIG. 36, the liquid can be infused into the applicator tip through. . .

DETD To facilitate the expansion of the applicator tip, thereby maximizing the surface contact between the nasal cavity wall and applicator tip, it may be desirable to incorporate a spring element 122 within the applicator tip 118.. . .

DETD . . . it will be necessary to hold the spring 122 in its compressed state until it is properly positioned within the nasal cavity, at which time the spring can be released to allow the applicator to expand into the nasal cavity. In the wet/dry sponge 121 embodiment described with respect to FIGS. 39A and 39B, a sponge and spring can. . .

DETD . . . retractable sheath or collar 126 for holding the spring in its

compressed configuration. Once the applicator is positioned within the nasal cavity, the actuator can be retracted to release the spring, thereby expanding the applicator.

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

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

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

DETD An apparatus for treating a nasal cavity of a patient via a controlled and uniform delivery of BoNT may comprise an applicator having an inner member,. . . open-faced chambers. The outer member may also comprise an array of microneedles to facilitate the passage of BoNT across the nasal membrane. The inner member is configured for occupying space when the applicator is positioned within the nasal cavity such that the outer member is placed in contact with the wall of the nasal cavity. The inner member may be any compliant material such as a sponge, balloon or foam rubber. The impermeable lining. . . outer member to inner member and, accordingly, facilitates the transfer of BoNT from the applicator to the tissue of the nasal wall. As with applicator embodiments that have been previously discussed herein, the outer member can be pre soaked or filled with BoNT solution, infused with BoNT following placement in the nasal passageway, or pre-loaded with freeze-dried BoNT that can be reconstituted with infused saline.

DETD . . . embodiment, the inner member comprises (1) a low volume configuration to facilitate the applicator's insertion into and placement within the nasal passageway and (2) an expanded volume configuration for pressing the outer member against the walls of the nasal cavity. The expansion of the inner member relative to the outer member can also facilitate the controlled release of BoNT. . .

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

DETD . . . carrying BoNT. In this embodiment, the applicator tip may comprise a BoNT-loaded bioresorbable polymer that can be absorbed into the nasal cavity tissue. The tip can be configured such that the BoNT can be delivered to the nasal wall both immediately and as the coating is absorbed into the tissue.

DETD . . . this application, the device described with respect to FIGS. 33 and 34 can be used to deliver BoNT-LC to the nasal cavity instead of the BoNT intact molecule. In cases where this device is used to deliver BoNT-LC to the nasal cavity, any of the previously-described, energy-based delivery systems can be used to cause poration in the nasal tissue to facilitate delivery of the BoNT-LC to the tissue. Additionally or alternatively, this device can be equipped with an. . .

DETD In addition to BTX-LC, it may be desirable to deliver additional agents to the nasal passages and sinuses prior to, coincident with, or after deliver of the LC. Adjunctive therapies may include agents designed to. . .

DETD Decongestants such as epinephrine also cause constriction of the vasculature in the nasal passages, which in addition to temporarily reducing swelling of the target tissues, may decrease the risks of LC entering the. . .

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

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

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

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

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

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

L8 ANSWER 19 OF 31 USPATFULL on STN

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

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

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

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

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

L8 ANSWER 20 OF 31 BIOSIS COPYRIGHT (c) 2020 Clarivate Analytics on STN
ACCESSION NUMBER: 2012:369512 BIOSIS
DOCUMENT NUMBER: PREV201200369512
TITLE: Methods and systems for toxin delivery to the nasal cavity.
AUTHOR(S): Deem, Mark E. [Inventor]; Anonymous; Gifford, Hanson [Inventor]
CORPORATE SOURCE: Mountain View, CA USA
ASSIGNEE: The Foundry LLC
PATENT INFORMATION: US 08105817 20120131
SOURCE: Official Gazette of the United States Patent and Trademark Office Patents, (JAN 31 2012)
CODEN: OGUPE7. ISSN: 0098-1133.
DOCUMENT TYPE: Patent
LANGUAGE: English
ENTRY DATE: Entered STN: 9 May 2012
Last Updated on STN: 9 May 2012 Full-text
TI Methods and systems for toxin delivery to the nasal cavity.
AU Deem, Mark E. [Inventor]; Anonymous; Gifford, Hanson [Inventor]
AB Methods and systems for delivering toxin and toxin fragments to a patient's nasal cavity provide for both release of the toxin and delivery of energy which selectively porates target cells to enhance uptake. . .
IT Methods & Equipment
nasal cavity targeted toxin/toxin fragment delivery method: therapeutic and prophylactic techniques, clinical techniques; nasal cavity targeted toxin/toxin fragment delivery system: drug delivery device
AB Methods and systems for delivering toxin and toxin fragments to a patient's nasal cavity provide for both release of the toxin and delivery of energy which selectively porates target cells to enhance uptake of the toxin. The use of energy-mediated delivery is particularly advantageous with light chain fragment toxins which lack cell binding capacity.

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

NUMBER	KIND	DATE

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

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

DOCUMENT TYPE: Utility
FILE SEGMENT: APPLICATION
NUMBER OF CLAIMS: 68
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 24 Drawing Page(s)
LINE COUNT: 1435
CAS INDEXING IS AVAILABLE FOR THIS PATENT. Full-text
TI METHODS AND SYSTEMS FOR TOXIN DELIVERY TO THE NASAL CAVITY
IN Deem, Mark E., Mountain View, CA, UNITED STATES
AB Methods and systems for delivering toxin and toxin fragments to a patient's nasal cavity provide for both release of the toxin and delivery of energy which selectively porates target cells to enhance uptake. . .
SUMM . . . relates to methods and systems for delivering toxins, such as botulinum toxin light chain fragments, to target cells in a nasal cavity.
SUMM . . . the symptoms of rhinorrhea, is a condition resulting from inflammation and swelling of the patient's mucus membranes which line the nasal cavity Rhinitis and/or rhinorrea can arise from a number of conditions, most often results from allergies to pollen, dust, seasonal. . . also be caused by anatomic pathologies such as blockages (as in the case of sinusitis). Symptoms may include sneezing, itching, nasal congestion, and a runny nose.
SUMM . . . for rhinitis which relies on the use of botulinum toxin ("BoNT") for blocking mucus production by mucus-producing cells in the nasal membrane has been proposed. Botulinum and other neurotoxins are capable of disabling adrenergic cells, including epithelial or goblet cells which are responsible for the majority of mucus production in the nasal cavity membrane. Dr. Ira Sanders has demonstrated that introduction of intact botulinum toxin molecules into the nasal passages of canines can reduce mucus secretion by a significant amount.
SUMM . . . toxin is a neurotoxin which could have significant negative effects on a patient if accidentally released outside of the targeted nasal passages. Inadvertent distribution of the toxin to muscles of the oropharynx, mouth, tongue, or elsewhere could result in serious complications to the patient. Additionally, the use of botulinum-soaked gauze pads for delivering the toxin to the nasal cavities, as demonstrated by Dr. Sanders, will have limited ability to uniformly and selectively deliver the botulinum to the regions. . .
SUMM . . . be desirable to provide improved methods and systems for delivering toxins, such as botulinum and active botulinum fragments, to the nasal membrane of a patient, particularly a patient suffering from rhinitis or other conditions associated with nasal inflammation and conditions, such as sinus headaches and migraine headaches. The methods and systems should be capable of providing for selective and repeatable delivery of the toxins to defined target areas within the nasal cavities, including particular paranasal sinuses, the nasopharynx, and in some cases substantially the entire nasal cavity. The systems and methods should provide for the safe and effective delivery of the toxins, and in particular should reduce or eliminate the risk of toxin being delivered to non-targeted tissues outside of the nasal cavity. At least some of these objectives will be met by the inventions described herein below.
SUMM Rhinorrhea is the term describing the effluence of mucus from the lining of the nasal passages, nasopharynx, or paranasal sinuses Rhinorrhea can be a symptom of a number of diseases such as the common cold,. . . paranasal sinuses. Sinusitis may have a number of different causes, and can be the result of chronic inflammation of the nasal passages, for example as a result of chronic rhinitis

SUMM Allergic rhinitis is an immunologic response modulated by IgE and characterized predominantly by sneezing, rhinorrhea, nasal congestion, and pruritus of the nose. It may be seasonal (a condition commonly referred to as hay fever) or perennial.. . .

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

SUMM . . . no energy applied to untargeted regions. It will be appreciated that the energy may be applied to regions of the nasal membrane which are the same or different from the regions to which the toxin has been introduced. By controlling the. . . cells of interest while minimizing the amount of toxin which enters non-targeted cells. That is, only those cells in the nasal membrane which are exposed to both the toxin and the applied energy will preferentially be permeablized or porated to receive. . .

SUMM . . . to be delivered may comprise any neurotoxin capable of disabling mucus secretion in epithelial or goblet cells and other mucus-producing nasal cells. Preferably, the toxin comprises botulinum toxin, although other toxins such as ricin, exotoxin A, diphtheria toxin, cholera toxin, tetanus. . . use. In preferred aspects of the present invention, only an active fragment of the toxin will be delivered to the nasal cavity. Botulinum toxin and the other toxins listed above commonly comprise both a heavy chain and a light chain. The. . .

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

SUMM . . . be introduced to the target region through a catheter. For example, the catheter may carry a balloon which engages the nasal membrane in order to effect delivery of the toxin to the target cells. In a particular example, the balloon is. . . over at least a portion of its area so that the toxin may be released to specific areas of the nasal membrane, typically being incorporated into a suitable liquid, gel, or other fluid or fluidizable carrier. In other embodiments, the toxin. . .

SUMM . . . that the transducer may be located within or beneath the porous balloon which is used to deliver toxin to the nasal membrane. When electrical energy is used for poration, the electrodes may be on the catheter within or surrounding the region which delivers the energy to the nasal membrane. In other instances, the energy may be applied from a separate catheter or other device adapted for intranasal introduction.. . .

SUMM . . . invention further provides systems for delivering toxins to epithelial or goblet and other target cells as defined above in a nasal membrane. The systems may typically comprise a catheter adapted to introduce a toxin to a region adjacent to the target. . .

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

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

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

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

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

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

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

within the nasal passageway.

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

DETD The present invention is directed to methods and systems for delivering toxins to target cells within a patient's nasal cavity. The toxins may be intact toxins, such as botulinum toxin, ricin, exotoxin A, diphtheria toxin, cholera toxin, tetanus toxin,. . .

DETD Botulinum toxin blocks acetylcholine release from cells, such as the epithelial or goblet cells in the nasal membranes responsible for mucus hypersecretion, and can thus be effective even without energy-mediated delivery in accordance with the principles of. . . energy to permeablize or porate the cell membranes of the epithelial or goblet cells or other mucus-secreting cells of the nasal lining, in accordance with the present invention, allows botulinum and other toxins to be preferentially delivered to the targeted epithelial. . . the toxin light chains may be locally and specifically introduced into the target cells located within defined regions of the nasal membrane. Thus, even if the toxin fragments are accidentally dispersed beyond the desired target regions, the fragments will not generally. . .

DETD . . . a simplified single cell model. A targeted cell, e.g., an epithelial or goblet cell of the type which line the nasal cavity membrane, is shown in FIG. 2A. Fragmented neurotoxin such as BoNT-LC (LC) is introduced into the vicinity of the. . .

DETD . . . devices of the present invention may be adapted to introduce a BoNT-LC solution to a target region, such as the nasal passages and then effect selective membrane transport of the BoNT-LC into the cell using sonoporation.

DETD . . . embodiment of the present invention utilizing an ultrasonic element that may be particularly useful in delivery of the BoNT-LC to nasal tissue that provides a broad but targeted transport of the LC across the epithelial and goblet cell walls. In this. . .

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

DETD . . . the energy, or both, non-invasively. For example, as illustrated in FIG. 9, the patient may draw the toxin into the nasal cavity from a hand-held dispersion device DD. After a sufficient amount of the toxin has been infused into the nasal cavity, a separate hand-held transducer TD connected to an appropriate power supply PS will be energized and applied to the nasal cavities by passing the transducer over the appropriate regions of the forehead and nose. Optionally, the transducer can have a. . .

DETD While the toxins and porating energy of the present invention may be delivered to the nasal cavity in a variety of ways, the following provides a number of specific examples of catheters and other structures for delivering toxins to preselected portions of the nasal cavity. For example, as shown in FIG. 10, a balloon catheter 100 may be provided with a porous balloon 102. . . transducers 104 within the balloon, optionally mounted on the catheter body, ultrasonic poration energy can be delivered to the adjacent nasal membranes which are receiving the toxin solution. As illustrated in FIG. 10, the toxin is being delivered to a lower. . .

DETD . . . positioned to target an area of high epithelial or goblet cell (G) concentration, for example in the back of the nasal passages in the area of the nasopharynx. By targeting this area of the nasal membrane, a high percentage of mucus-secreting epithelial or goblet cells can be treated with a device which is relatively small. . .

DETD . . . effect of such externally applied ultrasonic energy can be enhanced by introducing microbubbles (free air) into the isolated sinuses and/or nasal passages which have been filled with toxin solution. For example, encapsulated microbubbles, which are generally useful as echocardiographic contrast agents,. . .

DETD Referring now to FIGS. 20 and 21, a catheter 40 is placed at the posterior outlet of the nasal passages in the region of the nasopharynx. The catheters configured to occlude outflow from these sinuses and passages into the. . . shown in FIG. 20, the catheter is delivered in through the mouth and guided into the posterior portion of the nasal cavities, typically using a guidewire. Once the nasopharynx of the posterior portion of the nasal cavity is occluded, toxin solution (BoNT) can be infused through the occluding catheter lumen, or through a separate infusion catheter or tube, in order to treat substantially the entire sinus and/or nasal cavity membrane at once

(FIG. 21). When the toxin solution is introduced through the catheter at the posterior region of the cavities, it will frequently be desirable to occlude the nostrils, for example using a nasal clip 105.

DETD . . . air bleed valves 106 which are used to occlude the nostrils in order to evacuate or bleed air from the nasal passages while filling the passages with the toxin solution. The nose plugs 105 could optionally include ultrasonic transducers in order to deliver ultrasonic or other acoustic energy into the solutions entrapped within the nasal cavities using the nostril plugs. Alternatively, of course, the ultrasound or other acoustic energy could be delivered from an external. . .

DETD . . . can deliver toxin incorporated into vesicles which may be configured as "resonance" bodies, which reduce the need to fill the nasal cavities with a liquid or other form of toxin. For example, lipid microspheres which incorporate the toxin may be sprayed or aerosolized onto target surfaces of the nasal epithelium. After the lipid or other resonance bodies are attached to the targeted epithelium membrane surface(s), the ultrasound energy can. . .

DETD Referring to FIG. 29, the toxin may be delivered as a conventional nasal spray (BoNT), as mentioned hereinbefore, and the poration energy can be delivered through a face mask. The poration energy might. . .

DETD FIGS. 33 and 34 illustrate a device for applying BoNT to the treatment area within the nasal cavity. This device comprises a handle 115 having a proximal section, a body and a distal section. The body of. . . 118 connected to each of the first end and second, wherein the applicator tips are configured for insertion into the nasal passageway, as shown in FIG. 35.

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

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

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

passageway.

DETD . . . could be preloaded with lyophilized BoNT and wetted with a liquid (e.g., saline) following placement of the applicator in the nasal passageway. The liquid can be introduced into the nasal passageway using a spray or a catheter, or the BoNT may simply be rewetted by the nasal secretions themselves. Alternatively, as described with respect to FIG. 36, the liquid can be infused into the applicator tip through. . .

DETD To facilitate the expansion of the applicator tip, thereby maximizing the surface contact between the nasal cavity wall and applicator tip, it may be desirable to incorporate a spring element 122 within the applicator tip 118.. . .

DETD . . . it will be necessary to hold the spring 122 in its compressed state until it is properly positioned within the nasal cavity, at which time the spring can be released to allow the applicator to expand into the nasal cavity. In the wet/dry sponge 121 embodiment described with respect to FIGS. 39A and 39B, a sponge and spring can. . .

DETD . . . retractable sheath or collar 126 for holding the spring in its compressed configuration. Once the applicator is positioned within the nasal cavity, the actuator can be retracted to release the spring, thereby expanding the applicator.

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

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

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

DETD An apparatus for treating a nasal cavity of a patient via a controlled and uniform delivery of BoNT may comprise an applicator having an inner member,. . . open-faced chambers. The outer member may also comprise an array of microneedles to facilitate the passage of BoNT across the nasal membrane. The inner member is configured for occupying space when the applicator is positioned within the nasal cavity such that the outer member is placed in contact with the wall of the nasal cavity. The inner member may be any compliant material such as a sponge, balloon or foam rubber. The impermeable lining. . . outer member to inner member and, accordingly, facilitates the transfer of BoNT from the applicator to the tissue of the nasal wall. As with applicator embodiments that have been previously discussed herein, the outer member can be pre soaked or filled with BoNT solution, infused with BoNT following placement in the nasal passageway, or pre-loaded with freeze-dried BoNT that can be reconstituted with infused saline.

DETD . . . embodiment, the inner member comprises (1) a low volume configuration to facilitate the applicator's insertion into and placement within the nasal passageway and (2) an expanded volume configuration for pressing the outer member against the walls of the nasal cavity. The expansion of the inner member relative to the outer member can also facilitate the controlled release of BoNT. . .

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

DETD . . . carrying BoNT. In this embodiment, the applicator tip may comprise a BoNT-loaded bioresorbable polymer that can be absorbed into the nasal cavity tissue. The tip can be configured such that the BoNT can be delivered to the nasal wall both immediately and as the coating is absorbed into the tissue.

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

Additionally or alternatively, this device can be equipped with an. . .

DETD In addition to BTX-LC, it may be desirable to deliver additional agents to the nasal passages and sinuses prior to, coincident with, or after deliver of the LC. Adjunctive therapies may include agents designed to. . .

DETD Decongestants such as epinephrine also cause constriction of the vasculature in the nasal passages, which in addition to temporarily reducing swelling of the target tissues, may decrease the risks of LC entering the. . .

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

L8 ANSWER 24 OF 31 BIOSIS COPYRIGHT (c) 2020 Clarivate Analytics on STN
ACCESSION NUMBER: 2010:122525 BIOSIS
DOCUMENT NUMBER: PREV201000122525
TITLE: Methods and systems for toxin delivery to the nasal cavity.
AUTHOR(S): Deem, Mark E. [Inventor]; Anonymous; Gifford, Hanson [Inventor]
CORPORATE SOURCE: Mountain View, CA USA
ASSIGNEE: The Foundry LLC
PATENT INFORMATION: US 07655243 20100202
SOURCE: Official Gazette of the United States Patent and Trademark Office Patents, (FEB 2 2010)
CODEN: OGUPE7. ISSN: 0098-1133.
DOCUMENT TYPE: Patent
LANGUAGE: English
ENTRY DATE: Entered STN: 24 Feb 2010
Last Updated on STN: 24 Feb 2010 Full-text
TI Methods and systems for toxin delivery to the nasal cavity.
AU Deem, Mark E. [Inventor]; Anonymous; Gifford, Hanson [Inventor]
AB Methods and systems for delivering toxin and toxin fragments to a patient's nasal cavity provide for both release of the toxin and delivery of energy which selectively porates target cells to enhance uptake. . .
IT Methods & Equipment
nasal cavity based toxin delivery system: drug delivery device
AB Methods and systems for delivering toxin and toxin fragments to a patient's nasal cavity provide for both release of the toxin and delivery of energy which selectively porates target cells to enhance uptake of the toxin. The use of energy-mediated delivery is particularly advantageous with light chain fragment toxins which lack cell binding capacity.

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

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

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

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

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

CAS INDEXING IS AVAILABLE FOR THIS PATENT. Full-text
TI METHODS AND SYSTEMS FOR TOXIN DELIVERY TO THE NASAL CAVITY
IN DEEM, MARK E., MOUNTAIN VIEW, CA, UNITED STATES
AB Methods and systems for delivering toxin and toxin fragments to a patient's nasal cavity provide for both release of the toxin and delivery of energy which selectively porates target cells to enhance uptake. . .
SUMM . . . relates to methods and systems for delivering toxins, such as botulinum toxin light chain fragments, to target cells in a nasal cavity.
SUMM . . . the symptoms of rhinorrhea, is a condition resulting from inflammation and swelling of the patient's mucus membranes which line the nasal cavity. Rhinitis and/or rhinorrea can arise from a number of conditions, most often results from allergies to pollen, dust, seasonal. . . also be caused by anatomic pathologies such as blockages (as in the case of sinusitis). Symptoms may include sneezing, itching, nasal congestion, and a runny nose.
SUMM . . . for rhinitis which relies on the use of botulinum toxin ("BoNT") for blocking mucus production by mucus-producing cells in the nasal membrane has been proposed. Botulinum and other neurotoxins are capable of disabling adrenergic cells, including epithelial or goblet cells which are responsible for the majority of mucus production in the nasal cavity membrane. Dr. Ira Sanders has demonstrated that introduction of intact botulinum toxin molecules into the nasal passages of canines can reduce mucus secretion by a significant amount.
SUMM . . . toxin is a neurotoxin which could have significant negative effects on a patient if accidentally released outside of the targeted nasal passages. Inadvertent distribution of the toxin to muscles of the oropharynx, mouth, tongue, or elsewhere could result in serious complications to the patient. Additionally, the use of botulinum-soaked gauze pads for delivering the toxin to the nasal cavities, as demonstrated by Dr. Sanders, will have limited ability to uniformly and selectively deliver the botulinum to the regions. . .
SUMM . . . be desirable to provide improved methods and systems for delivering toxins, such as botulinum and active botulinum fragments, to the nasal membrane of a patient, particularly a patient suffering from rhinitis or other conditions associated with nasal inflammation and conditions, such as sinus headaches and migraine headaches. The methods and systems should be capable of providing for selective and repeatable delivery of the toxins to defined target areas within the nasal cavities, including particular paranasal sinuses, the nasopharynx, and in some cases substantially the entire nasal cavity. The systems and methods should provide for the safe and effective delivery of the toxins, and in particular should reduce or eliminate the risk of toxin being delivered to non-targeted tissues outside of the nasal cavity. At least some of these objectives will be met by the inventions described herein below.
SUMM Rhinorrhea is the term describing the effluence of mucus from the lining of the nasal passages, nasopharynx, or paranasal sinuses. Rhinorrhea can be a symptom of a number of diseases such as the common cold,. . . paranasal sinuses. Sinusitis may have a number of different causes, and can be the result of chronic inflammation of the nasal passages, for example as a result of chronic rhinitis.
SUMM Allergic rhinitis is an immunologic response modulated by IgE and characterized predominantly by sneezing, rhinorrhea, nasal congestion, and pruritus of the nose. It may be seasonal (a condition commonly referred to as hay fever) or perennial.. . .
SUMM . . . ricin, exotoxin A, diphtheria toxin, cholera toxin, tetanus toxin, other neurotoxins, and active fragments thereof are delivered to a patient's nasal membrane while applying energy to target cells within the membrane under conditions which cause a reversible (or in some instances. . . delivery of the toxin into the cells. The region where the toxin is introduced may comprise any portion of the nasal cavity, such as a single paranasal sinus or portion thereof, a main nasal passage, two or more paranasal sinuses, or in some cases may comprise substantially the entire nasal cavity of the patient. A particular target region for the toxin may comprise the nasopharynx which is at the back of the nasal passage. The nasopharynx comprises a cluster of epithelial or goblet cells which are responsible for mucus secretion and which are. . .
SUMM . . . no energy applied to untargeted regions. It will be appreciated that the energy may be applied to regions of the nasal membrane which

are the same or different from the regions to which the toxin has been introduced. By controlling the. . . cells of interest while minimizing the amount of toxin which enters non-targeted cells. That is, only those cells in the nasal membrane which are exposed to both the toxin and the applied energy will preferentially be permeablized or porated to receive. . .

SUMM . . . to be delivered may comprise any neurotoxin capable of disabling mucus secretion in epithelial or goblet cells and other mucus-producing nasal cells. Preferably, the toxin comprises botulinum toxin, although other toxins such as ricin, exotoxin A, diphtheria toxin, cholera toxin, tetanus. . . use. In preferred aspects of the present invention, only an active fragment of the toxin will be delivered to the nasal cavity. Botulinum toxin and the other toxins listed above commonly comprise both a heavy chain and a light chain. The. . .

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

SUMM . . . be introduced to the target region through a catheter. For example, the catheter may carry a balloon which engages the nasal membrane in order to effect delivery of the toxin to the target cells. In a particular example, the balloon is. . . over at least a portion of its area so that the toxin may be released to specific areas of the nasal membrane, typically being incorporated into a suitable liquid, gel, or other fluid or fluidizable carrier. In other embodiments, the toxin. . .

SUMM . . . that the transducer may be located within or beneath the porous balloon which is used to deliver toxin to the nasal membrane. When electrical energy is used for poration, the electrodes may be on the catheter within or surrounding the region which delivers the energy to the nasal membrane. In other instances, the energy may be applied from a separate catheter or other device adapted for intranasal introduction.. . .

SUMM . . . invention further provides systems for delivering toxins to epithelial or goblet and other target cells as defined above in a nasal membrane. The systems may typically comprise a catheter adapted to introduce a toxin to a region adjacent to the target. . .

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

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

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

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

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

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

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

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

DETD The present invention is directed to methods and systems for delivering toxins to target cells within a patient's nasal cavity. The toxins may be intact toxins, such as botulinum toxin, ricin, exotoxin A, diphtheria toxin, cholera toxin, tetanus toxin,. . .

DETD Botulinum toxin blocks acetylcholine release from cells, such as the epithelial or goblet cells in the nasal membranes responsible for mucus hypersecretion, and can thus be effective even without energy-mediated delivery in accordance with the principles of. . . energy to permeablize or porate the cell membranes of the epithelial or goblet cells or other mucus-secreting cells of the nasal lining, in accordance with the present invention, allows botulinum and other toxins to be preferentially delivered to the targeted epithelial. . . the toxin light chains may be locally and specifically introduced into the target cells located within defined regions of the nasal membrane. Thus, even if the toxin fragments are accidentally dispersed beyond the desired target regions, the fragments will not generally. . .

DETD . . . a simplified single cell model. A targeted cell, e.g., an epithelial or goblet cell of the type which line the nasal cavity membrane, is shown in FIG. 2A. Fragmented neurotoxin such as BoNT-LC (LC)is introduced into the vicinity of the targeted. . .

DETD . . . devices of the present invention may be adapted to introduce a BoNT-LC solution to a target region, such as the nasal passages and then effect selective membrane transport of the BoNT-LC into the cell using sonoporation.

DETD . . . embodiment of the present invention utilizing an ultrasonic element that may be particularly useful in delivery of the BoNT-LC to nasal tissue that provides a broad but targeted transport of the LC across the epithelial and goblet cell walls. In this. . .

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

DETD . . . the energy, or both, non-invasively. For example, as illustrated in FIG. 9, the patient may draw the toxin into the nasal cavity from a hand-held dispersion device DD. After a sufficient amount of the toxin has been infused into the nasal cavity, a separate hand-held transducer TD connected to an appropriate power supply PS will be energized and applied to the nasal cavities by passing the transducer over the appropriate regions of the forehead and nose. Optionally, the transducer can have a. . .

DETD While the toxins and porating energy of the present invention may be delivered to the nasal cavity in a variety of ways, the following provides a number of specific examples of catheters and other structures for delivering toxins to preselected portions of the nasal cavity. For example, as shown in FIG. 10, a balloon catheter 100 may be provided with a porous balloon 102. . . transducers 104 within the balloon, optionally mounted on the catheter body, ultrasonic poration energy can be delivered to the adjacent nasal membranes which are receiving the toxin solution. As illustrated in FIG. 10, the toxin is being delivered to a lower. . .

DETD . . . positioned to target an area of high epithelial or goblet cell (G) concentration, for example in the back of the nasal passages in the area of the nasopharynx. By targeting this area of the nasal membrane, a high percentage of mucus-secreting epithelial or goblet cells can be treated with a device which is relatively small. . .

DETD . . . effect of such externally applied ultrasonic energy can be enhanced by introducing microbubbles (free air) into the isolated sinuses and/or nasal passages which have been filled with toxin solution. For example, encapsulated microbubbles, which are generally useful as echocardiographic contrast agents,. . .

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

DETD . . . air bleed valves 106 which are used to occlude the nostrils in order to evacuate or bleed air from the nasal passages while filling the passages with the toxin solution. The nose plugs 105 could optionally include ultrasonic transducers in order to deliver ultrasonic or other acoustic energy into the solutions entrapped within the nasal cavities using the nostril plugs. Alternatively, of course, the ultrasound or other acoustic energy could be delivered from an external. . .

DETD . . . can deliver toxin incorporated into vesicles which may be configured as "resonance" bodies, which reduce the need to fill the nasal cavities with a liquid or other form of toxin. For example, lipid microspheres which incorporate the toxin may be sprayed or aerosolized onto target surfaces of the nasal epithelium. After the lipid or other resonance bodies are attached to the targeted epithelium membrane surface(s), the ultrasound energy can. . .

DETD Referring to FIG. 29, the toxin may be delivered as a conventional

nasal spray (BoNT), as mentioned hereinbefore, and the poration energy can be delivered through a face mask. The poration energy might. . .

DETD FIGS. 33 and 34 illustrate a device for applying BoNT to the treatment area within the nasal cavity. This device comprises a handle 115 having a proximal section, a body and a distal section. The body of. . . 118 connected to each of the first end and second, wherein the applicator tips are configured for insertion into the nasal passageway, as shown in FIG. 35.

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

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

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

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

DETD . . . could be preloaded with lyophilized BoNT and wetted with a liquid (e.g., saline) following placement of the applicator in the nasal passageway. The liquid can be introduced into the nasal passageway using a spray or a catheter, or the BoNT may simply be rewetted by the nasal secretions themselves. Alternatively, as described with respect to FIG. 36, the liquid can be infused into the applicator tip through. . .

DETD To facilitate the expansion of the applicator tip, thereby maximizing the surface contact between the nasal cavity wall and applicator tip, it may be desirable to incorporate a spring element 122 within the applicator tip 118.. . .

DETD . . . it will be necessary to hold the spring 122 in its compressed state until it is properly positioned within the nasal cavity, at which time the spring can be released to allow the applicator to expand into the nasal cavity. In the wet/dry sponge 121 embodiment described with respect to FIGS. 39A and 39B, a sponge and spring can. . .

DETD . . . retractable sheath or collar 126 for holding the spring in its compressed configuration. Once the applicator is positioned within the nasal cavity, the actuator can be retracted to release the spring, thereby expanding the applicator.

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

DETD . . . also be desirable for the apparatus to be configured such that

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

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

DETD An apparatus for treating a nasal cavity of a patient via a controlled and uniform delivery of BoNT may comprise an applicator having an inner member,. . . open-faced chambers. The outer member may also comprise an array of microneedles to facilitate the passage of BoNT across the nasal membrane. The inner member is configured for occupying space when the applicator is positioned within the nasal cavity such that the outer member is placed in contact with the wall of the nasal cavity. The inner member may be any compliant material such as a sponge, balloon or foam rubber. The impermeable lining. . . outer member to inner member and, accordingly, facilitates the transfer of BoNT from the applicator to the tissue of the nasal wall. As with applicator embodiments that have been previously discussed herein, the outer member can be pre soaked or filled with BoNT solution, infused with BoNT following placement in the nasal passageway, or pre-loaded with freeze-dried BoNT that can be reconstituted with infused saline.

DETD . . . embodiment, the inner member comprises (1) a low volume configuration to facilitate the applicator's insertion into and placement within the nasal passageway and (2) an expanded volume configuration for pressing the outer member against the walls of the nasal cavity. The expansion of the inner member relative to the outer member can also facilitate the controlled release of BoNT. . .

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

DETD . . . carrying BoNT. In this embodiment, the applicator tip may comprise a BoNT-loaded bioresorbable polymer that can be absorbed into the nasal cavity tissue. The tip can be configured such that the BoNT can be delivered to the nasal wall both immediately and as the coating is absorbed into the tissue.

DETD . . . this application, the device described with respect to FIGS. 33 and 34 can be used to deliver BoNT-LC to the nasal cavity instead of the BoNT intact molecule. In cases where this device is used to deliver BoNT-LC to the nasal cavity, any of the previously-described, energy-based delivery systems can be used to cause poration in the nasal tissue to facilitate delivery of the BoNT-LC to the tissue. Additionally or alternatively, this device can be equipped with an. . .

DETD In addition to BTX-LC, it may be desirable to deliver additional agents to the nasal passages and sinuses prior to, coincident with, or after deliver of the LC. Adjunctive therapies may include agents designed to. . .

DETD Decongestants such as epinephrine also cause constriction of the vasculature in the nasal passages, which in addition to temporarily reducing swelling of the target tissues, may decrease the risks of LC entering the. . .

CLM What is claimed is:

1. A system for delivering toxins to target cells in a nasal membrane, said system comprising: a catheter adapted to introduce a toxin to a region proximate the target cells; an energy. . .

CLM What is claimed is:

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

CLM What is claimed is:

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

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

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

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

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

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

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

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

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

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

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

ASSIGNMENT HISTORY FOR US PATENT AVAILABLE IN LSUS DISPLAY FORMAT Full-text
TI Methods and systems for toxin delivery to the nasal cavity
IN Deem, Mark E.; Gifford, Hanson
AB Methods and systems for delivering toxin and toxin fragments to a patient's nasal cavity provide for both release of the toxin and delivery of energy which selectively porates target cells to enhance uptake. . .
ST system toxin delivery nasal cavity
IT Catheters

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

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

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

AB Methods and systems for delivering toxin and toxin fragments to a patient's nasal cavity provide for both release of the toxin and delivery of energy which selectively porates target cells to enhance uptake of the toxin. The use of energy-mediated delivery is particularly advantageous with light chain fragment toxins which lack cell binding capacity. The use of balloon catheters for delivering toxins to the nasopharynx is depicted (no data).

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

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

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

PRIORITY APPLN. INFO.:		
US 2006-60747771	P	20060519
US 2007-750963	A	20070518
US 2007-750967	A	20070518
US 2005-60702077	P	20050722
JP 2008-522980	A3	20060721
US 2006-459090	A2	20060721
WO 2007-US69391	W	20070521

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

ASSIGNMENT HISTORY FOR US PATENT AVAILABLE IN LSUS DISPLAY FORMAT
OTHER SOURCE(S): CASFORMULTNS 2007:1363693 Full-text
TI Apparatus, methods and systems for toxin delivery to the nasal cavity
IN Deem, Mark E.; Gifford, Hanson; Kim, Steven; Salamini, Alexey
AB App., methods and systems for delivering toxin and toxin fragments to a patient's nasal cavity provide for both release of the toxin and delivery of energy which selectively porates target cells to enhance uptake. . .
ST toxin delivery nasal cavity inflammation
IT Medical goods
(balloons; toxin delivery to the nasal cavity)
IT Coating materials
(bioresorbable; toxin delivery to the nasal cavity)
IT Medical goods
(springs; toxin delivery to the nasal cavity)
IT Anti-inflammatory agents
Inflammation
Medical sponges
Microwave
Nasal drug delivery systems
Nasal mucosa
Nose
Pulsed electric current
Sound and Ultrasound
Springs (mechanical)
X-ray
(toxin delivery to the nasal cavity)
IT Toxins
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(toxin delivery to the nasal cavity)
IT 93384-43-1, Botulin A 93384-44-2, Botulin B 93384-45-3, Botulin C 93384-46-4, Botulin D 93384-47-5, Botulin E 107231-15-2, Botulin F 107231-16-3, Botulin G
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(toxin delivery to the nasal cavity)
AB App., methods and systems for delivering toxin and toxin fragments to a patient's nasal cavity provide for both release of the toxin and delivery of energy which selectively porates target cells to enhance uptake of the toxin. The use of energy-mediated delivery is particularly advantageous with light chain fragment toxins which lack cell binding capacity.

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

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

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

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

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

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

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

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

DOCUMENT TYPE: Utility
FILE SEGMENT: APPLICATION
LEGAL REPRESENTATIVE: TOWNSEND AND TOWNSEND AND CREW, LLP, TWO EMBARCADERO CENTER, EIGHTH FLOOR, SAN FRANCISCO, CA, 94111-3834, US
NUMBER OF CLAIMS: 43
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 24 Drawing Page(s)
LINE COUNT: 1513
CAS INDEXING IS AVAILABLE FOR THIS PATENT. Full-text
TI APPARATUS FOR TOXIN DELIVERY TO THE NASAL CAVITY
IN Deem, Mark E., Mountain View, CA, UNITED STATES
AB Apparatus for delivering toxin and toxin fragments to a patient's nasal cavity provide for both release of the toxin and delivery of energy which selectively porates target cells to enhance uptake. . .
DRWD FIG. 9--depicts use on an external hand held transducer for enhancing cellular uptake of toxin delivered from a separate nasal aerosolizer.
DRWD FIG. 15--depicts sizing of a delivery balloon to control distribution of toxin released into the nasal cavity.
DRWD FIG. 17--depicts the use of multiple small balloons for selective toxin delivery into the nasal cavity.
DRWD FIGS. 22 and 23--depict nose plugs for occluding and optionally delivery poration energy to the nasal cavity.
DRWD . . . 28 and 30--depict use of a simple catheter having a shaped distal end for aerosolizing a toxin into a target nasal sinus though an ostium open to the sinus.
DRWD FIG. 29--depicts toxin delivery using a nasal spray and energy delivery using a face mask.
DRWD FIG. 33--depicts an applicator device for delivering toxin to the

nasal cavity having a handle and two applicator tips for placement within the nasal passageway.

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

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

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

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

DETD . . . toxin is a neurotoxin which could have significant negative effects on a patient if accidentally released outside of the targeted nasal passages. Inadvertent distribution of the toxin to muscles of the oropharynx, mouth, tongue, or elsewhere could result in serious complications to the patient. Additionally, the use of botulinum-soaked gauze pads for delivering the toxin to the nasal cavities, as demonstrated by Dr. Sanders, will have limited ability to uniformly and selectively deliver the botulinum to the regions. . .

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

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

DETD Rhinorrhea is the term describing the effluence of mucus from the lining of the nasal passages, nasopharynx, or paranasal sinuses. Rhinorrhea can be a symptom of a number of diseases such as the common cold,. . . paranasal sinuses. Sinusitis may have a number of different causes, and can be the result of chronic inflammation of the nasal passages, for example as a result of chronic rhinitis.

DETD Allergic rhinitis is an immunologic response modulated by IgE and characterized predominantly by sneezing, rhinorrhea, nasal congestion, and pruritus of the nose. It may be seasonal (a condition commonly referred to as hay fever) or perennial.. . .

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

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

DETD . . . the applicator tips can be configured with a low volume delivery configuration to facilitate placement of the apparatus within the nasal passageway and an expanded volume treatment configuration to facilitate contact with the nasal wall. A spring element can be used to expand the applicator tip. Additionally, an actuator and engagement member can be. . .

DETD In another aspect of the present invention, the toxin is loaded onto the applicator tips prior to insertion into the nasal passageway by, for example, dipping the applicator tips in a solution of toxin, coating the applicator tips with a lyophilized. . .

DETD . . . toxin source so that toxin can be infused into the applicator tips either prior to or following placement in the nasal passageway. Alternatively, a liquid such as saline can be infused to the applicator tips to reconstituted lyophilized toxin that was. . .

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

DETD . . . expanded volume configuration and an outer member for carrying the predetermined quantity of toxin and delivering the toxin to the nasal wall. The expansion of the inner member can also facilitate the controlled delivery of toxin to the nasal wall. The applicator may further comprise an impermeable lining separating the inner member and outer member and preventing toxin from. . .

DETD Rhinorrhea is the term describing the effluence of mucus from the lining of the nasal passages, nasopharynx, or paranasal sinuses. Rhinorrhea can be a symptom of a number of diseases such as the common cold,. . .

paranasal sinuses. Sinusitis may have a number of different causes, and can be the result of chronic inflammation of the nasal passages, for example as a result of chronic rhinitis.

DETD Allergic rhinitis is an immunologic response modulated by IgE and characterized predominantly by sneezing, rhinorrhea, nasal congestion, and pruritus of the nose. It may be seasonal (a condition commonly referred to as hay fever) or perennial.. . .

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

DETD . . . no energy applied to untargeted regions. It will be appreciated that the energy may be applied to regions of the nasal membrane which are the same or different from the regions to which the toxin has been introduced. By controlling the. . . cells of interest while minimizing the amount of toxin which enters non-targeted cells. That is, only those cells in the nasal membrane which are exposed to both the toxin and the applied energy will preferentially be permeablized or porated to receive. . .

DETD . . . to be delivered may comprise any neurotoxin capable of disabling mucus secretion in epithelial or goblet cells and other mucus-producing nasal cells. Preferably, the toxin comprises botulinum toxin, although other toxins such as ricin, exotoxin A, diphtheria toxin, cholera toxin, tetanus. . . use. In preferred aspects of the present invention, only an active fragment of the toxin will be delivered to the nasal cavity. Botulinum toxin and the other toxins listed above commonly comprise both a heavy chain and a light chain. The. . .

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

DETD . . . be introduced to the target region through a catheter. For example, the catheter may carry a balloon which engages the nasal membrane in order to effect delivery of the toxin to the target cells.

In a particular example, the balloon is. . . over at least a portion of its area so that the toxin may be released to specific areas of the nasal membrane, typically being incorporated into a suitable liquid, gel, or other fluid or fluidizable carrier. In other embodiments, the toxin. . .

DETD . . . that the transducer may be located within or beneath the porous balloon which is used to deliver toxin to the nasal membrane. When electrical energy is used for poration, the electrodes may be on the catheter within or surrounding the region which delivers the energy to the nasal membrane. In other instances, the energy may be applied from a separate catheter or other device adapted for intranasal introduction.. . .

DETD . . . invention further provides systems for delivering toxins to epithelial or goblet and other target cells as defined above in a nasal membrane. The systems may typically comprise a catheter adapted to introduce a toxin to a region adjacent to the target. . .

DETD The present invention is directed to methods and systems for delivering toxins to target cells within a patient's nasal cavity. The toxins may be intact toxins, such as botulinum toxin, ricin, exotoxin A, diphtheria toxin, cholera toxin, tetanus toxin,. . .

DETD Botulinum toxin blocks acetylcholine release from cells, such as the epithelial or goblet cells in the nasal membranes responsible for mucus hypersecretion, and can thus be effective even without energy-mediated delivery in accordance with the principles of. . . energy to permeablize or porate the cell membranes of the epithelial or goblet cells or other mucus-secreting cells of the nasal lining, in accordance with the present invention, allows botulinum and other toxins to be preferentially delivered to the targeted epithelial. . . the toxin light chains may be locally and specifically introduced into the target cells located within defined regions of the nasal membrane. Thus, even if the toxin fragments are accidentally dispersed beyond the desired target regions, the fragments will not generally. . .

DETD . . . a simplified single cell model. A targeted cell, e.g., an epithelial or goblet cell of the type which line the nasal cavity membrane, is shown in FIG. 2A. Fragmented neurotoxin such as BoNT-LC (LC) is introduced into the vicinity of the. . .

DETD . . . devices of the present invention may be adapted to introduce a BoNT-LC solution to a target region, such as the nasal passages and then effect selective membrane transport of the BoNT-LC into the cell using sonoporation.

DETD . . . embodiment of the present invention utilizing an ultrasonic element that may be particularly useful in delivery of the BoNT-LC to nasal tissue that provides a broad but targeted transport of the LC across the epithelial and goblet cell walls. In this. . .

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

DETD . . . the energy, or both, non-invasively. For example, as illustrated in FIG. 9, the patient may draw the toxin into the nasal cavity from a hand-held dispersion device DD. After a sufficient amount of the toxin has been infused into the nasal cavity, a separate hand-held transducer TD connected to an appropriate power supply PS will be energized and applied to the nasal cavities by passing the transducer over the appropriate regions of the forehead and nose. Optionally, the transducer can have a. . .

DETD While the toxins and porating energy of the present invention may be delivered to the nasal cavity in a variety of ways, the following provides a number of specific examples of catheters and other structures for delivering toxins to preselected portions of the nasal cavity. For example, as shown in FIG. 10, a balloon catheter 100 may be provided with a porous balloon 102. . . transducers 104 within the balloon, optionally mounted on the catheter body, ultrasonic poration energy can be delivered to the adjacent nasal membranes which are receiving the toxin solution. As illustrated in FIG. 10, the toxin is being delivered to a lower. . .

DETD . . . positioned to target an area of high epithelial or goblet cell (G) concentration, for example in the back of the nasal passages in the area of the nasopharynx. By targeting this area of the nasal membrane, a high percentage of mucus-secreting epithelial or goblet cells can be treated with a device which is relatively small. . .

DETD . . . effect of such externally applied ultrasonic energy can be enhanced by introducing microbubbles (free air) into the isolated

sinuses and/or nasal passages which have been filled with toxin solution. For example, encapsulated microbubbles, which are generally useful as echocardiographic contrast agents,. . .

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

DETD . . . air bleed valves 106 which are used to occlude the nostrils in order to evacuate or bleed air from the nasal passages while filling the passages with the toxin solution. The nose plugs 105 could optionally include ultrasonic transducers in order to deliver ultrasonic or other acoustic energy into the solutions entrapped within the nasal cavities using the nostril plugs. Alternatively, of course, the

ultrasound or other acoustic energy could be delivered from an external. . .

DETD . . . can deliver toxin incorporated into vesicles which may be configured as "resonance" bodies, which reduce the need to fill the nasal cavities with a liquid or other form of toxin. For example, lipid microspheres which incorporate the toxin may be sprayed or aerosolized onto target surfaces of the nasal epithelium. After the lipid or other resonance bodies are attached to the targeted epithelium membrane surface(s), the ultrasound energy can. . .

DETD Referring to FIG. 29, the toxin may be delivered as a conventional nasal spray (BoNT), as mentioned hereinbefore, and the poration energy can be delivered through a face mask. The poration energy might. . .

DETD FIGS. 33 and 34 illustrate a device for applying BoNT to the treatment area within the nasal cavity. This device comprises a handle 115 having a proximal section, a body and a distal section. The body of. . . 118 connected to each of the first end and second, wherein the applicator tips are configured for insertion into the nasal passageway, as shown in FIG. 35.

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

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

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

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

DETD . . . could be preloaded with lyophilized BoNT and wetted with a liquid (e.g., saline) following placement of the applicator in the nasal passageway. The liquid can be introduced into the nasal passageway using a spray or a catheter, or the BoNT may simply be rewetted by the nasal secretions themselves. Alternatively, as described with respect to FIG. 36, the liquid can be infused into the applicator tip through. . .

DETD To facilitate the expansion of the applicator tip, thereby maximizing the surface contact between the nasal cavity wall and applicator tip, it may be desirable to incorporate a spring element 122 within the applicator tip 118.. . .

DETD . . . it will be necessary to hold the spring 122 in its compressed state until it is properly positioned within the nasal cavity, at which time the spring can be released to allow the applicator to expand into the nasal cavity. In the wet/dry sponge 121 embodiment described with respect to FIGS. 39A and 39B, a sponge and spring can. . .

DETD . . . retractable sheath or collar 126 for holding the spring in its compressed configuration. Once the applicator is positioned within the nasal cavity, the actuator can be retracted to release the spring, thereby expanding the applicator.

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

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

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

DETD An apparatus for treating a nasal cavity of a patient via a controlled and uniform delivery of BoNT may comprise an applicator having an inner member,. . . open-faced chambers. The outer member may also comprise an array of microneedles to facilitate the passage of BoNT across the nasal membrane. Alternatively, the outer member may comprise a combination of the structures and materials mentioned above. For example, the outer. . . a predetermined quantity of toxin. The inner member is configured for occupying space when the applicator is positioned within the nasal cavity such that the outer member is placed in contact with the wall of the nasal cavity. The inner member may be any compliant material such as a sponge, balloon or foam rubber. The impermeable lining. . . outer member to inner member and, accordingly, facilitates the transfer of BoNT from the applicator to the tissue of the nasal wall. As with applicator embodiments that have been previously discussed herein, the outer member can be pre soaked or filled with BoNT solution, infused with BoNT following placement in the nasal passageway, or pre-loaded with freeze-dried BoNT that can be reconstituted with infused saline.

DETD . . . embodiment, the inner member comprises (1) a low volume configuration to facilitate the applicator's insertion into and placement within the nasal passageway and (2) an expanded volume configuration for pressing the outer member against the walls of the nasal cavity. The expansion of the inner member relative to the outer member can also facilitate the controlled release of BoNT. . .

DETD In any of the embodiments discussed herein, it may be desirable to adapt the applicator to the geometry of the nasal cavity. For example, in

embodiments comprising an outer member and inner member, the outer member can be configured to match the shape of the nasal cavity or portions of the nasal passageway following the expansion of the inner member. By achieving better contact, the delivery of toxin to and across the nasal membrane can be optimized.

DETD . . . carrying BoNT. In this embodiment, the applicator tip may comprise a BoNT-loaded bioresorbable polymer that can be absorbed into the nasal cavity tissue. The tip can be configured such that the BoNT can be delivered to the nasal wall both immediately and as the coating is absorbed into the tissue.

DETD . . . this application, the device described with respect to FIGS. 33 and 34 can be used to deliver BoNT-LC to the nasal cavity instead of the BoNT intact molecule. In cases where this device is used to deliver BoNT-LC to the nasal cavity, any of the previously-described, energy-based delivery systems can be used to cause poration in the

nasal tissue to facilitate delivery of the BoNT-LC to the tissue. Additionally or alternatively, this device can be equipped with an. . .

DETD In addition to BTX-LC, it may be desirable to deliver additional agents to the nasal passages and sinuses prior to, coincident with, or after deliver of the LC. Adjunctive therapies may include agents designed to. . .

DETD Decongestants such as epinephrine also cause constriction of the vasculature in the nasal passages, which in addition to temporarily reducing swelling of the target tissues, may decrease the risks of LC entering the. . .

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

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

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

CLM What is claimed is:
. . . of claim 6, wherein each applicator tip in the expanded volume treatment configuration is adapted to fit substantially within the nasal cavity of the patient.

CLM What is claimed is:
. . . claim 8, wherein each applicator tip is configured to be arranged in a compressed delivery configuration for placement within the nasal passageway and an expanded treatment configuration for delivering toxin to the region of nasal tissue.

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

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

CLM What is claimed is:
. . . 26. The apparatus of claim 25 further comprising an energy delivery applicator configured for delivering energy to the region of nasal tissue to enhance delivery of the toxin to the nasal tissue.

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

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

CLM What is claimed is:
. . . of claim 31, wherein the applicator is configured to be arranged in a low volume configuration for placement within the nasal passageway and an expanded volume configuration for delivering the toxin to the nasal tissue.

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

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

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

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

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

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

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

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

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



=> e gifford h?/au

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

=> e

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

=> s e5-12

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

=> s l9 and nasal

L10          47 L9 AND NASAL
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=> dup rem L10

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

=> d ibib kwic ab 1-39


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

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

                               NUMBER             DATE
                        -------------------     --------
PRIORITY INFORMATION:   US 2005-60702077        20050722 (60)
DOCUMENT TYPE:          Utility
FILE SEGMENT:           APPLICATION
NUMBER OF CLAIMS:       30
EXEMPLARY CLAIM:        1
NUMBER OF DRAWINGS:     27 Drawing Page(s)
LINE COUNT:             1712
CAS INDEXING IS AVAILABLE FOR THIS PATENT. Full-text
IN      Gifford, Hanson, Woodside, CA, UNITED STATES
SUMM    . . . relates to methods and systems for delivering toxins, such as
        botulinum toxin light chain fragments, to target cells in a nasal
        cavity.
SUMM    . . . the symptoms of rhinorrhea, is a condition resulting from
        inflammation and swelling of the patient's mucus membranes which line
        the nasal cavity. Rhinitis and/or rhinorrea can arise from a number of
        conditions, most often results from allergies to pollen, dust, seasonal.
        . . also be caused by anatomic pathologies such as blockages (as in
        the case of sinusitis). Symptoms may include sneezing, itching, nasal
        congestion, and a runny nose.
SUMM    . . . for rhinitis which relies on the use of botulinum toxin
        ("BoNT") for blocking mucus production by mucus-producing
        cells in the nasal membrane has been proposed. Botulinum and other
        neurotoxins are capable of disabling adrenergic cells, including
        epithelial or goblet cells which are responsible for the majority of
        mucus production in the nasal cavity membrane. Dr. Ira Sanders has
        demonstrated that introduction of intact botulinum toxin molecules into
        the nasal passages of canines can reduce mucus secretion by a
        significant amount.
SUMM    . . . toxin is a neurotoxin which could have significant negative
        effects on a patient if accidentally released outside of the targeted
        nasal passages. Inadvertent distribution of the toxin to muscles of
        the oropharynx, mouth, tongue, or elsewhere could result in serious
        complications to the patient. Additionally, the use of botulinum-soaked
        gauze pads for delivering the toxin to the nasal cavities, as
        demonstrated by Dr. Sanders, will have limited ability to uniformly and
        selectively deliver the botulinum to the regions. . .
SUMM    . . . be desirable to provide improved methods and systems for
        delivering toxins, such as botulinum and active botulinum fragments, to
```

the nasal membrane of a patient, particularly a patient suffering from rhinitis or other conditions associated with nasal inflammation and conditions, such as sinus headaches and migraine headaches. The methods and systems should be capable of providing for selective and repeatable delivery of the toxins to defined target areas within the nasal cavities, including particular paranasal sinuses, the nasopharynx, and in some cases substantially the entire nasal cavity. The systems and methods should provide for the safe and effective delivery of the toxins, and in particular should reduce or eliminate the risk of toxin being delivered to non-targeted tissues outside of the nasal cavity. At least some of these objectives will be met by the inventions described herein below. U.S. Pat. No. 5,766,605,. . .

SUMM Rhinorrhea is the term describing the effluence of mucus from the lining of the nasal passages, nasopharynx, or paranasal sinuses. Rhinorrhea can be a symptom of a number of diseases such as the common cold,. . . paranasal sinuses. Sinusitis may have a number of different causes, and can be the result of chronic inflammation of the nasal passages, for example as a result of chronic rhinitis.

SUMM Allergic rhinitis is an immunologic response modulated by IgE and characterized predominantly by sneezing, rhinorrhea, nasal congestion, and pruritus of the nose. It may be seasonal (a condition commonly referred to as hay fever) or perennial.. . .

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

SUMM . . . no energy applied to untargeted regions. It will be appreciated that the energy may be applied to regions of the nasal membrane which are the same or different from the regions to which the toxin has been introduced. By controlling the. . . cells of interest while minimizing the amount of toxin which enters non-targeted cells. That is, only those cells in the nasal membrane which are exposed to both the toxin and the applied energy will preferentially be permeablized or porated to receive. . .

SUMM . . . to be delivered may comprise any neurotoxin capable of disabling mucus secretion in epithelial or goblet cells and other mucus-producing nasal cells. Preferably, the toxin comprises botulinum toxin, although other toxins such as ricin, exotoxin A, diphtheria toxin, cholera toxin, tetanus. . . use. In preferred aspects of the present invention, only an active fragment of the toxin will be delivered to the nasal cavity. botulinum toxin and the other toxins listed above commonly comprise both a heavy chain and a light chain. The. . .

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

SUMM . . . be introduced to the target region through a catheter. For example, the catheter may carry a balloon which engages the nasal membrane in order to effect delivery of the toxin to the target cells. In a particular example, the balloon is. . . over at least a portion of its area so that the toxin may be released to specific areas of the nasal membrane, typically being incorporated into a suitable liquid, gel, or other fluid or fluidizable carrier. In other embodiments, the toxin. . .

SUMM . . . that the transducer may be located within or beneath the porous balloon which is used to deliver toxin to the nasal membrane. When electrical energy is used for poration, the electrodes may be on the catheter within or surrounding the region which delivers the energy to the nasal membrane. In other instances, the energy may be applied from a separate catheter or other device adapted for intranasal introduction.. . .

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

membrane. The systems may typically comprise a catheter adapted to introduce a toxin to a region adjacent to the target. . .

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

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

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

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

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

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

DETD . . . in a simplified single cell model. A targeted cell 10, e.g. a goblet cell of the type which line the nasal cavity membrane, is shown in FIG. 2A. Fragmented neurotoxin such as BoNT-LC (LC) is introduced into the vicinity of the. . .

DETD . . . present invention may be adapted to introduce a BoNT-LC solution to a target region, such as the lung or the nasal passage and then effect selective membrane transport of the BoNT-LC into the cell using sonoporation.

DETD . . . utilizing an ultrasonic element 92 that may be particularly useful in delivery of the BoNT-LC to bronchial tissue (lung) and/or nasal tissue that provides a broad but targeted transport of the LC across the target cell walls, for example, epithelial and. . .

DETD Delivery to Nasal Cavity

DETD . . . other embodiments, the present invention is directed to methods and systems for delivering toxins to target cells within a patient's nasal cavity. The toxins may be intact toxins, such as botulinum toxin, ricin, exotoxin A, diphtheria toxin, cholera toxin, tetanus toxin,. . .

DETD Botulinum toxin blocks acetylcholine release from cells, such as the epithelial or goblet cells in the nasal membranes responsible for mucus hypersecretion, and can thus be effective even without energy-mediated delivery in accordance with the principles of. . . energy to permeablize or porate the cell membranes of the epithelial or goblet cells or other mucus-secreting cells of the nasal lining, in accordance with the present invention, allows botulinum and other toxins to be preferentially delivered to the targeted epithelial. . . the toxin light chains may be locally and specifically introduced into the target cells located within defined regions of the nasal membrane. Thus, even if the toxin fragments are accidentally dispersed beyond the desired target regions, the fragments will not generally. . .

DETD . . . the energy, or both, non-invasively. For example, as illustrated in FIG. 17, the patient may draw the toxin into the nasal cavity from a hand-held dispersion device DD. After a sufficient amount of the toxin has been infused into the nasal cavity, a separate hand-held transducer TD connected to an appropriate power supply PS will be energized and applied to the nasal cavities by passing the transducer over the appropriate regions of the forehead and nose. Optionally, the transducer can have a. . .

DETD While the toxins and porating energy of the present invention may be delivered to the nasal cavity in a variety of ways, the following provides a number of specific examples of catheters and other structures for delivering toxins to preselected portions of the nasal cavity. For example, as shown in FIG. 18, a balloon catheter 1000 may be provided with a porous balloon 1002. . . transducers 1004 within the balloon, optionally mounted on the catheter body, ultrasonic poration energy can be delivered to the adjacent nasal membranes which are receiving the toxin solution. As illustrated in FIG. 18, the toxin is being delivered to a lower. . .

DETD . . . sized and positioned to target an area of high goblet cell (G) concentration, for example in the back of the nasal passages in the area of the nasopharynx. By targeting this area of the nasal membrane, a high percentage of mucus-secreting epithelial or goblet cells can be treated with a device which is relatively small. . .

DETD . . . effect of such externally applied ultrasonic energy can be enhanced by introducing microbubbles (free air) into the isolated

sinuses and/or nasal passages which have been filled with toxin solution. For example, encapsulated microbubbles, which are generally useful as echocardiographic contrast agents,. . .

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

DETD . . . air bleed valves 1006 which are used to occlude the nostrils in order to evacuate or bleed air from the nasal passages while filling the passages with the toxin solution. The nose plugs 1005 could optionally include ultrasonic transducers in order to deliver ultrasonic or other acoustic energy into the solutions entrapped within the nasal cavities using the nostril plugs. Alternatively, of course, the ultrasound or other acoustic energy could be delivered from an external. . .

DETD . . . can deliver toxin incorporated into vesicles which may be configured as “resonance” bodies, which reduce the need to fill the nasal cavities with a liquid or other form of toxin. For example, lipid microspheres which incorporate the toxin may be sprayed or aerosolized onto target surfaces of the nasal epithelium. After the lipid or other resonance bodies are attached to the targeted epithelium membrane surface(s), the ultrasound energy can. . .

DETD Referring to FIG. 37, the toxin may be delivered as a conventional nasal spray (BoNT), as mentioned hereinbefore, and the poration energy can be delivered through a face mask. The poration energy might. . .

DETD In addition to BTX-LC, it may be desirable to deliver additional agents to the nasal passages and sinuses prior to, coincident with, or after delivery of the LC. Adjunctive therapies may include agents designed to. . .

DETD Decongestants such as epinephrine also cause constriction of the vasculature in the nasal passages, which in addition to temporarily reducing swelling of the target tissues, may decrease the risks of LC entering the. . .

CLM What is claimed is:
1. A method of treating a nasal condition of a patient comprising: positioning a distal portion of a treatment device proximate to target tissue in a nasopharyngeal. . .

CLM What is claimed is:
17. A method of treating a nasal condition of a patient comprising: positioning a distal portion of a treatment device proximate to target tissue in a nasopharyngeal. . .

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

L11 ANSWER 6 OF 39 BIOSIS COPYRIGHT (c) 2020 Clarivate Analytics on STN
ACCESSION NUMBER: 2018:777166 BIOSIS
DOCUMENT NUMBER: PREV201800777166
TITLE: Methods and systems for toxin delivery to the nasal cavity.
AUTHOR(S): Deem, Mark E. [Inventor]; Anonymous; Gifford, Hanson [Inventor]
CORPORATE SOURCE: Mountain View, CA USA
ASSIGNEE: The Foundry LLC
PATENT INFORMATION: US 10052465 20180821
SOURCE: Official Gazette of the United States Patent and Trademark Office Patents, (AUG 21 2018)
CODEN: OGUPE7. ISSN: 0098-1133.
DOCUMENT TYPE: Patent
LANGUAGE: English
ENTRY DATE: Entered STN: 26 Sep 2018
Last Updated on STN: 3 Oct 2018 Full-text
TI Methods and systems for toxin delivery to the nasal cavity.
AU Deem, Mark E. [Inventor]; Anonymous; Gifford, Hanson [Inventor]
AB Methods and systems for delivering toxin and toxin fragments to a patient's nasal cavity provide for both release of the toxin and delivery of energy which selectively porates target cells to enhance uptake. . .
IT . . .
and Techniques; Equipment Apparatus Devices and Instrumentation; Pulmonary Medicine (Human Medicine, Medical Sciences)
IT Parts, Structures, & Systems of Organisms
nasal cavity: respiratory system
IT Chemicals & Biochemicals
toxins: toxin
AB Methods and systems for delivering toxin and toxin fragments to a patient's nasal cavity provide for both release of the toxin and delivery of energy which selectively porates target cells to enhance uptake of the toxin. The use of energy-mediated delivery is particularly advantageous with light chain fragment toxins which lack cell binding capacity.

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

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

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

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

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

L11 ANSWER 8 OF 39 USPATFULL on STN

ACCESSION NUMBER:	2018:303843 USPATFULL		
TITLE:	METHODS AND APPARATUS FOR DELIVERING A THERAPEUTIC AGENT TO NASPHARYNGEAL MUCOSA TARGETS		
INVENTOR(S):	MORRISS, John, San Francisco, CA, UNITED STATES REICH, Cary, Los Gatos, CA, UNITED STATES GIFFORD, Hanson, Woodside, CA, UNITED STATES		
APPLICANT(S):	The Foundry, LLC, Menlo Park, CA, UNITED STATES		
	NUMBER	KIND	DATE
PATENT INFORMATION:	US 20180264092	A1	20180920
APPLICATION INFO.:	US 2018-15988801	A1	20180524 (15)
RELATED APPLN. INFO.:	Division of Ser. No. US 2016-15089007, filed on 1 Apr 2016, Pat. No. US 10004789 Division of Ser. No. US 2014-14151767, filed on 9 Jan 2014, Pat. No. US 9327104 Continuation of Ser. No. WO 2012-US46089, filed on 10 Jul 2012, PENDING		
	NUMBER		DATE
PRIORITY INFORMATION:	US 2011-61507417		20110713 (61)
DOCUMENT TYPE:	Utility		
FILE SEGMENT:	APPLICATION		
NUMBER OF CLAIMS:	25		
EXEMPLARY CLAIM:	1-77		
NUMBER OF DRAWINGS:	7 Drawing Page(s)		
LINE COUNT:	829		

CAS INDEXING IS AVAILABLE FOR THIS PATENT. Full-text

IN GIFFORD, Hanson, Woodside, CA, UNITED STATES

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

SUMM Allergic rhinitis is an immunologic response modulated by immunoglobulin E (IgE) and characterized predominantly by sneezing, rhinorrhea, nasal congestion, and pruritus of the nose. It may be seasonal (a condition commonly referred to as hay fever) or perennial.. . .

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

SUMM . . . for rhinitis which relies on the use of botulinum toxin (BoNT) for blocking mucus production by mucus-producing cells in the nasal membrane has been proposed. Botulinum toxin and other neurotoxins are capable of disabling adrenergic cells, including epithelial or goblet cells which are responsible for the majority of mucus production in the nasal cavity membrane. It has been published in the scientific literature that introduction of botulinum toxin into the nasal passages of canines can reduce mucus secretion by a significant amount. This work is further discussed in scientific and patent. . .

SUMM . . . toxin is a neurotoxin which could have significant negative effects on a patient if accidentally released outside of the targeted nasal passages. Inadvertent distribution of the toxin to muscles of the oropharynx, mouth, tongue, or elsewhere could result in serious complications to the patient. Additionally, the use of botulinum-soaked gauze pads for delivering the toxin to the nasal cavities, as reported in the scientific literature, will have limited ability to uniformly and selectively deliver the botulinum to the. . .

SUMM . . . treatment site. Such improved methods and systems are preferably used to deliver a toxin, such as botulinum toxin to the nasal membrane of a patient, particularly in a patient suffering from rhinitis or other conditions associated with nasal inflammation and conditions, such as sinus headaches and migraine headaches. The methods and systems should be capable of providing for selective and repeatable delivery of an appropriate dose of the toxins to a defined target areas within the nasal cavities, including particular paranasal sinuses, the nasopharynx, and in some cases substantially the entire nasal cavity. The systems and methods should provide for the safe, accurate and effective delivery of a proper dose of the. . . toxins, and in particular should reduce or eliminate the risk of toxin being delivered to non-targeted tissues outside of the nasal cavity. At least some of these objectives will be met by the inventions described herein below.

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

SUMM . . . therapeutic agent. The therapeutic agent may be a toxin or a non-toxin and in preferred embodiments is delivered to the nasal cavity. When toxins are used, the invention provides for the delivery of the toxin to and across the nasal membrane tissue to treat various conditions and symptoms associated with nasal inflammation, including, rhinorrhea, rhinitis, sinusitis and hay fever.

SUMM The region where the toxin is introduced may comprise any portion of the nasal cavity, such as the turbinates, a single paranasal sinus or portion thereof, a main nasal passage, two or more paranasal sinuses, or in some cases may comprise substantially the entire nasal cavity of the patient. A particular target region for the toxin may comprise the nasopharynx which is at the back of the nasal passage. The nasopharynx comprises a cluster of epithelial or goblet cells which are responsible for mucus secretion and which are. . .

SUMM . . . and the toxin may comprise any neurotoxin capable of disabling mucus secretion in epithelial or goblet cells and other mucus-producing nasal cells. Preferably, the toxin comprises botulinum toxin, although other toxins such as ricin, exotoxin A, diphtheria toxin, cholera toxin, tetanus. . .

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

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

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

DETD . . . directed to methods and systems for delivering therapeutic agents such as toxins or non-toxins to target cells within a patient's nasal cavity. The toxins may be intact toxins, such as botulinum toxin, ricin, exotoxin A, diphtheria toxin, cholera toxin, tetanus toxin,. . .

DETD Botulinum toxin blocks acetylcholine release from cells, such as the epithelial or goblet cells in the nasal membranes responsible for mucus hypersecretion, and can thus be effective in accordance with the principles of the present invention. The. . . energy to permeablize or porate the cell membranes of the epithelial or goblet cells or other mucus-secreting cells of the nasal lining, may facilitate botulinum and other toxins to be preferentially delivered to the targeted

epithelial or goblet and other mucus-producing. . . the toxin light chains may be locally and specifically introduced into the target cells located within defined regions of the nasal membrane. Thus, even if the toxin fragments are accidentally dispersed beyond the desired target regions, the fragments will not generally. . .

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

L11 ANSWER 9 OF 39 USPATFULL on STN

ACCESSION NUMBER: 2018:153972 USPATFULL

TITLE: NASOLACRIMAL DRAINAGE SYSTEM IMPLANTS FOR DRUG THERAPY

INVENTOR(S): de Juan, JR., Eugene, San Francisco, CA, UNITED STATES
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	NUMBER	KIND	DATE
PATENT INFORMATION:	US 20180133150	A1	20180517
	US 10383817	B2	20190820
APPLICATION INFO.:	US 2017-15852619	A1	20171222 (15)

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

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

US 2006-60787775 20060331 (60)
DOCUMENT TYPE: Utility
FILE SEGMENT: APPLICATION
NUMBER OF CLAIMS: 47
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 30 Drawing Page(s)
LINE COUNT: 1976
CAS INDEXING IS AVAILABLE FOR THIS PATENT. Full-text
IN Gifford, Hanson S., Woodside, CA, UNITED STATES
DETD . . . extend through the drug core 112 to permit tear flow through the lumen for the delivery of therapeutic agent for nasal and systemic applications of the therapeutic agent. In addition or in combination with channel 112C, retention structure 132 and core. . .
AB An implant for insertion through a punctum and into a canalicular lumen of a patient. The implant includes a matrix of material, a therapeutic agent dispersed in the matrix of material, a sheath disposed over a portion of the matrix of material and configured to inhibit the therapeutic agent from being released from the matrix of material into the canalicular lumen and to allow the therapeutic agent to be released from a surface of the matrix of material to a tear film, and a retention structure configured to retain the implant within the canalicular lumen.

L11 ANSWER 10 OF 39 USPATFULL on STN
ACCESSION NUMBER: 2018:25606 USPATFULL
TITLE: DELIVERY DEVICES FOR NASOPHARYNGEAL MUCOSA TARGETS
INVENTOR(S): MORRISS, John, Emerald Hills, CA, UNITED STATES
GIFFORD, Hanson, Woodside, CA, UNITED STATES
APPLICANT(S): The Foundry, LLC, Menlo Park, CA, UNITED STATES

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

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

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

DOCUMENT TYPE: Utility
FILE SEGMENT: APPLICATION
NUMBER OF CLAIMS: 32
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 20 Drawing Page(s)
LINE COUNT: 1232
CAS INDEXING IS AVAILABLE FOR THIS PATENT. Full-text
IN GIFFORD, Hanson, Woodside, CA, UNITED STATES
AB . . . configuration to an expanded configuration. The expanded configuration is adapted to engage and conform to the mucosa tissue in a nasal cavity, and the contracted configuration has a size suitable for introduction into the nasal cavity. The drug reservoir holds a therapeutic agent and is at least partially covered by the porous pad. The drug. . .
SUMM Rhinitis is commonly referred to as "stuffy nose," and results from inflammation and swelling of the mucus membranes lining the nasal cavity. Rhinitis falls into two major categories--allergic and non-allergic (or vasomotor). Chronic rhinitis can result in chronic inflammation of the nasal passages resulting in sinusitis, an infection or inflammation of the paranasal sinuses. Rhinitis includes the symptoms of rhinorrhea which is commonly referred to as "runny nose." Rhinorrhea describes the effluence of mucus from the lining of the nasal passages, nasopharynx, or paranasal sinuses. Rhinorrhea can be a symptom of a number of diseases such as the common cold,. . .
SUMM Allergic rhinitis is an immunologic response modulated by immunoglobulin E (IgE) and characterized predominantly by sneezing, rhinorrhea, nasal congestion, and pruritus of the nose. It may be seasonal (a condition commonly referred to as hay fever) or perennial.. . .
SUMM . . . be caused by anatomic pathologies such as blockages, as seen in the case of sinusitis. Symptoms may include sneezing, itching, nasal congestion, and a runny nose. Non-allergic rhinitis is a diagnosis of

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

SUMM . . . for rhinitis which relies on the use of botulinum toxin (BoNT) for blocking mucus production by mucus-producing cells in the nasal membrane has been proposed. Botulinum toxin and other neurotoxins are capable of disabling adrenergic cells, including epithelial or goblet cells which are responsible for the majority of mucus production in the nasal cavity membrane. It has been published in the scientific literature that introduction of botulinum toxin into the nasal passages of canines can reduce mucus secretion by a significant amount.

SUMM . . . toxin is a neurotoxin which could have significant negative effects on a patient if accidentally released outside of the targeted nasal passages. Inadvertent distribution of the toxin to muscles of the oropharynx, mouth, tongue, or elsewhere could result in serious complications. . . a needle being inserted into their nostril. Moreover, the use of a needle to inject a toxin deep within the nasal cavity can be very difficult. Topical application of toxins also may have short comings, particularly in terms of the accuracy of delivery of the toxin. For example, the use of botulinum-soaked gauze pads for delivering the toxin to the nasal cavities, as reported in the scientific literature, have limited ability to uniformly and selectively deliver the botulinum to the regions. . .

SUMM . . . treatment site. Such improved methods and systems are preferably used to deliver a toxin, such as botulinum toxin to the nasal membrane of a patient, particularly in a patient suffering from rhinitis or other conditions associated with nasal inflammation and conditions, such as sinus headaches and migraine headaches. Other therapeutic agents including non-toxins may also be delivered. Such. . . initial shape for insertion and may be easily deployed or activated to expand and fill the desired area of the nasal cavity. The methods and systems should be capable of providing for selective and repeatable delivery of an appropriate dose of the toxins to a defined target areas within the nasal cavities, including particular paranasal sinuses, the nasopharynx, and in some cases substantially the entire nasal cavity. The systems and methods should provide for the safe, accurate and effective delivery of a proper dose of the. . . toxins, and in particular should reduce or eliminate the risk of toxin being delivered to non-targeted tissues outside of the nasal cavity. At least some of these objectives will be met by the inventions described herein below.

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

SUMM Briefly and in general terms, the present invention provides methods and systems for delivery of a therapeutic agent to the nasal cavity. The therapeutic agent may be a toxin or a non-toxin. The present disclosure focuses on preferred embodiments where the invention provides for the delivery of toxin to and across the nasal membrane tissue to treat various conditions and symptoms associated with nasal inflammation, including, rhinorrhea, rhinitis, sinusitis and hay fever. One of skill in the art will appreciate that this is not. . .

SUMM The region where the toxin is introduced may comprise any portion of the nasal cavity, such as a single paranasal sinus or portion thereof, a main nasal passage, two or more paranasal sinuses, or in some cases may comprise substantially the entire nasal cavity of the patient. A particular target region for the toxin may comprise the nasopharynx which is at the back of the nasal passage. The nasopharynx comprises a cluster of epithelial or goblet cells which are responsible for mucus secretion and which are. . .

SUMM . . . and the toxin may comprise any neurotoxin capable of disabling mucus secretion in epithelial or goblet cells and other mucus-producing nasal cells. Preferably, the toxin comprises botulinum toxin, although other toxins such as ricin, exotoxin A, diphtheria toxin, cholera toxin, tetanus. . .

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

agents including toxins or non-toxins to target cells within a patient's nasal cavity. The toxins may be intact toxins, such as botulinum toxin, ricin, exotoxin A, diphtheria toxin, cholera toxin, tetanus toxin,. . .

DETD Botulinum toxin blocks acetylcholine release from cells, such as the epithelial or goblet cells in the nasal membranes responsible for mucus hypersecretion, and can thus be effective in accordance with the principles of the present invention. The. . . energy to permeablize or porate the cell membranes of the epithelial or goblet cells or other mucus-secreting cells of the nasal lining, may facilitate botulinum and other toxins to be preferentially delivered to the targeted epithelial or goblet and other mucus-producing. . . the toxin light chains may be locally and specifically introduced into the target cells located within defined regions of the nasal membrane. Thus, even if the toxin fragments are accidentally dispersed beyond the desired target regions, the fragments will not generally. . .

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

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

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

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

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

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

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

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

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

DETD FIGS. 7A-7B illustrate an exemplary method of delivering a therapeutic agent to the nasal cavity with a foam contact element. The delivery device 230 includes an elongate shaft 240 having a foam contact element. . . the foam contact element 234 to constrain the foam contact element into a collapsed configuration that facilitates insertion into the nasal cavity via a nostril. In FIG. 7B, the delivery device 230 has been advanced into the nasal cavity via a nostril, and sheath 232 has been proximally retracted, thereby allowing the foam contact element to expand into. . . shape of the foam contact element may be varied as

discussed above in order to engage specific regions of the nasal cavity. Possible targets include any of the turbinates as well as the nasal septum, uncinate process, inferior, superior, and lateral extents of the nasopharynx. The therapeutic agent, such as botulinum toxin may then. . . even larger surface area. The size of the foam contact element may be selected depending on the size of the nasal cavity, or the size of the target area to treat. In alternative embodiments, multiple delivery devices may be used to. . .

DETD FIGS. 8A-8B illustrate another exemplary embodiment of delivering a therapeutic agent to the nasal cavity. The delivery device includes a plurality of flexible shafts 254, each having a foam contact element 256 disposed on. . . elements 256. Thus sheath 252 helps constrain the shafts 254 into a lower profile for ease of insertion into the nasal cavity. In FIG. 8B, the delivery device has been advanced into the nasal cavity via a nostril. The sheath 252 has been retracted relative to the plurality of flexible shafts 254 allowing the. . . Use of multiple flexible shafts and contact elements allow the device to reach smaller, harder to reach areas within the nasal cavity, as well as to more easily navigate around obstructions or through narrow gaps. A

delivery device may be used. . .

DETD FIGS. 9A-9B illustrate still another exemplary embodiment of a method for delivering a therapeutic agent to the nasal cavity. A porous reservoir (not illustrated, but similar to that previously described above) may include a small diameter flexible tube. . . The foam covered flexible tube 280 may be loaded into a syringe 276 for advancement through a nostril into the nasal cavity as seen in FIG. 9A. Once the syringe is advanced into the nasal cavity, the syringe plunger may be actuated and the foam covered flexible tube 280 is pushed out of the syringe into the nasal cavity as seen in FIG. 9B. Once unconstrained by the syringe, the foam expands to fill the nasal cavity. A string 278 is coupled to the foam covered flexible tube, and a free end of the string 278. . . be pulled in order to remove the foam covered flexible tube. Multiple foam covered tubes may be inserted into the nasal cavity in order to deliver the therapeutic agent to a larger surface area.

DETD FIGS. 12A-12B illustrate an exemplary method of advancing a drug delivery device having looped elements into the nasal cavity. The drug delivery device in FIGS. 12A-12B only has a single looped element, but one of skill in the. . . porous drug reservoir is retracted into and constrained by sheath 342 for minimum profile that can be advanced into the nasal cavity via a nostril. Once the device has been introduced into the nasal cavity, the sheath may be retracted (or the loop may be advanced) so that the loop becomes unconstrained and it. . .

DETD FIGS. 13A-13C illustrate use of a porous balloon to deliver a therapeutic agent to the nasal cavity. A catheter 372 includes an elongate flexible shaft 374 having a porous balloon 376 disposed at the distal end. . . component to be fluidly coupled to the catheter 372. In FIG. 13B, the catheter 372 is advanced toward the patient's nasal cavity, and the distal tip is inserted into the nostril. An optional valve member 380 may be coupled to connector. . . prevent backflow of the therapeutic agent. In FIG. 13C, the balloon 376 is advanced into a desired portion of the nasal cavity, and a syringe or other reservoir device (not illustrated) is coupled to valve 380, and the therapeutic agent is. . . drug is delivered to different areas of the anatomy. Also, in some embodiments, multiple balloons may be inserted into the nasal cavity for simultaneous delivery of a larger quantity of drug to a larger surface area. A final filling of the. . .

DETD . . . fluid such as a gas (e.g. air or nitrogen) or saline in order to reduce the remaining volume of the nasal cavity. Thus, the small remaining volume of the nasal cavity can easily be filled with the inflated outer balloon or spongy layer 388. Therefore the expanded volume of the. . . balloon is preferably greater than the expanded volume of the outer balloon or spongy layer. Because the volume of the nasal cavity has been reduced, the therapeutic agent may be delivered in a higher concentration and lower volume and it will. . .

DETD . . . of a drug delivery device having a tissue penetrating needle that may be used to deliver a therapeutic agent to nasal cavity. The delivery device includes an outer syringe barrel 404 and an inner syringe barrel 408. In preferred embodiments, the. . .

DETD . . . may help reduce patient anxiety associated with seeing a needle. Also, the sleeve is flexible, and therefore can navigate the

nasal anatomy easier than a more rigid needle. And once the device has been positioned in a desired area of the nasal cavity, the sleeve will act as a guide to help the needle smoothly advance through the anatomy to the target.. . .

DETD . . . 15A-15B illustrate exemplary usage of the device in FIGS. 14A-14C. The sleeve 402 is advanced through a nostril into the nasal cavity as seen in FIG. 15A. Advancement of the sleeve is performed while the needle is retracted into the outer. . .

DETD FIGS. 16A-16C illustrate the use of a patch to delivery a therapeutic agent to a nasal cavity. The patch 422 may be similar to transdermal drug delivery patches, and it may include a porous reservoir for. . . 428, and that is joined to a flexible adhesive structure for temporary attachment to the target tissue, such as a nasal turbinate 420. The adhesive areas 424 of the patch 422 may be arranged to ensure that the patch will stick. . . 430 may be folded in the opposite direction to be placed in the meatus between a turbinate 420 and the nasal septum or another turbinate as seen in FIG. 16C.

DETD . . . the patient exhales. Exhalation produces a strong airflow out of the lungs and closes the soft palate to seal the nasal cavity from the mouth and inferior pharynx. This prevents toxins from entering the lungs. Additionally, multiple smaller doses may be. . .

DETD . . . the device of FIG. 17. Cilial transport 464 causes the drug to flow thereby further spreading the drug in the nasal cavity.

CLM What is claimed is:

. . . configuration to an expanded configuration, the expanded configuration being adapted to engage and conform to the mucosa tissue in a nasal cavity, and the contracted configuration having a size suitable for introduction into the nasal cavity; and a drug reservoir holding a therapeutic agent, the drug reservoir being at least partially covered by the porous. . .

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

L11 ANSWER 11 OF 39 USPATFULL on STN

ACCESSION NUMBER:	2018:1883 USPATFULL
TITLE:	CORNEAL DENERVATION FOR TREATMENT OF OCULAR PAIN
INVENTOR(S):	ALSTER, YAIR, TEL-AVIV, ISRAEL GIFFORD, HANSON S., WOODSIDE, CA, UNITED STATES REICH, CARY J., LOS GATOS, CA, UNITED STATES DE JUAN, JR., EUGENE, SAN FRANCISCO, CA, UNITED STATES SCHOLL, JOHN A., SAN RAMON, CA, UNITED STATES ALEJANDRO, JOSE D., SUNNYVALE, CA, UNITED STATES SUTTON, DOUGLAS, PACIFICA, CA, UNITED STATES RAFAELI, OMER, TEL-AVIV, ISRAEL
APPLICANT(S):	NEXISVISION, INC., Menlo Park, CA, UNITED STATES

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 20180000639	A1	20180104
	US 10596038	B2	20200324
APPLICATION INFO.:	US 2017-15684010	A1	20170823 (15)

RELATED APPLN. INFO.: Continuation of Ser. No. US 2012-13503841, filed on 20 Aug 2012, ABANDONED A 371 of International Ser. No. WO 2010-US53854, filed on 22 Oct 2010

	NUMBER	DATE
PRIORITY INFORMATION:	US 2009-61279612	20091023 (61)

DOCUMENT TYPE:	Utility
FILE SEGMENT:	APPLICATION
NUMBER OF CLAIMS:	20

EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 33 Drawing Page(s)
LINE COUNT: 1236 Full-text
IN GIFFORD, HANSON S., WOODSIDE, CA, UNITED STATES
DRWD . . . applicator as in FIG. 5A comprising at least two electrodes to deliver electrical energy to the cornea with a first nasal portion of the applicator and a second temporal portion of the applicator.
DETD . . . portion of tissue and as second outer portion of tissue. Many of the nerves extending into the cornea extend substantially nasal to temporal and temporal to nasal, such that a first outer portion 110A located on a first nasally disposed portion of the cornea and a second. . .
DETD . . . as in FIG. 5A comprising at least two electrodes 556 to deliver electrical energy to the cornea with a first nasal portion 550A of the applicator and a second temporal portion 550B of the applicator. When the first portion and second portion are substantially symmetrical, the applicator can be used on either eye, such that the nasal portion 550A can be used on the temporal portion of the opposite eye and the temporal portion 550B can be used on the nasal portion of the eye.
AB Methods and apparatus for the treatment of the eye to reduce pain can treat at least an outer region of the tissue so as to denervate nerves extending into the inner region and reduce the pain. For example, the cornea of the eye may comprise an inner region having an epithelial defect, and an outer portion of the cornea can be treated to reduce pain of the epithelial defect. The outer portion of the cornea can be treated to denervate nerves extending from the outer portion to the inner portion. The outer portion can be treated in many ways to denervate the nerve, for example with one or more of heat, cold or a denervating noxious substance such as capsaicin. The denervation of the nerve can be reversible, such that corneal innervation can return following treatment.

L11 ANSWER 12 OF 39 BIOSIS COPYRIGHT (c) 2020 Clarivate Analytics on STN
ACCESSION NUMBER: 2017:585488 BIOSIS
DOCUMENT NUMBER: PREV201700585488
TITLE: Methods and systems for toxin delivery to the nasal cavity.
AUTHOR(S): Deem, Mark E. [Inventor]; Anonymous; Gifford, Hanson [Inventor]
CORPORATE SOURCE: Mountain View, CA USA
ASSIGNEE: The Foundry LLC
PATENT INFORMATION: US 09700707 20170711
SOURCE: Official Gazette of the United States Patent and Trademark Office Patents, (JUL 11 2017)
CODEN: OGUPE7. ISSN: 0098-1133.
DOCUMENT TYPE: Patent
LANGUAGE: English
ENTRY DATE: Entered STN: 2 Aug 2017
Last Updated on STN: 2 Aug 2017 Full-text
TI Methods and systems for toxin delivery to the nasal cavity.
AU Deem, Mark E. [Inventor]; Anonymous; Gifford, Hanson [Inventor]
AB Methods and systems for delivering toxin and toxin fragments to a patient's nasal cavity provide for both release of the toxin and delivery of energy which selectively porates target cells to enhance uptake. . .
AB Methods and systems for delivering toxin and toxin fragments to a patient's nasal cavity provide for both release of the toxin and delivery of energy which selectively porates target cells to enhance uptake of the toxin. The use of energy-mediated delivery is particularly advantageous with light chain fragment toxins which lack cell binding capacity.

L11 ANSWER 13 OF 39 USPATFULL on STN
ACCESSION NUMBER: 2017:349935 USPATFULL
TITLE: DRUG CORES FOR SUSTAINED RELEASE OF THERAPEUTIC AGENTS
INVENTOR(S): Utkhede, JR., Deepank, Surrey, CANADA
Shimizu, Robert, Laguna Niguel, CA, UNITED STATES
Jain, Rachna, Milpitas, CA, UNITED STATES
Boyd, Stephen, Murrieta, CA, UNITED STATES
Gifford, Hanson S, Woodside, CA, UNITED STATES

De Juan, Eugene, San Francisco, CA, UNITED STATES
Reich, Cary, Los Gatos, CA, UNITED STATES
APPLICANT(S): Mati Therapeutics Inc., Austin, TX, UNITED STATES

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 20170304194	A1	20171026
APPLICATION INFO.:	US 2017-15598035	A1	20170517 (15)

RELATED APPLN. INFO.: Continuation of Ser. No. US 2008-231986, filed on 5 Sep 2008, ABANDONED

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

DOCUMENT TYPE: Utility
FILE SEGMENT: APPLICATION
NUMBER OF CLAIMS: 28
EXEMPLARY CLAIM: 1-41
NUMBER OF DRAWINGS: 50 Drawing Page(s)
LINE COUNT: 7222
CAS INDEXING IS AVAILABLE FOR THIS PATENT. Full-text
IN Gifford, Hanson S, Woodside, CA, UNITED STATES
DETD . . . therapeutic target, e.g., the eye, while blocking release to non-target tissue, such as the interior of the canaliculus, or the nasal sinus.
DETD . . . various embodiments, the drug cores can be used for sustained release of therapeutic agents into the ears and/or Eustachian tubes, nasal and/or sinus cavities, urethra, skin, gastrointestinal tract (including colon, bowel duct, and the like), and in or near joints such. . .
DETD . . . extend through the drug core 112 to permit tear flow through the lumen for the delivery of therapeutic agent for nasal and systemic applications of the therapeutic agent. In addition or in combination with channel 112C, retention structure 132 and core. . .
DETD . . . other therapeutic agent to an eye (e.g., to treat an infection, inflammation, glaucoma or other ocular disease or disorder), a nasal passage (e.g., to treat a sinus or allergy disorder) or an inner ear system (e.g., to treat dizziness or a. . .
DETD . . . insert can be disposed in the second cavity to provide a sustained drug or other therapeutic agent release to a nasal passage or inner ear system, for example. An implant body septum can be positioned between the first cavity and the. . .
DETD . . . having structures derived from the punctual implants described above may allow elution of one or more therapeutic agent into a nasal cavity. Modifications or differences between such nasal implants and the punctual implants described above may include providing a passage for controlled release of medicated tear fluid through the canilicular lumen. Alternative nasal tissue structures may be quite different in overall form, optionally including any of a variety of known nasal cavity drug release shapes, but optionally taking advantage of one or more aspects of the drug cores or other drug. . .
AB A solid drug core insert can be manufactured by injecting a liquid mixture comprising a therapeutic agent and a matrix precursor into a sheath body. The injection can be conducted at subambient temperatures. The mixture is cured to form a solid drug-matrix core. The therapeutic agent can be a liquid at about room temperature that forms a dispersion of droplets in the matrix material. A surface of the solid drug core is exposed, for example by cutting the tube, and the exposed surface of the solid drug core releases therapeutic quantities of the therapeutic agent when implanted into the patient. In some embodiments, the insert body inhibits release of the therapeutic agent, for example with a material substantially impermeable to the therapeutic agent, such that the therapeutic quantities are released through the exposed surface, thereby avoiding release of the therapeutic agent to non-target tissues.

L11 ANSWER 14 OF 39 USPATFULL on STN
ACCESSION NUMBER: 2017:306785 USPATFULL
TITLE: METHODS AND SYSTEMS FOR TOXIN DELIVERY TO THE NASAL

CAVITY
INVENTOR(S): Deem, Mark E., Mountain View, CA, UNITED STATES
Gifford, Hanson, Woodside, CA, UNITED STATES
APPLICANT(S): The Foundry, LLC, Menlo Park, CA, UNITED STATES

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

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

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

DOCUMENT TYPE: Utility
FILE SEGMENT: APPLICATION
NUMBER OF CLAIMS: 35
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 24 Drawing Page(s)
LINE COUNT: 1394
CAS INDEXING IS AVAILABLE FOR THIS PATENT. Full-text
TI METHODS AND SYSTEMS FOR TOXIN DELIVERY TO THE NASAL CAVITY
IN Gifford, Hanson, Woodside, CA, UNITED STATES
AB Methods and systems for delivering toxin and toxin fragments to a patient's nasal cavity provide for both release of the toxin and delivery of energy which selectively porates target cells to enhance uptake. . .
SUMM . . . relates to methods and systems for delivering toxins, such as botulinum toxin light chain fragments, to target cells in a nasal cavity.
SUMM . . . the symptoms of rhinorrhea, is a condition resulting from inflammation and swelling of the patient's mucus membranes which line the nasal cavity. Rhinitis and/or rhinorrea can arise from a number of conditions, most often results from allergies to pollen, dust, seasonal. . . also be caused by anatomic pathologies such as blockages (as in the case of sinusitis). Symptoms may include sneezing, itching, nasal congestion, and a runny nose.
SUMM . . . for rhinitis which relies on the use of botulinum toxin ("BoNT") for blocking mucus production by mucus-producing cells in the nasal membrane has been proposed. Botulinum and other neurotoxins are capable of disabling adrenergic cells, including epithelial or goblet cells which are responsible for the majority of mucus production in the nasal cavity membrane. Dr. Ira Sanders has demonstrated that introduction of intact botulinum toxin molecules into the nasal passages of canines can reduce mucus secretion by a significant amount.
SUMM . . . toxin is a neurotoxin which could have significant negative effects on a patient if accidentally released outside of the targeted nasal passages. Inadvertent distribution of the toxin to muscles of the oropharynx, mouth, tongue, or elsewhere could result in serious complications to the patient. Additionally, the use of botulinum-soaked gauze pads for delivering the toxin to the nasal cavities, as demonstrated by Dr. Sanders, will have limited ability to uniformly and selectively deliver the botulinum to the regions. . .
SUMM . . . be desirable to provide improved methods and systems for delivering toxins, such as botulinum and active botulinum fragments, to the nasal membrane of a patient, particularly a patient suffering from rhinitis or other conditions associated with nasal inflammation and conditions, such as sinus headaches and migraine headaches. The methods and systems should be capable of providing for selective and repeatable delivery of the toxins to defined target areas within the nasal cavities, including particular paranasal sinuses, the nasopharynx, and

in some cases substantially the entire nasal cavity. The systems and methods should provide for the safe and effective delivery of the toxins, and in particular should reduce or eliminate the risk of toxin being delivered to non-targeted tissues outside of the nasal cavity. At least some of these objectives will be met by the inventions described herein below.

SUMM Rhinorrhea is the term describing the effluence of mucus from the lining of the nasal passages, nasopharynx, or paranasal sinuses. Rhinorrhea can be a symptom of a number of diseases such as the common cold,. . . paranasal sinuses. Sinusitis may have a number of different causes, and can be the result of chronic inflammation of the nasal passages, for example as a result of chronic rhinitis.

SUMM Allergic rhinitis is an immunologic response modulated by IgE and characterized predominantly by sneezing, rhinorrhea, nasal congestion, and pruritus of the nose. It may be seasonal (a condition commonly referred to as hay fever) or perennial.. . .

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

SUMM . . . no energy applied to untargeted regions. It will be appreciated that the energy may be applied to regions of the nasal membrane which are the same or different from the regions to which the toxin has been introduced. By controlling the. . . cells of interest while minimizing the amount of toxin which enters non-targeted cells. That is, only those cells in the nasal membrane which are exposed to both the toxin and the applied energy will preferentially be permeablized or porated to receive. . .

SUMM . . . to be delivered may comprise any neurotoxin capable of disabling mucus secretion in epithelial or goblet cells and other mucus-producing nasal cells. Preferably, the toxin comprises botulinum toxin, although other toxins such as ricin, exotoxin A, diphtheria toxin, cholera toxin, tetanus. . . use. In preferred aspects of the present invention, only an active fragment of the toxin will be delivered to the nasal cavity. Botulinum toxin and the other toxins listed above commonly comprise both a heavy chain and a light chain. The. . .

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

SUMM . . . be introduced to the target region through a catheter. For example, the catheter may carry a balloon which engages the nasal membrane in order to effect delivery of the toxin to the target cells. In a particular example, the balloon is. . . over at least a portion of its area so that the toxin may be released to specific areas of the nasal membrane, typically being incorporated into a suitable liquid, gel, or other fluid or fluidizable carrier. In other embodiments, the toxin. . .

SUMM . . . that the transducer may be located within or beneath the porous balloon which is used to deliver toxin to the nasal membrane. When electrical energy is used for poration, the electrodes may be on the catheter within or surrounding the region which delivers the energy to the nasal membrane. In other instances, the energy may be applied from a separate catheter or other device adapted for intranasal introduction.. . .

SUMM . . . invention further provides systems for delivering toxins to epithelial or goblet and other target cells as defined above in a nasal membrane. The systems may typically comprise a catheter adapted to introduce a toxin to a region adjacent to the target. . .

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

DRWD FIG. 15 depicts sizing of a delivery balloon to control distribution of

toxin released into the nasal cavity.

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

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

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

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

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

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

DETD The present invention is directed to methods and systems for delivering toxins to target cells within a patient's nasal cavity. The toxins may be intact toxins, such as botulinum toxin, ricin, exotoxin A, diphtheria toxin, cholera toxin, tetanus toxin,. . .

DETD Botulinum toxin blocks acetylcholine release from cells, such as the epithelial or goblet cells in the nasal membranes responsible for mucus hypersecretion, and can thus be effective even without energy-mediated delivery in accordance with the principles of. . . energy to permeablize or porate the cell membranes of the epithelial or goblet cells or other mucus-secreting cells of the nasal lining, in accordance with the present invention, allows botulinum and other toxins to be preferentially delivered to the targeted epithelial. . . the toxin light chains may be locally and specifically introduced into the target cells located within defined regions of the nasal membrane. Thus, even if the toxin fragments are accidentally dispersed beyond the desired target regions, the fragments will not generally. . .

DETD . . . a simplified single cell model. A targeted cell, e.g., an epithelial or goblet cell of the type which line the nasal cavity membrane, is shown in FIG. 2A. Fragmented neurotoxin such as BoNT-LC (LC) is introduced into the vicinity of the. . .

DETD . . . devices of the present invention may be adapted to introduce a BoNT-LC solution to a target region, such as the nasal passages and then effect selective membrane transport of the BoNT-LC into the cell using sonoporation.

DETD . . . embodiment of the present invention utilizing an ultrasonic element that may be particularly useful in delivery of the BoNT-LC to nasal tissue that provides a broad but targeted transport of the LC across the epithelial and goblet cell walls. In this. . .

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

DETD . . . the energy, or both, non-invasively. For example, as illustrated in FIG. 9, the patient may draw the toxin into the nasal cavity from a hand-held dispersion device DD. After a sufficient amount of the toxin has been infused into the nasal cavity, a separate hand-held transducer TD connected to an appropriate power supply PS will be energized and applied to the nasal cavities by passing the transducer over the appropriate regions of the forehead and nose. Optionally, the transducer can have a. . .

DETD While the toxins and porating energy of the present invention may be delivered to the nasal cavity in a variety of ways, the following provides a number of specific examples of catheters and other structures for delivering toxins to preselected portions of the nasal cavity. For example, as shown in FIG. 10, a balloon catheter 100 may be provided with a porous balloon 102. . . transducers 104 within the balloon, optionally mounted on the catheter body, ultrasonic poration energy can be delivered to the adjacent nasal membranes which are receiving the toxin solution. As illustrated in FIG. 10, the toxin is being delivered to a lower. . .

DETD . . . positioned to target an area of high epithelial or goblet cell (G) concentration, for example in the back of the nasal passages in the area of the nasopharynx. By targeting this area of the nasal membrane, a high percentage of mucus-secreting epithelial or goblet cells can be treated with a device which is relatively small. . .

DETD . . . effect of such externally applied ultrasonic energy can be enhanced by introducing microbubbles (free air) into the isolated sinuses and/or nasal passages which have been filled with toxin

solution. For example, encapsulated microbubbles, which are generally useful as echocardiographic contrast agents,. . .

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

DETD . . . air bleed valves 106 which are used to occlude the nostrils in order to evacuate or bleed air from the nasal passages while filling the passages with the toxin solution. The nose plugs 105 could optionally include ultrasonic transducers in order to deliver ultrasonic or other acoustic energy into the solutions entrapped within the nasal cavities using the nostril plugs. Alternatively, of course, the ultrasound or other acoustic energy could be delivered from an external. . .

DETD . . . can deliver toxin incorporated into vesicles which may be configured as "resonance" bodies, which reduce the need to fill the nasal cavities with a liquid or other form of toxin. For example, lipid microspheres which incorporate the toxin may be sprayed or aerosolized onto target surfaces of the nasal epithelium. After the lipid or other resonance bodies are attached to the targeted epithelium membrane surface(s), the ultrasound energy can. . .

DETD Referring to FIG. 29, the toxin may be delivered as a conventional nasal spray (BoNT), as mentioned hereinbefore, and the poration energy can be delivered through a face mask. The poration energy might. . .

DETD FIGS. 33 and 34 illustrate a device for applying BoNT to the treatment area within the nasal cavity. This device comprises a handle 115 having a proximal section, a body and a distal section. The body of. . . 118 connected to each of the first end and second, wherein the applicator tips are configured for insertion into the nasal passageway, as shown in FIG. 35.

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

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

DETD To facilitate the insertion of the tip applicator through the nostril and into the nasal passageway, it may be desirable for the applicator tip to initially have a low volume configuration. Once properly positioned in the nasal passageway, it would be desirable for the

applicator to have an expanded volume configuration for maximizing contact with the nasal turbinates. In one exemplary embodiment, the tip applicator may comprise a sponge such that the sponge 121 is in a. . . 39A) and an expanded configuration when wet (FIG. 39B), wherein the sponge 121 is configured to fit securely within the nasal

passageway.

DETD . . . could be preloaded with lyophilized BoNT and wetted with a liquid (e.g., saline) following placement of the applicator in the nasal passageway. The liquid can be introduced into the nasal passageway using a spray or a catheter, or the BoNT may simply be rewetted by the nasal secretions themselves. Alternatively, as described with respect to FIG. 36, the liquid can be infused into the applicator tip through. . .

DETD To facilitate the expansion of the applicator tip, thereby maximizing the surface contact between the nasal cavity wall and applicator tip, it may be desirable to incorporate a spring element 122 within the applicator tip 118.. . .

DETD . . . it will be necessary to hold the spring 122 in its compressed state until it is properly positioned within the nasal cavity, at which time the spring can be released to allow the applicator to expand into the nasal cavity. In the wet/dry sponge 121 embodiment described with respect to FIGS. 39A and 39B, a sponge and spring can. . .

DETD . . . retractable sheath or collar 126 for holding the spring in its compressed configuration. Once the applicator is positioned within the nasal cavity, the actuator can be retracted to release the spring, thereby expanding the applicator.

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

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

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

DETD An apparatus for treating a nasal cavity of a patient via a controlled and uniform delivery of BoNT may comprise an applicator having an inner member,. . . open-faced chambers. The outer member may also comprise an array of microneedles to facilitate the passage of BoNT across the nasal membrane. The inner member is configured for occupying space when the applicator is positioned within the nasal cavity such that the outer member is placed in contact with the wall of the nasal cavity. The inner member may be any compliant material such as a sponge, balloon or foam rubber. The impermeable lining. . . outer member to inner member and, accordingly, facilitates the transfer of BoNT from the applicator to the tissue of the nasal wall. As with applicator embodiments that have been previously discussed herein, the outer member can be pre soaked or filled with BoNT solution, infused with BoNT following placement in the nasal passageway, or pre-loaded with freeze-dried BoNT that can be reconstituted with infused saline.

DETD . . . embodiment, the inner member comprises (1) a low volume configuration to facilitate the applicator's insertion into and placement within the nasal passageway and (2) an expanded volume configuration for pressing the outer member against the walls of the nasal cavity. The expansion of the inner member relative to the outer member can also facilitate the controlled release of BoNT. . .

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

the nasal membrane can be optimized.

DETD . . . carrying BoNT. In this embodiment, the applicator tip may comprise a BoNT-loaded bioresorbable polymer that can be absorbed into the nasal cavity tissue. The tip can be configured such that the BoNT can be delivered to the nasal wall both immediately and as the coating is absorbed into the tissue.

DETD . . . this application, the device described with respect to FIGS. 33 and 34 can be used to deliver BoNT-LC to the nasal cavity instead of the BoNT intact molecule. In cases where this device is used to deliver BoNT-LC to the nasal cavity, any of the previously-described, energy-based delivery systems can be used to cause poration in the nasal tissue to facilitate delivery of the BoNT-LC to the tissue. Additionally or alternatively, this device can be equipped with an. . .

DETD In addition to BTX-LC, it may be desirable to deliver additional agents to the nasal passages and sinuses prior to, coincident with, or after deliver of the LC. Adjunctive therapies may include agents designed to. . .

DETD Decongestants such as epinephrine also cause constriction of the vasculature in the nasal passages, which in addition to temporarily reducing swelling of the target tissues, may decrease the risks of LC entering the. . .

CLM What is claimed is:

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

CLM What is claimed is:

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

CLM What is claimed is:

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

CLM What is claimed is:

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

CLM What is claimed is:

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

CLM What is claimed is:

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

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

L11 ANSWER 15 OF 39 USPATFULL on STN
ACCESSION NUMBER: 2017:148318 USPATFULL
TITLE: NASOLACRIMAL DRAINAGE SYSTEM IMPLANTS FOR DRUG THERAPY
INVENTOR(S): de Juan, Jr., Eugene, San Francisco, CA, UNITED STATES
Boyd, Stephen, Murrieta, CA, UNITED STATES
Reich, Cary, Los Gatos, CA, UNITED STATES
Rapacki, Alan, Redwood, CA, UNITED STATES
Gifford, Hanson S, Woodside, CA, UNITED STATES
Deem, Mark, Mountain View, CA, UNITED STATES
APPLICANT(S): Mati Therapeutics Inc., Austin, TX, UNITED STATES

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 20170128361	A1	20170511
	US 9849082	B2	20171226
APPLICATION INFO.:	US 2017-15405991	A1	20170113 (15)

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

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

DOCUMENT TYPE: Utility
FILE SEGMENT: APPLICATION
NUMBER OF CLAIMS: 25
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 30 Drawing Page(s)
LINE COUNT: 1862
CAS INDEXING IS AVAILABLE FOR THIS PATENT. Full-text
IN Gifford, Hanson S, Woodside, CA, UNITED STATES
DETD . . . extend through the drug core 112 to permit tear flow through the lumen for the delivery of therapeutic agent for nasal and systemic applications of the therapeutic agent. In addition or in combination with channel 112C, retention structure 132 and core. . .
AB An implant for insertion through a punctum and into a canalicular lumen of a patient. The implant includes a matrix of material, a therapeutic agent dispersed in the matrix of material, a sheath disposed over a portion of the matrix of material and configured to inhibit the therapeutic agent from being released from the matrix of material into the canalicular lumen and to allow the therapeutic agent to be released from a surface of the matrix of material to a tear film, and a retention structure configured to retain the implant within the canalicular lumen.

L11 ANSWER 16 OF 39 BIOSIS COPYRIGHT (c) 2020 Clarivate Analytics on STN
DUPLICATE 1
ACCESSION NUMBER: 2017:53857 BIOSIS
DOCUMENT NUMBER: PREV201700053857
TITLE: Apparatus for toxin delivery to the nasal cavity.
AUTHOR(S): Deem, Mark E. [Inventor]; Anonymous; Gifford, Hanson [Inventor]; Kim, Steven [Inventor]; Salamini, Alexey [Inventor]
CORPORATE SOURCE: Mountain View, CA USA
ASSIGNEE: THE FOUNDRY LLC
PATENT INFORMATION: US 09511210 20161206
SOURCE: Official Gazette of the United States Patent and Trademark Office Patents, (DEC 6 2016)
CODEN: OGUPE7. ISSN: 0098-1133.

DOCUMENT TYPE: Patent
LANGUAGE: English
ENTRY DATE: Entered STN: 28 Dec 2016
Last Updated on STN: 1 Mar 2017 Full-text
TI Apparatus for toxin delivery to the nasal cavity.
AU Deem, Mark E. [Inventor]; Anonymous; Gifford, Hanson [Inventor]; Kim, Steven [Inventor]; Salamini, Alexey [Inventor]
AB Apparatus for delivering toxin and toxin fragments to a patient's nasal cavity provide for both release of the toxin and delivery of energy which selectively porates target cells to enhance uptake. . .
AB Apparatus for delivering toxin and toxin fragments to a patient's nasal cavity provide for both release of the toxin and delivery of energy which selectively porates target cells to enhance uptake of the toxin. The use of energy-mediated delivery is particularly advantageous with light chain fragment toxins which lack cell binding capacity.

L11 ANSWER 17 OF 39 USPATFULL on STN
ACCESSION NUMBER: 2016:242484 USPATFULL
TITLE: METHODS AND APPARATUS FOR DELIVERING A THERAPEUTIC AGENT TO NASPHARYNGEAL MUCOSA TARGETS
INVENTOR(S): MORRISS, John, San Francisco, CA, UNITED STATES
REICH, Cary, Los Gatos, CA, UNITED STATES
GIFFORD, Hanson, Woodside, CA, UNITED STATES
APPLICANT(S): The Foundry, LLC, Menlo Park, CA, UNITED STATES

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 20160213758	A1	20160728
	US 10004789	B2	20180626
APPLICATION INFO.:	US 2016-15089007	A1	20160401 (15)

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

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

DOCUMENT TYPE: Utility
FILE SEGMENT: APPLICATION
NUMBER OF CLAIMS: 23
EXEMPLARY CLAIM: 1-57
NUMBER OF DRAWINGS: 7 Drawing Page(s)
LINE COUNT: 820
CAS INDEXING IS AVAILABLE FOR THIS PATENT. Full-text
IN GIFFORD, Hanson, Woodside, CA, UNITED STATES
SUMM Rhinitis is commonly referred to as "stuffy nose," and results from inflammation and swelling of the mucus membranes lining the nasal cavity Rhinitis falls into two major categories--allergic and non-allergic (or vasomotor). Chronic rhinitis can result in chronic inflammation of the nasal passages resulting in sinusitis, an infection or inflammation of the paranasal sinuses. Rhinitis includes the symptoms of rhinorrhea which is commonly referred to as "runny nose." Rhinorrhea describes the effluence of mucus from the lining of the nasal passages, nasopharynx, or paranasal sinuses. Rhinorrhea can be a symptom of a number of diseases such as the common cold,. . .
SUMM Allergic rhinitis is an immunologic response modulated by immunoglobulin E (IgE) and characterized predominantly by sneezing, rhinorrhea, nasal congestion, and pruritus of the nose. It may be seasonal (a condition commonly referred to as hay fever) or perennial.. . .
SUMM . . . be caused by anatomic pathologies such as blockages, as seen in the case of sinusitis. Symptoms may include sneezing, itching, nasal congestion, and a runny nose. Non-allergic rhinitis is a diagnosis of rhinitis without any IgE mediation, as documented by allergen. . .
SUMM . . . for rhinitis which relies on the use of botulinum toxin (BoNT) for blocking mucus production by mucus-producing cells in the nasal membrane has been proposed. Botulinum toxin and other neurotoxins are capable of disabling adrenergic cells, including epithelial or goblet cells which are responsible for the majority of mucus production in the nasal cavity membrane. It has been published in the scientific literature that introduction of botulinum toxin into the nasal passages of canines can reduce mucus secretion by a significant amount.

This work is further discussed in scientific and patent. . .

SUMM . . . toxin is a neurotoxin which could have significant negative effects on a patient if accidentally released outside of the targeted nasal passages. Inadvertent distribution of the toxin to muscles of the oropharynx, mouth, tongue, or elsewhere could result in serious complications to the patient. Additionally, the use of botulinum-soaked gauze pads for delivering the toxin to the nasal cavities, as reported in the scientific literature, will have limited ability to uniformly and selectively deliver the botulinum to the. . .

SUMM . . . treatment site. Such improved methods and systems are preferably used to deliver a toxin, such as botulinum toxin to the nasal membrane of a patient, particularly in a patient suffering from rhinitis or other conditions associated with nasal inflammation and conditions, such as sinus headaches and migraine headaches. The methods and systems should be capable of providing for selective and repeatable delivery of an appropriate dose of the toxins to a defined target areas within the nasal cavities, including particular paranasal sinuses, the nasopharynx, and in some cases substantially the entire nasal cavity. The systems and methods should provide for the safe, accurate and effective delivery of a proper dose of the. . . toxins, and in particular should reduce or eliminate the risk of toxin being delivered to non-targeted tissues outside of the nasal cavity. At least some of these objectives will be met by the inventions described herein below.

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

SUMM . . . therapeutic agent. The therapeutic agent may be a toxin or a non-toxin and in preferred embodiments is delivered to the nasal cavity. When toxins are used, the invention provides for the delivery of the toxin to and across the nasal membrane tissue to treat various conditions and symptoms associated with nasal inflammation, including, rhinorrhea, rhinitis, sinusitis and hay fever.

SUMM The region where the toxin is introduced may comprise any portion of the nasal cavity, such as the turbinates, a single paranasal sinus or portion thereof, a main nasal passage, two or more paranasal sinuses, or in some cases may comprise substantially the entire nasal cavity of the patient. A particular target region for the toxin may comprise the nasopharynx which is at the back of the nasal passage. The nasopharynx comprises a cluster of epithelial or goblet cells which are responsible for mucus secretion and which are. . .

SUMM . . . and the toxin may comprise any neurotoxin capable of disabling mucus secretion in epithelial or goblet cells and other mucus-producing nasal cells. Preferably, the toxin comprises botulinum toxin, although other toxins such as ricin, exotoxin A, diphtheria toxin, cholera toxin, tetanus. . .

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

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

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

DETD . . . directed to methods and systems for delivering therapeutic agents such as toxins or non-toxins to target cells within a patient's nasal cavity. The toxins may be intact toxins, such as botulinum toxin, ricin, exotoxin A, diphtheria toxin, cholera toxin, tetanus toxin,. . .

DETD Botulinum toxin blocks acetylcholine release from cells, such as the epithelial or goblet cells in the nasal membranes responsible for mucus hypersecretion, and can thus be effective in accordance with the principles of the present invention. The. . . energy to permeablize or porate the cell membranes of the epithelial or goblet cells or other mucus-secreting cells of the nasal lining, may facilitate botulinum and other toxins to be preferentially delivered to the targeted epithelial or goblet and other mucus-producing. . . the toxin light chains may be locally and specifically introduced into the target cells located within defined regions of the nasal membrane. Thus, even if the toxin fragments are accidentally dispersed beyond the desired target regions, the fragments will not generally. . .

DETD FIG. 1 illustrates the basic anatomy of the nasal cavity. The entrance to the nasal cavity is via the external naris. Long, narrow, and curled bone shelves line a portion of the nasal cavity. These bones

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

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

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

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

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

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

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

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

DETD The nasal volume of the first 5.2 cm of the nasal passage has been estimated by Kjoergaard to be about 5.43 cm.sup.3±1.31 cm.sup.3 per side based on acoustic rhinometry. Topical application of toxins to the nasal cavity have been reported by Rohrbach to use a sponge filled with 40 U (per side) with a concentration of 25 U/ml of toxin. Delivering the same 40 U dose to the nasal cavity with foam having a 10× expansion factor would require approximately 0.5 ml of an 80 U/ml liquid drug solution.

DETD Experiment 3. Volunteers evaluated the sensation of various 3:1 mixtures of foam after the foam was delivered to their nasal cavities. In some instances, the pump dispenser was used to deliver the foam directly to the nostril, while in other. . . pump was used to generate the foam and then the foam was transferred to a syringe for delivery to the nasal passage. The test subjects reported that soap and SDS had a mild

stinging sensation in their nose, while Tween did. . . by pinching the nostril. Use of simethicone as an anti-foaming agent did result in sneezing and a sensation of post nasal drip. The 3:1 solution of saline and Tween appears to be a promising mixture for producing foam that remains self. . .

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

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

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

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

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

L11 ANSWER 18 OF 39 USPATFULL on STN

ACCESSION NUMBER: 2016:10112 USPATFULL

TITLE: NASOLACRIMAL DRAINAGE SYSTEM IMPLANTS FOR DRUG THERAPY

INVENTOR(S): de Juan, JR., Eugene, San Francisco, CA, UNITED STATES
Boyd, Stephen, Murrieta, CA, UNITED STATES
Reich, Cary, Los Gatos, CA, UNITED STATES
Rapacki, Alan, Redwood, CA, UNITED STATES
Gifford, Hanson S., Woodside, CA, UNITED STATES
Deem, Mark, Mountain View, CA, UNITED STATES

APPLICANT(S): Mati Therapeutics Inc, Austin, TX, UNITED STATES

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

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

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

DOCUMENT TYPE: Utility

FILE SEGMENT: APPLICATION

NUMBER OF CLAIMS: 14

EXEMPLARY CLAIM: 1

NUMBER OF DRAWINGS: 30 Drawing Page(s)

LINE COUNT: 1850

CAS INDEXING IS AVAILABLE FOR THIS PATENT. Full-text

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

DETD . . . extend through the drug core 112 to permit tear flow through

the lumen for the delivery of therapeutic agent for nasal and systemic applications of the therapeutic agent. In addition or in combination with channel 112C, retention structure 132 and core. . .

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

L11 ANSWER 19 OF 39 USPATFULL on STN

ACCESSION NUMBER: 2015:413714 USPATFULL

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

INVENTOR(S): Deem, Mark E., Mountain View, CA, UNITED STATES
Gifford, Hanson, Woodside, CA, UNITED STATES

APPLICANT(S): The Foundry LLC, Menlo Park, CA, UNITED STATES

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

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

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

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

TI METHODS AND SYSTEMS FOR TOXIN DELIVERY TO THE NASAL CAVITY

IN Gifford, Hanson, Woodside, CA, UNITED STATES

AB Methods and systems for delivering toxin and toxin fragments to a patient's nasal cavity provide for both release of the toxin and delivery of energy which selectively porates target cells to enhance uptake. . .

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

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

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

SUMM . . . toxin is a neurotoxin which could have significant negative effects on a patient if accidentally released outside of the targeted

nasal passages. Inadvertent distribution of the toxin to muscles of the oropharynx, mouth, tongue, or elsewhere could result in serious complications to the patient. Additionally, the use of botulinum-soaked gauze pads for delivering the toxin to the nasal cavities, as demonstrated by Dr. Sanders, will have limited ability to uniformly and selectively deliver the botulinum to the regions. . .

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

SUMM Rhinorrhea is the term describing the effluence of mucus from the lining of the nasal passages, nasopharynx, or paranasal sinuses. Rhinorrhea can be a symptom of a number of diseases such as the common cold,. . . paranasal sinuses. Sinusitis may have a number of different causes, and can be the result of chronic inflammation of the nasal passages, for example as a result of chronic rhinitis.

SUMM Allergic rhinitis is an immunologic response modulated by IgE and characterized predominantly by sneezing, rhinorrhea, nasal congestion, and pruritus of the nose. It may be seasonal (a condition commonly referred to as hay fever) or perennial.. . .

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

SUMM . . . no energy applied to untargeted regions. It will be appreciated that the energy may be applied to regions of the nasal membrane which are the same or different from the regions to which the toxin has been introduced. By controlling the. . . cells of interest while minimizing the amount of toxin which enters non-targeted cells. That is, only those cells in the nasal membrane which are exposed to both the toxin and the applied energy will preferentially be permeablized or porated to receive. . .

SUMM . . . to be delivered may comprise any neurotoxin capable of disabling mucus secretion in epithelial or goblet cells and other mucus-producing nasal cells. Preferably, the toxin comprises botulinum toxin, although other toxins such as ricin, exotoxin A, diphtheria toxin, cholera toxin, tetanus. . . use. In preferred aspects of the present invention, only an active fragment of the toxin will be delivered to the nasal cavity. Botulinum toxin and the other toxins listed above commonly comprise both a heavy chain and a light chain. The. . .

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

SUMM . . . be introduced to the target region through a catheter. For example, the catheter may carry a balloon which engages the nasal membrane in order to effect delivery of the toxin to the target cells. In a particular example, the balloon is. . . over at least a portion of its area so that the toxin may be released to specific areas of the nasal membrane, typically being incorporated into a suitable liquid, gel, or other fluid or fluidizable carrier. In other embodiments, the toxin. . .

SUMM . . . that the transducer may be located within or beneath the porous

balloon which is used to deliver toxin to the nasal membrane. When electrical energy is used for poration, the electrodes may be on the catheter within or surrounding the region which delivers the energy to the nasal membrane. In other instances, the energy may be applied from a separate catheter or other device adapted for intranasal introduction.. . .

SUMM . . . invention further provides systems for delivering toxins to epithelial or goblet and other target cells as defined above in a nasal membrane. The systems may typically comprise a catheter adapted to introduce a toxin to a region adjacent to the target. . .

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

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

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

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

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

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

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

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

DETD The present invention is directed to methods and systems for delivering toxins to target cells within a patient's nasal cavity. The toxins may be intact toxins, such as botulinum toxin, ricin, exotoxin A, diphtheria toxin, cholera toxin, tetanus toxin,. . .

DETD Botulinum toxin blocks acetylcholine release from cells, such as the epithelial or goblet cells in the nasal membranes responsible for mucus hypersecretion, and can thus be effective even without energy-mediated delivery in accordance with the principles of. . . energy to permeablize or porate the cell membranes of the epithelial or goblet cells or other mucus-secreting cells of the nasal lining, in accordance with the present invention, allows botulinum and other toxins to be preferentially delivered to the targeted epithelial. . . the toxin light chains may be locally and specifically introduced into the target cells located within defined regions of the nasal membrane. Thus, even if the toxin fragments are accidentally dispersed beyond the desired target regions, the fragments will not generally. . .

DETD . . . a simplified single cell model. A targeted cell, e.g., an epithelial or goblet cell of the type which line the nasal cavity membrane, is shown in FIG. 2A. Fragmented neurotoxin such as BoNT-LC (LC) is introduced into the vicinity of the. . .

DETD . . . devices of the present invention may be adapted to introduce a BoNT-LC solution to a target region, such as the nasal passages and then effect selective membrane transport of the BoNT-LC into the cell using sonoporation.

DETD . . . embodiment of the present invention utilizing an ultrasonic element that may be particularly useful in delivery of the BoNT-LC to nasal tissue that provides a broad but targeted transport of the LC across the epithelial and goblet cell walls. In this. . .

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

DETD . . . the energy, or both, non-invasively. For example, as illustrated in FIG. 9, the patient may draw the toxin into the nasal cavity from a hand-held dispersion device DD. After a sufficient amount of the toxin has been infused into the nasal cavity, a separate hand-held transducer TD connected to an appropriate power supply PS will be energized and applied to the nasal cavities by passing the transducer over the appropriate regions of the forehead and nose. Optionally, the transducer can have a. . .

DETD While the toxins and porating energy of the present invention may be delivered to the nasal cavity in a variety of ways, the following provides a number of specific examples of catheters and other structures for delivering toxins to preselected portions of the nasal cavity. For

example, as shown in FIG. 10, a balloon catheter 100 may be provided with a porous balloon 102. . . transducers 104 within the balloon, optionally mounted on the catheter body, ultrasonic poration energy can be delivered to the adjacent nasal membranes which are receiving the toxin solution. As illustrated in FIG. 10, the toxin is being delivered to a lower. . .

DETD . . . positioned to target an area of high epithelial or goblet cell (G) concentration, for example in the back of the nasal passages in the area of the nasopharynx. By targeting this area of the nasal membrane, a high percentage of mucus-secreting epithelial or goblet cells can be treated with a device which is relatively small. . .

DETD . . . effect of such externally applied ultrasonic energy can be enhanced by introducing microbubbles (free air) into the isolated sinuses and/or nasal passages which have been filled with toxin solution. For example, encapsulated microbubbles, which are generally useful as echocardiographic contrast agents,. . .

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

DETD . . . air bleed valves 106 which are used to occlude the nostrils in order to evacuate or bleed air from the nasal passages while filling the passages with the toxin solution. The nose plugs 105 could optionally include ultrasonic transducers in order to deliver ultrasonic or other acoustic energy into the solutions entrapped within the nasal cavities using the nostril plugs. Alternatively, of course, the ultrasound or other acoustic energy could be delivered from an external. . .

DETD . . . can deliver toxin incorporated into vesicles which may be configured as "resonance" bodies, which reduce the need to fill the nasal cavities with a liquid or other form of toxin. For example, lipid microspheres which incorporate the toxin may be sprayed or aerosolized onto target surfaces of the nasal epithelium. After the lipid or other resonance bodies are attached to the targeted epithelium membrane surface(s), the ultrasound energy can. . .

DETD Referring to FIG. 29, the toxin may be delivered as a conventional nasal spray (BoNT), as mentioned hereinbefore, and the poration energy can be delivered through a face mask. The poration energy might. . .

DETD FIGS. 33 and 34 illustrate a device for applying BoNT to the treatment area within the nasal cavity. This device comprises a handle 115 having a proximal section, a body and a distal section. The body of. . . 118 connected to each of the first end and second, wherein the applicator tips are configured for insertion into the nasal passageway, as shown in FIG. 35.

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

DETD . . . may be configured to provide an outward lateral force such that the applicator tips 118 are firmly contacted against the nasal turbinates when placed in the nasal passageway. With reference to FIG. 37A, the operator would apply inward pressure in the direction of the arrows to the. . . to inserting the applicator tips into the nose. Once the applicator tips of the device are properly inserted into the nasal passageway, this pressure would be released such that the outward bias in the handle transitions the handle from a compressed configuration to an expanded configuration, as shown in FIG. 37B,

wherein the applicator tips are pressed against the nasal turbinates. The applicator tips can be held against the turbinates by the outward bias for sufficient time to allow a therapeutically effective amount of BoNT to be absorbed by the nasal cavity wall.

DETD To facilitate the insertion of the tip applicator through the nostril and into the nasal passageway, it may be desirable for the applicator tip to initially have a low volume configuration. Once properly positioned in the nasal passageway, it would be desirable for the applicator to have an expanded volume configuration for maximizing contact with the nasal turbinates. In one exemplary embodiment, the tip applicator may comprise a sponge such that the sponge 121 is in a.

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

DETD . . . could be preloaded with lyophilized BoNT and wetted with a liquid (e.g., saline) following placement of the applicator in the nasal passageway. The liquid can be introduced into the nasal passageway using a spray or a catheter, or the BoNT may simply be rewetted by the nasal secretions themselves. Alternatively, as described with respect to FIG. 36, the liquid can be infused into the applicator tip through. . .

DETD To facilitate the expansion of the applicator tip, thereby maximizing the surface contact between the nasal cavity wall and applicator tip, it may be desirable to incorporate a spring element 122 within the applicator tip 118.. . .

DETD . . . it will be necessary to hold the spring 122 in its compressed state until it is properly positioned within the nasal cavity, at which time the spring can be released to allow the applicator to expand into the nasal cavity. In the wet/dry sponge 121 embodiment described with respect to FIGS. 39A and 39B, a sponge and spring can. . .

DETD . . . retractable sheath or collar 126 for holding the spring in its compressed configuration. Once the applicator is positioned within the nasal cavity, the actuator can be retracted to release the spring, thereby expanding the applicator.

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

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

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

DETD An apparatus for treating a nasal cavity of a patient via a controlled and uniform delivery of BoNT may comprise an applicator having an inner member,. . . open-faced chambers. The outer member may also comprise an array of microneedles to facilitate the passage of BoNT across the nasal membrane. The inner member is configured for occupying space when the applicator is positioned within the nasal cavity such that the outer member is placed in contact with the wall of the nasal cavity. The inner member may be any compliant material such as a sponge, balloon or foam rubber. The impermeable lining. . . outer member to inner member and, accordingly, facilitates the transfer of BoNT from the applicator to the tissue of the nasal wall. As with applicator embodiments that have been previously discussed herein, the outer member can be pre soaked or filled with BoNT solution, infused with BoNT

following placement in the nasal passageway, or pre-loaded with freeze-dried BoNT that can be reconstituted with infused saline.

DETD . . . embodiment, the inner member comprises (1) a low volume configuration to facilitate the applicator's insertion into and placement within the nasal passageway and (2) an expanded volume configuration for pressing the outer member against the walls of the nasal cavity. The expansion of the inner member relative to the outer member can also facilitate the controlled release of BoNT. . .

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

DETD . . . carrying BoNT. In this embodiment, the applicator tip may comprise a BoNT-loaded bioresorbable polymer that can be absorbed into the nasal cavity tissue. The tip can be configured such that the BoNT can be delivered to the nasal wall both immediately and as the coating is absorbed into the tissue.

DETD . . . this application, the device described with respect to FIGS. 33 and 34 can be used to deliver BoNT-LC to the nasal cavity instead of the BoNT intact molecule. In cases where this device is used to deliver BoNT-LC to the nasal cavity, any of the previously-described, energy-based delivery systems can be used to cause poration in the nasal tissue to facilitate delivery of the BoNT-LC to the tissue. Additionally or alternatively, this device can be equipped with an. . .

DETD In addition to BTX-LC, it may be desirable to deliver additional agents to the nasal passages and sinuses prior to, coincident with, or after deliver of the LC. Adjunctive therapies may include agents designed to. . .

DETD Decongestants such as epinephrine also cause constriction of the vasculature in the nasal passages, which in addition to temporarily reducing swelling of the target tissues, may decrease the risks of LC entering the. . .

CLM What is claimed is:

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

CLM What is claimed is:

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

CLM What is claimed is:

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

CLM What is claimed is:

15. The method of claim 14, wherein the applicator tip is inserted into the nasal cavity with the handle in the compressed configuration.

CLM What is claimed is:

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

CLM What is claimed is:

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

CLM What is claimed is:

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

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

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

L11 ANSWER 20 OF 39 CA COPYRIGHT 2020 ACS on STN DUPLICATE 2
ACCESSION NUMBER: 161:396131 CA
TITLE: Delivery devices for nasopharyngeal mucosa targets
INVENTOR(S): Morriss, John; Gifford, Hanson
PATENT ASSIGNEE(S): The Foundry, LLC, USA
SOURCE: U.S. Pat. Appl. Publ., 32pp., Cont. of Appl. No. PCT/US2012/046258.
CODEN: USXXCO
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.		DATE
US 20140243793	A1	20140828	US 2014-14151588		20140109
US 9867972	B2	20180116			
CN 107510872	A	20171226	CN 2017-10703190		20120711
EP 2731654	B1	20181226	EP 2012-811642		20120711
US 20180021555	A1	20180125	US 2017-15679243		20170817
PRIORITY APPLN. INFO.:			US 2011-61507422	P	20110713
			WO 2012-US46258	A1	20120711
			CN 2012-80044685	A3	20120711
			US 2014-14151588	A1	20140109

ASSIGNMENT HISTORY FOR US PATENT AVAILABLE IN LSUS DISPLAY FORMAT Full-text
IN Morriss, John; Gifford, Hanson
AB . . . configuration to an expanded configuration. The expanded configuration is adapted to engage and conform to the mucosa tissue in a nasal cavity, and the contracted configuration has a size suitable for introduction into the nasal cavity. The drug reservoir holds a therapeutic agent and is at least partially covered by the porous pad. The drug. . .
IT Dissolution
Medical adhesives
Mucus
Needles (tools)
Pharmaceutical nasal sprays
Pressure
Rhinitis
Syringes
Targeted drug delivery systems
Valves
Wetting
(delivery devices for nasopharyngeal mucosa targets)
IT Mucosal drug delivery systems
Nasal drug delivery systems
Nasal mucosa

(nasopharyngeal; delivery devices for nasopharyngeal mucosa targets)
AB A system for delivering a therapeutic agent to nasopharyngeal mucosa tissue has a shaft, a porous pad of compliant material coupled to the shaft near the distal end, and a drug reservoir. The porous pad is configured to expand from a contracted configuration to an expanded configuration. The expanded configuration is adapted to engage and conform to the mucosa tissue in a nasal cavity, and the contracted configuration has a size suitable for introduction into the nasal cavity. The drug reservoir holds a therapeutic agent and is at least partially covered by the porous pad. The drug reservoir is configured to release a fixed vol. of the therapeutic agent into the porous pad within a period of less than about 120 min, and has a wall with a plurality of channels fluidly coupled with the porous pad. Detailed scheme of the device design is provided.
OS.CITING REF COUNT: 1 THERE ARE 1 CAPLUS RECORDS THAT CITE THIS RECORD (1 CITINGS)

L11 ANSWER 21 OF 39 BIOSIS COPYRIGHT (c) 2020 Clarivate Analytics on STN
ACCESSION NUMBER: 2014:257758 BIOSIS
DOCUMENT NUMBER: PREV201400257758
TITLE: Methods and systems for toxin delivery to the nasal cavity.
AUTHOR(S): Deem, Mark E. [Inventor]; Anonymous; Gifford, Hanson [Inventor]
CORPORATE SOURCE: Mountain View, CA USA
ASSIGNEE: The Foundry LLC
PATENT INFORMATION: US 08636684 20140128
SOURCE: Official Gazette of the United States Patent and Trademark Office Patents, (JAN 28 2014)
CODEN: OGUPE7. ISSN: 0098-1133.
DOCUMENT TYPE: Patent
LANGUAGE: English
ENTRY DATE: Entered STN: 19 Mar 2014
Last Updated on STN: 19 Mar 2014 Full-text
TI Methods and systems for toxin delivery to the nasal cavity.
AU Deem, Mark E. [Inventor]; Anonymous; Gifford, Hanson [Inventor]
AB Methods and systems for delivering toxin and toxin fragments to a patient's nasal cavity provide for both release of the toxin and delivery of energy which selectively porates target cells to enhance uptake. . .
IT Methods & Equipment
nasal cavity providing toxin delivery system: medical equipment;
nasal cavity providing toxin delivery method: clinical techniques
AB Methods and systems for delivering toxin and toxin fragments to a patient's nasal cavity provide for both release of the toxin and delivery of energy which selectively porates target cells to enhance uptake of the toxin. The use of energy-mediated delivery is particularly advantageous with light chain fragment toxins which lack cell binding capacity.

L11 ANSWER 22 OF 39 USPATFULL on STN
ACCESSION NUMBER: 2014:368120 USPATFULL
TITLE: DRUG DELIVERY METHODS, STRUCTURES, AND COMPOSITIONS FOR NASOLACRIMAL SYSTEM
INVENTOR(S): de Juan, JR., Eugene, San Francisco, CA, UNITED STATES
Reich, Cary, Los Gatos, CA, UNITED STATES
Boyd, Stephen, Murrieta, CA, UNITED STATES
Gifford, Hanson S., Woodside, CA, UNITED STATES
Deem, Mark, Mountain View, CA, UNITED STATES
APPLICANT(S): Mati Therapeutics, Austin, TX, UNITED STATES

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

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

NUMBER	DATE

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

L11 ANSWER 23 OF 39 USPATFULL on STN
ACCESSION NUMBER: 2014:272055 USPATFULL
TITLE: METHODS AND APPARATUS FOR DELIVERING A THERAPEUTIC AGENT TO NASOPHARYNGEAL MUCOSA TARGETS
INVENTOR(S): Morriss, John, San Francisco, CA, UNITED STATES
Reich, Cary, Los Gatos, CA, UNITED STATES
Gifford, Hanson, Woodside, CA, UNITED STATES
PATENT ASSIGNEE(S): The Foundry, LLC, Menlo Park, CA, UNITED STATES (U.S. corporation)

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 20140242064	A1	20140828
	US 9327104	B2	20160503
APPLICATION INFO.:	US 2014-14151767	A1	20140109 (14)

RELATED APPLN. INFO.: Continuation of Ser. No. WO 2012-US46089, filed on 10 Jul 2012, PENDING

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

DOCUMENT TYPE: Utility
FILE SEGMENT: APPLICATION
NUMBER OF CLAIMS: 46
EXEMPLARY CLAIM: 1-33
NUMBER OF DRAWINGS: 7 Drawing Page(s)
LINE COUNT: 887
CAS INDEXING IS AVAILABLE FOR THIS PATENT. Full-text
IN Gifford, Hanson, Woodside, CA, UNITED STATES
SUMM Rhinitis is commonly referred to as "stuffy nose," and results from inflammation and swelling of the mucus membranes lining the nasal cavity Rhinitis falls into two major categories--allergic and non-allergic (or vasomotor). Chronic rhinitis can result in chronic inflammation of the nasal passages resulting in sinusitis, an infection or inflammation of the paranasal sinuses. Rhinitis includes the symptoms of rhinorrhea which is commonly referred to as "runny nose." Rhinorrhea describes the effluence of mucus from the lining of the nasal passages, nasopharynx, or paranasal sinuses. Rhinorrhea can be a symptom of a number of diseases such as the common cold,. . .
SUMM Allergic rhinitis is an immunologic response modulated by immunoglobulin E (IgE) and characterized predominantly by sneezing, rhinorrhea, nasal congestion, and pruritus of the nose. It may be seasonal (a condition commonly referred to as hay fever) or perennial.. . .
SUMM . . . be caused by anatomic pathologies such as blockages, as seen in

the case of sinusitis. Symptoms may include sneezing, itching, nasal congestion, and a runny nose. Non-allergic rhinitis is a diagnosis of rhinitis without any IgE mediation, as documented by allergen. . .

SUMM . . . for rhinitis which relies on the use of botulinum toxin (BoNT) for blocking mucus production by mucus-producing cells in the nasal membrane has been proposed. Botulinum toxin and other neurotoxins are capable of disabling adrenergic cells, including epithelial or goblet cells which are responsible for the majority of mucus production in the nasal cavity membrane. It has been published in the scientific literature that introduction of botulinum toxin into the nasal passages of canines can reduce mucus secretion by a significant amount. This work is further discussed in scientific and patent. . .

SUMM . . . toxin is a neurotoxin which could have significant negative effects on a patient if accidentally released outside of the targeted nasal passages. Inadvertent distribution of the toxin to muscles of the oropharynx, mouth, tongue, or elsewhere could result in serious complications to the patient. Additionally, the use of botulinum-soaked gauze pads for delivering the toxin to the nasal cavities, as reported in the scientific literature, will have limited ability to uniformly and selectively deliver the botulinum to the. . .

SUMM . . . treatment site. Such improved methods and systems are preferably used to deliver a toxin, such as botulinum toxin to the nasal membrane of a patient, particularly in a patient suffering from rhinitis or other conditions associated with nasal inflammation and conditions, such as sinus headaches and migraine headaches. The methods and systems should be capable of providing for selective and repeatable delivery of an appropriate dose of the toxins to a defined target areas within the nasal cavities, including particular paranasal sinuses, the nasopharynx, and in some cases substantially the entire nasal cavity. The systems and methods should provide for the safe, accurate and effective delivery of a proper dose of the. . . toxins, and in particular should reduce or eliminate the risk of toxin being delivered to non-targeted tissues outside of the nasal cavity. At least some of these objectives will be met by the inventions described herein below.

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

SUMM . . . therapeutic agent. The therapeutic agent may be a toxin or a non-toxin and in preferred embodiments is delivered to the nasal cavity. When toxins are used, the invention provides for the delivery of the toxin to and across the nasal membrane tissue to treat various conditions and symptoms associated with nasal inflammation, including, rhinorrhea, rhinitis, sinusitis and hay fever.

SUMM The region where the toxin is introduced may comprise any portion of the nasal cavity, such as the turbinates, a single paranasal sinus or portion thereof, a main nasal passage, two or more paranasal sinuses, or in some cases may comprise substantially the entire nasal cavity of the patient. A particular target region for the toxin may comprise the nasopharynx which is at the back of the nasal passage. The nasopharynx comprises a cluster of epithelial or goblet cells which are responsible for mucus secretion and which are. . .

SUMM . . . and the toxin may comprise any neurotoxin capable of disabling mucus secretion in epithelial or goblet cells and other mucus-producing nasal cells. Preferably, the toxin comprises botulinum toxin, although other toxins such as ricin, exotoxin A, diphtheria toxin, cholera toxin, tetanus. . .

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

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

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

DETD . . . directed to methods and systems for delivering therapeutic agents such as toxins or non-toxins to target cells within a patient's nasal cavity. The toxins may be intact toxins, such as botulinum toxin, ricin, exotoxin A, diphtheria toxin, cholera toxin, tetanus toxin,. . .

DETD Botulinum toxin blocks acetylcholine release from cells, such as the epithelial or goblet cells in the nasal membranes responsible for mucus hypersecretion, and can thus be effective in accordance with the principles of the present invention. The. . . energy to permeablize

or porate the cell membranes of the epithelial or goblet cells or other mucus-secreting cells of the nasal lining, may facilitate botulinum and other toxins to be preferentially delivered to the targeted epithelial or goblet and other mucus-producing. . . the toxin light chains may be locally and specifically introduced into the target cells located within defined regions of the nasal membrane. Thus, even if the toxin fragments are accidentally dispersed beyond the desired target regions, the fragments will not generally. . .

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

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

used to deliver the foam into the nasal cavity.

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

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

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

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

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

DETD The nasal volume of the first 5.2 cm of the nasal passage has been estimated by Kjoergaard to be about 5.43 cm.sup.3±1.31 cm.sup.3 per side based on acoustic rhinometry. Topical application of toxins to the

nasal cavity have been reported by Rohrbach to use a sponge filled with 40 U (per side) with a concentration of 25 U/ml of toxin. Delivering the same 40 U dose to the nasal cavity with foam having a 10× expansion factor would require approximately 0.5 ml of an 80 U/ml liquid drug solution.

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

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

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

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

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

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

L11 ANSWER 24 OF 39 USPATFULL on STN

ACCESSION NUMBER: 2014:265257 USPATFULL

TITLE: NASOLACRIMAL DRAINAGE SYSTEM IMPLANTS FOR DRUG THERAPY

INVENTOR(S): De Juan, JR., Eugene, San Francisco, CA, UNITED STATES
Boyd, Stephen, Murrieta, CA, UNITED STATES
Reich, Cary, Los Gatos, CA, UNITED STATES
Rapacki, Alan, Redwood, CA, UNITED STATES
Gifford, Hanson S., Woodside, CA, UNITED STATES
Deem, Mark, Mountain View, CA, UNITED STATES

PATENT ASSIGNEE(S): Mati Therapeutics Inc., Austin, TX, UNITED STATES (U.S. corporation)

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

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

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

DOCUMENT TYPE: Utility

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

L11 ANSWER 25 OF 39 USPATFULL on STN
ACCESSION NUMBER: 2014:208960 USPATFULL
TITLE: DRUG CORES FOR SUSTAINED RELEASE OF THERAPEUTIC AGENTS
INVENTOR(S): Utkhede, Deepank, Surrey, CANADA
Shimizu, Robert W., Laguna Niguel, CA, UNITED STATES
Jain, Rachna, Milpitas, CA, UNITED STATES
Boyd, Stephen, Murrieta, CA, UNITED STATES
Gifford, Hanson S., Woodside, CA, UNITED STATES
De Juan, JR., Eugene, San Francisco, CA, UNITED STATES
Reich, Cary J., Los Gatos, CA, UNITED STATES
PATENT ASSIGNEE(S): Mati Therapeutics, Inc., Austin, TX, UNITED STATES (non-U.S. corporation)

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 20140186420	A1	20140703
APPLICATION INFO.:	US 2013-14098317	A1	20131205 (14)

RELATED APPLN. INFO.: Continuation of Ser. No. US 2012-13367823, filed on 7 Feb 2012, Pat. No. US 8628792 Division of Ser. No. US 2008-231986, filed on 5 Sep 2008, PENDING

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

DOCUMENT TYPE: Utility
FILE SEGMENT: APPLICATION
NUMBER OF CLAIMS: 19
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 50 Drawing Page(s)
LINE COUNT: 7171
CAS INDEXING IS AVAILABLE FOR THIS PATENT. Full-text
IN Gifford, Hanson S., Woodside, CA, UNITED STATES
DETD . . . therapeutic target, e.g., the eye, while blocking release to non-target tissue, such as the interior of the canaliculus, or the nasal sinus.
DETD . . . various embodiments, the drug cores can be used for sustained release of therapeutic agents into the ears and/or Eustachian tubes, nasal and/or sinus cavities, urethra, skin, gastrointestinal tract (including colon, bowel duct, and the like), and in or near joints such. . .
DETD . . . extend through the drug core 112 to permit tear flow through the lumen for the delivery of therapeutic agent for nasal and systemic applications of the therapeutic agent. In addition or in combination with channel 112C, retention structure 132 and core. . .
DETD . . . other therapeutic agent to an eye (e.g., to treat an infection, inflammation, glaucoma or other ocular disease or disorder), a nasal passage (e.g., to treat a sinus or allergy disorder) or an inner ear system (e.g., to treat dizziness or a. . .

DETD . . . insert can be disposed in the second cavity to provide a sustained drug or other therapeutic agent release to a nasal passage or inner ear system, for example. An implant body septum can be positioned between the first cavity and the. . .

DETD . . . having structures derived from the punctual implants described above may allow elution of one or more therapeutic agent into a nasal cavity. Modifications or differences between such nasal implants and the punctual implants described above may include providing a passage for controlled release of medicated tear fluid through the canilicular lumen. Alternative nasal tissue structures may be quite different in overall form, optionally including any of a variety of known nasal cavity drug release shapes, but optionally taking advantage of one or more aspects of the drug cores or other drug. . .

AB A solid drug core insert can be manufactured by injecting a liquid mixture comprising a therapeutic agent and a matrix precursor into a sheath body. The injection can be conducted at subambient temperatures. The mixture is cured to form a solid drug-matrix core. The therapeutic agent can be a liquid at about room temperature that forms a dispersion of droplets in the matrix material. A surface of the solid drug core is exposed, for example by cutting the tube, and the exposed surface of the solid drug core releases therapeutic quantities of the therapeutic agent when implanted into the patient. In some embodiments, the insert body inhibits release of the therapeutic agent, for example with a material substantially impermeable to the therapeutic agent, such that the therapeutic quantities are released through the exposed surface, thereby avoiding release of the therapeutic agent to non-target tissues.

L11 ANSWER 26 OF 39 USPATFULL on STN

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

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

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

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

DOCUMENT TYPE:	Utility
FILE SEGMENT:	APPLICATION
NUMBER OF CLAIMS:	31
EXEMPLARY CLAIM:	1
NUMBER OF DRAWINGS:	24 Drawing Page(s)
LINE COUNT:	1374

CAS INDEXING IS AVAILABLE FOR THIS PATENT. Full-text

TI METHODS AND SYSTEMS FOR TOXIN DELIVERY TO THE NASAL CAVITY

IN Gifford, Hanson, Woodside, CA, UNITED STATES

AB Methods and systems for delivering toxin and toxin fragments to a patient's nasal cavity provide for both release of the toxin and delivery of energy which selectively porates target cells to enhance uptake. . .

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

SUMM . . . the symptoms of rhinorrhea, is a condition resulting from inflammation and swelling of the patient's mucus membranes which line the nasal cavity. Rhinitis and/or rhinorrea can arise from a number of

conditions, most often results from allergies to pollen, dust, seasonal. . . also be caused by anatomic pathologies such as blockages (as in the case of sinusitis). Symptoms may include sneezing, itching, nasal congestion, and a runny nose.

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

SUMM . . . toxin is a neurotoxin which could have significant negative effects on a patient if accidentally released outside of the targeted nasal passages. Inadvertent distribution of the toxin to muscles of the oropharynx, mouth, tongue, or elsewhere could result in serious complications to the patient. Additionally, the use of botulinum-soaked gauze pads for delivering the toxin to the nasal cavities, as demonstrated by Dr. Sanders, will have limited ability to uniformly and selectively deliver the botulinum to the regions. . .

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

SUMM Rhinorrhea is the term describing the effluence of mucus from the lining of the nasal passages, nasopharynx, or paranasal sinuses. Rhinorrhea can be a symptom of a number of diseases such as the common cold,. . . paranasal sinuses. Sinusitis may have a number of different causes, and can be the result of chronic inflammation of the nasal passages, for example as a result of chronic rhinitis.

SUMM Allergic rhinitis is an immunologic response modulated by IgE and characterized predominantly by sneezing, rhinorrhea, nasal congestion, and pruritus of the nose. It may be seasonal (a condition commonly referred to as hay fever) or perennial.. . .

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

SUMM . . . no energy applied to untargeted regions. It will be appreciated that the energy may be applied to regions of the nasal membrane which are the same or different from the regions to which the toxin has been introduced. By controlling the. . . cells of interest while minimizing the amount of toxin which enters non-targeted cells. That is, only those cells in the nasal membrane which are exposed to both the toxin and the applied energy will preferentially be permeablized or porated to receive. . .

SUMM . . . to be delivered may comprise any neurotoxin capable of disabling mucus secretion in epithelial or goblet cells and other mucus-producing nasal cells. Preferably, the toxin comprises botulinum toxin, although other toxins such as ricin, exotoxin A, diphtheria toxin, cholera toxin, tetanus. . . use. In preferred aspects of the present invention, only an active fragment of the toxin will be delivered to the nasal cavity. Botulinum toxin and the other toxins

listed above commonly comprise both a heavy chain and a light chain. The. . .

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

SUMM . . . be introduced to the target region through a catheter. For example, the catheter may carry a balloon which engages the nasal membrane in order to effect delivery of the toxin to the target cells. In a particular example, the balloon is. . . over at least a portion of its area so that the toxin may be released to specific areas of the nasal membrane, typically being incorporated into a suitable liquid, gel, or other fluid or fluidizable carrier. In other embodiments, the toxin. . .

SUMM . . . that the transducer may be located within or beneath the porous balloon which is used to deliver toxin to the nasal membrane. When electrical energy is used for poration, the electrodes may be on the catheter within or surrounding the region which delivers the energy to the nasal membrane. In other instances, the energy may be applied from a separate catheter or other device adapted for intranasal introduction.. . .

SUMM . . . invention further provides systems for delivering toxins to epithelial or goblet and other target cells as defined above in a nasal membrane. The systems may typically comprise a catheter adapted to introduce a toxin to a region adjacent to the target. . .

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

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

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

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

poration energy to the nasal cavity.

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

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

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

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

DETD The present invention is directed to methods and systems for delivering toxins to target cells within a patient's nasal cavity. The toxins may be intact toxins, such as botulinum toxin, ricin, exotoxin A, diphtheria toxin, cholera toxin, tetanus toxin,. . .

DETD Botulinum toxin blocks acetylcholine release from cells, such as the epithelial or goblet cells in the nasal membranes responsible for mucus hypersecretion, and can thus be effective even without energy-mediated delivery in accordance with the principles of. . . energy to permeablize or porate the cell membranes of the epithelial or goblet cells or other mucus-secreting cells of the nasal lining, in accordance with the present invention, allows botulinum and other toxins to be preferentially delivered to the targeted epithelial. . . the toxin light chains may be locally and specifically introduced into the target cells located within defined regions of the nasal membrane. Thus, even if the toxin fragments are accidentally dispersed beyond the desired target regions, the fragments will not generally. . .

DETD . . . a simplified single cell model. A targeted cell, e.g., an epithelial or goblet cell of the type which line the nasal cavity membrane, is shown in FIG. 2A. Fragmented neurotoxin such as BoNT-LC (LC) is introduced into the vicinity of the. . .

DETD . . . devices of the present invention may be adapted to introduce a BoNT-LC solution to a target region, such as the nasal passages and then effect selective membrane transport of the BoNT-LC into the cell using sonoporation.

DETD . . . embodiment of the present invention utilizing an ultrasonic element that may be particularly useful in delivery of the BoNT-LC to nasal tissue that provides a broad but targeted transport of the LC across the epithelial and goblet cell walls. In this. . .

DETD . . . of producing a porative effect at the cellular level, including

electrodes, ultrasonic elements and the like, for treatment in the nasal passages.

DETD . . . the energy, or both, non-invasively. For example, as illustrated in FIG. 9, the patient may draw the toxin into the nasal cavity from a hand-held dispersion device DD. After a sufficient amount of the toxin has been infused into the nasal cavity, a separate hand-held transducer TD connected to an appropriate power supply PS will be energized and applied to the nasal cavities by passing the transducer over the appropriate regions of the forehead and nose. Optionally, the transducer can have a. . .

DETD While the toxins and porating energy of the present invention may be delivered to the nasal cavity in a variety of ways, the following provides a number of specific examples of catheters and other structures for delivering toxins to preselected portions of the nasal cavity. For example, as shown in FIG. 10, a balloon catheter 100 may be provided with a porous balloon 102. . . transducers 104 within the balloon, optionally mounted on the catheter body, ultrasonic poration energy can be delivered to the adjacent nasal membranes which are receiving the toxin solution. As illustrated in FIG. 10, the toxin is being delivered to a lower. . .

DETD . . . positioned to target an area of high epithelial or goblet cell (G) concentration, for example in the back of the nasal passages in the area of the nasopharynx. By targeting this area of the nasal membrane, a high percentage of mucus-secreting epithelial or goblet cells can be treated with a device which is relatively small. . .

DETD . . . effect of such externally applied ultrasonic energy can be enhanced by introducing microbubbles (free air) into the isolated sinuses and/or nasal passages which have been filled with toxin solution. For example, encapsulated microbubbles, which are generally useful as echocardiographic contrast agents,. . .

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

DETD . . . air bleed valves 106 which are used to occlude the nostrils in order to evacuate or bleed air from the nasal passages while filling the passages with the toxin solution. The nose plugs 105 could optionally include ultrasonic transducers in order to deliver ultrasonic or other acoustic energy into the solutions entrapped within the nasal cavities using the nostril plugs. Alternatively, of course, the ultrasound or other acoustic energy could be delivered from an external. . .

DETD . . . can deliver toxin incorporated into vesicles which may be configured as "resonance" bodies, which reduce the need to fill the nasal cavities with a liquid or other form of toxin. For example, lipid microspheres which incorporate the toxin may be sprayed or aerosolized onto target surfaces of the nasal epithelium. After the lipid or other resonance bodies are attached to the targeted epithelium membrane surface(s), the ultrasound energy can. . .

DETD Referring to FIG. 29, the toxin may be delivered as a conventional nasal spray (BoNT), as mentioned hereinbefore, and the poration energy can be delivered through a face mask. The poration energy might. . .

DETD FIGS. 33 and 34 illustrate a device for applying BoNT to the treatment area within the nasal cavity. This device comprises a handle 115 having a proximal section, a body and a distal section. The body of. . . 118 connected to each of the first end and second, wherein the applicator tips are configured for insertion into the nasal passageway, as shown in FIG. 35.

DETD Once within the nasal cavity, the applicator tips 117 and 118 can apply BoNT to the nasal passageway and, specifically, the turbinates along the nasal wall. The BoNT can be applied or affixed to the applicator tips as a liquid solution, gel, foam, cream, lotion and/or a lyophilized compound prior to being positioned within the nasal

passageway. Alternatively, as illustrated in FIG. 36, the handle can be configured with an infusion channel 119 for delivering the BoNT to the applicator tips following placement in the nasal passageway. In this configuration, the handle may further comprise an access port at its proximal section that is in fluid. . .

DETD . . . may be configured to provide an outward lateral force such that the applicator tips 118 are firmly contacted against the nasal turbinates when placed in the nasal passageway. With reference to FIG. 37A, the operator would apply inward pressure in the direction of the arrows to the. . . to inserting the applicator tips into the nose. Once the applicator tips of the device are properly inserted into the nasal passageway, this pressure would be released such that the outward bias in the handle transitions the handle from a compressed configuration to an expanded configuration, as shown in FIG. 37B, wherein the applicator tips are pressed against the nasal turbinates. The applicator tips can be held against the turbinates by the outward bias for sufficient time to allow a therapeutically effective amount of BoNT to be absorbed by the nasal cavity wall.

DETD To facilitate the insertion of the tip applicator through the nostril and into the nasal passageway, it may be desirable for the applicator tip to initially have a low volume configuration. Once properly positioned in the nasal passageway, it would be desirable for the applicator to have an expanded volume configuration for maximizing contact with the nasal turbinates. In one exemplary embodiment, the tip applicator may comprise a sponge such that the sponge 121 is in a. . . 39A) and an expanded configuration when wet (FIG. 39B), wherein

the sponge 121 is configured to fit securely within the nasal passageway.

DETD . . . could be preloaded with lyophilized BoNT and wetted with a liquid (e.g., saline) following placement of the applicator in the nasal passageway. The liquid can be introduced into the nasal passageway using a spray or a catheter, or the BoNT may simply be rewetted by the nasal secretions themselves. Alternatively, as described with respect to FIG. 36, the liquid can be infused into the applicator tip through. . .

DETD To facilitate the expansion of the applicator tip, thereby maximizing the surface contact between the nasal cavity wall and applicator tip, it may be desirable to incorporate a spring element 122 within the applicator tip 118.. . .

DETD . . . it will be necessary to hold the spring 122 in its compressed state until it is properly positioned within the nasal cavity, at which time the spring can be released to allow the applicator to expand into the nasal cavity. In the wet/dry sponge 121 embodiment described with respect to FIGS. 39A and 39B, a sponge and spring can. . .

DETD . . . retractable sheath or collar 126 for holding the spring in its compressed configuration. Once the applicator is positioned within the nasal cavity, the actuator can be retracted to release the spring, thereby expanding the applicator.

DETD . . . for the spring-assisted expansion of the applicator tip to be directionally biased to maximize contact with the wall of the nasal cavity and optimize contact pressure with the nasal turbinates. For example, the spring element can be dimensioned and configured such that the applicator expands laterally towards the turbinates of the nasal cavity. Alternatively or additionally, portions of the applicator tip may comprise an impermeable lining such that delivery of BoNT to certain portions of the nasal cavity is optimized and undesirable migration of BoNT solution is minimized.

DETD . . . also be desirable for the apparatus to be configured such that only the amount of toxin necessary to treat the nasal cavity is loaded on the applicator tip and applied to the nasal wall. It this embodiment, it would be desirable for the applicator to carry a predetermined quantity of toxin, wherein the. . . to be configured such that most, if not all, of the toxin carried on the applicator is delivered to the nasal wall, wherein little to no toxin runs, escapes or migrates to non-target portions of body tissue.

DETD . . . be configured to provide a controlled delivery of toxin to facilitate absorption of the toxin into the walls of the nasal cavity. An applicator providing a controlled delivery of toxin can be configured such that the rate of toxin delivery is proportionate with the rate of BoNT absorption across the nasal membrane. Such a controlled delivery will ensure that the toxin is absorbed into the nasal tissue and not

dispersed elsewhere in the body.

DETD An apparatus for treating a nasal cavity of a patient via a controlled and uniform delivery of BoNT may comprise an applicator having an inner member,. . . open-faced chambers. The outer member may also comprise an array of microneedles to facilitate the passage of BoNT across the nasal membrane. The inner member is configured for occupying space when the applicator is positioned within the nasal cavity such that the outer member is placed in contact with the wall of the nasal cavity. The inner member may be any compliant material such as a sponge, balloon or foam rubber. The impermeable lining. . . outer member to inner member and, accordingly, facilitates the transfer of BoNT from the applicator to the tissue of the nasal wall. As with applicator embodiments that have been previously discussed herein, the outer member can be pre soaked or filled with BoNT solution, infused with BoNT following placement in the nasal passageway, or pre-loaded with freeze-dried BoNT that can be reconstituted with infused saline.

DETD . . . embodiment, the inner member comprises (1) a low volume configuration to facilitate the applicator's insertion into and placement within the nasal passageway and (2) an expanded volume configuration for pressing the outer member against the walls of the nasal cavity. The expansion of the inner member relative to the outer member can also facilitate the controlled release of BoNT. . .

DETD In any of the embodiments discussed herein, it may be desirable to adapt the applicator to the geometry of the nasal cavity. For example, in embodiments comprising an outer member and inner member, the outer member can be configured to match the shape of the nasal cavity or portions of the nasal passageway following the expansion of the inner member. By achieving better contact, the delivery of toxin to and across the nasal membrane can be optimized.

DETD . . . carrying BoNT. In this embodiment, the applicator tip may comprise a BoNT-loaded bioresorbable polymer that can be absorbed into the nasal cavity tissue. The tip can be configured such that the BoNT can be delivered to the nasal wall both immediately and as the coating is absorbed into the tissue.

DETD . . . this application, the device described with respect to FIGS. 33 and 34 can be used to deliver BoNT-LC to the nasal cavity instead of the BoNT intact molecule. In cases where this device is used to deliver BoNT-LC to the nasal cavity, any of the previously-described, energy-based delivery systems can be used to cause poration in the nasal tissue to facilitate delivery of the BoNT-LC to the tissue. Additionally or alternatively, this device can be equipped with an. . .

DETD In addition to BTX-LC, it may be desirable to deliver additional agents to the nasal passages and sinuses prior to, coincident with, or after deliver of the LC. Adjunctive therapies may include agents designed to. . .

DETD Decongestants such as epinephrine also cause constriction of the vasculature in the nasal passages, which in addition to temporarily reducing swelling of the target tissues, may decrease the risks of LC entering the. . .

CLM What is claimed is:

1. A system for treating a nasal condition in a patient, said system comprising: an apparatus insertable into a nasal cavity of the patient, the apparatus comprising an outer expandable member and an inner expandable member disposed within the outer expandable member and configured to expand within the nasal cavity, wherein expansion of the inner expandable member causes expansion of the outer expandable member such that the outer expandable member is placed in contact with a wall of the nasal cavity; and a toxin either: (i) carried by the outer expandable member or (ii) disposed in a space between the. . . members, wherein the outer expandable member is configured to deliver the toxin to target cells in the wall of the nasal cavity.

CLM What is claimed is:

. . . system of claim 1, wherein the inner expandable member comprises a low volume configuration adapted to facilitate insertion into the nasal cavity and an expanded volume configuration adapted to place the outer expandable member in contact with the wall of the nasal cavity.

CLM What is claimed is:

19. A method for treating a nasal condition in a patient, said method comprising: inserting an apparatus into a nasal cavity of the patient,

wherein the apparatus comprises an inner and an outer expandable member; expanding the inner expandable member thereby causing the outer expandable member to expand and contact a wall of the nasal cavity; and delivering a toxin from the outer expandable member to target cells in the wall of the nasal cavity.

CLM What is claimed is:
30. The method of claim 19, wherein expanding the inner balloon substantially fills the nasal cavity, thereby inhibiting release of the toxin into portions of the nasal cavity other than the wall.

CLM What is claimed is:
. . . 31. The method of claim 30, wherein delivering the toxin comprises delivering a therapeutic dose to the wall of the nasal cavity while inhibiting release of the toxin into other portions of the nasal cavity.

AB Methods and systems for delivering toxin and toxin fragments to a patient's nasal cavity provide for both release of the toxin and delivery of energy which selectively porates target cells to enhance uptake of the toxin. The use of energy-mediated delivery is particularly advantageous with light chain fragment toxins which lack cell binding capacity.

L11 ANSWER 27 OF 39 CA COPYRIGHT 2020 ACS on STN DUPLICATE 3
ACCESSION NUMBER: 158:197331 CA
TITLE: Methods and apparatus for delivering a therapeutic agent to nasopharyngeal mucosa targets
INVENTOR(S): Moriss, John; Reich, Cary; Gifford, Hanson
PATENT ASSIGNEE(S): The Foundry, LLC, USA
SOURCE: PCT Int. Appl., 40pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2013009761	A1	20130117	WO 2012-US46089	20120710
EP 2731590	A1	20140521	EP 2012-811983	20120710
EP 2731590	B1	20180523		
CN 103874481	A	20140618	CN 2012-80044533	20120710
CN 103874481	B	20160928		
US 20140242064	A1	20140828	US 2014-14151767	20140109
US 9327104	B2	20160503		
US 20160213758	A1	20160728	US 2016-15089007	20160401
US 10004789	B2	20180626		
US 20180264092	A1	20180920	US 2018-15988801	20180524

PRIORITY APPLN. INFO.: US 2011-61507417 P 20110713
WO 2012-US46089 W 20120710
US 2014-14151767 A3 20140109
US 2016-15089007 A3 20160401
ASSIGNMENT HISTORY FOR US PATENT AVAILABLE IN LSUS DISPLAY FORMAT
OTHER SOURCE(S): CASFORMULTNS 2013:87239 Full-text
IN Moriss, John; Reich, Cary; Gifford, Hanson
IT Nasal drug delivery systems
(nasopharyngeal mucosa; methods and app. for delivering therapeutic agent to nasopharyngeal mucosa targets)
AB A system for delivering a therapeutic agent to a nasopharyngeal mucosa target comprises a foam generating mechanism, a gas, a therapeutic agent in liq. form that inhibits mucus prodn., and a delivery device. Actuation of the foam generating mechanism entraps gaseous bubbles from the gas in the liq. thereby forming a foam. The therapeutic agent is dispersed in the foam which has an expanded configuration adapted to fill a nasopharyngeal space and deliver the therapeutic agent to the mucosa targets. The delivery device is for delivering the foam to the nasopharyngeal space. The foam may also have a collapsed configuration for removal from the nasopharyngeal space or for concn. of the therapeutic agent onto the mucosa. Thus, 0.9 % sodium chloride aq. soln. was combined with a surfactant; surfactants included liq. soaps, sodium dodecyl sulfate (SDS) or Polysorbate 20; the liq. soaps contained water, vegetable oils (such as coconut, castor, soybean, apricot kernel, sunflower seed, meadow

flower seed, and shea butter), and potassium hydroxide; various ratios of saline to surfactant were used; a 3:1 ratio of saline to surfactant easily generated foam when passed through a foam generating mechanism; the foam generating mechanism included a pump dispenser similar to a hand soap pump or a whipped cream canister with nitrous oxide cartridges; a 6:1 ratio also produced foam, but the foam had shorter longevity than the foam formed with a 3:1 ratio of saline to surfactant; using the 3:1 ratio with a pump bottle contg. saline, and either soap, SDS, or Tween produced foams of similar appearance; the foams were white, with a distribution of small uniform bubbles and remained self supporting for at least 15 min.

OS.CITING REF COUNT: 1 THERE ARE 1 CAPLUS RECORDS THAT CITE THIS RECORD (1 CITINGS)

REFERENCE COUNT: 11 THERE ARE 11 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L11 ANSWER 28 OF 39 USPATFULL on STN

ACCESSION NUMBER: 2013:74774 USPATFULL

TITLE: Corneal Denervation for Treatment of Ocular Pain

INVENTOR(S): Alster, Yair, Palo Alto, CA, UNITED STATES
Gifford, Hanson S., Woodside, CA, UNITED STATES
Reich, Cary J., Los Gatos, CA, UNITED STATES
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PATENT ASSIGNEE(S): NexisVision, Inc., Menlo Park, CA, UNITED STATES (U.S. corporation)

	NUMBER	KIND	DATE	
PATENT INFORMATION:	US 20130066283	A1	20130314	
APPLICATION INFO.:	US 2012-13503841	A1	20101022	(13)
	WO 2010-US53854		20101022	
			20120820	PCT 371 date

	NUMBER	DATE
PRIORITY INFORMATION:	US 2009-61279612	20091023 (61)

DOCUMENT TYPE: Utility

FILE SEGMENT: APPLICATION

NUMBER OF CLAIMS: 14

EXEMPLARY CLAIM: 1-148

NUMBER OF DRAWINGS: 33 Drawing Page(s)

LINE COUNT: 1252 Full-text

IN Gifford, Hanson S., Woodside, CA, UNITED STATES

DRWD . . . applicator as in FIG. 5A comprising at least two electrodes to deliver electrical energy to the cornea with a first nasal portion of the applicator and a second temporal portion of the applicator.

DETD . . . portion of tissue and as second outer portion of tissue. Many of the nerves extending into the cornea extend substantially nasal to temporal and temporal to nasal, such that a first outer portion 110A located on a first nasally disposed portion of the cornea and a second. . .

DETD . . . as in FIG. 5A comprising at least two electrodes 556 to deliver electrical energy to the cornea with a first nasal portion 550A of the applicator and a second temporal portion 550B of the applicator. When the first portion and second portion are substantially symmetrical, the applicator can be used on either eye, such that the nasal portion 550A can be used on the temporal portion of the opposite eye and the temporal portion 550B can be used on the nasal portion of the eye.

AB Methods and apparatus for the treatment of the eye to reduce pain can treat at least an outer region of the tissue so as to denervate nerves extending into the inner region and reduce the pain. For example, the cornea of the eye may comprise an inner region having an epithelial defect, and an outer portion of the cornea can be treated to reduce pain of the epithelial defect. The outer portion of the cornea can be treated to denervate nerves extending from the outer portion to the inner portion. The outer portion can be treated in many ways to denervate the nerve, for example with one or more of heat, cold or a denervating noxious substance such as capsaicin. The denervation of the nerve can be

reversible, such that corneal innervation can return following treatment.

L11 ANSWER 29 OF 39 BIOSIS COPYRIGHT (c) 2020 Clarivate Analytics on STN
ACCESSION NUMBER: 2012:369512 BIOSIS
DOCUMENT NUMBER: PREV201200369512
TITLE: Methods and systems for toxin delivery to the nasal cavity.
AUTHOR(S): Deem, Mark E. [Inventor]; Anonymous; Gifford, Hanson [Inventor]
CORPORATE SOURCE: Mountain View, CA USA
ASSIGNEE: The Foundry LLC
PATENT INFORMATION: US 08105817 20120131
SOURCE: Official Gazette of the United States Patent and Trademark Office Patents, (JAN 31 2012)
CODEN: OGUPE7. ISSN: 0098-1133.
DOCUMENT TYPE: Patent
LANGUAGE: English
ENTRY DATE: Entered STN: 9 May 2012
Last Updated on STN: 9 May 2012 Full-text
TI Methods and systems for toxin delivery to the nasal cavity.
AU Deem, Mark E. [Inventor]; Anonymous; Gifford, Hanson [Inventor]
AB Methods and systems for delivering toxin and toxin fragments to a patient's nasal cavity provide for both release of the toxin and delivery of energy which selectively porates target cells to enhance uptake. . .
IT Methods & Equipment
nasal cavity targeted toxin/toxin fragment delivery method: therapeutic and prophylactic techniques, clinical techniques; nasal cavity targeted toxin/toxin fragment delivery system: drug delivery device
AB Methods and systems for delivering toxin and toxin fragments to a patient's nasal cavity provide for both release of the toxin and delivery of energy which selectively porates target cells to enhance uptake of the toxin. The use of energy-mediated delivery is particularly advantageous with light chain fragment toxins which lack cell binding capacity.

L11 ANSWER 30 OF 39 USPATFULL on STN
ACCESSION NUMBER: 2012:210534 USPATFULL
TITLE: DRUG CORES FOR SUSTAINED RELEASE OF THERAPEUTIC AGENTS
INVENTOR(S): Utkhede, Deepank, Surrey, CANADA
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Jain, Rachna, Milpitas, CA, UNITED STATES
Boyd, Stephen, Murrieta, CA, UNITED STATES
Gifford, Hanson S., Woodside, CA, UNITED STATES
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Reich, Cary J., Los Gatos, CA, UNITED STATES
PATENT ASSIGNEE(S): QLT INC., Vancouver, CANADA (non-U.S. corporation)

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 20120187594	A1	20120726
	US 8628792	B2	20140114
APPLICATION INFO.:	US 2012-13367823	A1	20120207 (13)

RELATED APPLN. INFO.: Continuation of Ser. No. US 2008-231986, filed on 5 Sep 2008, PENDING

	NUMBER	DATE
PRIORITY INFORMATION:	US 2008-61049317	20080430 (61)
	US 2007-60970820	20070907 (60)
	US 2007-60970699	20070907 (60)
	US 2007-60970709	20070907 (60)

DOCUMENT TYPE: Utility
FILE SEGMENT: APPLICATION
NUMBER OF CLAIMS: 41
EXEMPLARY CLAIM: 1-29
NUMBER OF DRAWINGS: 50 Drawing Page(s)
LINE COUNT: 7250

CAS INDEXING IS AVAILABLE FOR THIS PATENT. Full-text
IN Gifford, Hanson S., Woodside, CA, UNITED STATES
DETD . . . therapeutic target, e.g., the eye, while blocking release to non-target tissue, such as the interior of the canaliculus, or the nasal sinus.
DETD . . . various embodiments, the drug cores can be used for sustained release of therapeutic agents into the ears and/or Eustachian tubes, nasal and/or sinus cavities, urethra, skin, gastrointestinal tract (including colon, bowel duct, and the like), and in or near joints such. . .
DETD . . . extend through the drug core 112 to permit tear flow through the lumen for the delivery of therapeutic agent for nasal and systemic applications of the therapeutic agent. In addition or in combination with channel 112C, retention structure 132 and core. . .
DETD . . . other therapeutic agent to an eye (e.g., to treat an infection, inflammation, glaucoma or other ocular disease or disorder), a nasal passage (e.g., to treat a sinus or allergy disorder) or an inner ear system (e.g., to treat dizziness or a. . .
DETD . . . insert can be disposed in the second cavity to provide a sustained drug or other therapeutic agent release to a nasal passage or inner ear system, for example. An implant body septum can be positioned between the first cavity and the. . .
DETD . . . having structures derived from the punctual implants described above may allow elution of one or more therapeutic agent into a nasal cavity. Modifications or differences between such nasal implants and the punctual implants described above may include providing a passage for controlled release of medicated tear fluid through the canilicular lumen. Alternative nasal tissue structures may be quite different in overall form, optionally including any of a variety of known nasal cavity drug release shapes, but optionally taking advantage of one or more aspects of the drug cores or other drug. . .
AB A solid drug core insert can be manufactured by injecting a liquid mixture comprising a therapeutic agent and a matrix precursor into a sheath body. The injection can be conducted at subambient temperatures. The mixture is cured to form a solid drug-matrix core. The therapeutic agent can be a liquid at about room temperature that forms a dispersion of droplets in the matrix material. A surface of the solid drug core is exposed, for example by cutting the tube, and the exposed surface of the solid drug core releases therapeutic quantities of the therapeutic agent when implanted into the patient. In some embodiments, the insert body inhibits release of the therapeutic agent, for example with a material substantially impermeable to the therapeutic agent, such that the therapeutic quantities are released through the exposed surface, thereby avoiding release of the therapeutic agent to non-target tissues.

L11 ANSWER 31 OF 39 USPATFULL on STN

ACCESSION NUMBER:	2012:99920 USPATFULL		
TITLE:	METHODS AND SYSTEMS FOR TOXIN DELIVERY TO THE NASAL CAVITY		
INVENTOR(S):	Deem, Mark E., Mountain View, CA, UNITED STATES Gifford, Hanson, Woodside, CA, UNITED STATES		
PATENT ASSIGNEE(S):	The Foundry, LLC, Menlo Park, CA, UNITED STATES (U.S. corporation)		
	NUMBER	KIND	DATE
PATENT INFORMATION:	US 20120089078	A1	20120412
	US 8636684	B2	20140128
APPLICATION INFO.:	US 2011-13328203	A1	20111216 (13)
RELATED APPLN. INFO.:	Continuation of Ser. No. US 2009-636477, filed on 11 Dec 2009, Pat. No. US 8105817 Division of Ser. No. US 2007-750963, filed on 18 May 2007, Pat. No. US 7655243 Continuation-in-part of Ser. No. US 2006-459090, filed on 21 Jul 2006, Pat. No. US 7608275		
	NUMBER		DATE
PRIORITY INFORMATION:	US 2005-60702077		20050722 (60)
	US 2006-60747771		20060519 (60)
DOCUMENT TYPE:	Utility		
FILE SEGMENT:	APPLICATION		

NUMBER OF CLAIMS: 68
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 24 Drawing Page(s)
LINE COUNT: 1435
CAS INDEXING IS AVAILABLE FOR THIS PATENT. Full-text
TI METHODS AND SYSTEMS FOR TOXIN DELIVERY TO THE NASAL CAVITY
IN Gifford, Hanson, Woodside, CA, UNITED STATES
AB Methods and systems for delivering toxin and toxin fragments to a patient's nasal cavity provide for both release of the toxin and delivery of energy which selectively porates target cells to enhance uptake. . .
SUMM . . . relates to methods and systems for delivering toxins, such as botulinum toxin light chain fragments, to target cells in a nasal cavity.
SUMM . . . the symptoms of rhinorrhea, is a condition resulting from inflammation and swelling of the patient's mucus membranes which line the nasal cavity Rhinitis and/or rhinorrea can arise from a number of conditions, most often results from allergies to pollen, dust, seasonal. . . also be caused by anatomic pathologies such as blockages (as in the case of sinusitis). Symptoms may include sneezing, itching, nasal congestion, and a runny nose.
SUMM . . . for rhinitis which relies on the use of botulinum toxin ("BoNT") for blocking mucus production by mucus-producing cells in the nasal membrane has been proposed. Botulinum and other neurotoxins are capable of disabling adrenergic cells, including epithelial or goblet cells which are responsible for the majority of mucus production in the nasal cavity membrane. Dr. Ira Sanders has demonstrated that introduction of intact botulinum toxin molecules into the nasal passages of canines can reduce mucus secretion by a significant amount.
SUMM . . . toxin is a neurotoxin which could have significant negative effects on a patient if accidentally released outside of the targeted nasal passages. Inadvertent distribution of the toxin to muscles of the oropharynx, mouth, tongue, or elsewhere could result in serious complications to the patient. Additionally, the use of botulinum-soaked gauze pads for delivering the toxin to the nasal cavities, as demonstrated by Dr. Sanders, will have limited ability to uniformly and selectively deliver the botulinum to the regions. . .
SUMM . . . be desirable to provide improved methods and systems for delivering toxins, such as botulinum and active botulinum fragments, to the nasal membrane of a patient, particularly a patient suffering from rhinitis or other conditions associated with nasal inflammation and conditions, such as sinus headaches and migraine headaches. The methods and systems should be capable of providing for selective and repeatable delivery of the toxins to defined target areas within the nasal cavities, including particular paranasal sinuses, the nasopharynx, and in some cases substantially the entire nasal cavity. The systems and methods should provide for the safe and effective delivery of the toxins, and in particular should reduce or eliminate the risk of toxin being delivered to non-targeted tissues outside of the nasal cavity. At least some of these objectives will be met by the inventions described herein below.
SUMM Rhinorrhea is the term describing the effluence of mucus from the lining of the nasal passages, nasopharynx, or paranasal sinuses Rhinorrhea can be a symptom of a number of diseases such as the common cold,. . . paranasal sinuses. Sinusitis may have a number of different causes, and can be the result of chronic inflammation of the nasal passages, for example as a result of chronic rhinitis
SUMM Allergic rhinitis is an immunologic response modulated by IgE and characterized predominantly by sneezing, rhinorrhea, nasal congestion, and pruritus of the nose. It may be seasonal (a condition commonly referred to as hay fever) or perennial.. . .
SUMM . . . ricin, exotoxin A, diphtheria toxin, cholera toxin, tetanus toxin, other neurotoxins, and active fragments thereof are delivered to a patient's nasal membrane while applying energy to target cells within the membrane under conditions which cause a reversible (or in some instances. . . delivery of the toxin into the cells. The region where the toxin is introduced may comprise any portion of the nasal cavity, such as a single paranasal sinus or portion thereof, a main nasal passage, two or more paranasal sinuses, or in some cases may comprise substantially the entire nasal cavity of the patient. A particular target region for the toxin may comprise the nasopharynx which is at the back of the nasal passage. The nasopharynx comprises a

cluster of epithelial or goblet cells which are responsible for mucus secretion and which are. . .

SUMM . . . no energy applied to untargeted regions. It will be appreciated that the energy may be applied to regions of the nasal membrane which are the same or different from the regions to which the toxin has been introduced. By controlling the. . . cells of interest while minimizing the amount of toxin which enters non-targeted cells. That is, only those cells in the nasal membrane which are exposed to both the toxin and the applied energy will preferentially be permeablized or porated to receive. . .

SUMM . . . to be delivered may comprise any neurotoxin capable of disabling mucus secretion in epithelial or goblet cells and other mucus-producing nasal cells. Preferably, the toxin comprises botulinum toxin, although other toxins such as ricin, exotoxin A, diphtheria toxin, cholera toxin, tetanus. . . use. In preferred aspects of the present invention, only an active fragment of the toxin will be delivered to the nasal cavity. Botulinum toxin and the other toxins listed above commonly comprise both a heavy chain and a light chain. The. . .

SUMM . . . external ultrasonic transducers and/or ultrasound wave guides capable of delivering focused or unfocused ultrasound into the target tissues of the nasal cavity.

SUMM . . . be introduced to the target region through a catheter. For example, the catheter may carry a balloon which engages the nasal membrane in order to effect delivery of the toxin to the target cells. In a particular example, the balloon is. . . over at least a portion of its area so that the toxin may be released to specific areas of the nasal membrane, typically being incorporated into a suitable liquid, gel, or other fluid or fluidizable carrier. In other embodiments, the toxin. . .

SUMM . . . that the transducer may be located within or beneath the porous balloon which is used to deliver toxin to the nasal membrane. When electrical energy is used for poration, the electrodes may be on the catheter within or surrounding the region which delivers the energy to the nasal membrane. In other instances, the energy may be applied from a separate catheter or other device adapted for intranasal introduction.. . .

SUMM . . . invention further provides systems for delivering toxins to epithelial or goblet and other target cells as defined above in a nasal membrane. The systems may typically comprise a catheter adapted to introduce a toxin to a region adjacent to the target. . .

DRWD FIG. 9--depicts use on an external hand held transducer for enhancing cellular uptake of toxin delivered from a separate nasal aerosolizer.

DRWD FIG. 15--depicts sizing of a delivery balloon to control distribution of toxin released into the nasal cavity.

DRWD FIG. 17--depicts the use of multiple small balloons for selective toxin delivery into the nasal cavity.

DRWD FIGS. 22 and 23--depict nose plugs for occluding and optionally delivery poration energy to the nasal cavity.

DRWD . . . 28 and 30--depict use of a simple catheter having a shaped distal end for aerosolizing a toxin into a target nasal sinus though an ostium open to the sinus.

DRWD FIG. 29--depicts toxin delivery using a nasal spray and energy delivery using a face mask.

DRWD FIG. 33--depicts an applicator device for delivering toxin to the nasal cavity having a handle and two applicator tips for placement within the nasal passageway.

DRWD FIG. 35--depicts the applicator device illustrated in FIG. 33 when placed within the nasal passageway.

DETD The present invention is directed to methods and systems for delivering toxins to target cells within a patient's nasal cavity. The toxins may be intact toxins, such as botulinum toxin, ricin, exotoxin A, diphtheria toxin, cholera toxin, tetanus toxin,. . .

DETD Botulinum toxin blocks acetylcholine release from cells, such as the epithelial or goblet cells in the nasal membranes responsible for mucus hypersecretion, and can thus be effective even without energy-mediated delivery in accordance with the principles of. . . energy to permeablize or porate the cell membranes of the epithelial or goblet cells or other mucus-secreting cells of the nasal lining, in accordance with the present invention, allows botulinum and other toxins to be preferentially delivered to the targeted epithelial. . . the

toxin light chains may be locally and specifically introduced into the target cells located within defined regions of the nasal membrane. Thus, even if the toxin fragments are accidentally dispersed beyond the desired target regions, the fragments will not generally. . .

DETD . . . a simplified single cell model. A targeted cell, e.g., an epithelial or goblet cell of the type which line the nasal cavity membrane, is shown in FIG. 2A. Fragmented neurotoxin such as BoNT-LC (LC) is introduced into the vicinity of the. . .

DETD . . . devices of the present invention may be adapted to introduce a BoNT-LC solution to a target region, such as the nasal passages and then effect selective membrane transport of the BoNT-LC into the cell using sonoporation.

DETD . . . embodiment of the present invention utilizing an ultrasonic element that may be particularly useful in delivery of the BoNT-LC to nasal tissue that provides a broad but targeted transport of the LC across the epithelial and goblet cell walls. In this. . .

DETD . . . of producing a porative effect at the cellular level, including electrodes, ultrasonic elements and the like, for treatment in the nasal passages.

DETD . . . the energy, or both, non-invasively. For example, as illustrated in FIG. 9, the patient may draw the toxin into the nasal cavity from a hand-held dispersion device DD. After a sufficient amount of the toxin has been infused into the nasal cavity, a separate hand-held transducer TD connected to an appropriate power supply PS will be energized and applied to the nasal cavities by passing the transducer over the appropriate regions of the forehead and nose. Optionally, the transducer can have a. . .

DETD While the toxins and porating energy of the present invention may be delivered to the nasal cavity in a variety of ways, the following provides a number of specific examples of catheters and other structures for delivering toxins to preselected portions of the nasal cavity. For example, as shown in FIG. 10, a balloon catheter 100 may be provided with a porous balloon 102. . . transducers 104 within the balloon, optionally mounted on the catheter body, ultrasonic poration energy can be delivered to the adjacent nasal membranes which are receiving the toxin solution. As illustrated in FIG. 10, the toxin is being delivered to a lower. . .

DETD . . . positioned to target an area of high epithelial or goblet cell (G) concentration, for example in the back of the nasal passages in the area of the nasopharynx. By targeting this area of the nasal membrane, a high percentage of mucus-secreting epithelial or goblet cells can be treated with a device which is relatively small. . .

DETD . . . effect of such externally applied ultrasonic energy can be enhanced by introducing microbubbles (free air) into the isolated sinuses and/or nasal passages which have been filled with toxin solution. For example, encapsulated microbubbles, which are generally useful as echocardiographic contrast agents,. . .

DETD Referring now to FIGS. 20 and 21, a catheter 40 is placed at the posterior outlet of the nasal passages in the region of the nasopharynx. The catheters configured to occlude outflow from these sinuses and passages into the. . . shown in FIG. 20, the catheter is delivered in through the mouth and guided into the posterior portion of the nasal cavities, typically using a guidewire. Once the nasopharynx of the posterior portion of the nasal cavity is occluded, toxin solution (BoNT) can be infused through the occluding catheter lumen, or through a separate infusion catheter or tube, in order to treat substantially the entire sinus and/or nasal cavity membrane at once (FIG. 21). When the toxin solution is introduced through the catheter at the posterior region of the cavities, it will frequently be desirable to occlude the nostrils, for example using a nasal clip 105.

DETD . . . air bleed valves 106 which are used to occlude the nostrils in order to evacuate or bleed air from the nasal passages while filling the passages with the toxin solution. The nose plugs 105 could optionally include ultrasonic transducers in order to deliver ultrasonic or other acoustic energy into the solutions entrapped within the nasal cavities using the nostril plugs. Alternatively, of course, the ultrasound or other acoustic energy could be delivered from an external. . .

DETD . . . can deliver toxin incorporated into vesicles which may be configured as "resonance" bodies, which reduce the need to fill the nasal cavities with a liquid or other form of toxin. For example, lipid microspheres which incorporate the toxin may be sprayed or

aerosolized onto target surfaces of the nasal epithelium. After the lipid or other resonance bodies are attached to the targeted epithelium membrane surface(s), the ultrasound energy can. . .

DETD Referring to FIG. 29, the toxin may be delivered as a conventional nasal spray (BoNT), as mentioned hereinbefore, and the poration energy can be delivered through a face mask. The poration energy might. . .

DETD FIGS. 33 and 34 illustrate a device for applying BoNT to the treatment area within the nasal cavity. This device comprises a handle 115 having a proximal section, a body and a distal section. The body of. . . 118 connected to each of the first end and second, wherein the applicator tips are configured for insertion into the nasal passageway, as shown in FIG. 35.

DETD Once within the nasal cavity, the applicator tips 117 and 118 can apply BoNT to the nasal passageway and, specifically, the turbinates along the nasal wall. The BoNT can be applied or affixed to the applicator tips as a liquid solution, gel, foam, cream, lotion and/or a lyophilized compound prior to being positioned within the nasal passageway. Alternatively, as illustrated in FIG. 36, the handle can be configured with an infusion channel 119 for delivering the BoNT to the applicator tips following placement in the nasal passageway. In this configuration, the handle may further comprise an access port at its proximal section that is in fluid. . .

DETD . . . may be configured to provide an outward lateral force such that the applicator tips 118 are firmly contacted against the nasal turbinates when placed in the nasal passageway. With reference to FIG. 37A, the operator would apply inward pressure in the direction of the arrows to the. . . to inserting the applicator tips into the nose. Once the applicator tips of the device are properly inserted into the nasal passageway, this pressure would be released such that the outward bias in the handle transitions the handle from a compressed configuration to an expanded configuration, as shown in FIG. 37B, wherein the applicator tips are pressed against the nasal turbinates. The applicator tips can be held against the turbinates by the outward bias for sufficient time to allow a therapeutically effective amount of BoNT to be absorbed by the nasal cavity wall.

DETD To facilitate the insertion of the tip applicator through the nostril and into the nasal passageway, it may be desirable for the applicator tip to initially have a low volume configuration. Once properly positioned in the nasal passageway, it would be desirable for the applicator to have an expanded volume configuration for maximizing contact with the nasal turbinates. In one exemplary embodiment, the tip applicator may comprise a sponge such that the sponge 121 is in a. . . 39A) and an expanded configuration when wet (FIG. 39B), wherein the sponge 121 is configured to fit securely within the nasal passageway.

DETD . . . could be preloaded with lyophilized BoNT and wetted with a liquid (e.g., saline) following placement of the applicator in the nasal passageway. The liquid can be introduced into the nasal passageway using a spray or a catheter, or the BoNT may simply be rewetted by the nasal secretions themselves. Alternatively, as described with respect to FIG. 36, the liquid can be infused into the applicator tip through. . .

DETD To facilitate the expansion of the applicator tip, thereby maximizing the surface contact between the nasal cavity wall and applicator tip, it may be desirable to incorporate a spring element 122 within the applicator tip 118.. . .

DETD . . . it will be necessary to hold the spring 122 in its compressed state until it is properly positioned within the nasal cavity, at which time the spring can be released to allow the applicator to expand into the nasal cavity. In the wet/dry sponge 121 embodiment described with respect to FIGS. 39A and 39B, a sponge and spring can. . .

DETD . . . retractable sheath or collar 126 for holding the spring in its compressed configuration. Once the applicator is positioned within the nasal cavity, the actuator can be retracted to release the spring, thereby expanding the applicator.

DETD . . . for the spring-assisted expansion of the applicator tip to be directionally biased to maximize contact with the wall of the nasal cavity and optimize contact pressure with the nasal turbinates. For example, the spring element can be dimensioned and configured such that the applicator expands laterally towards the turbinates of the nasal cavity. Alternatively or additionally, portions of the applicator tip

may comprise an impermeable lining such that delivery of BoNT to certain portions of the nasal cavity is optimized and undesirable migration of BoNT solution is minimized

DETD . . . also be desirable for the apparatus to be configured such that only the amount of toxin necessary to treat the nasal cavity is loaded on the applicator tip and applied to the nasal wall. It this embodiment, it would be desirable for the applicator to carry a predetermined quantity of toxin, wherein the. . . to be configured such that most, if not all, of the toxin carried on the applicator is delivered to the nasal wall, wherein little to no toxin runs, escapes or migrates to non-target portions of body tissue.

DETD . . . be configured to provide a controlled delivery of toxin to facilitate absorption of the toxin into the walls of the nasal cavity. An applicator providing a controlled delivery of toxin can be configured such that the rate of toxin delivery is proportionate with the rate of BoNT absorption across the nasal membrane. Such a controlled delivery will ensure that the toxin is absorbed into the nasal tissue and not dispersed elsewhere in the body.

DETD An apparatus for treating a nasal cavity of a patient via a controlled and uniform delivery of BoNT may comprise an applicator having an inner member,. . . open-faced chambers. The outer member may also comprise an array of microneedles to facilitate the passage of BoNT across the nasal membrane. The inner member is configured for occupying space when the applicator is positioned within the nasal cavity such that the outer member is placed in contact with the wall of the nasal cavity. The inner member may be any compliant material such as a sponge, balloon or foam rubber. The impermeable lining. . . outer member to inner member and, accordingly, facilitates the transfer of BoNT from the applicator to the tissue of the nasal wall. As with applicator embodiments that have been previously discussed herein, the outer member can be pre soaked or filled with BoNT solution, infused with BoNT following placement in the nasal passageway, or pre-loaded with freeze-dried BoNT that can be reconstituted with infused saline.

DETD . . . embodiment, the inner member comprises (1) a low volume configuration to facilitate the applicator's insertion into and placement within the nasal passageway and (2) an expanded volume configuration for pressing the outer member against the walls of the nasal cavity. The expansion of the inner member relative to the outer member can also facilitate the controlled release of BoNT. . .

DETD In any of the embodiments discussed herein, it may be desirable to adapt the applicator to the geometry of the nasal cavity. For example, in embodiments comprising an outer member and inner member, the outer member can be configured to match the shape of the nasal cavity or portions of the nasal passageway following the expansion of the inner member. By achieving better contact, the delivery of toxin to and across the nasal membrane can be optimized

DETD . . . carrying BoNT. In this embodiment, the applicator tip may comprise a BoNT-loaded bioresorbable polymer that can be absorbed into the nasal cavity tissue. The tip can be configured such that the BoNT can be delivered to the nasal wall both immediately and as the coating is absorbed into the tissue.

DETD . . . this application, the device described with respect to FIGS. 33 and 34 can be used to deliver BoNT-LC to the nasal cavity instead of the BoNT intact molecule. In cases where this device is used to deliver BoNT-LC to the nasal cavity, any of the previously-described, energy-based delivery systems can be used to cause poration in the nasal tissue to facilitate delivery of the BoNT-LC to the tissue. Additionally or alternatively, this device can be equipped with an. . .

DETD In addition to BTX-LC, it may be desirable to deliver additional agents to the nasal passages and sinuses prior to, coincident with, or after deliver of the LC. Adjunctive therapies may include agents designed to. . .

DETD Decongestants such as epinephrine also cause constriction of the vasculature in the nasal passages, which in addition to temporarily reducing swelling of the target tissues, may decrease the risks of LC entering the. . .

CLM What is claimed is:

2. A method of treating a nasal condition comprising: positioning one or more occlusion devices in a nasal cavity to fluidly isolate a treatment region therein from a remaining portion of the nasal cavity, the treatment region containing target cells; and introducing a toxin to

the treatment region while the one or more occlusion devices block the toxin from entering the remaining portion of the nasal cavity, wherein the toxin inhibits mucous secretion in the target.

CLM What is claimed is:
. . . method of claim 2, wherein the one or more occlusion devices comprise one or more plugs positioned to block a nasal passage of the patient.

CLM What is claimed is:
27. The method of claim 2, wherein the treatment region comprises at least one paranasal sinus, a main nasal passage, or a nasal turbinate.

CLM What is claimed is:
28. The method of claim 2, wherein the treatment region comprises substantially the entire nasal cavity.

CLM What is claimed is:
34. A method of treating a nasal condition in a patient, said method comprising: introducing a gel or foam carrier comprising a toxin to a treatment region in a nasal cavity containing target cells, wherein the toxin is delivered from the gel or foam carrier to the target cells so. . .

CLM What is claimed is:
39. The method of claim 34, further comprising filling a targeted airway of the nasal cavity of the patient with the gel or foam carrier.

CLM What is claimed is:
40. The method of claim 39, further comprising fluidly isolating a treatment region of the nasal cavity, wherein the toxin is introduced into the treatment region.

CLM What is claimed is:
41. The method of claim 34, wherein the gel or foam carrier remains in place in the nasal cavity following introduction while the toxin is delivered to the target cells.

CLM What is claimed is:
62. The method of claim 34, wherein the treatment region comprises at least one paranasal sinus, a main nasal passage, or a nasal turbinate.

CLM What is claimed is:
63. The method of claim 34, wherein the treatment region comprises substantially the entire nasal cavity.

AB Methods and systems for delivering toxin and toxin fragments to a patient's nasal cavity provide for both release of the toxin and delivery of energy which selectively porates target cells to enhance uptake of the toxin. The use of energy-mediated delivery is particularly advantageous with light chain fragment toxins which lack cell binding capacity.

L11 ANSWER 32 OF 39 BIOSIS COPYRIGHT (c) 2020 Clarivate Analytics on STN
ACCESSION NUMBER: 2010:122525 BIOSIS
DOCUMENT NUMBER: PREV201000122525
TITLE: Methods and systems for toxin delivery to the nasal cavity.
AUTHOR(S): Deem, Mark E. [Inventor]; Anonymous; Gifford, Hanson [Inventor]
CORPORATE SOURCE: Mountain View, CA USA
ASSIGNEE: The Foundry LLC
PATENT INFORMATION: US 07655243 20100202
SOURCE: Official Gazette of the United States Patent and Trademark Office Patents, (FEB 2 2010)
CODEN: OGUPE7. ISSN: 0098-1133.
DOCUMENT TYPE: Patent
LANGUAGE: English
ENTRY DATE: Entered STN: 24 Feb 2010
Last Updated on STN: 24 Feb 2010 Full-text
TI Methods and systems for toxin delivery to the nasal cavity.
AU Deem, Mark E. [Inventor]; Anonymous; Gifford, Hanson [Inventor]
AB Methods and systems for delivering toxin and toxin fragments to a

patient's nasal cavity provide for both release of the toxin and delivery of energy which selectively porates target cells to enhance uptake. . .

IT Methods & Equipment
nasal cavity based toxin delivery system: drug delivery device

AB Methods and systems for delivering toxin and toxin fragments to a patient's nasal cavity provide for both release of the toxin and delivery of energy which selectively porates target cells to enhance uptake of the toxin. The use of energy-mediated delivery is particularly advantageous with light chain fragment toxins which lack cell binding capacity.

L11 ANSWER 33 OF 39 USPATFULL on STN

ACCESSION NUMBER:	2010:98403 USPATFULL		
TITLE:	METHODS AND SYSTEMS FOR TOXIN DELIVERY TO THE NASAL CAVITY		
INVENTOR(S):	DEEM, MARK E., MOUNTAIN VIEW, CA, UNITED STATES GIFFORD, HANSON, WOODSIDE, CA, UNITED STATES		
PATENT ASSIGNEE(S):	THE FOUNDY, LLC, MENLO PARK, CA, UNITED STATES (U.S. corporation)		
	NUMBER	KIND	DATE
PATENT INFORMATION:	US 20100087775	A1	20100408
	US 8105817	B2	20120131
APPLICATION INFO.:	US 2009-636477	A1	20091211 (12)
RELATED APPLN. INFO.:	Division of Ser. No. US 2007-750963, filed on 18 May 2007, Pat. No. US 7655243 Continuation-in-part of Ser. No. US 2006-459090, filed on 21 Jul 2006, Pat. No. US 7608275		
	NUMBER		DATE
PRIORITY INFORMATION:	US 2006-60747771		20060519 (60)
	US 2005-60702077		20050722 (60)
DOCUMENT TYPE:	Utility		
FILE SEGMENT:	APPLICATION		
LEGAL REPRESENTATIVE:	TOWNSEND AND TOWNSEND AND CREW, LLP, TWO EMBARCADERO CENTER, EIGHTH FLOOR, SAN FRANCISCO, CA, 94111-3834, US		
NUMBER OF CLAIMS:	31		
EXEMPLARY CLAIM:	1		
NUMBER OF DRAWINGS:	24 Drawing Page(s)		
LINE COUNT:	1356		

CAS INDEXING IS AVAILABLE FOR THIS PATENT. Full-text

TI METHODS AND SYSTEMS FOR TOXIN DELIVERY TO THE NASAL CAVITY

IN GIFFORD, HANSON, WOODSIDE, CA, UNITED STATES

AB Methods and systems for delivering toxin and toxin fragments to a patient's nasal cavity provide for both release of the toxin and delivery of energy which selectively porates target cells to enhance uptake. . .

SUMM . . . relates to methods and systems for delivering toxins, such as botulinum toxin light chain fragments, to target cells in a nasal cavity.

SUMM . . . the symptoms of rhinorrhea, is a condition resulting from inflammation and swelling of the patient's mucus membranes which line the nasal cavity. Rhinitis and/or rhinorrea can arise from a number of conditions, most often results from allergies to pollen, dust, seasonal. . . also be caused by anatomic pathologies such as blockages (as in the case of sinusitis). Symptoms may include sneezing, itching, nasal congestion, and a runny nose.

SUMM . . . for rhinitis which relies on the use of botulinum toxin ("BoNT") for blocking mucus production by mucus-producing cells in the nasal membrane has been proposed. Botulinum and other neurotoxins are capable of disabling adrenergic cells, including epithelial or goblet cells which are responsible for the majority of mucus production in the nasal cavity membrane. Dr. Ira Sanders has demonstrated that introduction of intact botulinum toxin molecules into the nasal passages of canines can reduce mucus secretion by a significant amount.

SUMM . . . toxin is a neurotoxin which could have significant negative effects on a patient if accidentally released outside of the targeted nasal passages. Inadvertent distribution of the toxin to muscles of

the oropharynx, mouth, tongue, or elsewhere could result in serious complications to the patient. Additionally, the use of botulinum-soaked gauze pads for delivering the toxin to the nasal cavities, as demonstrated by Dr. Sanders, will have limited ability to uniformly and selectively deliver the botulinum to the regions. . .

SUMM . . . be desirable to provide improved methods and systems for delivering toxins, such as botulinum and active botulinum fragments, to the nasal membrane of a patient, particularly a patient suffering from rhinitis or other conditions associated with nasal inflammation and conditions, such as sinus headaches and migraine headaches. The methods and systems should be capable of providing for selective and repeatable delivery of the toxins to defined target areas within the nasal cavities, including particular paranasal sinuses, the nasopharynx, and in some cases substantially the entire nasal cavity. The systems and methods should provide for the safe and effective delivery of the toxins, and in particular should reduce or eliminate the risk of toxin being delivered to non-targeted tissues outside of the nasal cavity. At least some of these objectives will be met by the inventions described herein below.

SUMM Rhinorrhea is the term describing the effluence of mucus from the lining of the nasal passages, nasopharynx, or paranasal sinuses. Rhinorrhea can be a symptom of a number of diseases such as the common cold,. . . paranasal sinuses. Sinusitis may have a number of different causes, and can be the result of chronic inflammation of the nasal passages, for example as a result of chronic rhinitis.

SUMM Allergic rhinitis is an immunologic response modulated by IgE and characterized predominantly by sneezing, rhinorrhea, nasal congestion, and pruritus of the nose. It may be seasonal (a condition commonly referred to as hay fever) or perennial.. . .

SUMM . . . ricin, exotoxin A, diphtheria toxin, cholera toxin, tetanus toxin, other neurotoxins, and active fragments thereof are delivered to a patient's nasal membrane while applying energy to target cells within the membrane under conditions which cause a reversible (or in some instances. . . delivery of the toxin into the cells. The region where the toxin is introduced may comprise any portion of the nasal cavity, such as a single paranasal sinus or portion thereof, a main nasal passage, two or more paranasal sinuses, or in some cases may comprise substantially the entire nasal cavity of the patient. A particular target region for the toxin may comprise the nasopharynx which is at the back of the nasal passage. The nasopharynx comprises a cluster of epithelial or goblet cells which are responsible for mucus secretion and which are. . .

SUMM . . . no energy applied to untargeted regions. It will be appreciated that the energy may be applied to regions of the nasal membrane which are the same or different from the regions to which the toxin has been introduced. By controlling the. . . cells of interest while minimizing the amount of toxin which enters non-targeted cells. That is, only those cells in the nasal membrane which are exposed to both the toxin and the applied energy will preferentially be permeablized or porated to receive. . .

SUMM . . . to be delivered may comprise any neurotoxin capable of disabling mucus secretion in epithelial or goblet cells and other mucus-producing nasal cells. Preferably, the toxin comprises botulinum toxin, although other toxins such as ricin, exotoxin A, diphtheria toxin, cholera toxin, tetanus. . . use. In preferred aspects of the present invention, only an active fragment of the toxin will be delivered to the nasal cavity. Botulinum toxin and the other toxins listed above commonly comprise both a heavy chain and a light chain. The. . .

SUMM . . . external ultrasonic transducers and/or ultrasound wave guides capable of delivering focused or unfocused ultrasound into the target tissues of the nasal cavity.

SUMM . . . be introduced to the target region through a catheter. For example, the catheter may carry a balloon which engages the nasal membrane in order to effect delivery of the toxin to the target cells. In a particular example, the balloon is. . . over at least a portion of its area so that the toxin may be released to specific areas of the nasal membrane, typically being incorporated into a suitable liquid, gel, or other fluid or fluidizable carrier. In other embodiments, the toxin. . .

SUMM . . . that the transducer may be located within or beneath the porous balloon which is used to deliver toxin to the nasal membrane. When

electrical energy is used for poration, the electrodes may be on the catheter within or surrounding the region which delivers the energy to the nasal membrane. In other instances, the energy may be applied from a separate catheter or other device adapted for intranasal introduction.. . .

SUMM . . . invention further provides systems for delivering toxins to epithelial or goblet and other target cells as defined above in a nasal membrane. The systems may typically comprise a catheter adapted to introduce a toxin to a region adjacent to the target. . .

DRWD FIG. 9--depicts use on an external hand held transducer for enhancing cellular uptake of toxin delivered from a separate nasal aerosolizer.

DRWD FIG. 15--depicts sizing of a delivery balloon to control distribution of toxin released into the nasal cavity.

DRWD FIG. 17--depicts the use of multiple small balloons for selective toxin delivery into the nasal cavity.

DRWD FIGS. 22 and 23--depict nose plugs for occluding and optionally delivery poration energy to the nasal cavity.

DRWD . . . 28 and 30--depict use of a simple catheter having a shaped distal end for aerosolizing a toxin into a target nasal sinus though an ostium open to the sinus.

DRWD FIG. 29--depicts toxin delivery using a nasal spray and energy delivery using a face mask.

DRWD FIG. 33--depicts an applicator device for delivering toxin to the nasal cavity having a handle and two applicator tips for placement within the nasal passageway.

DRWD FIG. 35--depicts the applicator device illustrated in FIG. 33 when placed within the nasal passageway.

DETD The present invention is directed to methods and systems for delivering toxins to target cells within a patient's nasal cavity. The toxins may be intact toxins, such as botulinum toxin, ricin, exotoxin A, diphtheria toxin, cholera toxin, tetanus toxin,. . .

DETD Botulinum toxin blocks acetylcholine release from cells, such as the epithelial or goblet cells in the nasal membranes responsible for mucus hypersecretion, and can thus be effective even without energy-mediated delivery in accordance with the principles of. . . energy to permeablize or porate the cell membranes of the epithelial or goblet cells or other mucus-secreting cells of the nasal lining, in accordance with the present invention, allows botulinum and other toxins to be preferentially delivered to the targeted epithelial. . . the toxin light chains may be locally and specifically introduced into the target cells located within defined regions of the nasal membrane. Thus, even if the toxin fragments are accidentally dispersed beyond the desired target regions, the fragments will not generally. . .

DETD . . . a simplified single cell model. A targeted cell, e.g., an epithelial or goblet cell of the type which line the nasal cavity membrane, is shown in FIG. 2A. Fragmented neurotoxin such as BoNT-LC (LC)is introduced into the vicinity of the targeted. . .

DETD . . . devices of the present invention may be adapted to introduce a BoNT-LC solution to a target region, such as the nasal passages and then effect selective membrane transport of the BoNT-LC into the cell using sonoporation.

DETD . . . embodiment of the present invention utilizing an ultrasonic element that may be particularly useful in delivery of the BoNT-LC to nasal tissue that provides a broad but targeted transport of the LC across the epithelial and goblet cell walls. In this. . .

DETD . . . of producing a porative effect at the cellular level, including electrodes, ultrasonic elements and the like, for treatment in the nasal passages.

DETD . . . the energy, or both, non-invasively. For example, as illustrated in FIG. 9, the patient may draw the toxin into the nasal cavity from a hand-held dispersion device DD. After a sufficient amount of the toxin has been infused into the nasal cavity, a separate hand-held transducer TD connected to an appropriate power supply PS will be energized and applied to the nasal cavities by passing the transducer over the appropriate regions of the forehead and nose. Optionally, the transducer can have a. . .

DETD While the toxins and porating energy of the present invention may be delivered to the nasal cavity in a variety of ways, the following provides a number of specific examples of catheters and other structures for delivering toxins to preselected portions of the nasal cavity. For example, as shown in FIG. 10, a balloon catheter 100 may be provided

with a porous balloon 102. . . transducers 104 within the balloon, optionally mounted on the catheter body, ultrasonic poration energy can be delivered to the adjacent nasal membranes which are receiving the toxin solution. As illustrated in FIG. 10, the toxin is being delivered to a lower. . .

DETD . . . positioned to target an area of high epithelial or goblet cell (G) concentration, for example in the back of the nasal passages in the area of the nasopharynx. By targeting this area of the nasal membrane, a high percentage of mucus-secreting epithelial or goblet cells can be treated with a device which is relatively small. . .

DETD . . . effect of such externally applied ultrasonic energy can be enhanced by introducing microbubbles (free air) into the isolated sinuses and/or nasal passages which have been filled with toxin solution. For example, encapsulated microbubbles, which are generally useful as echocardiographic contrast agents,. . .

DETD Referring now to FIGS. 20 and 21, a catheter 40 is placed at the posterior outlet of the nasal passages in the region of the nasopharynx. The catheters configured to occlude outflow from these sinuses and passages into the. . . shown in FIG. 20, the catheter is delivered in through the mouth and guided into the posterior portion of the nasal cavities, typically using a guidewire. Once the nasopharynx of the posterior portion of the nasal cavity is occluded, toxin solution (BoNT) can be infused through the occluding catheter lumen, or through a separate infusion catheter or tube, in order to treat substantially the entire sinus and/or nasal cavity membrane at once (FIG. 21). When the toxin solution is introduced through the catheter at the posterior region of the cavities, it will frequently be desirable to occlude the nostrils, for example using a nasal clip 105.

DETD . . . air bleed valves 106 which are used to occlude the nostrils in order to evacuate or bleed air from the nasal passages while filling the passages with the toxin solution. The nose plugs 105 could optionally include ultrasonic transducers in order to deliver ultrasonic or other acoustic energy into the solutions entrapped within the nasal cavities using the nostril plugs. Alternatively, of course, the ultrasound or other acoustic energy could be delivered from an external. . .

DETD . . . can deliver toxin incorporated into vesicles which may be configured as "resonance" bodies, which reduce the need to fill the nasal cavities with a liquid or other form of toxin. For example, lipid microspheres which incorporate the toxin may be sprayed or aerosolized onto target surfaces of the nasal epithelium. After the lipid or other resonance bodies are attached to the targeted epithelium membrane surface(s), the ultrasound energy can. . .

DETD Referring to FIG. 29, the toxin may be delivered as a conventional nasal spray (BoNT), as mentioned hereinbefore, and the poration energy can be delivered through a face mask. The poration energy might. . .

DETD FIGS. 33 and 34 illustrate a device for applying BoNT to the treatment area within the nasal cavity. This device comprises a handle 115 having a proximal section, a body and a distal section. The body of. . . 118 connected to each of the first end and second, wherein the applicator tips are configured for insertion into the nasal passageway, as shown in FIG. 35.

DETD Once within the nasal cavity, the applicator tips 117 and 118 can apply BoNT to the nasal passageway and, specifically, the turbinates along the nasal wall. The BoNT can be applied or affixed to the applicator tips as a liquid solution, gel, foam, cream, lotion and/or a lyophilized compound prior to being positioned within the nasal passageway. Alternatively, as illustrated in FIG. 36, the handle can be configured with an infusion channel 119 for delivering the BoNT to the applicator tips following placement in the nasal passageway. In this configuration, the handle may further comprise an access port at its proximal section that is in fluid. . .

DETD . . . may be configured to provide an outward lateral force such that the applicator tips 118 are firmly contacted against the nasal turbinates when placed in the nasal passageway. With reference to FIG. 37A, the operator would apply inward pressure in the direction of the arrows to the. . . to inserting the applicator tips into the nose. Once the applicator tips of the device are properly inserted into the nasal passageway, this pressure would be released such that the outward bias in the handle transitions the handle from a compressed configuration to an expanded configuration, as shown in FIG. 37B, wherein the applicator tips are pressed against the nasal turbinates.

The applicator tips can be held against the turbinates by the outward bias for sufficient time to allow a therapeutically effective amount of BoNT to be absorbed by the nasal cavity wall.

DETD To facilitate the insertion of the tip applicator through the nostril and into the nasal passageway, it may be desirable for the applicator tip to initially have a low volume configuration. Once properly positioned in the nasal passageway, it would be desirable for the applicator to have an expanded volume configuration for maximizing contact with the nasal turbinates. In one exemplary embodiment, the tip applicator may comprise a sponge such that the sponge 121 is in a. . . 39A) and an expanded configuration when wet (FIG. 39B), wherein

the sponge 121 is configured to fit securely within the nasal passageway.

DETD . . . could be preloaded with lyophilized BoNT and wetted with a liquid (e.g., saline) following placement of the applicator in the nasal passageway. The liquid can be introduced into the nasal passageway using a spray or a catheter, or the BoNT may simply be rewetted by the nasal secretions themselves. Alternatively, as described with respect to FIG. 36, the liquid can be infused into the applicator tip through. . .

DETD To facilitate the expansion of the applicator tip, thereby maximizing the surface contact between the nasal cavity wall and applicator tip, it may be desirable to incorporate a spring element 122 within the applicator tip 118.. . .

DETD . . . it will be necessary to hold the spring 122 in its compressed state until it is properly positioned within the nasal cavity, at which time the spring can be released to allow the applicator to expand into the nasal cavity. In the wet/dry sponge 121 embodiment described with respect to FIGS. 39A and 39B, a sponge and spring can. . .

DETD . . . retractable sheath or collar 126 for holding the spring in its compressed configuration. Once the applicator is positioned within the nasal cavity, the actuator can be retracted to release the spring, thereby expanding the applicator.

DETD . . . for the spring-assisted expansion of the applicator tip to be directionally biased to maximize contact with the wall of the nasal cavity and optimize contact pressure with the nasal turbinates. For example, the spring element can be dimensioned and configured such that the applicator expands laterally towards the turbinates of the nasal cavity. Alternatively or additionally, portions of the applicator tip may comprise an impermeable lining such that delivery of BoNT to certain portions of the nasal cavity is optimized and undesirable migration of BoNT solution is minimized.

DETD . . . also be desirable for the apparatus to be configured such that only the amount of toxin necessary to treat the nasal cavity is loaded on the applicator tip and applied to the nasal wall. It this embodiment, it would be desirable for the applicator to carry a predetermined quantity of toxin, wherein the. . . to be configured such that most, if not all, of the toxin carried on the applicator is delivered to the nasal wall, wherein little to no toxin runs, escapes or migrates to non-target portions of body tissue.

DETD . . . be configured to provide a controlled delivery of toxin to facilitate absorption of the toxin into the walls of the nasal cavity. An applicator providing a controlled delivery of toxin can be configured such that the rate of toxin delivery is proportionate with the rate of BoNT absorption across the nasal membrane. Such a controlled delivery will ensure that the toxin is absorbed into the nasal tissue and not dispersed elsewhere in the body.

DETD An apparatus for treating a nasal cavity of a patient via a controlled and uniform delivery of BoNT may comprise an applicator having an inner member,. . . open-faced chambers. The outer member may also comprise an array of microneedles to facilitate the passage of BoNT across the nasal membrane. The inner member is configured for occupying space when the applicator is positioned within the nasal cavity such that the outer member is placed in contact with the wall of the nasal cavity. The inner member may be any compliant material such as a sponge, balloon or foam rubber. The impermeable lining. . . outer member to inner member and, accordingly, facilitates the transfer of BoNT from the applicator to the tissue of the nasal wall. As with applicator embodiments that have been previously discussed herein, the outer member can be pre soaked or filled with BoNT solution, infused with BoNT following placement in the nasal passageway, or pre-loaded with

freeze-dried BoNT that can be reconstituted with infused saline.

DETD . . . embodiment, the inner member comprises (1) a low volume configuration to facilitate the applicator's insertion into and placement within the nasal passageway and (2) an expanded volume configuration for pressing the outer member against the walls of the nasal cavity. The expansion of the inner member relative to the outer member can also facilitate the controlled release of BoNT. . .

DETD In any of the embodiments discussed herein, it may be desirable to adapt the applicator to the geometry of the nasal cavity. For example, in embodiments comprising an outer member and inner member, the outer member can be configured to match the shape of the nasal cavity or portions of the nasal passageway following the expansion of the inner member. By achieving better contact, the delivery of toxin to and across the nasal membrane can be optimized.

DETD . . . carrying BoNT. In this embodiment, the applicator tip may comprise a BoNT-loaded bioresorbable polymer that can be absorbed into the nasal cavity tissue. The tip can be configured such that the BoNT can be delivered to the nasal wall both immediately and as the coating is absorbed into the tissue.

DETD . . . this application, the device described with respect to FIGS. 33 and 34 can be used to deliver BoNT-LC to the nasal cavity instead of the BoNT intact molecule. In cases where this device is used to deliver BoNT-LC to the nasal cavity, any of the previously-described, energy-based delivery systems can be used to cause poration in the nasal tissue to facilitate delivery of the BoNT-LC to the tissue. Additionally or alternatively, this device can be equipped with an. . .

DETD In addition to BTX-LC, it may be desirable to deliver additional agents to the nasal passages and sinuses prior to, coincident with, or after deliver of the LC. Adjunctive therapies may include agents designed to. . .

DETD Decongestants such as epinephrine also cause constriction of the vasculature in the nasal passages, which in addition to temporarily reducing swelling of the target tissues, may decrease the risks of LC entering the. . .

CLM What is claimed is:
1. A system for delivering toxins to target cells in a nasal membrane, said system comprising: a catheter adapted to introduce a toxin to a region proximate the target cells; an energy. . .

CLM What is claimed is:
. . . A system as in claim 1, wherein the energy applicator comprises a wave guide configured to be positioned within a nasal passageway.

CLM What is claimed is:
30. A system as in claim 17, wherein the balloon is configured to be positioned within a nasal passageway.

AB Methods and systems for delivering toxin and toxin fragments to a patient's nasal cavity provide for both release of the toxin and delivery of energy which selectively porates target cells to enhance uptake of the toxin. The use of energy-mediated delivery is particularly advantageous with light chain fragment toxins which lack cell binding capacity.

L11 ANSWER 34 OF 39 USPATFULL on STN
ACCESSION NUMBER: 2009:115740 USPATFULL
TITLE: Drug cores for sustained release of therapeutic agents
INVENTOR(S): Utkhede, Deepank, Surrey, CANADA
Shimizu, Robert W., Laguna Niguel, CA, UNITED STATES
Jain, Rachna, Milpitas, CA, UNITED STATES
Boyd, Stephen, Murrieta, CA, UNITED STATES
Gifford, Hanson S., Woodside, CA, UNITED STATES
de Juan, JR., Eugene, San Francisco, CA, UNITED STATES
Reich, Cary J., Los Gatos, CA, UNITED STATES
PATENT ASSIGNEE(S): QLT Plug Delivery, Inc. - QPDI, Menlo Park, CA, UNITED STATES (U.S. corporation)

	NUMBER	KIND	DATE	
PATENT INFORMATION:	US 20090104243	A1	20090423	
APPLICATION INFO.:	US 2008-231986	A1	20080905	(12)

	NUMBER	DATE
PRIORITY INFORMATION:	US 2007-60970699	20070907 (60)
	US 2007-60970709	20070907 (60)
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DOCUMENT TYPE: Utility
FILE SEGMENT: APPLICATION
LEGAL REPRESENTATIVE: SCHWEGMAN, LUNDBERG & WOESSNER, P.A., P.O. BOX 2938, MINNEAPOLIS, MN, 55402, US
NUMBER OF CLAIMS: 32
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 50 Drawing Page(s)
LINE COUNT: 7264
CAS INDEXING IS AVAILABLE FOR THIS PATENT. Full-text
IN Gifford, Hanson S., Woodside, CA, UNITED STATES
DETD . . . therapeutic target, e.g., the eye, while blocking release to non-target tissue, such as the interior of the canaliculus, or the nasal sinus.
DETD . . . various embodiments, the drug cores can be used for sustained release of therapeutic agents into the ears and/or Eustachian tubes, nasal and/or sinus cavities, urethra, skin, gastrointestinal tract (including colon, bowel duct, and the like), and in or near joints such. . .
DETD . . . extend through the drug core 112 to permit tear flow through the lumen for the delivery of therapeutic agent for nasal and systemic applications of the therapeutic agent. In addition or in combination with channel 112C, retention structure 132 and core. . .
DETD . . . other therapeutic agent to an eye (e.g., to treat an infection, inflammation, glaucoma or other ocular disease or disorder), a nasal passage (e.g., to treat a sinus or allergy disorder) or an inner ear system (e.g., to treat dizziness or a. . .
DETD . . . insert can be disposed in the second cavity to provide a sustained drug or other therapeutic agent release to a nasal passage or inner ear system, for example. An implant body septum can be positioned between the first cavity and the. . .
DETD . . . having structures derived from the punctual implants described above may allow elution of one or more therapeutic agent into a nasal cavity. Modifications or differences between such nasal implants and the punctual implants described above may include providing a passage for controlled release of medicated tear fluid through the canilicular lumen. Alternative nasal tissue structures may be quite different in overall form, optionally including any of a variety of known nasal cavity drug release shapes, but optionally taking advantage of one or more aspects of the drug cores or other drug. . .
AB A solid drug core insert can be manufactured by injecting a liquid mixture comprising a therapeutic agent and a matrix precursor into a sheath body. The injection can be conducted at subambient temperatures. The mixture is cured to form a solid drug-matrix core. The therapeutic agent can be a liquid at about room temperature that forms a dispersion of droplets in the matrix material. A surface of the solid drug core is exposed, for example by cutting the tube, and the exposed surface of the solid drug core releases therapeutic quantities of the therapeutic agent when implanted into the patient. In some embodiments, the insert body inhibits release of the therapeutic agent, for example with a material substantially impermeable to the therapeutic agent, such that the therapeutic quantities are released through the exposed surface, thereby avoiding release of the therapeutic agent to non-target tissues.

L11 ANSWER 35 OF 39 CA COPYRIGHT 2020 ACS on STN DUPLICATE 4
ACCESSION NUMBER: 148:175883 CA
TITLE: Methods and systems for toxin delivery to the nasal cavity
INVENTOR(S): Deem, Mark E.; Gifford, Hanson
PATENT ASSIGNEE(S): The Foundry Inc., USA
SOURCE: U.S. Pat. Appl. Publ., 38pp., Cont.-in-part of U. S. Ser. No. 459,090.
CODEN: USXXCO
DOCUMENT TYPE: Patent
LANGUAGE: English

FAMILY ACC. NUM. COUNT: 4
PATENT INFORMATION:

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PRIORITY APPLN. INFO.:	US 2005-60702077	P	20050722
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	JP 2008-522980	A3	20060721
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	US 2012-13660629	A1	20121025
	US 2013-14139710	A1	20131223
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	JP 2015-120827	A3	20150616
	US 2015-14841514	A1	20150831
	US 2016-15358187	A1	20161122
	US 2018-16036381	A1	20180716

ASSIGNMENT HISTORY FOR US PATENT AVAILABLE IN LSUS DISPLAY FORMAT Full-text
TI Methods and systems for toxin delivery to the nasal cavity
IN Deem, Mark E.; Gifford, Hanson
AB Methods and systems for delivering toxin and toxin fragments to a patient's nasal cavity provide for both release of the toxin and delivery of energy which selectively porates target cells to enhance uptake. . .
ST system toxin delivery nasal cavity
IT Catheters
Epithelium
Headache
Human

Microwave
Migraine
Nasopharynx
Nose
Sound and Ultrasound
(methods and systems for toxin delivery to nasal cavity)

IT Toxins
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(methods and systems for toxin delivery to nasal cavity)

IT 93384-43-1, Botulin A 93384-44-2, Botulin B 93384-45-3, Botulin C 93384-46-4, Botulin D 93384-47-5, Botulin E 107231-12-9, Botulinum toxin 107231-15-2, Botulin F 107231-16-3, Botulin G
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(methods and systems for toxin delivery to nasal cavity)

AB Methods and systems for delivering toxin and toxin fragments to a patient's nasal cavity provide for both release of the toxin and delivery of energy which selectively porates target cells to enhance uptake of the toxin. The use of energy-mediated delivery is particularly advantageous with light chain fragment toxins which lack cell binding capacity. The use of balloon catheters for delivering toxins to the nasopharynx is depicted (no data).

OS.CITING REF COUNT: 16 THERE ARE 16 CAPLUS RECORDS THAT CITE THIS RECORD (26 CITINGS)
REFERENCE COUNT: 75 THERE ARE 75 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L11 ANSWER 36 OF 39 CA COPYRIGHT 2020 ACS on STN DUPLICATE 5
ACCESSION NUMBER: 147:548133 CA
TITLE: Apparatus, methods and systems for toxin delivery to the nasal cavity
INVENTOR(S): Deem, Mark E.; Gifford, Hanson; Kim, Steven; Salamini, Alexey
PATENT ASSIGNEE(S): The Foundry Inc., USA
SOURCE: PCT Int. Appl., 68 pp., Chemical Indexing Equivalent to 166:33837 (US)
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 4
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2007137235	A2	20071129	WO 2007-US69391	20070521
WO 2007137235	A3	20080522		
US 20080021369	A1	20080124	US 2007-750963	20070518
US 7655243	B2	20100202		
US 9511210	B2	20161206	US 2007-750967	20070518
US 20070267011	A1	20071122		
EP 2021022	A2	20090211	EP 2007-784000	20070521
EP 2021022	B1	20170412		
JP 2009538641	T	20091112	JP 2009-511262	20070521
JP 5183627	B2	20130417		
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US 20150150625	A1	20150604	US 2015-14601529	20150121
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JP 6290139	B2	20180307		
JP 2017038963	A	20170223	JP 2016-227703	20161124

PRIORITY APPLN. INFO.:

US 2006-60747771	P	20060519
US 2007-750963	A	20070518
US 2007-750967	A	20070518
US 2005-60702077	P	20050722
JP 2008-522980	A3	20060721
US 2006-459090	A2	20060721
WO 2007-US69391	W	20070521
US 2009-559278	A1	20090914
US 2011-13253595	A1	20111005
US 2012-13660629	A1	20121025

ASSIGNMENT HISTORY FOR US PATENT AVAILABLE IN LSUS DISPLAY FORMAT
OTHER SOURCE(S): CASFORMULTNS 2007:1363693 Full-text
TI Apparatus, methods and systems for toxin delivery to the nasal cavity
IN Deem, Mark E.; Gifford, Hanson; Kim, Steven; Salamini, Alexey
AB App., methods and systems for delivering toxin and toxin fragments to a patient's nasal cavity provide for both release of the toxin and delivery of energy which selectively porates target cells to enhance uptake. . .
ST toxin delivery nasal cavity inflammation
IT Medical goods
(balloons; toxin delivery to the nasal cavity)
IT Coating materials
(bioresorbable; toxin delivery to the nasal cavity)
IT Medical goods
(springs; toxin delivery to the nasal cavity)
IT Anti-inflammatory agents
Inflammation
Medical sponges
Microwave
Nasal drug delivery systems
Nasal mucosa
Nose
Pulsed electric current
Sound and Ultrasound
Springs (mechanical)
X-ray
(toxin delivery to the nasal cavity)
IT Toxins
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(toxin delivery to the nasal cavity)
IT 93384-43-1, Botulin A 93384-44-2, Botulin B 93384-45-3, Botulin C 93384-46-4, Botulin D 93384-47-5, Botulin E 107231-15-2, Botulin F 107231-16-3, Botulin G
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(toxin delivery to the nasal cavity)
AB App., methods and systems for delivering toxin and toxin fragments to a patient's nasal cavity provide for both release of the toxin and delivery of energy which selectively porates target cells to enhance uptake of the toxin. The use of energy-mediated delivery is particularly advantageous with light chain fragment toxins which lack cell binding capacity.

L11 ANSWER 37 OF 39 USPATFULL on STN
ACCESSION NUMBER: 2007:308397 USPATFULL
TITLE: Drug Delivery Methods, Structures, and Compositions for Nasolacrimal System
INVENTOR(S): de Juan, Eugene JR., San Francisco, CA, UNITED STATES
Reich, Cary, Los Gatos, CA, UNITED STATES
Boyd, Stephen, Murrieta, CA, UNITED STATES
Gifford, Hanson G. III, Woodside, CA, UNITED STATES
Deem, Mark, Mountain View, CA, UNITED STATES
PATENT ASSIGNEE(S): FORSIGHT LABS, LLC, Menlo Park, CA, UNITED STATES, 94025 (U.S. corporation)

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 20070269487	A1	20071122
	US 8795711	B2	20140805
APPLICATION INFO.:	US 2007-695537	A1	20070402 (11)

	NUMBER	DATE
PRIORITY INFORMATION:	US 2006-60787775	20060331 (60)
	US 2006-60871864	20061226 (60)

DOCUMENT TYPE: Utility
FILE SEGMENT: APPLICATION
LEGAL REPRESENTATIVE: TOWNSEND AND TOWNSEND AND CREW, LLP, TWO EMBARCADERO CENTER, EIGHTH FLOOR, SAN FRANCISCO, CA, 94111-3834, US
NUMBER OF CLAIMS: 53
EXEMPLARY CLAIM: 1

NUMBER OF DRAWINGS: 25 Drawing Page(s)
LINE COUNT: 1911
CAS INDEXING IS AVAILABLE FOR THIS PATENT. Full-text
IN Gifford, Hanson G. III, Woodside, CA, UNITED STATES
DETD . . . extend through the drug core 112 to permit tear flow through the lumen for the delivery of therapeutic agent for nasal and systemic applications of the therapeutic agent. In addition or in combination with channel 112C, retention structure 132 and core. . .
AB An implant for insertion into a punctum of a patient comprises a body. The body has a distal end, a proximal end, and an axis therebetween. The distal end of the body is insertable distally through the punctum into the canalicular lumen. The body comprises a therapeutic agent included within an agent matrix drug core. Exposure of the agent matrix to the tear fluid effects an effective therapeutic agent release into the tear fluid over a sustained period. The body has a sheath disposed over the agent matrix to inhibit release of the agent away from the proximal end. The body also has an outer surface configured to engage luminal wall tissues so as to inhibit expulsion when disposed therein. In specific embodiments, the agent matrix comprises a non-bioabsorbable polymer, for example silicone in a non-homogenous mixture with the agent.

L11 ANSWER 38 OF 39 USPATFULL on STN
ACCESSION NUMBER: 2007:305933 USPATFULL
TITLE: APPARATUS FOR TOXIN DELIVERY TO THE NASAL CAVITY
INVENTOR(S): Deem, Mark E., Mountain View, CA, UNITED STATES
Gifford, Hanson, Woodside, CA, UNITED STATES
Kim, Steven, Los Altos, CA, UNITED STATES
Salamini, Alexey, San Francisco, CA, UNITED STATES
PATENT ASSIGNEE(S): The Foundry Inc., Menlo Park, CA, UNITED STATES (U.S. corporation)

	NUMBER	KIND	DATE	
PATENT INFORMATION:	US 20070267011	A1	20071122	
	US 9511210	B2	20161206	
APPLICATION INFO.:	US 2007-750967	A1	20070518	(11)

	NUMBER	DATE
PRIORITY INFORMATION:	US 2006-60747771	20060519 (60)

DOCUMENT TYPE: Utility
FILE SEGMENT: APPLICATION
LEGAL REPRESENTATIVE: TOWNSEND AND TOWNSEND AND CREW, LLP, TWO EMBARCADERO CENTER, EIGHTH FLOOR, SAN FRANCISCO, CA, 94111-3834, US
NUMBER OF CLAIMS: 43
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 24 Drawing Page(s)
LINE COUNT: 1513
CAS INDEXING IS AVAILABLE FOR THIS PATENT. Full-text
TI APPARATUS FOR TOXIN DELIVERY TO THE NASAL CAVITY
IN Gifford, Hanson, Woodside, CA, UNITED STATES
AB Apparatus for delivering toxin and toxin fragments to a patient's nasal cavity provide for both release of the toxin and delivery of energy which selectively porates target cells to enhance uptake. . .
DRWD FIG. 9--depicts use on an external hand held transducer for enhancing cellular uptake of toxin delivered from a separate nasal aerosolizer.
DRWD FIG. 15--depicts sizing of a delivery balloon to control distribution of toxin released into the nasal cavity.
DRWD FIG. 17--depicts the use of multiple small balloons for selective toxin delivery into the nasal cavity.
DRWD FIGS. 22 and 23--depict nose plugs for occluding and optionally delivery poration energy to the nasal cavity.
DRWD . . . 28 and 30--depict use of a simple catheter having a shaped distal end for aerosolizing a toxin into a target nasal sinus though an ostium open to the sinus.
DRWD FIG. 29--depicts toxin delivery using a nasal spray and energy delivery using a face mask.
DRWD FIG. 33--depicts an applicator device for delivering toxin to the nasal cavity having a handle and two applicator tips for placement within the nasal passageway.
DRWD FIG. 35--depicts the applicator device illustrated in FIG. 33 when

placed within the nasal passageway.

DETD . . . relates to methods and systems for delivering toxins, such as botulinum toxin light chain fragments, to target cells in a nasal cavity.

DETD . . . the symptoms of rhinorrhea, is a condition resulting from inflammation and swelling of the patient's mucus membranes which line the nasal cavity. Rhinitis and/or rhinorrea can arise from a number of conditions, most often results from allergies to pollen, dust, seasonal. . . also be caused by anatomic pathologies such as blockages (as in the case of sinusitis). Symptoms may include sneezing, itching, nasal congestion, and a runny nose.

DETD . . . for rhinitis which relies on the use of botulinum toxin ("BoNT") for blocking mucus production by mucus-producing cells in the nasal membrane has been proposed. Botulinum and other neurotoxins are capable of disabling adrenergic cells, including epithelial or goblet cells which are responsible for the majority of mucus production in the nasal cavity membrane. Dr. Ira Sanders has demonstrated that introduction of intact botulinum toxin molecules into the nasal passages of canines can reduce mucus secretion by a significant amount.

DETD . . . toxin is a neurotoxin which could have significant negative effects on a patient if accidentally released outside of the targeted nasal passages. Inadvertent distribution of the toxin to muscles of the oropharynx, mouth, tongue, or elsewhere could result in serious complications to the patient. Additionally, the use of botulinum-soaked gauze pads for delivering the toxin to the nasal cavities, as demonstrated by Dr. Sanders, will have limited ability to uniformly and selectively deliver the botulinum to the regions. . .

DETD . . . be desirable to provide improved methods and systems for delivering toxins, such as botulinum and active botulinum fragments, to the nasal membrane of a patient, particularly a patient suffering from rhinitis or other conditions associated with nasal inflammation and conditions, such as sinus headaches and migraine headaches. The methods and systems should be capable of providing for selective and repeatable delivery of the toxins to defined target areas within the nasal cavities, including particular paranasal sinuses, the nasopharynx, and in some cases substantially the entire nasal cavity. The systems and methods should provide for the safe and effective delivery of the toxins, and in particular should reduce or eliminate the risk of toxin being delivered to non-targeted tissues outside of the nasal cavity. At least some of these objectives will be met by the inventions described herein below.

DETD Briefly and in general terms, the present invention provides methods and systems for toxin delivery to the nasal cavity. The invention provides for the delivery of toxin to and across the nasal membrane tissue to treat various conditions and symptoms associated with nasal inflammation, including, rhinorrhea, rhinitis, sinusitis and hay fever.

DETD Rhinorrhea is the term describing the effluence of mucus from the lining of the nasal passages, nasopharynx, or paranasal sinuses. Rhinorrhea can be a symptom of a number of diseases such as the common cold,. . . paranasal sinuses. Sinusitis may have a number of different causes, and can be the result of chronic inflammation of the nasal passages, for example as a result of chronic rhinitis.

DETD Allergic rhinitis is an immunologic response modulated by IgE and characterized predominantly by sneezing, rhinorrhea, nasal congestion, and pruritus of the nose. It may be seasonal (a condition commonly referred to as hay fever) or perennial.. . .

DETD According to embodiments of the present invention, a toxin, such as botulinum toxin, is administered to the tissue of the nasal cavity using an apparatus comprising a handle and at least one applicator tip configured for insertion into a patient's nostril and placement within the patient's nasal passageway to facilitate deliver of the toxin via the applicator.

DETD . . . the present invention, the apparatus can be configured to facilitate contact between the applicator tips and the turbinates of the nasal wall and optimize toxin deliver to the nasal membrane. This can be achieved by incorporating a spring element into the handle of the apparatus, such as a v-shaped. . . spring. The outward bias from this spring element can result in an expanded treatment configuration for delivering toxin to the nasal tissue.

DETD . . . the applicator tips can be configured with a low volume delivery configuration to facilitate placement of the apparatus within the nasal passageway and an expanded volume treatment configuration to

facilitate contact with the nasal wall. A spring element can be used to expand the applicator tip. Additionally, an actuator and engagement member can be. . .

DETD In another aspect of the present invention, the toxin is loaded onto the applicator tips prior to insertion into the nasal passageway by, for example, dipping the applicator tips in a solution of toxin, coating the applicator tips with a lyophilized. . .

DETD . . . toxin source so that toxin can be infused into the applicator tips either prior to or following placement in the nasal passageway. Alternatively, a liquid such as saline can be infused to the applicator tips to reconstituted lyophilized toxin that was. . .

DETD . . . another aspect of the present invention, a toxin fragment, such as light chain botulinum toxin, can be administered to the nasal tissue and energy can be delivered to the tissue to cause poration in the cells of the nasal membrane and enhance delivery of the toxin to the tissue.

DETD . . . expanded volume configuration and an outer member for carrying the predetermined quantity of toxin and delivering the toxin to the nasal wall. The expansion of the inner member can also facilitate the controlled delivery of toxin to the nasal wall. The applicator may further comprise an impermeable lining separating the inner member and outer member and preventing toxin from. . .

DETD Rhinorrhea is the term describing the effluence of mucus from the lining of the nasal passages, nasopharynx, or paranasal sinuses. Rhinorrhea can be a symptom of a number of diseases such as the common cold,. . .

paranasal sinuses. Sinusitis may have a number of different causes, and can be the result of chronic inflammation of the nasal passages, for example as a result of chronic rhinitis.

DETD Allergic rhinitis is an immunologic response modulated by IgE and characterized predominantly by sneezing, rhinorrhea, nasal congestion, and pruritus of the nose. It may be seasonal (a condition commonly referred to as hay fever) or perennial.. . .

DETD . . . ricin, exotoxin A, diphtheria toxin, cholera toxin, tetanus toxin, other neurotoxins, and active fragments thereof are delivered to a patient's nasal membrane while applying energy to target cells within the membrane under conditions which cause a reversible (or in some instances. . . delivery of the toxin into the cells. The region where the toxin is introduced may comprise any portion of the nasal cavity, such as a single paranasal sinus or portion thereof, a main nasal passage, two or more paranasal sinuses, or in some cases may comprise substantially the entire nasal cavity of the patient. A particular target region for the toxin may comprise the nasopharynx which is at the back of the nasal passage. The nasopharynx comprises a cluster of epithelial or goblet cells which are responsible for mucus secretion and which are. . .

DETD . . . no energy applied to untargeted regions. It will be appreciated that the energy may be applied to regions of the nasal membrane which are the same or different from the regions to which the toxin has been introduced. By controlling the. . . cells of interest while minimizing the amount of toxin which enters non-targeted cells. That is, only those cells in the nasal membrane which are exposed to both the toxin and the applied energy will preferentially be permeablized or porated to receive. . .

DETD . . . to be delivered may comprise any neurotoxin capable of disabling mucus secretion in epithelial or goblet cells and other mucus-producing nasal cells. Preferably, the toxin comprises botulinum toxin, although other toxins such as ricin, exotoxin A, diphtheria toxin, cholera toxin, tetanus. . . use. In preferred aspects of the present invention, only an active fragment of the toxin will be delivered to the nasal cavity. Botulinum toxin and the other toxins listed above commonly comprise both a heavy chain and a light chain. The. . .

DETD . . . external ultrasonic transducers and/or ultrasound wave guides capable of delivering focused or unfocused ultrasound into the target tissues of the nasal cavity.

DETD . . . be introduced to the target region through a catheter. For example, the catheter may carry a balloon which engages the nasal membrane in order to effect delivery of the toxin to the target cells. In a particular example, the balloon is. . . over at least a portion of its area so that the toxin may be released to specific areas of the nasal membrane, typically being incorporated into a suitable liquid,

gel, or other fluid or fluidizable carrier. In other embodiments, the toxin. . .

DETD . . . that the transducer may be located within or beneath the porous balloon which is used to deliver toxin to the nasal membrane. When electrical energy is used for poration, the electrodes may be on the catheter within or surrounding the region which delivers the energy to the nasal membrane. In other instances, the energy may be applied from a separate catheter or other device adapted for intranasal introduction.. . .

DETD . . . invention further provides systems for delivering toxins to epithelial or goblet and other target cells as defined above in a nasal membrane. The systems may typically comprise a catheter adapted to introduce a toxin to a region adjacent to the target. . .

DETD The present invention is directed to methods and systems for delivering toxins to target cells within a patient's nasal cavity. The toxins may be intact toxins, such as botulinum toxin, ricin, exotoxin A, diphtheria toxin, cholera toxin, tetanus toxin,. . .

DETD Botulinum toxin blocks acetylcholine release from cells, such as the epithelial or goblet cells in the nasal membranes responsible for mucus hypersecretion, and can thus be effective even without energy-mediated delivery in accordance with the principles of. . . energy to permeablize or porate the cell membranes of the epithelial or goblet cells or other mucus-secreting cells of the nasal lining, in accordance with the present invention, allows botulinum and other toxins to be preferentially delivered to the targeted epithelial. . . the toxin light chains may be locally and specifically introduced into the target cells located within defined regions of the nasal membrane. Thus, even if the toxin fragments are accidentally dispersed beyond the desired target regions, the fragments will not generally. . .

DETD . . . a simplified single cell model. A targeted cell, e.g., an epithelial or goblet cell of the type which line the nasal cavity membrane, is shown in FIG. 2A. Fragmented neurotoxin such as BoNT-LC (LC) is introduced into the vicinity of the. . .

DETD . . . devices of the present invention may be adapted to introduce a BoNT-LC solution to a target region, such as the nasal passages and then effect selective membrane transport of the BoNT-LC into the cell using sonoporation.

DETD . . . embodiment of the present invention utilizing an ultrasonic element that may be particularly useful in delivery of the BoNT-LC to nasal tissue that provides a broad but targeted transport of the LC across the epithelial and goblet cell walls. In this. . .

DETD . . . of producing a porative effect at the cellular level, including electrodes, ultrasonic elements and the like, for treatment in the nasal passages.

DETD . . . the energy, or both, non-invasively. For example, as illustrated in FIG. 9, the patient may draw the toxin into the nasal cavity from a hand-held dispersion device DD. After a sufficient amount of the toxin has been infused into the nasal cavity, a separate hand-held transducer TD connected to an appropriate power supply PS will be energized and applied to the nasal cavities by passing the transducer over the appropriate regions of the forehead and nose. Optionally, the transducer can have a. . .

DETD While the toxins and porating energy of the present invention may be delivered to the nasal cavity in a variety of ways, the following provides a number of specific examples of catheters and other structures for delivering toxins to preselected portions of the nasal cavity. For example, as shown in FIG. 10, a balloon catheter 100 may be provided with a porous balloon 102. . . transducers 104 within the balloon, optionally mounted on the catheter body, ultrasonic poration energy can be delivered to the adjacent nasal membranes which are receiving the toxin solution. As illustrated in FIG. 10, the toxin is being delivered to a lower. . .

DETD . . . positioned to target an area of high epithelial or goblet cell (G) concentration, for example in the back of the nasal passages in the area of the nasopharynx. By targeting this area of the nasal membrane, a high percentage of mucus-secreting epithelial or goblet cells can be treated with a device which is relatively small. . .

DETD . . . effect of such externally applied ultrasonic energy can be enhanced by introducing microbubbles (free air) into the isolated sinuses and/or nasal passages which have been filled with toxin solution. For example, encapsulated microbubbles, which are generally useful as echocardiographic contrast agents,. . .

DETD Referring now to FIGS. 20 and 21, a catheter 40 is placed at the posterior outlet of the nasal passages in the region of the nasopharynx. The catheters configured to occlude outflow from these sinuses and passages into the. . . shown in FIG. 20, the catheter is delivered in through the mouth and guided into the posterior portion of the nasal cavities, typically using a guidewire. Once the nasopharynx of the posterior portion of the nasal cavity is occluded, toxin solution (BoNT) can be infused through the occluding catheter lumen, or through a separate infusion catheter or tube, in order to treat substantially the entire sinus and/or nasal cavity membrane at once (FIG. 21). When the toxin solution is introduced through the catheter at the posterior region of the cavities, it will frequently be desirable to occlude the nostrils, for example using a nasal clip 105.

DETD . . . air bleed valves 106 which are used to occlude the nostrils in order to evacuate or bleed air from the nasal passages while filling the passages with the toxin solution. The nose plugs 105 could optionally include ultrasonic transducers in order to deliver ultrasonic or other acoustic energy into the solutions entrapped within the nasal cavities using the nostril plugs. Alternatively, of course, the

ultrasound or other acoustic energy could be delivered from an external. . .

DETD . . . can deliver toxin incorporated into vesicles which may be configured as "resonance" bodies, which reduce the need to fill the nasal cavities with a liquid or other form of toxin. For example, lipid microspheres which incorporate the toxin may be sprayed or aerosolized onto target surfaces of the nasal epithelium. After the lipid or other resonance bodies are attached to the targeted epithelium membrane surface(s), the ultrasound energy can. . .

DETD Referring to FIG. 29, the toxin may be delivered as a conventional nasal spray (BoNT), as mentioned hereinbefore, and the poration energy can be delivered through a face mask. The poration energy might. . .

DETD FIGS. 33 and 34 illustrate a device for applying BoNT to the treatment area within the nasal cavity. This device comprises a handle 115 having a proximal section, a body and a distal section. The body of. . . 118 connected to each of the first end and second, wherein the applicator tips are configured for insertion into the nasal passageway, as shown in FIG. 35.

DETD Once within the nasal cavity, the applicator tips 117 and 118 can apply BoNT to the nasal passageway and, specifically, the turbinates along the nasal wall. The BoNT can be applied or affixed to the applicator tips as a liquid solution, gel, foam, cream, lotion and/or a lyophilized compound prior to being positioned within the nasal passageway. Alternatively, as illustrated in FIG. 36, the handle can be configured with an infusion channel 119 for delivering the BoNT to the applicator tips following placement in the nasal passageway. In this configuration, the handle may further comprise an access port at its proximal section that is in fluid. . .

DETD . . . may be configured to provide an outward lateral force such that the applicator tips 118 are firmly contacted against the nasal turbinates when placed in the nasal passageway. With reference to FIG. 37A, the operator would apply inward pressure in the direction of the arrows to the. . . to inserting the applicator tips into the nose. Once the applicator tips of the device are properly inserted into the nasal passageway, this pressure would be released such that the outward bias in the handle transitions the handle from a compressed configuration to an expanded configuration, as shown in FIG. 37B, wherein the applicator tips are pressed against the nasal turbinates. The applicator tips can be held against the turbinates by the outward bias for sufficient time to allow a therapeutically effective amount of BoNT to be absorbed by the nasal cavity wall.

DETD To facilitate the insertion of the tip applicator through the nostril and into the nasal passageway, it may be desirable for the applicator tip to initially have a low volume configuration. Once properly positioned in the nasal passageway, it would be desirable for the applicator to have an expanded volume configuration for maximizing contact with the nasal turbinates. In one exemplary embodiment, the tip applicator may comprise a sponge such that the sponge 121 is in a. . . 39A) and an expanded configuration when wet (FIG. 39B), wherein the sponge 121 is configured to fit securely within the nasal passageway.

DETD . . . could be preloaded with lyophilized BoNT and wetted with a

liquid (e.g., saline) following placement of the applicator in the nasal passageway. The liquid can be introduced into the nasal passageway using a spray or a catheter, or the BoNT may simply be rewetted by the nasal secretions themselves. Alternatively, as described with respect to FIG. 36, the liquid can be infused into the applicator tip through. . .

DETD To facilitate the expansion of the applicator tip, thereby maximizing the surface contact between the nasal cavity wall and applicator tip, it may be desirable to incorporate a spring element 122 within the applicator tip 118.. . .

DETD . . . it will be necessary to hold the spring 122 in its compressed state until it is properly positioned within the nasal cavity, at which time the spring can be released to allow the applicator to expand into the nasal cavity. In the wet/dry sponge 121 embodiment described with respect to FIGS. 39A and 39B, a sponge and spring can. . .

DETD . . . retractable sheath or collar 126 for holding the spring in its compressed configuration. Once the applicator is positioned within the nasal cavity, the actuator can be retracted to release the spring, thereby expanding the applicator.

DETD . . . for the spring-assisted expansion of the applicator tip to be directionally biased to maximize contact with the wall of the nasal cavity and optimize contact pressure with the nasal turbinates. For example, the spring element can be dimensioned and configured such that the applicator expands laterally towards the turbinates of the nasal cavity. Alternatively or additionally, portions of the applicator tip may comprise an impermeable lining such that delivery of BoNT to certain portions of the nasal cavity is optimized and undesirable migration of BoNT solution is minimized.

DETD . . . also be desirable for the apparatus to be configured such that only the amount of toxin necessary to treat the nasal cavity is loaded on the applicator tip and applied to the nasal wall. It this embodiment, it would be desirable for the applicator to carry a predetermined quantity of toxin, wherein the. . . to be configured such that most, if not all, of the toxin carried on the applicator is delivered to the nasal wall, wherein little to no toxin runs, escapes or migrates to non-target portions of body tissue.

DETD . . . be configured to provide a controlled delivery of toxin to facilitate absorption of the toxin into the walls of the nasal cavity. An applicator providing a controlled delivery of toxin can be configured such that the rate of toxin delivery is proportionate with the rate of BoNT absorption across the nasal membrane. Such a controlled delivery will ensure that the toxin is absorbed into the nasal tissue and not dispersed elsewhere in the body.

DETD An apparatus for treating a nasal cavity of a patient via a controlled and uniform delivery of BoNT may comprise an applicator having an inner member,. . . open-faced chambers. The outer member may also comprise an array of microneedles to facilitate the passage of BoNT across the nasal membrane. Alternatively, the outer member may comprise a combination of the structures and materials mentioned above. For example, the outer. . . a predetermined quantity of toxin. The inner member is configured for occupying space when the applicator is positioned within the nasal cavity such that the outer member is placed in contact with the wall of the nasal cavity. The inner member may be any compliant material such as a sponge, balloon or foam rubber. The impermeable lining. . . outer member to inner member and, accordingly, facilitates the transfer of BoNT from the applicator to the tissue of the nasal wall. As with applicator embodiments that have been previously discussed herein, the outer member can be pre soaked or filled with BoNT solution, infused with BoNT following placement in the nasal passageway, or pre-loaded with freeze-dried BoNT that can be reconstituted with infused saline.

DETD . . . embodiment, the inner member comprises (1) a low volume configuration to facilitate the applicator's insertion into and placement within the nasal passageway and (2) an expanded volume configuration for pressing the outer member against the walls of the nasal cavity. The expansion of the inner member relative to the outer member can also facilitate the controlled release of BoNT. . .

DETD In any of the embodiments discussed herein, it may be desirable to adapt the applicator to the geometry of the nasal cavity. For example, in embodiments comprising an outer member and inner member, the outer member can be configured to match the shape of the nasal cavity or portions of the nasal passageway following the expansion of the inner

member. By achieving better contact, the delivery of toxin to and across the nasal membrane can be optimized.

DETD . . . carrying BoNT. In this embodiment, the applicator tip may comprise a BoNT-loaded bioresorbable polymer that can be absorbed into the nasal cavity tissue. The tip can be configured such that the BoNT can be delivered to the nasal wall both immediately and as the coating is absorbed into the tissue.

DETD . . . this application, the device described with respect to FIGS. 33 and 34 can be used to deliver BoNT-LC to the nasal cavity instead of the BoNT intact molecule. In cases where this device is used to deliver BoNT-LC to the nasal cavity, any of the previously-described, energy-based delivery systems can be used to cause poration in the

nasal tissue to facilitate delivery of the BoNT-LC to the tissue. Additionally or alternatively, this device can be equipped with an. . .

DETD In addition to BTX-LC, it may be desirable to deliver additional agents to the nasal passages and sinuses prior to, coincident with, or after deliver of the LC. Adjunctive therapies may include agents designed to. . .

DETD Decongestants such as epinephrine also cause constriction of the vasculature in the nasal passages, which in addition to temporarily reducing swelling of the target tissues, may decrease the risks of LC entering the. . .

CLM What is claimed is:
1. An apparatus for treating inflammation of a nasal membrane of a patient comprising: a handle comprising a proximal section, a first member and a second member, wherein the. . . tip and second applicator tip are each configured for insertion into a nostril of the patient and placement within a nasal passageway of the patient and wherein each applicator tip is configured for delivering a toxin to a region of nasal tissue within the nasal cavity of the patient, thereby treating the inflammation.

CLM What is claimed is:
4. The apparatus of claim 2, wherein the handle is configured to be arranged in a compressed delivery configuration for placement of the applicator tips within the nasal passageway and an expanded treatment configuration for delivering toxin to the region of nasal tissue.

CLM What is claimed is:
. . . 5, wherein each applicator tip is configured to be arranged in a low volume delivery configuration for placement within the nasal passageway and an expanded volume treatment configuration for delivering toxin to the region of nasal tissue.

CLM What is claimed is:
. . . of claim 6, wherein each applicator tip in the expanded volume treatment configuration is adapted to fit substantially within the nasal cavity of the patient.

CLM What is claimed is:
. . . claim 8, wherein each applicator tip is configured to be arranged in a compressed delivery configuration for placement within the nasal passageway and an expanded treatment configuration for delivering toxin to the region of nasal tissue.

CLM What is claimed is:
. . . apparatus of claim 17, wherein the applicator tips are configured to receive the toxin prior to being positioned in the nasal passageway.

CLM What is claimed is:
. . . The apparatus of claim 17, wherein the applicator tips are configured to receive the toxin after being positioned in the nasal passageway.

CLM What is claimed is:
. . . 26. The apparatus of claim 25 further comprising an energy delivery applicator configured for delivering energy to the region of nasal tissue to enhance delivery of the toxin to the nasal tissue.

CLM What is claimed is:
. . . applicator is adapted to deliver energy under conditions which cause

poration of at least one cell in the region of nasal tissue.

CLM What is claimed is:
31. An apparatus for treating a condition associated with inflammation of a nasal membrane of a patient selected from the group consisting of rhinitis, rhinorrhea, hay fever and combinations thereof, said apparatus comprising: an applicator configured for (a) insertion into a nostril of the patient, (b) placement within a nasal passageway of the patient, and (c) delivering a therapeutically effective amount of a toxin to a region of nasal tissue within the nasal cavity of the patient; wherein the applicator comprises an inner member and outer member.

CLM What is claimed is:
. . . of claim 31, wherein the applicator is configured to be arranged in a low volume configuration for placement within the nasal passageway and an expanded volume configuration for delivering the toxin to the nasal tissue.

CLM What is claimed is:
40. The apparatus of claim 39, wherein expansion of the inner member facilitates delivery of the toxin to the nasal tissue.

CLM What is claimed is:
41. An apparatus for treating a condition associated with inflammation of a nasal membrane of a patient selected from the group consisting of rhinitis, rhinorrhea, hay fever and combinations thereof, said apparatus comprising:. . . tip and second applicator tip are each configured for insertion into a nostril of the patient and placement within a nasal passageway of the patient and wherein each applicator tip is configured for delivering a therapeutically effective amount of a toxin to a region of nasal tissue within the nasal cavity of the patient, thereby treating the condition.

CLM What is claimed is:
. . . element is configured to provide the applicator tips with an outward bias when the applicator tips are placed within the nasal passageway.

CLM What is claimed is:
43. The apparatus of claim 42, wherein the outward bias presses each applicator tip against a turbinate in the nasal cavity.

AB Apparatus for delivering toxin and toxin fragments to a patient's nasal cavity provide for both release of the toxin and delivery of energy which selectively porates target cells to enhance uptake of the toxin. The use of energy-mediated delivery is particularly advantageous with light chain fragment toxins which lack cell binding capacity.

L11 ANSWER 39 OF 39 USPATFULL on STN

ACCESSION NUMBER:	2007:277801 USPATFULL
TITLE:	Nasolacrimal Drainage System Implants for Drug Therapy
INVENTOR(S):	de Juan, Eugene JR., San Francisco, CA, UNITED STATES Boyd, Stephen, Murrieta, CA, UNITED STATES Reich, Cary, Los Gatos, CA, UNITED STATES Rapacki, Alan, Redwood City, CA, UNITED STATES Gifford, Hanson S. III, Woodside, CA, UNITED STATES Deem, Mark, Mountain View, CA, UNITED STATES
PATENT ASSIGNEE(S):	ForSight Labs, LLC, Menlo Park, CA, UNITED STATES (U.S. corporation)

	NUMBER	KIND	DATE	
PATENT INFORMATION:	US 20070243230	A1	20071018	
	US 7998497	B2	20110816	
APPLICATION INFO.:	US 2007-695545	A1	20070402	(11)

	NUMBER	DATE	
PRIORITY INFORMATION:	US 2006-60787775	20060331	(60)
	US 2006-60871864	20061226	(60)
DOCUMENT TYPE:	Utility		
FILE SEGMENT:	APPLICATION		

LEGAL REPRESENTATIVE: TOWNSEND AND TOWNSEND AND CREW, LLP, TWO EMBARCADERO CENTER, EIGHTH FLOOR, SAN FRANCISCO, CA, 94111-3834, US
NUMBER OF CLAIMS: 47
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 30 Drawing Page(s)
LINE COUNT: 1982
CAS INDEXING IS AVAILABLE FOR THIS PATENT. Full-text
IN Gifford, Hanson S. III, Woodside, CA, UNITED STATES
DETD . . . extend through the drug core 112 to permit tear flow through the lumen for the delivery of therapeutic agent for nasal and systemic applications of the therapeutic agent. In addition or in combination with channel 112C, retention structure 132 and core. . .
AB Implant devices, systems and methods for insertion into a punctum of a patient optionally comprises a drug core and a sheath body disposed over the drug core. The drug core includes a therapeutic agent deliverable into the eye, and the sheath defines at least one exposed surface of the drug core. The exposed surface(s) of the drug core may contact a tear or tear film fluid and release the therapeutic agent at therapeutic levels over a sustained period when the implant is implanted for use. The implant may include a retention element to retain the drug core and sheath body near the punctum, optionally comprising a shape memory alloy that can resiliently expand. An occlusive element may be attached to the retention element to at least partially occlude tear flow through the canalicular lumen.

=>

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Appl. No.:	17/151,938
Filed:	January 19, 2021
Docket No.:	19264.0001USC8

RESPONSE

Commissioner for Patents
P.O. Box 1450
Alexandria, Virginia 22313-1450

Attention: Commissioner for Patents

Please consider and enter the following amendments and/or remarks in response to the recent office action for this patent application.

If a petition for an extension of time under 37 C.F.R. § 1.136(a) is necessary to maintain the pendency of this patent application in connection with this response, and is not otherwise requested in this patent application, it is requested that the Commissioner consider this paper to be a petition for an appropriate extension of time and an authorization for the Commissioner to charge the fee as set forth in 37 C.F.R. § 1.17(a) corresponding to the needed extension of time to Deposit Account No. 13-2725

Remarks

This is in response to the non-final Office Action mailed December 5, 2022. Reconsideration and allowance are requested for at least the following reasons.

Claim Rejections – Double Patenting

Claims 1-20 are rejected on the grounds of non-statutory double patenting as being unpatentable over claims 1-20 of U.S. Patent No. 10,894,011. This rejection is respectfully traversed.

While the correctness of the rejection is not conceded, a terminal disclaimer is filed herewith to address the rejection. Reconsideration is requested.

Conclusion

Favorable reconsideration is requested. Please contact the undersigned with any questions regarding this patent application.

Respectfully submitted,

MERCHANT & GOULD P.C.
P.O. Box 2903
Minneapolis, Minnesota 55402-0903
(612) 332-5300

Date: March 1, 2023

/Robert A. Kalinsky/
Name: Robert A. Kalinsky
Reg. No.: 50,471

UNITED STATES
PATENT AND TRADEMARK OFFICE

P.O. Box 1450
Alexandria, VA 22313 - 1450
www.uspto.gov

ELECTRONIC PAYMENT RECEIPT

APPLICATION #	RECEIPT DATE / TIME	ATTORNEY DOCKET #
17/151,938	03/01/2023 01:46:26 PM ET	19264.0001USC8

Title of Invention

SYSTEMS AND METHODS FOR DELIVERY OF A THERAPEUTIC AGENT

Application Information

APPLICATION TYPE	Utility - Nonprovisional Application under 35 USC 111(a)	PATENT #	-
CONFIRMATION #	1034	FILED BY	Theresa Powless
PATENT CENTER #	61672055	AUTHORIZED BY	Robert Kalinsky
CUSTOMER #	23552	FILING DATE	01/19/2021
CORRESPONDENCE ADDRESS	-	FIRST NAMED INVENTOR	Mark E. Deem

Payment Information

PAYMENT METHOD	PAYMENT TRANSACTION ID	PAYMENT AUTHORIZED BY
CARD / 4938	E202331D48097543	Theresa Powless

PRE-AUTHORIZED ACCOUNT	PRE-AUTHORIZED CATEGORY
132725	37 CFR 1.16 (National application filing, search, and examination fees); 37 CFR 1.17 (Patent application and reexamination processing fees); 37 CFR 1.19 (Document supply fees); 37 CFR 1.20 (Post Issuance fees); 37 CFR 1.21 (Miscellaneous fees and charges)

FEE CODE	DESCRIPTION	ITEM PRICE($)	QUANTITY	ITEM TOTAL($)
2814	STATUTORY DISCLAIMER, INCLUDING TERMINAL DISCLAIMER	170.00	1	170.00
			TOTAL AMOUNT:	$170.00

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 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

P.O. Box 1450
Alexandria, VA 22313 - 1450
www.uspto.gov

ELECTRONIC ACKNOWLEDGEMENT RECEIPT

APPLICATION #	RECEIPT DATE / TIME	ATTORNEY DOCKET #
17/151,938	**03/01/2023 01:46:26 PM ET**	**19264.0001USC8**

Title of Invention

SYSTEMS AND METHODS FOR DELIVERY OF A THERAPEUTIC AGENT

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APPLICATION TYPE	Utility - Nonprovisional Application under 35 USC 111(a)	PATENT #	-
CONFIRMATION #	1034	FILED BY	Theresa Powless
PATENT CENTER #	61672055	FILING DATE	01/19/2021
CUSTOMER #	23552	FIRST NAMED INVENTOR	Mark E. Deem
CORRESPONDENCE ADDRESS	-	AUTHORIZED BY	Robert Kalinsky

Documents

TOTAL DOCUMENTS: 2

DOCUMENT	PAGES	DESCRIPTION	SIZE (KB)
2023-03-01--Response to FOA--19264.0001USC8.PDF	2	Response After Final Action	72 KB
2023-03-01--Terminal Disclaimer 10894011--19264.0001USC8.PDF	2	Terminal Disclaimer Filed	241 KB

Digest

DOCUMENT	MESSAGE DIGEST(SHA-512)
2023-03-01--Response to FOA-	5B52BA1359347BA6C059E16D7B843CF850C2397DAFC09B4AE

-19264.0001USC8.PDF	E0CBD84E7BCB5402457EFFF24133F9107BADB7DAFE47A88397E5EE2E9548B12AAD609DE49C965D3
2023-03-01--Terminal Disclaimer 10894011--19264.0001USC8.PDF	C5E234BA928A1A5538695697A8CE23E0A0FE4E2716BDB3D039B88EAF33B0240A8EA9009A9CA80BFB89E19DAA28EAFBA06392BD66BCA0917E69DA16E521630A82

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 filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application

National Stage of an International Application under 35 U.S.C. 371

If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office

If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

PTO/AIA/26 (04-14)
Approved for use through 05/31/2024. OMB 0651-0031
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it displays a valid OMB control number.

TERMINAL DISCLAIMER TO OBVIATE A DOUBLE PATENTING REJECTION OVER A "PRIOR" PATENT	Docket Number (Optional) 19264.0001USC8

In re Application of: The Foundry, LLC

Application No.: 17/151,938

Filed: January 19, 2021

For: SYSTEMS AND METHODS FOR DELIVERY OF A THERAPEUTIC AGENT

The applicant, The Foundry, LLC, owner 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 **prior patent** No. 10,894,011 as the term of said **prior patent** is presently shortened by any terminal disclaimer. The applicant hereby agrees that any patent so granted on the instant application shall be enforceable only for and during such period that it and the **prior patent** are commonly owned. This agreement runs with any patent granted on the instant application and is binding upon the grantee, its successors or assigns.

In making the above disclaimer, the applicant does not disclaim the terminal part of the term of any patent granted on the instant application that would extend to the expiration date of the full statutory term of the **prior patent**, "as the term of said **prior patent** is presently shortened by any terminal disclaimer," in the event that said **prior patent** later:

expires for failure to pay a maintenance fee;
is held unenforceable;
is found invalid by a court of competent jurisdiction;
is statutorily disclaimed in whole or terminally disclaimed under 37 CFR 1.321;
has all claims canceled by a reexamination certificate;
is reissued; or
is in any manner terminated prior to the expiration of its full statutory term as presently shortened by any terminal disclaimer.

Check either box 1 or 2 below, if appropriate.

1. ☐ The undersigned is the applicant. If the applicant is an assignee, the undersigned is authorized to act on behalf of the assignee.

I hereby acknowledge that any willful false statements made are punishable under 18 U.S.C. 1001 by fine or imprisonment of not more than five (5) years, or both.

2. ☑ The undersigned is an attorney or agent of record. Reg. No. 50,471

/Robert A. Kalinsky/ — Signature
March 1, 2023 — Date

Robert A. Kalinsky — Typed or printed name

Attorney of Record — Title
612.332.5300 — Telephone Number

☑ Terminal disclaimer fee under 37 CFR 1.20(d) included.

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.

A Federal agency may not conduct or sponsor, and a person is not required to respond to, nor shall a person be subject to a penalty for failure to comply with an information collection subject to the requirements of the Paperwork Reduction Act of 1995, unless the information collection has a currently valid OMB Control Number. The OMB Control Number for this information collection is 0651-0031. Public burden for this form is estimated to average 12 minutes per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the information collection. Send comments regarding this burden estimate or any other aspect of this information collection, including suggestions for reducing this burden to the Chief Administrative Officer, United States Patent and Trademark Office, P.O. Box 1450, Alexandria, VA 22313-1450 or email InformationCollection@uspto.gov. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **If filing this completed form by mail, 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.

Privacy Act Statement

The Privacy Act of 1974 (P.L. 93-579) requires that you be given certain information in connection with your submission of the attached form related to a patent application or patent. The United States Patent and Trademark Office (USPTO) collects the information in this record under authority of 35 U.S.C. 2. The USPTO's system of records is used to manage all applicant and owner information including name, citizenship, residence, post office address, and other information with respect to inventors and their legal representatives pertaining to the applicant's/owner's activities in connection with the invention for which a patent is sought or has been granted. The applicable Privacy Act System of Records Notice for the information collected in this form is COMMERCE/PAT-TM-7 Patent Application Files, available in the Federal Register at 78 FR 19243 (March 29, 2013). https://www.govinfo.gov/content/pkg/FR-2013-03-29/pdf/2013-07341.pdf

Routine uses of the information in this record may include disclosure to: 1) law enforcement, in the event that the system of records indicates a violation or potential violation of law; 2) a Federal, state, local, or international agency, in response to its request; 3) a contractor of the USPTO having need for the information in order to perform a contract; 4) the Department of Justice for determination of whether the Freedom of Information Act (FOIA) requires disclosure of the record; 5) a Member of Congress submitting a request involving an individual to whom the record pertains, when the individual has requested the Member's assistance with respect to the subject matter of the record; 6) a court, magistrate, or administrative tribunal, in the course of presenting evidence, including disclosures to opposing counsel in the course of settlement negotiations; 7) the Administrator, General Services Administration (GSA), or their designee, during an inspection of records conducted by GSA under authority of 44 U.S.C. 2904 and 2906, in accordance with the GSA regulations and any other relevant (i.e., GSA or Commerce) directive, where such disclosure shall not be used to make determinations about individuals; 8) another federal agency for purposes of National Security review (35 U.S.C. 181) and for review pursuant to the Atomic Energy Act (42 U.S.C. 218(c)); 9) the Office of Personnel Management (OPM) for personnel research purposes; and 9) the Office of Management and Budget (OMB) for legislative coordination and clearance.

If you do not furnish the information requested on this form, the USPTO may not be able to process and/or examine your submission, which may result in termination of proceedings, abandonment of the application, and/or expiration of the patent.

Additional Uses

Additional USPTO uses of the information in this record may include disclosure to: 1) the International Bureau of the World Intellectual Property Organization, if the record is related to an international application filed under the Patent Cooperation Treaty; 2) the public i) after publication of the application pursuant to 35 U.S.C. 122(b), ii) after issuance of a patent pursuant to 35 U.S.C. 151, iii) if the record was filed in an application which became abandoned or in which the proceedings were terminated and which application is referenced by either a published application, an application open to public inspections, or an issued patent, or iv) without publication of the application or patent under the specific circumstances provided for by 37 CFR 1.14(a)(1)(v)-(vii); and/or 3) the National Archives and Records Administration, for inspection of records.

Application Number * 17/151,938 *	Application/Control No. 17/151,938	Applicant(s)/Patent under Reexamination Deem et al.	
	Examiner NAVARRO, ALBERT MARK	Art Unit 1645	

Document Code - DISQ	Internal Document - DO NOT MAIL

TERMINAL DISCLAIMER	☑ APPROVED	☐ DISAPPROVED
Date Filed: 01 March 2023	This patent is subject to a Terminal Disclaimer	

Approved/Disapproved by:

/CHARRISSA S BROWN/

Technology Center: PLRC

Telephone: (571)272-1558

_____

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

NOTICE OF ALLOWANCE AND FEE(S) DUE

23552 7590 03/13/2023

MERCHANT & GOULD P.C.
P.O. BOX 2903
MINNEAPOLIS, MN 55402-0903

EXAMINER
NAVARRO, ALBERT MARK

ART UNIT	PAPER NUMBER
1645	

DATE MAILED: 03/13/2023

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
17/151,938	01/19/2021	Mark E. Deem	19264.0001USC8	1034

TITLE OF INVENTION: SYSTEMS AND METHODS FOR DELIVERY OF A THERAPEUTIC AGENT

APPLN. TYPE	ENTITY STATUS	ISSUE FEE DUE	PUBLICATION FEE DUE	PREV. PAID ISSUE FEE	TOTAL FEE(S) DUE	DATE DUE
nonprovisional	SMALL	$480	$0.00	$0.00	$480	06/13/2023

THE APPLICATION IDENTIFIED ABOVE HAS BEEN EXAMINED AND IS ALLOWED FOR ISSUANCE AS A PATENT. PROSECUTION ON THE MERITS IS CLOSED. THIS NOTICE OF ALLOWANCE IS NOT A GRANT OF PATENT RIGHTS. THIS APPLICATION IS SUBJECT TO WITHDRAWAL FROM ISSUE AT THE INITIATIVE OF THE OFFICE OR UPON PETITION BY THE APPLICANT. SEE 37 CFR 1.313 AND MPEP 1308.

THE ISSUE FEE AND PUBLICATION FEE (IF REQUIRED) MUST BE PAID WITHIN THREE MONTHS FROM THE MAILING DATE OF THIS NOTICE OR THIS APPLICATION SHALL BE REGARDED AS ABANDONED. THIS STATUTORY PERIOD CANNOT BE EXTENDED. SEE 35 U.S.C. 151. THE ISSUE FEE DUE INDICATED ABOVE DOES NOT REFLECT A CREDIT FOR ANY PREVIOUSLY PAID ISSUE FEE IN THIS APPLICATION. IF AN ISSUE FEE HAS PREVIOUSLY BEEN PAID IN THIS APPLICATION (AS SHOWN ABOVE), THE RETURN OF PART B OF THIS FORM WILL BE CONSIDERED A REQUEST TO REAPPLY THE PREVIOUSLY PAID ISSUE FEE TOWARD THE ISSUE FEE NOW DUE.

HOW TO REPLY TO THIS NOTICE:

I. Review the ENTITY STATUS shown above. If the ENTITY STATUS is shown as SMALL or MICRO, verify whether entitlement to that entity status still applies.

If the ENTITY STATUS is the same as shown above, pay the TOTAL FEE(S) DUE shown above.

If the ENTITY STATUS is changed from that shown above, on PART B - FEE(S) TRANSMITTAL, complete section number 5 titled "Change in Entity Status (from status indicated above)".

For purposes of this notice, small entity fees are 40% the amount of undiscounted fees, and micro entity fees are 20% the amount of undiscounted fees.

II. PART B - FEE(S) TRANSMITTAL, or its equivalent, must be completed and returned to the United States Patent and Trademark Office (USPTO) with your ISSUE FEE and PUBLICATION FEE (if required). If you are charging the fee(s) to your deposit account, section "4b" of Part B - Fee(s) Transmittal should be completed. If an equivalent of Part B is filed, a request to reapply a previously paid issue fee must be clearly made, and delays in processing may occur due to the difficulty in recognizing the paper as an equivalent of Part B.

III. All communications regarding this application must give the application number. Please direct all communications prior to issuance to Mail Stop ISSUE FEE unless advised to the contrary.

IMPORTANT REMINDER: Maintenance fees are due in utility patents issuing on applications filed on or after Dec. 12, 1980. It is patentee's responsibility to ensure timely payment of maintenance fees when due. More information is available at www.uspto.gov/PatentMaintenanceFees.

PART B - FEE(S) TRANSMITTAL

Complete and send this form, together with applicable fee(s), by mail or fax, or via EFS-Web.

By mail, send to: Mail Stop ISSUE FEE
Commissioner for Patents
P.O. Box 1450
Alexandria, Virginia 22313-1450

By fax, send to: (571)-273-2885

INSTRUCTIONS: This form should be used for transmitting the ISSUE FEE and PUBLICATION FEE (if required). Blocks 1 through 5 should be completed where appropriate. All further correspondence including the Patent, advance orders and notification of maintenance fees will be mailed to the current correspondence address as indicated unless corrected below or directed otherwise in Block 1, by (a) specifying a new correspondence address; and/or (b) indicating a separate "FEE ADDRESS" for maintenance fee notifications.

CURRENT CORRESPONDENCE ADDRESS (Note: Use Block 1 for any change of address)

23552 7590 03/13/2023

MERCHANT & GOULD P.C.
P.O. BOX 2903
MINNEAPOLIS, MN 55402-0903

Note: A certificate of mailing can only be used for domestic mailings of the Fee(s) Transmittal. This certificate cannot be used for any other accompanying papers. Each additional paper, such as an assignment or formal drawing, must have its own certificate of mailing or transmission.

Certificate of Mailing or Transmission

I hereby certify that this Fee(s) Transmittal is being deposited with the United States Postal Service with sufficient postage for first class mail in an envelope addressed to the Mail Stop ISSUE FEE address above, or being transmitted to the USPTO via EFS-Web or by facsimile to (571) 273-2885, on the date below.

(Typed or printed name)
(Signature)
(Date)

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
17/151,938	01/19/2021	Mark E. Deem	19264.0001USC8	1034

TITLE OF INVENTION: SYSTEMS AND METHODS FOR DELIVERY OF A THERAPEUTIC AGENT

APPLN. TYPE	ENTITY STATUS	ISSUE FEE DUE	PUBLICATION FEE DUE	PREV. PAID ISSUE FEE	TOTAL FEE(S) DUE	DATE DUE
nonprovisional	SMALL	$480	$0.00	$0.00	$480	06/13/2023

EXAMINER	ART UNIT	CLASS-SUBCLASS
NAVARRO, ALBERT MARK	1645	424-190100

1. Change of correspondence address or indication of "Fee Address" (37 CFR 1.363).

❑ Change of correspondence address (or Change of Correspondence Address form PTO/AIA/122 or PTO/SB/122) attached.

❑ "Fee Address" indication (or "Fee Address" Indication form PTO/AIA/47 or PTO/SB/47; Rev 03-02 or more recent) attached. **Use of a Customer Number is required.**

2. For printing on the patent front page, list
(1) The names of up to 3 registered patent attorneys or agents OR, alternatively,
(2) The name of a single firm (having as a member a registered attorney or agent) and the names of up to 2 registered patent attorneys or agents. If no name is listed, no name will be printed.

1 _____
2 _____
3 _____

3. ASSIGNEE NAME AND RESIDENCE DATA TO BE PRINTED ON THE PATENT (print or type)

PLEASE NOTE: Unless an assignee is identified below, no assignee data will appear on the patent. If an assignee is identified below, the document must have been previously recorded, or filed for recordation, as set forth in 37 CFR 3.11 and 37 CFR 3.81(a). Completion of this form is NOT a substitute for filing an assignment.

(A) NAME OF ASSIGNEE (B) RESIDENCE: (CITY and STATE OR COUNTRY)

Please check the appropriate assignee category or categories (will not be printed on the patent) : ❑ Individual ❑ Corporation or other private group entity ❑ Government

4a. Fees submitted: ❑ Issue Fee ❑ Publication Fee (if required) ❑ Advance Order - # of Copies _____

4b. Method of Payment: *(Please first reapply any previously paid fee shown above)*

❑ Electronic Payment via EFS-Web ❑ Enclosed check ❑ Non-electronic payment by credit card (Attach form PTO-2038)

❑ The Director is hereby authorized to charge the required fee(s), any deficiency, or credit any overpayment to Deposit Account No. _____

5. **Change in Entity Status** (from status indicated above)

❑ Applicant certifying micro entity status. See 37 CFR 1.29

❑ Applicant asserting small entity status. See 37 CFR 1.27

❑ Applicant changing to regular undiscounted fee status.

NOTE: Absent a valid certification of Micro Entity Status (see forms PTO/SB/15A and 15B), issue fee payment in the micro entity amount will not be accepted at the risk of application abandonment.
NOTE: If the application was previously under micro entity status, checking this box will be taken to be a notification of loss of entitlement to micro entity status.
NOTE: Checking this box will be taken to be a notification of loss of entitlement to small or micro entity status, as applicable.

NOTE: This form must be signed in accordance with 37 CFR 1.31 and 1.33. See 37 CFR 1.4 for signature requirements and certifications.

Authorized Signature _____ Date _____

Typed or printed name _____ Registration No. _____

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United States Patent and Trademark Office
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www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
17/151,938	01/19/2021	Mark E. Deem	19264.0001USC8	1034

23552 7590 03/13/2023

MERCHANT & GOULD P.C.
P.O. BOX 2903
MINNEAPOLIS, MN 55402-0903

EXAMINER	
NAVARRO, ALBERT MARK	
ART UNIT	PAPER NUMBER
1645	

DATE MAILED: 03/13/2023

Determination of Patent Term Adjustment under 35 U.S.C. 154 (b)
(Applications filed on or after May 29, 2000)

The Office has discontinued providing a Patent Term Adjustment (PTA) calculation with the Notice of Allowance.

Section 1(h)(2) of the AIA Technical Corrections Act amended 35 U.S.C. 154(b)(3)(B)(i) to eliminate the requirement that the Office provide a patent term adjustment determination with the notice of allowance. See Revisions to Patent Term Adjustment, 78 Fed. Reg. 19416, 19417 (Apr. 1, 2013). Therefore, the Office is no longer providing an initial patent term adjustment determination with the notice of allowance. The Office will continue to provide a patent term adjustment determination with the Issue Notification Letter that is mailed to applicant approximately three weeks prior to the issue date of the patent, and will include the patent term adjustment on the patent. Any request for reconsideration of the patent term adjustment determination (or reinstatement of patent term adjustment) should follow the process outlined in 37 CFR 1.705.

Any questions regarding the Patent Term Extension or Adjustment determination should be directed to the Office of Patent Legal Administration at (571)-272-7702. Questions relating to issue and publication fee payments should be directed to the Customer Service Center of the Office of Patent Publication at 1-(888)-786-0101 or (571)-272-4200.

OMB Clearance and PRA Burden Statement for PTOL-85 Part B

The Paperwork Reduction Act (PRA) of 1995 requires Federal agencies to obtain Office of Management and Budget approval before requesting most types of information from the public. When OMB approves an agency request to collect information from the public, OMB (i) provides a valid OMB Control Number and expiration date for the agency to display on the instrument that will be used to collect the information and (ii) requires the agency to inform the public about the OMB Control Number's legal significance in accordance with 5 CFR 1320.5(b).

The information collected by PTOL-85 Part B is required by 37 CFR 1.311. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 30 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, Virginia 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, Virginia 22313-1450. Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it displays a valid OMB control number.

Privacy Act Statement

The Privacy Act of 1974 (P.L. 93-579) requires that you be given certain information in connection with your submission of the attached form related to a patent application or patent. Accordingly, pursuant to the requirements of the Act, please be advised that: (1) the general authority for the collection of this information is 35 U.S.C. 2(b)(2); (2) furnishing of the information solicited is voluntary; and (3) the principal purpose for which the information is used by the U.S. Patent and Trademark Office is to process and/or examine your submission related to a patent application or patent. If you do not furnish the requested information, the U.S. Patent and Trademark Office may not be able to process and/or examine your submission, which may result in termination of proceedings or abandonment of the application or expiration of the patent.

The information provided by you in this form will be subject to the following routine uses:

1. The information on this form will be treated confidentially to the extent allowed under the Freedom of Information Act (5 U.S.C. 552) and the Privacy Act (5 U.S.C 552a). Records from this system of records may be disclosed to the Department of Justice to determine whether disclosure of these records is required by the Freedom of Information Act.
2. A record from this system of records may be disclosed, as a routine use, in the course of presenting evidence to a court, magistrate, or administrative tribunal, including disclosures to opposing counsel in the course of settlement negotiations.
3. A record in this system of records may be disclosed, as a routine use, to a Member of Congress submitting a request involving an individual, to whom the record pertains, when the individual has requested assistance from the Member with respect to the subject matter of the record.
4. A record in this system of records may be disclosed, as a routine use, to a contractor of the Agency having need for the information in order to perform a contract. Recipients of information shall be required to comply with the requirements of the Privacy Act of 1974, as amended, pursuant to 5 U.S.C. 552a(m).
5. A record related to an International Application filed under the Patent Cooperation Treaty in this system of records may be disclosed, as a routine use, to the International Bureau of the World Intellectual Property Organization, pursuant to the Patent Cooperation Treaty.
6. A record in this system of records may be disclosed, as a routine use, to another federal agency for purposes of National Security review (35 U.S.C. 181) and for review pursuant to the Atomic Energy Act (42 U.S.C. 218(c)).
7. A record from this system of records may be disclosed, as a routine use, to the Administrator, General Services, or his/her designee, during an inspection of records conducted by GSA as part of that agency's responsibility to recommend improvements in records management practices and programs, under authority of 44 U.S.C. 2904 and 2906. Such disclosure shall be made in accordance with the GSA regulations governing inspection of records for this purpose, and any other relevant (i.e., GSA or Commerce) directive. Such disclosure shall not be used to make determinations about individuals.
8. A record from this system of records may be disclosed, as a routine use, to the public after either publication of the application pursuant to 35 U.S.C. 122(b) or issuance of a patent pursuant to 35 U.S.C. 151. Further, a record may be disclosed, subject to the limitations of 37 CFR 1.14, as a routine use, to the public if the record was filed in an application which became abandoned or in which the proceedings were terminated and which application is referenced by either a published application, an application open to public inspection or an issued patent.
9. A record from this system of records may be disclosed, as a routine use, to a Federal, State, or local law enforcement agency, if the USPTO becomes aware of a violation or potential violation of law or regulation.

Notice of Allowability	Application No. 17/151,938	Applicant(s) Deem et al.	
	Examiner Mark NAVARRO	Art Unit 1645	AIA (FITF) Status No

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address--

All claims being allowable, PROSECUTION ON THE MERITS IS (OR REMAINS) CLOSED in this application. If not included herewith (or previously mailed), a Notice of Allowance (PTOL-85) or other appropriate communication will be mailed in due course. **THIS NOTICE OF ALLOWABILITY IS NOT A GRANT OF PATENT RIGHTS.** This application is subject to withdrawal from issue at the initiative of the Office or upon petition by the applicant. See 37 CFR 1.313 and MPEP 1308.

1. ☑ This communication is responsive to the terminal disclaimer filed March 1, 2023, which has been recorded.
   ☐ A declaration(s)/affidavit(s) under **37 CFR 1.130(b)** was/were filed on _____.

2. ☐ An election was made by the applicant in response to a restriction requirement set forth during the interview on _____; the restriction requirement and election have been incorporated into this action.

3. ☑ The allowed claim(s) is/are See Continuation Sheet . As a result of the allowed claim(s), you may be eligible to benefit from the **Patent Prosecution Highway** program at a participating intellectual property office for the corresponding application. For more information, please see **http://www.uspto.gov/patents/init_events/pph/index.jsp** or send an inquiry to **PPHfeedback@uspto.gov.**

4. ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

   Certified copies:

   a) ☐ All b) ☐ Some* c) ☐ None of the:

   1. ☐ Certified copies of the priority documents have been received.
   2. ☐ Certified copies of the priority documents have been received in Application No. _____ .
   3. ☐ Copies of the certified copies of the priority documents have been received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

   * Certified copies not received: _____ .

Applicant has THREE MONTHS FROM THE "MAILING DATE" of this communication to file a reply complying with the requirements noted below. Failure to timely comply will result in ABANDONMENT of this application.
THIS THREE-MONTH PERIOD IS NOT EXTENDABLE.

5. ☐ CORRECTED DRAWINGS (as "replacement sheets") must be submitted.
   ☐ including changes required by the attached Examiner's Amendment / Comment or in the Office action of Paper No./Mail Date _____ .

   Identifying indicia such as the application number (see 37 CFR 1.84(c)) should be written on the drawings in the front (not the back) of each sheet. Replacement sheet(s) should be labeled as such in the header according to 37 CFR 1.121(d).

6. ☐ DEPOSIT OF and/or INFORMATION about the deposit of BIOLOGICAL MATERIAL must be submitted. Note the attached Examiner's comment regarding REQUIREMENT FOR THE DEPOSIT OF BIOLOGICAL MATERIAL.

Attachment(s)

1. ☐ Notice of References Cited (PTO-892)
2. ☐ Information Disclosure Statements (PTO/SB/08), Paper No./Mail Date _____.
3. ☐ Examiner's Comment Regarding Requirement for Deposit of Biological Material _____.
4. ☐ Interview Summary (PTO-413), Paper No./Mail Date. _____.
5. ☐ Examiner's Amendment/Comment
6. ☐ Examiner's Statement of Reasons for Allowance
7. ☐ Other _____.

/ALBERT M NAVARRO/
Primary Examiner, Art Unit 1645

Continuation of 3. The allowed claim(s) is/are: 29-43, renumbered as 1-15, respectively

Issue Classification	Application/Control No.	Applicant(s)/Patent Under Reexamination
	17/151,938	Deem et al.
	Examiner	**Art Unit**
	Mark NAVARRO	1645

CPC								
Symbol							**Type**	**Version**
A61K	/	9	/	0021			F	2013-01-01
A61K	/	38	/	164			I	2013-01-01
A61K	/	38	/	168			I	2013-01-01
A61K	/	38	/	4893			I	2013-01-01
A61K	/	41	/	00			I	2013-01-01
A61K	/	41	/	0028			I	2013-01-01
A61N	/	1	/	327			I	2013-01-01
A61K	/	9	/	0078			I	2013-01-01
A61N	/	1	/	08			I	2013-01-01
A61N	/	1	/	303			I	2013-01-01
A61N	/	7	/	00			I	2013-01-01
A61B	/	18	/	1492			I	2013-01-01
A61B	/	18	/	1815			I	2013-01-01
A61N	/	5	/	10			I	2013-01-01
A61K	/	41	/	0047			I	2013-01-01
A61M	/	37	/	00			I	2013-01-01
A61M	/	37	/	0092			I	2013-01-01
C12Y	/	304	/	24069			I	2013-01-01
Y02A	/	50	/	30			A	2018-01-01
A61B	/	2018	/	0016			A	2013-01-01
A61B	/	2018	/	00214			A	2013-01-01
A61B	/	2018	/	00434			A	2013-01-01
A61B	/	2018	/	1861			A	2013-01-01
A61N	/	2007	/	003			A	2013-01-01
A61M	/	2210	/	1035			A	2013-01-01

CPC Combination Sets								
Symbol					**Type**	**Set**	**Ranking**	**Version**
A61K	/	38	/	4893	I	1	1	2013-01-01
A61K	/	2300	/	00	I	1	2	2013-01-01

NONE		**Total Claims Allowed:**	
(Assistant Examiner)	(Date)	15	
/ALBERT M NAVARRO/ Primary Examiner, Art Unit 1645	07 March 2023	O.G. Print Claim(s)	O.G. Print Figure
(Primary Examiner)	(Date)	1	NONE

Issue Classification	Application/Control No.	Applicant(s)/Patent Under Reexamination
	17/151,938	Deem et al.
	Examiner	**Art Unit**
	Mark NAVARRO	1645

INTERNATIONAL CLASSIFICATION					
CLAIMED					
C12M	/	1	/	00	
NON-CLAIMED					
	/		/		

US ORIGINAL CLASSIFICATION	
CLASS	**SUBCLASS**
435	283.1

CROSS REFERENCES(S)						
CLASS	**SUBCLASS (ONE SUBCLASS PER BLOCK)**					

NONE (Assistant Examiner) (Date)	**Total Claims Allowed:** 15	
/ALBERT M NAVARRO/ Primary Examiner, Art Unit 1645 (Primary Examiner) 07 March 2023 (Date)	O.G. Print Claim(s) 1	O.G. Print Figure NONE

Issue Classification	Application/Control No.	Applicant(s)/Patent Under Reexamination
	17/151,938	Deem et al.
	Examiner	**Art Unit**
	Mark NAVARRO	1645

☑ Claims renumbered in the same order as presented by applicant ☐ CPA ☑ T.D. ☐ R.1.47

CLAIMS

Final	Original	Final	Original	Final	Original	Final	Original	Final	Original	Final	Original	Final	Original	Final	Original

NONE		**Total Claims Allowed:**	
(Assistant Examiner)	(Date)	15	
/ALBERT M NAVARRO/ Primary Examiner, Art Unit 1645	07 March 2023	O.G. Print Claim(s)	O.G. Print Figure
(Primary Examiner)	(Date)	1	NONE

Search Notes	Application/Control No.	Applicant(s)/Patent Under Reexamination
	17/151,938	Deem et al.
	Examiner	Art Unit
	Mark NAVARRO	1645

CPC - Searched*		
Symbol	Date	Examiner
A61K 9/0021	03/07/2023	MN

CPC Combination Sets - Searched*		
Symbol	Date	Examiner

US Classification - Searched*			
Class	Subclass	Date	Examiner

* See search history printout included with this form or the SEARCH NOTES box below to determine the scope of the search.

Search Notes		
Search Notes	Date	Examiner
Medline, Biosis, Ca, Caplus, Embase, PCTfull, USPatfull, terms: update search history 16/842,209, 16/659,893, 16/036,381, 15/358,187, 14/601,529, 13/660,629, 13/253,595, 12/559,278, 11/459,090	03/07/2023	MN

Interference Search			
US Class/CPC Symbol	US Subclass/CPC Group	Date	Examiner
A61K	9/0021	03/07/2023	MN

OK
TO
ENTER
/MN/
3/7/2023

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Appl. No.:	17/151,938
Filed:	January 19, 2021
Docket No.:	19264.0001USC8

RESPONSE

Commissioner for Patents
P.O. Box 1450
Alexandria, Virginia 22313-1450

Attention: Commissioner for Patents

Please consider and enter the following amendments and/or remarks in response to the recent office action for this patent application.

If a petition for an extension of time under 37 C.F.R. § 1.136(a) is necessary to maintain the pendency of this patent application in connection with this response, and is not otherwise requested in this patent application, it is requested that the Commissioner consider this paper to be a petition for an appropriate extension of time and an authorization for the Commissioner to charge the fee as set forth in 37 C.F.R. § 1.17(a) corresponding to the needed extension of time to Deposit Account No. 13-2725

Remarks

This is in response to the non-final Office Action mailed December 5, 2022. Reconsideration and allowance are requested for at least the following reasons.

Claim Rejections – Double Patenting

Claims 1-20 are rejected on the grounds of non-statutory double patenting as being unpatentable over claims 1-20 of U.S. Patent No. 10,894,011. This rejection is respectfully traversed.

While the correctness of the rejection is not conceded, a terminal disclaimer is filed herewith to address the rejection. Reconsideration is requested.

Conclusion

Favorable reconsideration is requested. Please contact the undersigned with any questions regarding this patent application.

Respectfully submitted,

MERCHANT & GOULD P.C.
P.O. Box 2903
Minneapolis, Minnesota 55402-0903
(612) 332-5300

Date: March 1, 2023

/Robert A. Kalinsky/
Name: Robert A. Kalinsky
Reg. No.: 50,471

* * * * * * * * * * Welcome to STN International * * * * * * * * * *

NEWS 1 OCT 4 MARPAT(R) Enhanced with Patent Status Data
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NEWS 6 FEB 21 USGENE database reload provides updated BLAST and GETSIM versions and new searching capabilities
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NEWS 13 APR 4 The enhanced Derwent World Patents Index(R) is now available on STNext
NEWS 14 APR 4 The Derwent Chemistry Resource (DCR) is now available as a standalone database on STNext
NEWS 15 JUN 22 CAS Customer Center Hours Expanded!
NEWS 16 JUN 22 Claims for Four Additional Patent Authorities Added to CA/CAplus
NEWS 17 JUN 24 SMARTracker SDI Option Now Supported in Derwent Files
NEWS 18 JUN 24 Expanded Claims Coverage and Enhanced HIT Displays of Claims Data in Derwent World Patents Index(R)
NEWS 19 AUG 08 Identification of Substances from Claims Simplified in CAS PatentPak
NEWS 20 SEP 5 September 2022 update to Emtree(R) Now Available in Embase(R)
NEWS 21 SEP 9 Enhanced Coverage of Malaysia, Saudi Arabia, and Georgia Increases Comprehensiveness of INPADOC
NEWS 22 SEP 14 New Preference Setting for Transcript Options Helps Better Manage Transcripts, Increase Their Efficiency
NEWS 23 SEP 22 CAS STNext Structure Editor Update Preserves Functionality, Increases Flexibility
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                                                     ENTRY         SESSION
FULL ESTIMATED COST                                   0.24            0.24

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=> s syphilis (25a) detect?

            6 FILES SEARCHED...

L1        6146 SYPHILIS (25A) DETECT?

=> s l1 (300a) cardiolipin?

L2         187 L1 (300A) CARDIOLIPIN?

=> s l2 (300a) lecithin?

L3          33 L2 (300A) LECITHIN?

=> s l2 and lecithin?

L4          70 L2 AND LECITHIN?

=> s l4 and cholesterol?

L5          61 L4 AND CHOLESTEROL?

=> dup rem l5

PROCESSING COMPLETED FOR L5
L6           39 DUP REM L5 (22 DUPLICATES REMOVED)

=> d ibib kwic 1-39


L6   ANSWER 1 OF 39  CA  COPYRIGHT 2022 ACS on STN     DUPLICATE 1
ACCESSION NUMBER:        179:130667  CA Full-text
TITLE:                   Post-COVID-19 biologically false-positive VDRL: A
                         report
AUTHOR(S):               Ahmed, Ghazal; George C, Anju; Ganguly, Satyaki
CORPORATE SOURCE:        Department of Dermatology, Venereology and Leprosy,
                         All India Institute of Medical Sciences, Raipur,
                         417408, India
SOURCE:                  International Journal of STD & AIDS (2022), 33(5),
                         525-526
```

CODEN: INSAE3; ISSN: 1758-1052
DIGITAL OBJECT ID: 10.1177/09564624221076278
PUBLISHER: Sage Publications Ltd.
DOCUMENT TYPE: Journal; (online computer file)
LANGUAGE: English
AB The venereal disease ref. lab. (VDRL) test of syphilis detects antibodies to a non-specific cardiolipin\lecithin-cholesterol antigen. It is a biol. false pos. (BFP) when VDRL is reactive, but a specific treponemal test is non-reactive. To. . .
IT Antibodies and Immunoglobulins
Cardiolipins
Lecithins
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(post-COVID-19 biol. false-pos. VDRL)

L6 ANSWER 2 OF 39 CA COPYRIGHT 2022 ACS on STN DUPLICATE 2
ACCESSION NUMBER: 178:330963 CA Full-text
TITLE: Electrochemical platform for anti-cardiolipin antibody detection in human syphilitic serum
AUTHOR(S): Do Egito, Elton M. N.; Silva-Junior, Alberto G.; Lucena, Raiza P. S.; Oliveira, Maria D. L.; Andrade, Cesar A. S.
CORPORATE SOURCE: Programa de Pos-Graduacao em Inovacao Terapeutica, Universidade Federal de Pernambuco, Recife, 50670-901, Brazil
SOURCE: Current Research in Biotechnology (2022), 4, 58-65
CODEN: CRBUC6; ISSN: 2590-2628
DIGITAL OBJECT ID: 10.1016/j.crbiot.2022.01.001
PUBLISHER: Elsevier B.V.
DOCUMENT TYPE: Journal; (online computer file)
LANGUAGE: English
REFERENCE COUNT: 44 THERE ARE 44 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT
AB . . . complex samples. In this work, we used a self-assembled monolayer (3-mercaptopropyl)trimethoxysilane (MPTS) to immobilize an antigenic colloidal suspension (contg. cardiolipin, cholesterol, and lecithin) as a biorecognition element in a platform for detecting anti-cardiolipin (anti-C) antibodies in infected human serum. The biosensor platform was. . .
IT Atomic force microscopy
Blood analysis
Blood serum
Cyclic voltammetry
Diagnosis
Dielectric spectroscopy
Electrochemical biosensors
Homo sapiens
Human
Surface structure
Surface treatment
Syphilis
Treponema pallidum
(electrochem. platform for anti-cardiolipin antibody detection in human syphilitic serum)
IT Cardiolipins
Lecithins
RL: ARU (Analytical role, unclassified); ANST (Analytical study)
(electrochem. platform for anti-cardiolipin antibody detection in human syphilitic serum)

L6 ANSWER 3 OF 39 USPATFULL on STN
ACCESSION NUMBER: 2021:181550 USPATFULL Full-text
TITLE: COMBINATION TREPONEMAL AND NON-TREPONEMAL SYPHILIS TEST
INVENTOR(S): Kaul, Ravi, Davis, CA, UNITED STATES
Zheng, Weiming, Emeryville, CA, UNITED STATES
Walker, Roger, Benicia, CA, UNITED STATES
APPLICANT(S): Bio-Rad Laboratories, Inc., Hercules, CA, UNITED STATES

NUMBER	KIND	DATE

PATENT INFORMATION: US 20210156859 A1 20210527
APPLICATION INFO.: US 2021-17170577 A1 20210208 (17)
RELATED APPLN. INFO.: Continuation of Ser. No. US 2020-16832608, filed on 27 Mar 2020, Pat. No. US 10942182 Division of Ser. No. US 2019-16405588, filed on 7 May 2019, Pat. No. US 10648981 Continuation of Ser. No. US 2017-15701272, filed on 11 Sep 2017, Pat. No. US 10324091 Continuation of Ser. No. WO 2016-US21379, filed on 8 Mar 2016, PENDING

	NUMBER	DATE
PRIORITY INFORMATION:	US 2015-62181685	20150618 (62)
	US 2015-62131062	20150310 (62)

DOCUMENT TYPE: Utility
FILE SEGMENT: APPLICATION
NUMBER OF CLAIMS: 20
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 2 Drawing Page(s)
LINE COUNT: 1199
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

SUMM Syphilis is a sexually transmitted disease (STD) caused by the spirochete bacterium Treponema pallidum. Serological tests for syphilis can be classified into two groups, nontreponemal and treponemal tests. Nontreponemal tests detect nontreponemal antibodies (reagin) against lipoidal material released from damaged host cells. The most widely used nontreponemal tests are Venereal Diseases Research Laboratory (VDRL) and rapid plasma reagin (RPR) tests, which are tests (usually flocculation tests) employing a cardiolipin-lecithin-cholesterol-based antigen. Nontreponemal tests have the advantage of being widely available, inexpensive and convenient to perform. Results for these tests usually. . .

SUMM Provided herein are kits to detect nontreponemal and treponemal antibodies in a sample from an individual suspected of having a syphilis infection. In some embodiments, the kit includes (i) a solid support (e.g., microparticles, beads, or surface such as a chip, microtiter plate, membrane, or glass) coated with a lipoidal antigen (e.g., cardiolipin, lecithin, cholesterol, or a mixture thereof); and (ii) a solid support (e.g., microparticles, beads, or surface such as a chip, microtiter plate,. . .

SUMM In some embodiments, the lipoidal antigen is cardiolipin, lecithin or cholesterol. In some embodiments, the Treponema pallidum antigen is r15, r17, r47, a mixture thereof, or a fusion of r17 and. . .

SUMM Further provided are methods of detecting the presence of syphilis antibodies in a sample, e.g., a biological sample from an individual, e.g., a human. In some embodiments, the method comprises (a) contacting the sample with (i) solid support (e.g., microparticles, beads, or surface) coated with lipoidal antigen (e.g., cardiolipin-lecitin-cholesterol antigen) and (ii) solid support (e.g., microparticles, beads, or surface) coated with Treponema pallidum antigen in the same compartment, thereby. . . remove unbound sample; (c) contacting the sample-support mixture with a labeled, anti-immunoglobulin (Ig) antibody (e.g., anti-human Ig antibody); and (d) detecting the presence of syphilis antibodies by detecting the label on the anti-Ig antibody. In some embodiments, step (a) and/or step (c) are carried out in a buffer. . .

DETD . . . and r47 fusion protein), and a nontreponemal test (e.g., beads labeled with a second label and an antigen mixture of cardiolipin-lecithin-cholesterol). The combination test can also comprise labeled anti-human IgG and labeled anti-human IgM reporters (e.g., anti-hIgG-PE and anti-hIgM-PE) to quantify. . .

DETD In this case, the multiplex assay includes a hydophobic component, e.g., a solid support coupled to lipid antigen (e.g., cardiolipin-lecithin-cholesterol), and a hydrophilic component e.g., solid support coupled to a syphilis antigen (e.g., r15, r17, r47, or mixtures or fusions. . .

DETD The nontreponemal antigen mixture can be in an ethanol solution of cardiolipin (a diphosphatidylglycerol purified from beef heart or synthetic), lecithin (from hen egg yolk, soybean, or synthetic), and cholesterol, wherein the weight ratio of cardiolipin, lecithin and cholesterol is in the range of 0.03-1 mg/mL, 0.01-3 mg/mL, and 0.1-10 mg/mL respectively. Other organic solvents like methanol, chloroform,

benzene. . . solubilize the nontreponemal (RPR or VDRL) antigen. The examples show use of VDRL antigen with 0.3 mg/mL cardiolipin, 2.1 mg/mL lecithin, and 9 mg/mL cholesterol.

DETD . . . in the range of approximately 0.01 to 0.5 M or 0.05-0.2 M. In some embodiments, the storage buffer further comprises cholesterol.

DETD The conjugate reagent buffer optionally also include cholesterol in concentrations of 30-150 μg/mL, 30-100 μg/mL, 30 μg/mL, 35 μg/mL, 40 μg/mL or 50 μg/mL. In some embodiments, the cholesterol is bovine cholesterol.

DETD . . . beads coated with a recombinant treponemal r17-r47 fusion protein (Rec Tp17/r47 fusion) and PEI-functionalized beads coated with non-treponemal antigens cardiolipin, lecithin, and cholesterol were mixed in assay buffer (50 mM MOPS, 150 mM NaCl, 0.05% BSA, 10 mM EDTA, 0.1% CHAPS, 20% glycerol,. . .

DETD . . . to the presence of phosphate group) could not be coupled directly on activated carboxylated beads. In order to bind cardiolipin, cholesterol, and lecithin (a trio of lipids) we changed the net charge on magnetic beads by covalently coupling a positively charged group such. . .

CLM What is claimed is:
1. A kit comprising: (i) a solid support coated with cardiolipin-lecithin-cholesterol antigen, wherein the cardiolipin-lecithin-cholesterol antigen is non-covalently attached to the solid support by ionic interaction; and (ii) a solid support coated with Treponema pallidum. . .

CLM What is claimed is:
2. The kit of claim 1, wherein the cardiolipin-lecithin-cholesterol antigen and Treponema pallidum antigen are in the same compartment.

CLM What is claimed is:
. . . claim 1, wherein the solid support of (i) is prepared by incubating a cationic surface of the solid support with cardiolipin-lecithin-cholesterol antigen in a coupling buffer to coat the solid support with cardiolipin-lecithin-cholesterol by ionic interaction.

CLM What is claimed is:
. . . kit of claim 1, wherein the solid support of (i) is functionalized with polyethylenimine to coat the solid support with cardiolipin-lecithin-cholesterol antigen.

CLM What is claimed is:
11. A method of detecting the presence of syphilis antibodies in a sample comprising: (a) contacting the sample with (i) a solid support non-covalently attached to cardiolipin-lecithin-cholesterol antigen, wherein the cardiolipin-lecithin-cholesterol antigen is attached to the solid support by ionic interaction; and (ii) a solid support coated with Treponema pallidum antigen,. . . unbound sample; (c) contacting the solid supports of (i) and (ii) with a labeled, anti-human immunoglobulin (Ig) antibody; and (d) detecting the presence of syphilis antibodies by detecting the label on the anti-human Ig antibody.

CLM What is claimed is:
12. The method of claim 11, wherein the cardiolipin-lecithin-cholesterol antigen and the Treponema pallidum antigen are attached to the same solid support.

CLM What is claimed is:
. . . 11, wherein the solid support of (i) is prepared by incubating a cationic surface of the solid support with the cardiolipin-lecithin-cholesterol antigen in a coupling buffer to coat the solid support with cardiolipin-lecithin-cholesterol by ionic interaction.

CLM What is claimed is:
. . . 11, wherein the surface of the solid support of (i) is functionalized with polyethylenimine to coat the solid surface with cardiolipin-lecithin-cholesterol antigen.

L6 ANSWER 4 OF 39 USPATFULL on STN
ACCESSION NUMBER: 2020:258223 USPATFULL Full-text
TITLE: COMBINATION TREPONEMAL AND NON-TREPONEMAL SYPHILIS TEST
INVENTOR(S): Kaul, Ravi, Davis, CA, UNITED STATES
Zheng, Weiming, Emeryville, CA, UNITED STATES
Walker, Roger, Benicia, CA, UNITED STATES
APPLICANT(S): Bio-Rad Laboratories, Inc., Hercules, CA, UNITED STATES

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 20200225230	A1	20200716
	US 10942182	B2	20210309
APPLICATION INFO.:	US 2020-16832608	A1	20200327 (16)

RELATED APPLN. INFO.: Division of Ser. No. US 2019-16405588, filed on 7 May 2019, Pat. No. US 10648981 Continuation of Ser. No. US 2017-15701272, filed on 11 Sep 2017, Pat. No. US 10324091 Continuation of Ser. No. WO 2016-US21379, filed on 8 Mar 2016, PENDING

	NUMBER	DATE
PRIORITY INFORMATION:	US 2015-62181685	20150618 (62)
	US 2015-62131062	20150310 (62)

DOCUMENT TYPE: Utility
FILE SEGMENT: APPLICATION
NUMBER OF CLAIMS: 20
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 2 Drawing Page(s)
LINE COUNT: 1164
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

SUMM Syphilis is a sexually transmitted disease (STD) caused by the spirochete bacterium Treponema pallidum. Serological tests for syphilis can be classified into two groups, nontreponemal and treponemal tests. Nontreponemal tests detect nontreponemal antibodies (reagin) against lipoidal material released from damaged host cells. The most widely used nontreponemal tests are Venereal Diseases Research Laboratory (VDRL) and rapid plasma reagin (RPR) tests, which are tests (usually flocculation tests) employing a cardiolipin-lecithin-cholesterol-based antigen. Nontreponemal tests have the advantage of being widely available, inexpensive and convenient to perform. Results for these tests usually. . .

SUMM Provided herein are kits to detect nontreponemal and treponemal antibodies in a sample from an individual suspected of having a syphilis infection. In some embodiments, the kit includes (i) a solid support (e.g., microparticles, beads, or surface such as a chip, microtiter plate, membrane, or glass) coated with a lipoidal antigen (e.g., cardiolipin, lecithin, cholesterol, or a mixture thereof); and (ii) a solid support (e.g., microparticles, beads, or surface such as a chip, microtiter plate,. . .

SUMM In some embodiments, the lipoidal antigen is cardiolipin, lecithin or cholesterol. In some embodiments, the Treponema pallidum antigen is r15, r17, r47, a mixture thereof, or a fusion of r17 and. . .

SUMM Further provided are methods of detecting the presence of syphilis antibodies in a sample, e.g., a biological sample from an individual, e.g., a human. In some embodiments, the method comprises (a) contacting the sample with (i) solid support (e.g., microparticles, beads, or surface) coated with lipoidal antigen (e.g., cardiolipin-lecitin-cholesterol antigen) and (ii) solid support (e.g., microparticles, beads, or surface) coated with Treponema pallidum antigen in the same compartment, thereby. . . remove unbound sample; (c) contacting the sample-support mixture with a labeled, anti-immunoglobulin (Ig) antibody (e.g., anti-human Ig antibody); and (d) detecting the presence of syphilis antibodies by detecting the label on the anti-Ig antibody. In some embodiments, step (a) and/or step (c) are carried out in a buffer. . .

DETD . . . and r47 fusion protein), and a nontreponemal test (e.g., beads labeled with a second label and an antigen mixture of cardiolipin-lecithin-cholesterol). The combination test can also comprise labeled anti-human IgG and labeled anti-human IgM reporters (e.g., anti-hIgG-PE and anti-hIgM-PE) to quantify. . .

DETD In this case, the multiplex assay includes a hydophobic component, e.g., a solid support coupled to lipid antigen (e.g.,

cardiolipin-lecithin-cholesterol), and a hydrophilic component e.g., solid support coupled to a syphilis antigen (e.g., r15, r17, r47, or mixtures or fusions. . .

DETD The nontreponemal antigen mixture can be in an ethanol solution of cardiolipin (a diphosphatidylglycerol purified from beef heart or synthetic), lecithin (from hen egg yolk, soybean, or synthetic), and cholesterol, wherein the weight ratio of cardiolipin, lecithin and cholesterol is in the range of 0.03-1 mg/mL, 0.01-3 mg/mL, and 0.1-10 mg/mL respectively. Other organic solvents like methanol, chloroform, benzene. . . solubilize the nontreponemal (RPR or VDRL) antigen. The examples show use of VDRL antigen with 0.3 mg/mL cardiolipin, 2.1 mg/mL lecithin, and 9 mg/mL cholesterol.

DETD . . . in the range of approximately 0.01 to 0.5 M or 0.05-0.2 M. In some embodiments, the storage buffer further comprises cholesterol.

DETD The conjugate reagent buffer optionally also include cholesterol in concentrations of 30-150 μg/mL, 30-100 μg/mL, 30 μg/mL, 35 μg/mL, 40 μg/mL or 50 μg/mL. In some embodiments, the cholesterol is bovine cholesterol.

DETD . . . beads coated with a recombinant treponemal r17-r47 fusion protein (Rec Tp17/r47 fusion) and PEI-functionalized beads coated with non-treponemal antigens cardiolipin, lecithin, and cholesterol were mixed in assay buffer (50 mM MOPS, 150 mM NaCl, 0.05% BSA, 10 mM EDTA, 0.1% CHAPS, 20% glycerol,. . .

DETD . . . to the presence of phosphate group) could not be coupled directly on activated carboxylated beads. In order to bind cardiolipin, cholesterol, and lecithin (a trio of lipids) we changed the net charge on magnetic beads by covalently coupling a positively charged group such. . .

CLM What is claimed is:
1. A kit comprising: (i) beads coated with cardiolipin-lecithin-cholesterol antigen; and (ii) beads coated with Treponema pallidum antigen.

CLM What is claimed is:
3. The kit of claim 1, wherein the beads of (i) are non-covalently attached to the cardiolipin-lecithin-cholesterol antigen.

CLM What is claimed is:
5. The kit of claim 3, wherein the beads of (i) are prepared by incubating cationic beads with cardiolipin-lecithin-cholesterol antigen in a coupling buffer to coat the beads with cardiolipin-lecithin-cholesterol by ionic interaction.

CLM What is claimed is:
. . . 6. The kit of claim 1, wherein the beads of (i) are functionalized with polyethylenimine to coat the beads with cardiolipin-lecithin-cholesterol antigen.

L6 ANSWER 5 OF 39 CA COPYRIGHT 2022 ACS on STN DUPLICATE 3
ACCESSION NUMBER: 172:14052 CA Full-text
TITLE: Syphilis non-specific antibody quality control setting serum, preparation method, application and kit for syphilis detection
INVENTOR(S): Zheng, Heping; Qin, Xiaolin
PATENT ASSIGNEE(S): Dermatology Hospital of Southern Medical University, Peop. Rep. China
SOURCE: Faming Zhuanli Shenqing, 14pp.
CODEN: CNXXEV
DOCUMENT TYPE: Patent
LANGUAGE: Chinese
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
CN 110456086	A	20191115	CN 2019-10714707	20190802

PRIORITY APPLN. INFO.: CN 2019-10714707 20190802
PATENT STATUS PATENT INFORMATION:

PATENT NO.	KIND	STATUS	STATUS DATE

CN 110456086 A Alive 20201121

IT Cardiolipins
Lecithins
RL: ARG (Analytical reagent use); ANST (Analytical study); USES (Uses)
(syphilis non-specific antibody quality control setting serum, prepn. method, application and kit for syphilis detection)

IT 57-88-5, Cholesterol, uses
RL: ARG (Analytical reagent use); ANST (Analytical study); USES (Uses)
(syphilis non-specific antibody quality control setting serum, prepn. method, application and kit for syphilis detection)

L6 ANSWER 6 OF 39 USPATFULL on STN

ACCESSION NUMBER:	2019:303731 USPATFULL Full-text		
TITLE:	COMBINATION TREPONEMAL AND NON-TREPONEMAL SYPHILIS TEST		
INVENTOR(S):	Kaul, Ravi, Davis, CA, UNITED STATES Zheng, Weiming, Emeryville, CA, UNITED STATES Walker, Roger, Benicia, CA, UNITED STATES		
APPLICANT(S):	Bio-Rad Laboratories, Inc., Hercules, CA, UNITED STATES		
	NUMBER	KIND	DATE
PATENT INFORMATION:	US 20190265240	A1	20190829
	US 10648981	B2	20200512
APPLICATION INFO.:	US 2019-16405588	A1	20190507 (16)
RELATED APPLN. INFO.:	Continuation of Ser. No. US 2017-15701272, filed on 11 Sep 2017, Pat. No. US 10324091 Continuation of Ser. No. WO 2016-US21379, filed on 8 Mar 2016, PENDING		
	NUMBER		DATE
PRIORITY INFORMATION:	US 2015-62181685		20150618 (62)
	US 2015-62131062		20150310 (62)
DOCUMENT TYPE:	Utility		
FILE SEGMENT:	APPLICATION		
NUMBER OF CLAIMS:	9		
EXEMPLARY CLAIM:	1		
NUMBER OF DRAWINGS:	2 Drawing Page(s)		
LINE COUNT:	1152		

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

SUMM Syphilis is a sexually transmitted disease (STD) caused by the spirochete bacterium Treponema pallidum . Serological tests for syphilis can be classified into two groups, nontreponemal and treponemal tests. Nontreponemal tests detect nontreponemal antibodies (reagin) against lipoidal material released from damaged host cells. The most widely used nontreponemal tests are Venereal Diseases Research Laboratory (VDRL) and rapid plasma reagin (RPR) tests, which are tests (usually flocculation tests) employing a cardiolipin-lecithin-cholesterol-based antigen. Nontreponemal tests have the advantage of being widely available, inexpensive and convenient to perform. Results for these tests usually. . .

SUMM Provided herein are kits to detect nontreponemal and treponemal antibodies in a sample from an individual suspected of having a syphilis infection. In some embodiments, the kit includes (i) a solid support (e.g., microparticles, beads, or surface such as a chip, microtiter plate, membrane, or glass) coated with a lipoidal antigen (e.g., cardiolipin, lecithin, cholesterol, or a mixture thereof); and (ii) a solid support (e.g., microparticles, beads, or surface such as a chip, microtiter plate,. . .

SUMM In some embodiments, the lipoidal antigen is cardiolipin, lecithin or cholesterol. In some embodiments, the Treponema pallidum antigen is r15, r17, r47, a mixture thereof, or a fusion of r17 and. . .

SUMM Further provided are methods of detecting the presence of syphilis antibodies in a sample, e.g., a biological sample from an individual, e.g., a human. In some embodiments, the method comprises (a) contacting the sample with (i) solid support (e.g., microparticles, beads, or surface) coated with lipoidal antigen (e.g., cardiolipin-lecitin-cholesterol antigen) and (ii) solid support (e.g., microparticles, beads, or surface) coated with Treponema pallidum antigen in the same compartment, thereby. . . remove unbound sample; (c) contacting the sample-support mixture with a labeled,

anti-immunoglobulin (Ig) antibody (e.g., anti-human Ig antibody); and (d) detecting the presence of syphilis antibodies by detecting the label on the anti-Ig antibody. In some embodiments, step (a) and/or step (c) are carried out in a buffer. . .

DETD . . . and r47 fusion protein), and a nontreponemal test (e.g., beads labeled with a second label and an antigen mixture of cardiolipin-lecithin-cholesterol). The combination test can also comprise labeled anti-human IgG and labeled anti-human IgM reporters (e.g., anti-hIgG-PE and anti-hIgM-PE) to quantify. . .

DETD In this case, the multiplex assay includes a hydophobic component, e.g., a solid support coupled to lipid antigen (e.g., cardiolipin-lecithin-cholesterol), and a hydrophilic component e.g., solid support coupled to a syphilis antigen (e.g., r15, r17, r47, or mixtures or fusions. . .

DETD The nontreponemal antigen mixture can be in an ethanol solution of cardiolipin (a diphosphatidylglycerol purified from beef heart or synthetic), lecithin (from hen egg yolk, soybean, or synthetic), and cholesterol, wherein the weight ratio of cardiolipin, lecithin and cholesterol is in the range of 0.03-1 mg/mL, 0.01-3 mg/mL, and 0.1-10 mg/mL respectively. Other organic solvents like methanol, chloroform, benzene. . . solubilize the nontreponemal (RPR or VDRL) antigen. The examples show use of VDRL antigen with 0.3 mg/mL cardiolipin, 2.1 mg/mL lecithin, and 9 mg/mL cholesterol.

DETD . . . in the range of approximately 0.01 to 0.5 M or 0.05-0.2 M. In some embodiments, the storage buffer further comprises cholesterol.

DETD The conjugate reagent buffer optionally also include cholesterol in concentrations of 30-150 μg/mL, 30-100 μg/mL, 30 μg/mL, 35 μg/mL, 40 μg/mL or 50 μg/mL. In some embodiments, the cholesterol is bovine cholesterol.

DETD . . . beads coated with a recombinant treponemal r17-r47 fusion protein (Rec Tp17/r47 fusion) and PEI-functionalized beads coated with non-treponemal antigens cardiolipin, lecithin, and cholesterol were mixed in assay buffer (50 mM MOPS, 150 mM NaCl, 0.05% BSA, 10 mM EDTA, 0.1% CHAPS, 20% glycerol,. . .

DETD . . . to the presence of phosphate group) could not be coupled directly on activated carboxylated beads. In order to bind cardiolipin, cholesterol, and lecithin (a trio of lipids) we changed the net charge on magnetic beads by covalently coupling a positively charged group such. . .

CLM What is claimed is:
1. A kit comprising: (i) beads coated with cardiolipin-lecithin-cholesterol antigen; and (ii) beads coated with Treponema pallidum antigen.

CLM What is claimed is:
2. A method of detecting the presence of syphilis antibodies in a sample comprising: (a) contacting the sample with (i) beads coated with cardiolipin-lecitin-cholesterol antigen and (ii) beads coated with Treponema pallidum antigen in the same compartment, thereby forming a sample-bead mixture; (b) washing. . . sample-bead mixture to remove unbound sample; (c) contacting the sample-bead mixture with a labeled, anti-human immunoglobulin (Ig) antibody; and (d) detecting the presence of syphilis antibodies by detecting the label on the anti-human Ig antibody.

CLM What is claimed is:
9. The method of claim 2, wherein the beads of (i) are cationic, and the cardiolipin-lecitin-cholesterol antigen is attached to the beads via an ionic interaction; and/or the beads of (i) are functionalized with polyethylenimine.

L6 ANSWER 7 OF 39 EMBASE COPYRIGHT (c) 2022 Elsevier B.V. All rights reserved on STN

ACCESSION NUMBER: 0053142831 EMBASE Full-text
DOCUMENT NUMBER: 623263472
TITLE: Performance of the syphilis serology algorithm diagnosis.
AUTHOR: Balada-Llasat, Joan-Miquel (correspondence)
CORPORATE SOURCE: Ohio State Univ., Col. of Med, United States.
SOURCE: Journal of Immunology, (May 2018) Vol. 200, No. 1, Supp. Supplement 1. Abstract Number: 117.1.

Meeting Info: 105th Annual Meeting of the American Association of Immunologists, IMMUNOLOGY 2018. Austin, TX, United States. 04 May 2018-08 May 2018
ISSN: 1550-6606
PUBLISHER: American Association of Immunologists.
COUNTRY: Netherlands
DOCUMENT TYPE: Journal; Conference; (Conference Abstract)
FILE SEGMENT: CONF
FILE SEGMENT: Intellectual Indexing
LANGUAGE: English
SUMMARY LANGUAGE: English
ENTRY DATE: Entered Embase: 2 Aug 2018
Last Updated on Embase: 2 Aug 2018
Indexing Added: 2 Aug 2018
First Entered Embase or Embase Alert: 2 Aug 2018

AB . . . on microspheres to detect IgG to T. pallidum. If reactive, a nontreponemal test, rapid plasma reagin (RPR), is used to detect antibodies against cardiolipin-cholesterol-lecithin antigens, though not specific they are present in most patients with syphilis. If results are reactive with MFI but nonreactive with RPR, a second treponemal-specific antibody test using T. pallidum particle agglutination. . .

L6 ANSWER 8 OF 39 USPATFULL on STN
ACCESSION NUMBER: 2017:426008 USPATFULL Full-text
TITLE: COMBINATION TREPONEMAL AND NON-TREPONEMAL SYPHILIS TEST
INVENTOR(S): Kaul, Ravi, Davis, CA, UNITED STATES
Zheng, Weiming, Emeryville, CA, UNITED STATES
Walker, Roger, Benicia, CA, UNITED STATES
APPLICANT(S): Bio-Rad Laboratories, Inc., Hercules, CA, UNITED STATES

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 20170370931	A1	20171228
	US 10324091	B2	20190618
APPLICATION INFO.:	US 2017-15701272	A1	20170911 (15)

RELATED APPLN. INFO.: Continuation of Ser. No. WO 2016-US21379, filed on 8 Mar 2016, PENDING

	NUMBER	DATE
PRIORITY INFORMATION:	US 2015-62181685	20150618 (62)
	US 2015-62131062	20150310 (62)

DOCUMENT TYPE: Utility
FILE SEGMENT: APPLICATION
NUMBER OF CLAIMS: 20
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 2 Drawing Page(s)
LINE COUNT: 1203
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

SUMM Syphilis is a sexually transmitted disease (STD) caused by the spirochete bacterium Treponema pallidum. Serological tests for syphilis can be classified into two groups, nontreponemal and treponemal tests. Nontreponemal tests detect nontreponemal antibodies (reagin) against lipoidal material released from damaged host cells. The most widely used nontreponemal tests are Venereal Diseases Research Laboratory (VDRL) and rapid plasma reagin (RPR) tests, which are tests (usually flocculation tests) employing a cardiolipin-lecithin-cholesterol-based antigen. Nontreponemal tests have the advantage of being widely available, inexpensive and convenient to perform. Results for these tests usually. . .

SUMM Provided herein are kits to detect nontreponemal and treponemal antibodies in a sample from an individual suspected of having a syphilis infection. In some embodiments, the kit includes (i) a solid support (e.g., microparticles, beads, or surface such as a chip, microtiter plate, membrane, or glass) coated with a lipoidal antigen (e.g., cardiolipin, lecithin, cholesterol, or a mixture thereof); and (ii) a solid support (e.g., microparticles, beads, or surface such as a chip, microtiter plate,. . .

SUMM In some embodiments, the lipoidal antigen is cardiolipin, lecithin or cholesterol. In some embodiments, the Treponema pallidum antigen is

r15, r17, r47, a mixture thereof, or a fusion of r17 and. . .

SUMM Further provided are methods of detecting the presence of syphilis antibodies in a sample, e.g., a biological sample from an individual, e.g., a human. In some embodiments, the method comprises (a) contacting the sample with (i) solid support (e.g., microparticles, beads, or surface) coated with lipoidal antigen (e.g., cardiolipin-lecitin-cholesterol antigen) and (ii) solid support (e.g., microparticles, beads, or surface) coated with Treponema pallidum antigen in the same compartment, thereby. . . remove unbound sample; (c) contacting the sample-support mixture with a labeled, anti-immunoglobulin (Ig) antibody (e.g., anti-human Ig antibody); and (d) detecting the presence of syphilis antibodies by detecting the label on the anti-Ig antibody. In some embodiments, step (a) and/or step (c) are carried out in a buffer. . .

DETD . . . and r47 fusion protein), and a nontreponemal test (e.g., beads labeled with a second label and an antigen mixture of cardiolipin-lecithin-cholesterol). The combination test can also comprise labeled anti-human IgG and labeled anti-human IgM reporters (e.g., anti-hIgG-PE and anti-hIgM-PE) to quantify. . .

DETD In this case, the multiplex assay includes a hydophobic component, e.g., a solid support coupled to lipid antigen (e.g., cardiolipin-lecithin-cholesterol), and a hydrophilic component e.g., solid support coupled to a syphilis antigen (e.g., r15, r17, r47, or mixtures or fusions. . .

DETD The nontreponemal antigen mixture can be in an ethanol solution of cardiolipin (a diphosphatidylglycerol purified from beef heart or synthetic), lecithin (from hen egg yolk, soybean, or synthetic), and cholesterol, wherein the weight ratio of cardiolipin, lecithin and cholesterol is in the range of 0.03-1 mg/mL, 0.01-3 mg/mL, and 0.1-10 mg/mL respectively. Other organic solvents like methanol, chloroform, benzene. . . solubilize the nontreponemal (RPR or VDRL) antigen. The examples show use of VDRL antigen with 0.3 mg/mL cardiolipin, 2.1 mg/mL lecithin, and 9 mg/mL cholesterol.

DETD . . . in the range of approximately 0.01 to 0.5 M or 0.05-0.2 M. In some embodiments, the storage buffer further comprises cholesterol.

DETD The conjugate reagent buffer optionally also include cholesterol in concentrations of 30-150 μg/mL, 30-100 μg/mL, 30 μg/mL, 35 μg/mL, 40 μg/mL or 50 μg/mL. In some embodiments, the cholesterol is bovine cholesterol.

DETD . . . beads coated with a recombinant treponemal r17-r47 fusion protein (Rec Tp17/r47 fusion) and PEI-functionalized beads coated with non-treponemal antigens cardiolipin, lecithin, and cholesterol were mixed in assay buffer (50 mM MOPS, 150 mM NaCl, 0.05% BSA, 10 mM EDTA, 0.1% CHAPS, 20% glycerol,. . .

DETD . . . to the presence of phosphate group) could not be coupled directly on activated carboxylated beads. In order to bind cardiolipin, cholesterol, and lecithin (a trio of lipids) we changed the net charge on magnetic beads by covalently coupling a positively charged group such. . .

CLM What is claimed is:
1. A kit comprising: (i) beads coated with cardiolipin-lecithin-cholesterol antigen; and (ii) beads coated with Treponema pallidum antigen.

CLM What is claimed is:
8. The kit of claim 1, wherein the beads coated with cardiolipin-lecithin-cholesterol antigen are stored in storage solution lacking non-ionic detergent and/or the kit further comprises a wash or wash stock solution. . .

CLM What is claimed is:
10. The kit of claim 1, wherein the beads of (i) are cationic, and the cardiolipin-lecitin-cholesterol antigen is attached to the beads via an ionic interaction; and/or the beads of (i) are functionalized with polyethylenimine (PEI).
. . .

CLM What is claimed is:
13. A method of detecting the presence of syphilis antibodies in a sample comprising: (a) contacting the sample with (i) beads coated with cardiolipin-lecitin-cholesterol antigen and (ii) beads coated with Treponema pallidum antigen in the same compartment, thereby forming a sample-bead mixture; (b) washing. . . sample-bead mixture to remove unbound sample; (c) contacting the sample-bead mixture with a labeled,

anti-human immunoglobulin (Ig) antibody; and (d) detecting the presence of syphilis antibodies by detecting the label on the anti-human Ig antibody.

CLM What is claimed is:
20. The method of claim 13, wherein the beads of (i) are cationic, and the cardiolipin-lecitin-cholesterol antigen is attached to the beads via an ionic interaction; and/or the beads of (i) are functionalized with polyethylenimine.

L6 ANSWER 9 OF 39 PCTFULL COPYRIGHT 2022 LNU on STN
ACCESSION NUMBER: 2016144962 PCTFULL Full-text
ENTRY DATE: 20160919
UPDATE DATE: 20220606
ENTRY DATE (FULLTEXT): 20160919
DATA ENTRY DATE: 20160915
DATA UPDATE DATE: 20220531
TITLE (ENGLISH): COMBINATION TREPONEMAL AND NON-TREPONEMAL SYPHILIS TEST
TITLE (FRENCH): TEST DE LA SYPHILIS COMBINE TREPONEMIQUE ET NON TREPONEMIQUE
INVENTOR(S): KAUL, Ravi, 1000 Alfred Nobel Drive, Hercules, California 94547, US, for all designated states
ZHENG, Weiming, 1000 Alfred Nobel Drive, Hercules, California 94547, US, for all designated states
WALKER, Roger, 1000 Alfred Nobel Drive, Hercules, California 94547, US, for all designated states
PATENT APPLICANT(S): BIO-RAD LABORATORIES, INC., 1000 Alfred Nobel Drive, Hercules, California 94547, US, [NAT: US, RES: US], for all designated states
AGENT: LOCKYER, Jean M. et al., Kilpatrick Townsend & Stockton LLP, Two Embarcadero Center, 8th Floor, San Francisco, California 94111, US
LANGUAGE OF FILING: English
LANGUAGE OF PUBL.: English
DOCUMENT TYPE: Patent; (Fulltext)
PATENT INFORMATION: WO 2016144962 A1 20160915
DESIGNATED STATES:
W: AE AG AL AM AO AT AU AZ BA BB BG BH BN BR BW BY BZ CA CH CL CN CO CR CU CZ DE DK DM DO DZ EC EE EG ES FI GB GD GE GH GM GT HN HR HU ID IL IN IR IS JP KE KG KN KP KR KZ LA LC LK LR LS LU LY MA MD ME MG MK MN MW MX MY MZ NA NG NI NO NZ OM PA PE PG PH PL PT QA RO RS RU RW SA SC SD SE SG SK SL SM ST SV SY TH TJ TM TN TR TT TZ UA UG US UZ VC VN ZA ZM ZW
RW (ARIPO): BW GH GM KE LR LS MW MZ NA RW SD SL ST SZ TZ UG ZM ZW
RW (EAPO): AM AZ BY KG KZ RU TJ TM
RW (EPO): AL AT BE BG CH CY CZ DE DK EE ES FI FR GB GR HR HU IE IS IT LT LU LV MC MK MT NL NO PL PT RO RS SE SI SK SM TR
RW (OAPI): BF BJ CF CG CI CM GA GN GQ GW KM ML MR NE SN TD TG
APPLICATION INFO.: WO 2016-US21379 20160308
PRIORITY INFO.: US 2015-62131062 20150310
US 2015-62181685 20150618

DETDEN
[0002] Syphilis is a sexually transmitted disease (STD) caused by the spirochete bacterium Treponema pallidum. Serological tests for syphilis can be classified into two groups, nontreponemal and treponemal tests. Nontreponemal tests detect nontreponemal antibodies (reagin) against lipoidal material released from damaged host ceils. The most widely used nontreponemal tests are Venereal Diseases Research Laboratory (VDRL) and rapid plasma reagin (RPR) tests, which are tests (usually flocculation tests) employing a cardiolipin-lecithin-cholesterol-based antigen. Nontreponemal tests have the advantage of being widely available, inexpensive and convenient to perform. Results for these tests usually. . .

DETDEN
[0004] Provided herein are kits to detect nontreponemal and treponemal antibodies in a sample from an individual suspected of having a syphilis infection. In some embodiments, the kit includes (i) a solid support (e.g.,

microparticles, beads, or surface such as a chip, microtiter plate, membrane, or glass) coated with a lipoidal antigen (e.g., cardiolipin, lecithin, cholesterol, or a mixture thereof); and (ii) a solid support (e.g., microparticles, beads, or surface such as a chip, microtiter plate,. . . .

DETDEN
[0005] In some embodiments, the lipoidal antigen is cardiolipin, lecithin or cholesterol. In some embodiments, the Treponema pallidum antigen is rl5, rl7, r47, a mixture thereof, or a fusion of rl7 and. . .

DETDEN
[0010] Further pro vided are methods of detecting the presence of syphilis antibodies m a sample, e.g., a biological sample from an individual, e.g., a human. In some embodiments, the method comprises (a) contacting the sample with (i) solid support (e.g., microparticles, beads, or surface) coated with lipoidal antigen (e.g., cardiolipin-iecitin-cholesterol antigen) and (ii) solid support (e.g., microparticles, beads, or surface) coated with Treponema pallidum antigen in the same compartment, thereby. . . remove unbound sample; (X212E) contacting the sample-support mixture with a labeled, anti-immunoglobulin (Ig) antibody (e.g., anti-human Ig antibody); and (d) detecting the presence of syphilis antibodies by detecting the label on the anti-Ig antibody. In some embodiments, step (a) and/or step (c) are carried out in a buffer. . .

DETDEN . . .
[0042] In this case, the multiplex assay includes a hydophobic component, e.g., a solid support coupled to lipid antigen (e.g., cardiolipin-lecithin-choiesterol), and a hydrophilic component e.g., solid support coupled to a syphilis antigen (e.g., r]5, rl7, r47, or mixtures or fusions. . .

DETDEN . . .
The nontreponemal antigen mixture can be in an ethanol solution of cardiolipin (a diphosphatidylglycerol purified from beef heart or synthetic), lecithin (from hen egg yolk, soybean, or synthetic), and cholesterol, wherein the weight ratio of cardiolipin, lecithin and cholesterol is in the range of 0.03-1 mg/mL, 0.01-3 mg/mL, and 0.1-10 mg/mL respectively.

DETDEN . . .
solubilize the nontreponemal (RPR or VDRL) antigen. The examples show' use of VDRL antigen with 0.3 mg/mL cardiolipin, 2.1 mg/mL lecithin, and 9 mg/mL cholesterol.

DETDEN . . .
in the range of approximately 0.01 to 0.5 Μ or 0.05-0.2 Μ. In some embodiments, the storage buffer further comprises cholesterol.

DETDEN
[0052] The conjugate reagent buffer optionally also include cholesterol in concentrations of 30-150 pg/mL, 30-100 pg/mL, 30 pg/mL, 35 pg/mL, 40 pg/mL or 50 pg/mL. In some embodiments, the cholesterol is bovine cholesterol.

DETDEN . . .
beads coated with a recombinant treponemal rl7-r47 fusion protein (Rec Tp17Μ7 fusion) and PEI-functionalized beads coated with non-treponemal antigens cardiolipin, lecithin, and cholesterol were mixed in assay buffer (50mM MOPS, 150mM NaCi, 0.05% BSA, lOmM EDTA, 0.1% CHAPS, 20% glycerol, and 0.095% sodium. . .

DETDEN . . .
to the presence of phosphate group) could not be coupled directly on activated carboxylated beads. In order to bind cardiolipin, cholesterol, and lecithin (a trio of lipids) we changed the net charge on magnetic beads by covalently coupling a positively charged group such. . .

CLMEN
1. A kit comprising: (i) beads coated with cardiolipin-lecithin-choiesterol antigen: and (ii) beads coated with Treponema pallidum antigen.

CLMEN
11. Tire kit of any one of the foregoing claims , wherein the beads coated

with cardiolipin-lecithin-cholesterol antigen are stored in storage solution lacking non-ionic detergent.

CLMEN. . .
15. The kit of any one of the foregoing claims , wherein the heads of (i) are cationic, and the cardiolipin-lecitin-cholesterol antigen is attached to the beads via an ionic interaction.

CLMEN
30. The method of any one of claims 20-29 , wherein the beads of (i) are cationic, and the cardiolipin-lecitin-cholesterol antigen is attached to the beads via an ionic interaction.

L6 ANSWER 10 OF 39 USPATFULL on STN

ACCESSION NUMBER:	2015:425498 USPATFULL Full-text		
TITLE:	Serological Methods and Diagnostic Tests for Syphilis Antibodies		
INVENTOR(S):	Kiefer, David J., Miami Springs, FL, UNITED STATES Compain, Oscar R., Coral Gables, FL, UNITED STATES		
APPLICANT(S):	Awareness Technology Inc., Palm City, FL, UNITED STATES		
	NUMBER	KIND	DATE
PATENT INFORMATION:	US 20150377902	A1	20151231
	US 9482674	B2	20161101
APPLICATION INFO.:	US 2015-14850633	A1	20150910 (14)
RELATED APPLN. INFO.:	Continuation of Ser. No. US 2014-14561333, filed on 5 Dec 2014, Pat. No. US 9170259 Continuation of Ser. No. US 2014-14191014, filed on 26 Feb 2014, Pat. No. US 8945827		
	NUMBER		DATE
PRIORITY INFORMATION:	US 2013-61778544		20130313 (61)
DOCUMENT TYPE:	Utility		
FILE SEGMENT:	APPLICATION		
NUMBER OF CLAIMS:	1		
EXEMPLARY CLAIM:	1		
NUMBER OF DRAWINGS:	5 Drawing Page(s)		
LINE COUNT:	717		

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB A method of detecting antibodies to syphilis antigens includes providing a syphilis detection kit having a screening solid-phase platform with a screening portion coated with non-treponemal syphilis antigens. The screening portion is fabricated by initially dissolving cholesterol in an organic solvent and further diluting the dissolved cholesterol in an ethanol solution comprising cardiolipin and lecithin to form an antigen solution, permitting the antigen solution to evaporate at the screening portion and at least partially coating. . .

SUMM The VDRL Test is a non-treponemal serological screening for syphilis used to assess response to therapy, to detect CNS involvement, and as an aid in the diagnosis of congenital syphilis. The basis of the test is that antibody (IgG, IgM or IgA), produced by a patient with syphilis, reacts with a compound comprised of cardiolipin, cholesterol, and lecithin. The test is performed by mixing the patients serum with compound described above. Positive sera result in "flocculation." Simply put,. . .

SUMM . . . also is a manual test, with a qualitative, subjective, visual readout. The RPR Test utilizes a colloidal suspension of cardiolipin, cholesterol, and lecithin, mixed with micro-particulate carbon. Thus, the RPR Test uses the same antigen as the VDRL Test, but, in the RPR. . .

SUMM Three components comprise the VDRL antigen: cardiolipin; cholesterol; and lecithin. These components are lipid in nature. As such, they are not soluble in aqueous solution. In the classical VDRL test,. . .

SUMM . . . and specificity of the VDRL ELISA Test include the following:

1) The formulation, i.e., relative concentrations of the cardiolipin, cholesterol, lecithin antigen preparation, contributes to the sensitivity and specificity of the test.

2) The formulation of a post-coating solution prevents non-specific binding. . .

SUMM . . . component of the VDRL antigen preparation, is inherently unstable.

2) Cardiolipin and the other components of the antigen preparation, cholesterol and lecithin, are not soluble in aqueous solution and, therefore, cannot be bound to polystyrene wells by conventional measures.

SUMM The inventive systems and processes are not limited to particular cardiolipins or cholesterol. The inventive systems and processes are envisioned to use natural or purified-from-natural cardiolipins or even synthesized cardiolipins. It is possible. . . used even if they are inherently stable. The inventive systems and processes are envisioned to also be used with synthesized cholesterol and/or synthesized lecithin.

SUMM 1) The cholesterol is initially dissolved in an organic solvent, and is then further diluted in an ethanol solution containing cardiolipin and lecithin.

2) A small volume (e.g., 50 microliter) of the antigen solution is permitted to evaporate in place, in polystyrene. . .

SUMM . . . with the invention, a method of manufacturing a non-treponemal diagnostic test for syphilis infection includes the steps of initially dissolving cholesterol in an organic solvent and further diluting the dissolved cholesterol in an ethanol solution comprising cardiolipin and lecithin to form an antigen solution, permitting a volume of the antigen solution to evaporate in place within a container and. . .

SUMM . . . is also provided a method of manufacturing a non-treponemal diagnostic test for syphilis infection including the steps of initially dissolving cholesterol in an organic solvent and further diluting the dissolved cholesterol in an ethanol solution comprising cardiolipin and lecithin to form an antigen solution, permitting a volume of the antigen solution to evaporate in place within a container and. . . enzyme-labeled conjugate component of a syphilis infection test that is formulated to be compatible with a lipid nature of the cholesterol, the cardiolipin, and the lecithin, providing a sample diluent that is formulated to be compatible with the lipid nature of the cholesterol, the cardiolipin, and the lecithin, providing a wash fluid that is formulated to be compatible with the lipid nature of the cholesterol, the cardiolipin, and the lecithin, and providing an enzyme substrate that is formulated to be compatible with the lipid nature of the cholesterol, the cardiolipin, and the lecithin.

SUMM In accordance with yet a further mode of the invention, the cholesterol is a natural cholesterol, a purified-from-natural cholesterol, and/or a synthesized cholesterol.

SUMM In accordance with yet an additional mode of the invention, the lecithin is a natural lecithin, a purified-from-natural lecithin, and/or a synthesized lecithin.

SUMM . . . enzyme-labeled conjugate component of a syphilis infection test that is formulated to be compatible with a lipid nature of the cholesterol, the cardiolipin, and the lecithin is provided, a sample diluent that is formulated to be compatible with the lipid nature of the cholesterol, the cardiolipin, and the lecithin is provided, a wash fluid that is formulated to be compatible with the lipid nature of the cholesterol, the cardiolipin, and the lecithin is provided, and an enzyme substrate that is formulated to be compatible with the lipid nature of the cholesterol, the cardiolipin, and the lecithin is provided.

DETD . . . ELISA Test starts with the previous understanding that the antigen complex for syphilis is formed from a combination of cardiolipin, cholesterol and lecithin, which, due to its lipid nature, does not readily remain in a microwell. From this, it was necessary to find. . .

DETD As set forth above, the non-binding of the antigen complex to a microwell is due the lipid nature of cardiolipin, cholesterol and lecithin, which compounds are not soluble in aqueous solution. The inventors discovered, however, that these compounds can be dissolved in organic. . . the compounds used in the classical VDRL method, when diluted to one-tenth the concentration, i.e., 0.003% W/V cardiolipin, 0.09% W/V cholesterol and 0.02% W/V lecithin, produce the desired results when dried in wells in the VDRL-ELISA method. Furthermore, by examining the aforementioned compounds in the. . . antibodies than

any of the compounds individually or in any of the other relative proportions examined. Accordingly, in Step 210, cholesterol is dissolved in an organic solvent, such as acetone, chloroform, butanol, methanol, and/or ether. In Step 220, cardiolipin and lecithin are dissolved in ethanol, and the organic solvent mixture is further diluted in the ethanol solution containing the cardiolipin and lecithin. In Step 230, the two mixtures are combined and an amount of this mixture is placed in microwells, for example,. . .

DETD . . . bovine serum, gelatin, goat serum, horse serum, and milk protein, to name a few. Utilizing the known property that cardiolipin, cholesterol, and lecithin are not soluble in aqueous solution, in Step 260, the coated microwells are filled with a post-coating mixture of the. . .

CLM What is claimed is:
1. A method of manufacturing a non-treponemal diagnostic test for syphilis infection, which comprises: initially dissolving cholesterol in an organic solvent and further diluting the dissolved cholesterol in an ethanol solution comprising cardiolipin and lecithin to form an antigen solution; permitting a volume of the antigen solution to evaporate in place within a container and. . .

L6 ANSWER 11 OF 39 USPATFULL on STN
ACCESSION NUMBER: 2015:172809 USPATFULL Full-text
TITLE: Serological Methods and Diagnostic Tests for Syphilis Antibodies
INVENTOR(S): Kiefer, David J., Miami Springs, FL, UNITED STATES
Compain, Oscar R., Coral Gables, FL, UNITED STATES
APPLICANT(S): Awareness Technology Inc., Palm City, FL, UNITED STATES

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 20150153342	A1	20150604
	US 9170259	B2	20151027
APPLICATION INFO.:	US 2014-14561333	A1	20141205 (14)
RELATED APPLN. INFO.:	Continuation of Ser. No. US 2014-14191014, filed on 26 Feb 2014, Pat. No. US 8945827		

	NUMBER	DATE
PRIORITY INFORMATION:	US 2013-61778544	20130313 (61)

DOCUMENT TYPE: Utility
FILE SEGMENT: APPLICATION
NUMBER OF CLAIMS: 21
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 5 Drawing Page(s)
LINE COUNT: 820
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB A method of detecting antibodies to syphilis antigens includes providing a syphilis detection kit having a screening solid-phase platform with a screening portion coated with non-treponemal syphilis antigens. The screening portion is fabricated by initially dissolving cholesterol in an organic solvent and further diluting the dissolved cholesterol in an ethanol solution comprising cardiolipin and lecithin to form an antigen solution, permitting the antigen solution to evaporate at the screening portion and at least partially coating. . .

SUMM The VDRL Test is a non-treponemal serological screening for syphilis used to assess response to therapy, to detect CNS involvement, and as an aid in the diagnosis of congenital syphilis. The basis of the test is that antibody (IgG, IgM or IgA), produced by a patient with syphilis, reacts with a compound comprised of cardiolipin, cholesterol, and lecithin. The test is performed by mixing the patients serum with compound described above. Positive sera result in "flocculation." Simply put,. . .

SUMM . . . also is a manual test, with a qualitative, subjective, visual readout. The RPR Test utilizes a colloidal suspension of cardiolipin, cholesterol, and lecithin, mixed with micro-particulate carbon. Thus, the RPR Test uses the same antigen as the VDRL Test, but, in the RPR. . .

SUMM Three components comprise the VDRL antigen: cardiolipin; cholesterol; and lecithin. These components are lipid in nature. As such, they are

not soluble in aqueous solution. In the classical VDRL test,. . .
SUMM . . . and specificity of the VDRL ELISA Test include the following:

1) The formulation, i.e., relative concentrations of the cardiolipin, cholesterol, lecithin antigen preparation, contributes to the sensitivity and specificity of the test.
2) The formulation of a post-coating solution prevents non-specific binding. .
.
SUMM . . . a major component of the VDRL antigen preparation, is inherently unstable.
2) Cardiolipin and the other components of the antigen preparation, cholesterol and lecithin, are not soluble in aqueous solution and, therefore, cannot be bound to polystyrene wells by conventional measures.
SUMM The inventive systems and processes are not limited to particular cardiolipins or cholesterol. The inventive systems and processes are envisioned to use natural or purified-from-natural cardiolipins or even synthesized cardiolipins. It is possible. . . used even if they are inherently stable. The inventive systems and processes are envisioned to also be used with synthesized cholesterol and/or synthesized lecithin.
SUMM . . . used to prepare VDRL antigen coated wells that are stable and capable of producing reproducible test results:

1) The cholesterol is initially dissolved in an organic solvent, and is then further diluted in an ethanol solution containing cardiolipin and lecithin.
2) A small volume (e.g., 50 microliter) of the antigen solution is permitted to evaporate in place, in polystyrene microwells.
3) The. . .
SUMM . . . with the invention, a method of manufacturing a non-treponemal diagnostic test for syphilis infection includes the steps of initially dissolving cholesterol in an organic solvent and further diluting the dissolved cholesterol in an ethanol solution comprising cardiolipin and lecithin to form an antigen solution, permitting a volume of the antigen solution to evaporate in place within a container and. . .
SUMM . . . is also provided a method of manufacturing a non-treponemal diagnostic test for syphilis infection including the steps of initially dissolving cholesterol in an organic solvent and further diluting the dissolved cholesterol in an ethanol solution comprising cardiolipin and lecithin to form an antigen solution, permitting a volume of the antigen solution to evaporate in place within a container and. . . enzyme-labeled conjugate component of a syphilis infection test that is formulated to be compatible with a lipid nature of the cholesterol, the cardiolipin, and the lecithin, providing a sample diluent that is formulated to be compatible with the lipid nature of the cholesterol, the cardiolipin, and the lecithin, providing a wash fluid that is formulated to be compatible with the lipid nature of the cholesterol, the cardiolipin, and the lecithin, and providing an enzyme substrate that is formulated to be compatible with the lipid nature of the cholesterol, the cardiolipin, and the lecithin.
SUMM In accordance with yet a further mode of the invention, the cholesterol is a natural cholesterol, a purified-from-natural cholesterol, and/or a synthesized cholesterol.
SUMM In accordance with yet an additional mode of the invention, the lecithin is a natural lecithin, a purified-from-natural lecithin, and/or a synthesized lecithin.
SUMM . . . enzyme-labeled conjugate component of a syphilis infection test that is formulated to be compatible with a lipid nature of the cholesterol, the cardiolipin, and the lecithin is provided, a sample diluent that is formulated to be compatible with the lipid nature of the cholesterol, the cardiolipin, and the lecithin is provided, a wash fluid that is formulated to be compatible with the lipid nature of the cholesterol, the cardiolipin, and the lecithin is provided, and an enzyme substrate that is formulated to be compatible with the lipid nature of the cholesterol, the cardiolipin, and the lecithin is provided.
DETD . . . ELISA Test starts with the previous understanding that the antigen complex for syphilis is formed from a combination of cardiolipin, cholesterol and lecithin, which, due to its lipid nature, does not readily remain in a microwell. From this, it was necessary to find. . .
DETD As set forth above, the non-binding of the antigen complex to a

microwell is due the lipid nature of cardiolipin, cholesterol and lecithin, which compounds are not soluble in aqueous solution. The inventors discovered, however, that these compounds can be dissolved in organic. . . the compounds used in the classical VDRL method, when diluted to one-tenth the concentration, i.e., 0.003% W/V cardiolipin, 0.09% W/V cholesterol and 0.02% W/V lecithin, produce the desired results when dried in wells in the VDRL-ELISA method. Furthermore, by examining the aforementioned compounds in the. . . antibodies than any of the compounds individually or in any of the other relative proportions examined. Accordingly, in Step 210, cholesterol is dissolved in an organic solvent, such as acetone, chloroform, butanol, methanol, and/or ether. In Step 220, cardiolipin and lecithin are dissolved in ethanol, and the organic solvent mixture is further diluted in the ethanol solution containing the cardiolipin and lecithin. In Step 230, the two mixtures are combined and an amount of this mixture is placed in microwells, for example,. . .

DETD . . . bovine serum, gelatin, goat serum, horse serum, and milk protein, to name a few. Utilizing the known property that cardiolipin, cholesterol, and lecithin are not soluble in aqueous solution, in Step 260, the coated microwells are filled with a post-coating mixture of the. . .

CLM What is claimed is:
1. A method of manufacturing a non-treponemal diagnostic test for syphilis infection, which comprises: initially dissolving cholesterol in an organic solvent and further diluting the dissolved cholesterol in an ethanol solution comprising cardiolipin and lecithin to form an antigen solution; permitting a volume of the antigen solution to evaporate in place within a container and. . .

CLM What is claimed is:
7. The method according to claim 1, wherein the cholesterol is a natural cholesterol, a purified-from-natural cholesterol, and/or a synthesized cholesterol.

CLM What is claimed is:
9. The method according to claim 1, wherein the lecithin is a natural lecithin, a purified-from-natural lecithin, and/or a synthesized lecithin.

CLM What is claimed is:
17. The method according to claim 2, which further comprises: providing an enzyme-labeled conjugate component of a syphilis infection test that is formulated to be compatible with a lipid nature of the cholesterol, the cardiolipin, and the lecithin; providing a sample diluent that is formulated to be compatible with the lipid nature of the cholesterol, the cardiolipin, and the lecithin; providing a wash fluid that is formulated to be compatible with the lipid nature of the cholesterol, the cardiolipin, and the lecithin; and providing an enzyme substrate that is formulated to be compatible with the lipid nature of the cholesterol, the cardiolipin, and the lecithin.

CLM What is claimed is:
21. A method of manufacturing a non-treponemal diagnostic test for syphilis infection, which comprises: initially dissolving cholesterol in an organic solvent and further diluting the dissolved cholesterol in an ethanol solution comprising cardiolipin and lecithin to form an antigen solution; permitting a volume of the antigen solution to evaporate in place within a container and. . . enzyme-labeled conjugate component of a syphilis infection test that is formulated to be compatible with a lipid nature of the cholesterol, the cardiolipin, and the lecithin; providing a sample diluent that is formulated to be compatible with the lipid nature of the cholesterol, the cardiolipin, and the lecithin; providing a wash fluid that is formulated to be

compatible with the lipid nature of the cholesterol, the cardiolipin, and the lecithin; and providing an enzyme substrate that is formulated to be compatible with the lipid nature of the cholesterol, the cardiolipin, and the lecithin.

L6 ANSWER 12 OF 39 USPATFULL on STN
ACCESSION NUMBER: 2014:361073 USPATFULL Full-text

TITLE: OXIDIZED CARDIOLIPIN AND USES TO DETECT CARDIOLIPIN ANTIBODIES

INVENTOR(S): Castro, Arnold R., Monroe, GA, UNITED STATES
Mody, Himanshu Champaklal, Springville, UT, UNITED STATES

APPLICANT(S): Government of the United States of America as Represented by the Secretary of the Department of, Atlanta, GA, UNITED STATES

PATENT ASSIGNEE(S): The Government of the United States of America as represented by the Secretary of the Department of (U.S. corporation)
Arlington Scientific, Inc. (U.S. corporation)

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 20140322800	A1	20141030
	US 9081009	B2	20150714
APPLICATION INFO.:	US 2014-14329236	A1	20140711 (14)

RELATED APPLN. INFO.: Continuation of Ser. No. US 2013-14079634, filed on 13 Nov 2013, Pat. No. US 8778619 Continuation-in-part of Ser. No. US 2011-13027224, filed on 14 Feb 2011, PENDING Continuation of Ser. No. US 2008-94144, filed on 16 May 2008, Pat. No. US 7888043 A 371 of International Ser. No. WO 2006-US44572, filed on 17 Nov 2006

	NUMBER	DATE
PRIORITY INFORMATION:	US 2005-60737901	20051118 (60)

DOCUMENT TYPE: Utility
FILE SEGMENT: APPLICATION
NUMBER OF CLAIMS: 20
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 13 Drawing Page(s)
LINE COUNT: 3177
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB Compositions, methods and devices for the detection of anti-lipoidal antibodies and the diagnosis of disease, for example, syphilis, are described. In particular, oxidized cardiolipins, which may be conjugated with a variety of attachment molecules, such as BSA, KLH, biotin, synthetic protein MAPS, IgY, streptavidin, or avidin, are described. Such oxidized cardiolipin, alone or complexed with one or more attachment molecules, are useful to detect anti-lipoidal antibodies (such as IgG and IgM. . .

SUMM This disclosure relates to oxidized cardiolipin compositions and uses therefor; in particular, to methods of immobilizing oxidized cardiolipin to a solid support, and related immunoassays (such as ELISA), which assays and devices are useful, for example, for detection of anti-lipoidal IgG and IgM antibodies and/or diagnosis of disease (such as syphilis).

SUMM Tests for anti-lipoidal antibodies (often called "non-treponemal tests") are typically based on an antigen composed of naturally occurring cardiolipin, cholesterol and lecithin. The widely used non-treponemal tests (e.g., Venereal Disease Research Laboratory (VDRL) test and Rapid Plasma Reagin (RPR) test) monitor, either. . .

SUMM . . . method that permits attachment of cardiolipin (or lipoidal antigens comprising cardiolipin modified as described herein, phosphatidylcholine (also referred to as "lecithin"), and cholesterol) to a solid substrate (such as a multi-well plate) while maintaining the antigenicity and specificity of the antigen for anti-lipoidal. . .

SUMM . . . assay (ELISA) multi-well plate, are also provided. In some examples, such methods permit diagnosis of syphilis, determine the stage of syphilis infection (such as monitoring the progression of the disease), permit monitoring of syphilis therapy, or combinations thereof. In some examples, the methods permit detection of NTA IgM and IgG antibody content in a sample (such as a qualitative or quantitative measurement). In some examples. . . formation of a complex among an anti-lipoidal antibody (e.g., IgG, IgA, and/or IgM) in the biological sample and the oxidized cardiolipin on the solid support. Detection of the complex can diagnose syphilis, determine an amount of IgG, IgA, and/or IgM present, determine the stage of syphilis infection,

determine whether a treatment is working in a patient, or combinations thereof. In some examples, the method also includes. . . IgM, or both. In some examples, the method also includes contacting with or adding to the solid support a labeled cardiolipin molecule (such as a biotin-labeled cardiolipin, which can be detected using labeled streptavidin), which can bind to the anti-lipoidal antibody/oxidized complex on the solid support (if. . .

DRWD FIG. 8 shows a digital image of a thin-layer chromatograph of an oxidized cardiolipin-lecithin mixture. (A) A mixture of unmodified cardiolipin and unmodified lecithin in t-butanol; (B) an oxidized cardiolipin/lecithin mixture; (C) the upper, t-butanol phase following the oxidation of a cardiolipin/lecithin mixture; and (D) the lower, aqueous phase following the oxidation of a cardiolipin/lecithin mixture. The direction of migration of each sample is shown by an arrow.

DRWD FIG. 9 shows the chemical structures of four representative naturally occurring phosphatidylcholine (lecithin) molecules. For L-α-phosphatidylcholine (heart, bovine), the molecular formula is C.sub.42H.sub.80NO.sub.8P, the molecular weight is 758.07, the molecular weight (isotope) is. . .

DRWD FIG. 10 shows a digital image of a dot blot assay used to determine the antigenicity of six oxidized cardiolipin/lecithin-BSA or -KLH conjugates. The amounts of the respective antigens applied to each dot in the assay are given in the. . .

DETD . . . detecting formation of a complex between the anti-lipoidal antibody (e.g., IgG, IgA, and/or IgM) in the sample and the oxidized cardiolipin attached to the solid support. In some examples the complex further includes a detector reagent (e.g., a labeled anti-human antibody,. . . peroxidase (HRP) and the method further includes contacting the solid support (e.g., multi-well plate) with tetramethyl benzidine (TMB) and wherein detecting comprises detecting a signal spectrophotometrically at 450 nm. Detection of the formation of the complex detects an anti-lipoidal antibody associated with infection with syphilis. In those embodiments in which the device includes a conjugate pad in the path of flow from the sample application area to the cardiolipin capture area, the detected complex includes the mobile or mobilizable detector reagent. In other embodiments in which the detector reagent. . .

DETD . . . to disease states, such as infection by T. pallidum. Naturally occurring cardiolipin has traditionally been used, often in combination with cholesterol and lecithin, in flocculation tests to detect anti-lipoidal antibodies, for example, in the serum of T. pallidum-infected patients.

DETD Lecithin (a.k.a., phosphatidylcholine): A glycerophospholipid, which is usually the most abundant phospholipid in animal and plants. It is a key building. . .

DETD As used herein, the term "lecithin" includes both naturally occurring lecithins and any modified synthetic lecithin that has structural similarity to naturally occurring lecithin. For example, the fatty acids of synthetic lecithins may include the following:

DETD D. Cardiolipin/Lecithin Mixtures

DETD Mixtures of cardiolipin and lecithin may be oxidized by the same methods described above for cardiolipin alone; the only difference being that the starting material is a mixture of cardiolipin and lecithin. In the initial oxidation reaction, cardiolipin and lecithin can be mixed together in a weight ratio (cardiolipin:lecithin) between about 20:1 to about 1:1, or between about 1:1 to about 1:10, or between about 10:1 to about 1:10,. . . between about 5:1 to about 1:5, or between about 1:1 to about 1:5. In particular examples, the weight ratio of cardiolipin:lecithin includes about 20:1, about 10:1, about 5:1, about 2:1, about 1:1, about 1:2, about 1:3, about 1:5, or about 1:10.

DETD The provided method to oxidize cardiolipin and prepare cardiolipin-attachment molecule conjugates, which can be immobilized on a solid support (such as a well of a multi-well plate, or a. . . or PVDF) enables solid-surface-based immunoassays (such as, EIA, ELISA, flow-through devices, dipsticks, and lateral flow devices) for the detection of cardiolipin-binding analytes (such as anti-lipoidal antibodies in biological samples from T. pallidum-infected subjects). In some examples, a disclosed immunoassay permits detection of the presence (or absence) of anti-lipoidal antibodies (such as IgG and IgM,) in a biological sample for diagnosis of syphilis. IgG and IgM anti-lipoidal antibodies can be detected qualitatively or quantitatively.

DETD . . . embodiments involve combinations of oxidized cardiolipin and other antigens specific for anti-lipoidal antibody; for example, immobilized lipoidal antigen comprising cardiolipin, lecithin and cholesterol. Immobilization of lipoidal antigen is described in detail in PCT/US2006/024117, which is incorporated herein in its entirety by reference. In one example, a lipoidal antigen comprising cardiolipin (e.g., naturally occurring or synthetic cardiolipin), lecithin and cholesterol is contacted with a population of Fab fragments specific for the lipoidal antigen to provide a lipoidal antigen-Fab complex, which. . .

DETD In some examples, the method includes detecting non-treponemal (e.g., cardiolipin) antibodies (e.g., IgG and/or IgM), for example quantitatively. In some examples, the detected OD value represents the concentration of antibody present, which can eliminate the need to determine the titer of antibody. For example, the method can include detecting cardiolipin IgM antibodies quantitatively. Such a method can be used as a confirmatory test, for example to confirm the results of a qualitative assay. Detection of cardiolipin IgM antibodies permits detection or diagnosis of a recent T. palladium infection, and can be used to monitor the efficacy of treatment. For example, levels of cardiolipin IgM antibodies in some examples decrease following treatment, such as a decrease of at least 25%, at least 50%, at least 75%, at least 90%, or at least 95% as compared to an amount prior to treatment. Detection of cardiolipin IgM antibodies can also be used to detect or diagnose congenital syphilis.

DETD In some examples, the method includes detecting cardiolipin IgG antibodies quantitatively. Such a method can be used as a confirmatory test, for example to confirm the results of a qualitative assay. Detection of cardiolipin IgG antibodies can be used to monitor the

efficacy of treatment. For examples, levels of IgG antibodies in some examples. . . least 50%, at least 75%, at least 90%, or at least 95% as compared to an amount prior to treatment. Detection of IgG antibodies can also be used to determine the stages of syphilis.

DETD Oxidation of Mixtures of Cardiolipin and Lecithin

DETD This example describes the oxidation of mixtures of cardiolipin and lecithin, and demonstrates that oxidized mixtures of cardiolipin and lecithin perform at least as well as oxidized cardiolipin alone in the assays described in Examples 4-7.

DETD Cardiolipin and lecithin were mixed together in ratios of 1:1, 1:3, and 1:5 cardiolipin to lecithin by weight. The mixtures were then oxidized as described in Example 1. As shown in FIG. 8, lane A, a mixture of unmodified cardiolipin and unmodified lecithin resolves into two spots on a TLC strip. Unmodified cardiolipin migrates to the top of the TLC strip, as indicated by the dark spot furthest from the point of origin (see also, FIG. 2, lane A). Unmodified lecithin migrates somewhat more slowly on the TLC place and is shown as the dark spot approximately halfway between the cardiolipin. . .

DETD . . . acid side chains, and introduces carboxyl groups into one or more of the fatty acid side chains of cardiolipin and lecithin. Carboxyl groups present in oxidized molecules interact more strongly with the silica substrate of a TLC strip, which retards the migration of the oxidized forms along the strip. Hence, in oxidized mixtures of cardiolipin and lecithin, a pronounced smear in the direction of migration is observed (see FIG. 8, lanes B and C). In addition, oxidative. . . represented by a white spot (due to dye exclusion), which is coextensive with the point of origin. Following oxidation of cardiolipin/lecithin mixtures as described in this example, oxidized forms of cardiolipin were found predominantly in the t-butanol phase (shown in FIG.. . .

DETD A. BSA and KLH Conjugation of Oxidized Cardiolipin/Lecithin Mixtures

DETD Oxidized mixtures of cardiolipin and lecithin were conjugated to either BSA or KLH, as described in Method 3 of Example 2. The BSA- or KLH-conjugated cardiolipin/lecithin preparations are described in Table 5.

DETD

TABLE 5

Cardiolipin/Lecithin Mixtures

	Amount of Attachment

Cardiolipin (CL) Lecithin (L) Prep. No.	CL:L Ratio (by weight)	Attachment Molecule	Molecule Per Reaction (mg)
C/L 1	1:1	BSA	5
C/L 2	1:1	BSA	2
C/L 3	1:1	KLH	2

C/L. . .

DETD B. RPR Inhibition Test of Oxidized Cardiolipin/Lecithin Mixtures

DETD The antigenicities of the cardiolipin/lecithin preparations described in Table 5 were tested in the RPR Inhibition Test, as described in Example 3. As shown in Table 6, each of the cardiolipin/lecithin preparations completely inhibited the reactivity of syphilitic serum in the traditional RPR test.

DETD

TABLE 6

RPR Inhibition Test Results for Cardiolipin/Lecithin Mixtures

Cardiolipin/Lecithin Prep. Used for Serum Preincubation	Serum (Lot 50 L) Dilution 1:1	1:2	1:4	1:8	1:16	1:32
None (i.e., Control)	R	R	R.sub.(-). . .			

DETD This result demonstrates that the oxidized cardiolipin/lecithin mixtures very efficiently strip (i.e., remove) anti-lipoidal antibodies from the syphilitic serum, so that such serum is non-reactive in the. . .

DETD C. Immunodot Testing of Oxidized Cardiolipin/Lecithin Mixtures

DETD . . . (BioRad) with a goat anti-human IgG alkaline-phosphatase conjugate in accordance with the manufacturer's instructions. As shown in FIG. 10, oxidized cardiolipin/lecithin mixtures in the range 375 ng to 21 μg per dot reacted with syphilitic serum (Lot 94265; 1:50 dilution). In comparison, none of the tested amounts of the oxidized cardiolipin/lecithin preparations showed any significant reaction with normal, human serum (i.e., non-syphilitic serum).

DETD The preparations where cardiolipin and lecithin were oxidized in a 1:1 ratio (by weight) and then conjugated to either BSA or KLH (i.e., 1:1 BSA and. . .

DETD . . . example, gold-labeled oxidized cardiolipin-BSA, or gold-labeled oxidized cardioliping KLH conjugate, or a gold-labeled, BSA-conjugated mixture of oxidized cardiolipin and oxidized lecithin, or a gold-labeled, KLH-conjugated mixture of oxidized cardiolipin and oxidized lecithin.

L6 ANSWER 13 OF 39 USPATFULL on STN

ACCESSION NUMBER:	2014:305943 USPATFULL Full-text			
TITLE:	Serological Methods and Diagnostic Tests for Syphilis Antibodies			
INVENTOR(S):	Kiefer, David J., Miami Springs, FL, UNITED STATES Compain, Oscar R., Coral Gables, FL, UNITED STATES			
PATENT ASSIGNEE(S):	Awareness Technology Inc., Palm City, FL, UNITED STATES (U.S. corporation)			
	NUMBER	KIND	DATE	
PATENT INFORMATION:	US 20140273027	A1	20140918	
	US 8945827	B2	20150203	
APPLICATION INFO.:	US 2014-14191014	A1	20140226	(14)
	NUMBER		DATE	
PRIORITY INFORMATION:	US 2013-61778544		20130313	(61)
DOCUMENT TYPE:	Utility			
FILE SEGMENT:	APPLICATION			
NUMBER OF CLAIMS:	21			
EXEMPLARY CLAIM:	1			
NUMBER OF DRAWINGS:	5 Drawing Page(s)			
LINE COUNT:	850			

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB A non-treponemal diagnostic test for syphilis infection includes

initially dissolving cholesterol in an organic solvent and further diluting the dissolved cholesterol in an ethanol solution comprising cardiolipin and lecithin, permitting a volume of the antigen solution to evaporate in place within a container, rinsing the coated container with buffered. . . enzyme-labeled conjugate component of a syphilis infection test that is formulated to be compatible with a lipid nature of the cholesterol, the cardiolipin, and the lecithin VDRL antigens, providing a sample diluent that is formulated to be compatible with the lipid nature of the VDRL antigens,. . .

SUMM The VDRL Test is a non-treponemal serological screening for syphilis used to assess response to therapy, to detect CNS involvement, and as an aid in the diagnosis of congenital syphilis. The basis of the test is that antibody (IgG, IgM or IgA), produced by a patient with syphilis, reacts with a compound comprised of cardiolipin, cholesterol, and lecithin. The test is performed by mixing the patients serum with compound described above. Positive sera result in "flocculation." Simply put,. . .

SUMM . . . also is a manual test, with a qualitative, subjective, visual readout. The RPR Test utilizes a colloidal suspension of cardiolipin, cholesterol, and lecithin, mixed with micro-particulate carbon. Thus, the RPR Test uses the same antigen as the VDRL Test, but, in the RPR. . .

SUMM Three components comprise the VDRL antigen: cardiolipin; cholesterol; and lecithin. These components are lipid in nature. As such, they are not soluble in aqueous solution. In the classical VDRL test,. . .

SUMM . . . and specificity of the VDRL ELISA Test include the following:

1) The formulation, i.e., relative concentrations of the cardiolipin, cholesterol, lecithin antigen preparation, contributes to the sensitivity and specificity of the test.

2) The formulation of a post-coating solution prevents non-specific binding. . .

SUMM . . . a major component of the VDRL antigen preparation, is inherently unstable.

2) Cardiolipin and the other components of the antigen preparation, cholesterol and lecithin, are not soluble in aqueous solution and, therefore, cannot be bound to polystyrene wells by conventional measures.

SUMM The inventive systems and processes are not limited to particular cardiolipins or cholesterol. The inventive systems and processes are envisioned to use natural or purified-from-natural cardiolipins or even synthesized cardiolipins. It is possible. . . used even if they are inherently stable. The inventive systems and processes are envisioned to also be used with synthesized cholesterol and/or synthesized lecithin.

SUMM . . . used to prepare VDRL antigen coated wells that are stable and capable of producing reproducible test results:

1) The cholesterol is initially dissolved in an organic solvent, and is then further diluted in an ethanol solution containing cardiolipin and lecithin.

2) A small volume (e.g., 50 microliter) of the antigen solution is permitted to evaporate in place, in polystyrene microwells.

3) The. . .

SUMM . . . in accordance with the invention, a method of manufacturing a non-treponemal diagnostic test for syphilis infection, which comprises initially dissolving cholesterol in an organic solvent and further diluting the dissolved cholesterol in an ethanol solution comprising cardiolipin and lecithin to form an antigen solution, permitting a volume of the antigen solution to evaporate in place within a container and. . .

SUMM . . . view, there is also provided a method of manufacturing a non-treponemal diagnostic test for syphilis infection, which comprises initially dissolving cholesterol in an organic solvent and further diluting the dissolved cholesterol in an ethanol solution comprising cardiolipin and lecithin to form an antigen solution, permitting a volume of the antigen solution to evaporate in place within a container and. . . enzyme-labeled conjugate component of a syphilis infection test that is formulated to be compatible with a lipid nature of the cholesterol, the cardiolipin, and the lecithin, providing a sample diluent that is formulated to be compatible with the lipid nature of the cholesterol, the cardiolipin, and the lecithin, providing a wash fluid that is formulated to be compatible with the lipid nature of the

cholesterol, the cardiolipin, and the lecithin, and providing an enzyme substrate that is formulated to be compatible with the lipid nature of the cholesterol, the cardiolipin, and the lecithin.

SUMM . . . for syphilis infection comprising a container having an interior that is at least partially coated first with a mixture of cholesterol dissolved in an organic solvent and further diluted in an ethanol solution comprising cardiolipin and lecithin to form an interior antigen coating that is then overcoated with an inert protein dissolved in buffered saline, a vapor-proof. . . dry, an enzyme-labeled conjugate component of a syphilis infection test formulated to be compatible with a lipid nature of the cholesterol, the cardiolipin, and the lecithin, a sample diluent formulated to be compatible with the lipid nature of the cholesterol, the cardiolipin, and the lecithin, a wash fluid formulated to be compatible with the lipid nature of the cholesterol, the cardiolipin, and the lecithin, and an enzyme substrate formulated to be compatible with the lipid nature of the cholesterol, the cardiolipin, and the lecithin.

SUMM In accordance with an additional mode of the invention, the cholesterol is a natural cholesterol, a purified-from-natural cholesterol, and/or a synthesized cholesterol.

SUMM In accordance with yet a further mode of the invention, the lecithin is a natural lecithin, a purified-from-natural lecithin, and/or a synthesized lecithin.

SUMM . . . enzyme-labeled conjugate component of a syphilis infection test that is formulated to be compatible with a lipid nature of the cholesterol, the cardiolipin, and the lecithin, providing a sample diluent that is formulated to be compatible with the lipid nature of the cholesterol, the cardiolipin, and the lecithin, providing a wash fluid that is formulated to be compatible with the lipid nature of the cholesterol, the cardiolipin, and the lecithin, and providing an enzyme substrate that is formulated to be compatible with the lipid nature of the cholesterol, the cardiolipin, and the lecithin.

DETD . . . ELISA Test starts with the previous understanding that the antigen complex for syphilis is formed from a combination of cardiolipin, cholesterol and lecithin, which, due to its lipid nature, does not readily remain in a microwell. From this, it was necessary to find. . .

DETD As set forth above, the non-binding of the antigen complex to a microwell is due the lipid nature of cardiolipin, cholesterol and lecithin, which compounds are not soluble in aqueous solution. The inventors discovered, however, that these compounds can be dissolved in organic. . . the compounds used in the classical VDRL method, when diluted to one-tenth the concentration, i.e., 0.003% W/V cardiolipin, 0.09% W/V cholesterol and 0.02% W/V lecithin, produce the desired results when dried in wells in the VDRL-ELISA method. Furthermore, by examining the aforementioned compounds in the. . . antibodies than any of the compounds individually or in any of the other relative proportions examined. Accordingly, in Step 210, cholesterol is dissolved in an organic solvent, such as acetone, chloroform, butanol, methanol, and/or ether. In Step 220, cardiolipin and lecithin are dissolved in ethanol, and the organic solvent mixture is further diluted in the ethanol solution containing the cardiolipin and lecithin. In Step 230, the two mixtures are combined and an amount of this mixture is placed in microwells, for example,. . .

DETD . . . bovine serum, gelatin, goat serum, horse serum, and milk protein, to name a few. Utilizing the known property that cardiolipin, cholesterol, and lecithin are not soluble in aqueous solution, in Step 260, the coated microwells are filled with a post-coating mixture of the. . .

CLM What is claimed is:

1. A method of manufacturing a non-treponemal diagnostic test for syphilis infection, which comprises: initially dissolving cholesterol in an organic solvent and further diluting the dissolved cholesterol in an ethanol solution comprising cardiolipin and lecithin to form an antigen solution; permitting a volume of the antigen solution to evaporate in place within a container and. . .

CLM What is claimed is:

5. The method according to claim 1, wherein the cholesterol is a natural cholesterol, a purified-from-natural cholesterol, and/or a synthesized cholesterol.

CLM What is claimed is:

7. The method according to claim 1, wherein the lecithin is a natural lecithin, a purified-from-natural lecithin, and/or a synthesized lecithin.

CLM What is claimed is:
16. The method according to claim 1, which further comprises: providing an enzyme-labeled conjugate component of a syphilis infection test that is formulated to be compatible with a lipid nature of the cholesterol, the cardiolipin, and the lecithin; providing a sample diluent that is formulated to be compatible with the lipid nature of the cholesterol, the cardiolipin, and the lecithin; providing a wash fluid that is formulated to be compatible with the lipid nature of the cholesterol,

the cardiolipin, and the lecithin; and providing an enzyme substrate that is formulated to be compatible with the lipid nature of the cholesterol, the cardiolipin, and the lecithin.

CLM What is claimed is:
20. A method of manufacturing a non-treponemal diagnostic test for syphilis infection, which comprises: initially dissolving cholesterol in an organic solvent and further diluting the dissolved cholesterol in an ethanol solution comprising cardiolipin and lecithin to form an antigen solution; permitting a volume of the antigen solution to evaporate in place within a container and. . . enzyme-labeled conjugate component of a syphilis infection test that is formulated to be compatible with a lipid nature of the cholesterol, the cardiolipin, and the lecithin; providing a sample diluent that is formulated to be compatible with the lipid nature of the cholesterol, the cardiolipin, and the lecithin; providing a wash fluid that is formulated to be compatible with the lipid nature of the cholesterol, the cardiolipin, and the lecithin; and providing an enzyme substrate that is formulated to be compatible with the lipid nature of the cholesterol, the cardiolipin, and the lecithin.

CLM What is claimed is:
. . . for syphilis infection, comprising: a container having an interior that is at least partially coated first with a mixture of cholesterol dissolved in an organic solvent and further diluted in an ethanol solution comprising cardiolipin and lecithin to form an interior antigen coating that is then overcoated with an inert protein dissolved in buffered saline; a vapor-proof. . . dry; an enzyme-labeled conjugate component of a syphilis infection test formulated to be compatible with a lipid nature of the cholesterol, the cardiolipin, and the lecithin; a sample diluent formulated to be compatible with the lipid nature of the cholesterol, the cardiolipin, and the lecithin; a wash fluid formulated to be compatible with the lipid nature of the cholesterol, the cardiolipin, and the lecithin; and an enzyme substrate formulated to be compatible with the lipid nature of the cholesterol, the cardiolipin, and the lecithin.

L6 ANSWER 14 OF 39 USPATFULL on STN
ACCESSION NUMBER: 2014:96776 USPATFULL Full-text
TITLE: OXIDIZED CARDIOLIPIN AND USES TO DETECT CARDIOLIPIN ANTIBODIES
INVENTOR(S): Castro, Arnold R., Monroe, GA, UNITED STATES
Mody, Himanshu Champaklal, Springville, UT, UNITED STATES
PATENT ASSIGNEE(S): Arlington Scientific, Inc., Springville, UT, UNITED STATES (U.S. corporation)
Government of the U.S.A. as Represented by the Secretary of the Dept. of Health and Human Service, Atlanta, GA, UNITED STATES (U.S. corporation)

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 20140087398	A1	20140327
	US 8778619	B2	20140715
APPLICATION INFO.:	US 2013-14079634	A1	20131113 (14)

RELATED APPLN. INFO.: Continuation-in-part of Ser. No. US 2011-13027224, filed on 14 Feb 2011, PENDING Continuation of Ser. No. US 2008-94144, filed on 16 May 2008, Pat. No. US

7888043 A 371 of International Ser. No. WO 2006-US44572, filed on 17 Nov 2006

	NUMBER	DATE
PRIORITY INFORMATION:	US 2005-60737901	20051118 (60)

DOCUMENT TYPE: Utility
FILE SEGMENT: APPLICATION
NUMBER OF CLAIMS: 27
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 13 Drawing Page(s)
LINE COUNT: 3224
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB Compositions, methods and devices for the detection of anti-lipoidal antibodies and the diagnosis of disease, for example, syphilis, are described. In particular, oxidized cardiolipins, which may be conjugated with a variety of attachment molecules, such as BSA, KLH, biotin, synthetic protein MAPS, IgY, streptavidin, or avidin, are described. Such oxidized cardiolipin, alone or complexed with one or more attachment molecules, are useful to detect anti-lipoidal antibodies (such as IgG and IgM. . .

SUMM This disclosure relates to oxidized cardiolipin compositions and uses therefor; in particular, to methods of immobilizing oxidized cardiolipin to a solid support, and related immunoassays (such as ELISA), which assays and devices are useful, for example, for detection of anti-lipoidal IgG and IgM antibodies and/or diagnosis of disease (such as syphilis).

SUMM Tests for anti-lipoidal antibodies (often called "non-treponemal tests") are typically based on an antigen composed of naturally occurring cardiolipin, cholesterol and lecithin. The widely used non-treponemal tests (e.g., Venereal Disease Research Laboratory (VDRL) test and Rapid Plasma Reagin (RPR) test) monitor, either. . .

SUMM . . . method that permits attachment of cardiolipin (or lipoidal antigens comprising cardiolipin modified as described herein, phosphatidylcholine (also referred to as "lecithin"), and cholesterol) to a solid substrate (such as a multi-well plate) while maintaining the antigenicity and specificity of the antigen for anti-lipoidal. . .

SUMM . . . assay (ELISA) multi-well plate, are also provided. In some examples, such methods permit diagnosis of syphilis, determine the stage of syphilis infection (such as monitoring the progression of the disease), permit monitoring of syphilis therapy, or combinations thereof. In some examples, the methods permit detection of NTA IgM and IgG antibody content in a sample (such as a qualitative or quantitative measurement). In some examples. . . formation of a complex among an anti-lipoidal antibody (e.g., IgG, IgA, and/or IgM) in the biological sample and the oxidized cardiolipin on the solid support. Detection of the complex can diagnose syphilis, determine an amount of IgG, IgA, and/or IgM present, determine the stage of syphilis infection, determine whether a treatment is working in a patient, or combinations thereof. In some examples, the method also includes. . . IgM, or both. In some examples, the method also includes contacting with or adding to the solid support a labeled cardiolipin molecule (such as a biotin-labeled cardiolipin, which can be detected using labeled streptavidin), which can bind to the anti-lipoidal antibody/oxidized complex on the solid support (if. . .

DRWD FIG. 8 shows a digital image of a thin-layer chromatograph of an oxidized cardiolipin-lecithin mixture. (A) A mixture of unmodified cardiolipin and unmodified lecithin in t-butanol; (B) an oxidized cardiolipin/lecithin mixture; (C) the upper, t-butanol phase following the oxidation of a cardiolipin/lecithin mixture; and (D) the lower, aqueous phase following the oxidation of a cardiolipin/lecithin mixture. The direction of migration of each sample is shown by an arrow.

DRWD FIG. 9 shows the chemical structures of four representative naturally occurring phosphatidylcholine (lecithin) molecules. For L-α-phosphatidylcholine (heart, bovine), the molecular formula is C.sub.42H.sub.80NO.sub.8P, the molecular weight is 758.07, the molecular weight (isotope) is. . .

DRWD FIG. 10 shows a digital image of a dot blot assay used to determine the antigenicity of six oxidized cardiolipin/lecithin-BSA or -KLH conjugates. The amounts of the respective antigens applied to each dot in the assay are given in the. . .

DETD . . . detecting formation of a complex between the anti-lipoidal antibody (e.g., IgG, IgA, and/or IgM) in the sample and the oxidized cardiolipin attached to the solid support. In some examples the complex further includes a detector reagent (e.g., a labeled anti-human antibody,. . . peroxidase (HRP) and the method further includes contacting the solid support (e.g., multi-well plate) with tetramethyl benzidine (TMB) and wherein detecting comprises detecting a signal spectrophotometrically at 450 nm. Detection of the formation of the complex detects an anti-lipoidal antibody associated with infection with syphilis. In those embodiments in which the device includes a conjugate pad in the path of flow from the sample application area to the cardiolipin capture area, the detected complex includes the mobile or mobilizable detector reagent. In other embodiments in which the detector reagent. . .

DETD . . . to disease states, such as infection by T. pallidum. Naturally occurring cardiolipin has traditionally been used, often in combination with cholesterol and lecithin, in flocculation tests to detect anti-lipoidal antibodies, for example, in the serum of T. pallidum-infected patients.

DETD Lecithin (a.k.a., Phosphatidylcholine):

DETD As used herein, the term "lecithin" includes both naturally occurring lecithins and any modified synthetic lecithin that has structural similarity to naturally occurring lecithin. For example, the fatty acids of synthetic lecithins may include the following:

DETD D. Cardiolipin/Lecithin Mixtures

DETD Mixtures of cardiolipin and lecithin may be oxidized by the same methods described above for cardiolipin alone; the only difference being that the starting material is a mixture of cardiolipin and lecithin. In the initial oxidation reaction, cardiolipin and lecithin can be mixed together in a weight ratio (cardiolipin:lecithin) between about 20:1 to about 1:1, or between about 1:1 to about 1:10, or between about 10:1 to about 1:10,. . . between about 5:1 to about 1:5, or between about 1:1 to about 1:5. In particular examples, the weight ratio of cardiolipin:lecithin includes about 20:1, about 10:1, about 5:1, about 2:1, about 1:1, about 1:2, about 1:3, about 1:5, or about 1:10.

DETD The provided method to oxidize cardiolipin and prepare cardiolipin-attachment molecule conjugates, which can be immobilized on a solid support (such as a well of a multi-well plate, or a. . . or PVDF) enables solid-surface-based immunoassays (such as, EIA, ELISA, flow-through devices, dipsticks, and lateral flow devices) for the detection of cardiolipin-binding analytes (such as anti-lipoidal antibodies in biological samples from T. pallidum-infected subjects). In some examples, a disclosed immunoassay permits detection of the presence (or absence) of anti-lipoidal antibodies (such as IgG and IgM,) in a biological sample for diagnosis of syphilis. IgG and IgM anti-lipoidal antibodies can be detected qualitatively or quantitatively.

DETD . . . embodiments involve combinations of oxidized cardiolipin and other antigens specific for anti-lipoidal antibody; for example, immobilized lipoidal antigen comprising cardiolipin, lecithin and cholesterol Immobilization of lipoidal antigen is described in detail in PCT/US2006/024117, which is incorporated herein in its entirety by reference. In one example, a lipoidal antigen comprising cardiolipin (e.g., naturally occurring or synthetic cardiolipin), lecithin and cholesterol is contacted with a population of Fab fragments specific for the lipoidal antigen to provide a lipoidal antigen-Fab complex, which. . .

DETD In some examples, the method includes detecting non-treponemal (e.g., cardiolipin) antibodies (e.g., IgG and/or IgM), for example quantitatively. In some examples, the detected OD value represents the concentration of antibody present, which can eliminate the need to determine the titer of antibody. For example, the method can include detecting cardiolipin IgM antibodies quantitatively. Such a method can be used as a confirmatory test, for example to confirm the results of a qualitative assay. Detection of cardiolipin IgM antibodies permits detection or diagnosis of a recent T. palladium infection, and can be used to monitor the efficacy of treatment. For example, levels of cardiolipin IgM antibodies in some examples decrease following treatment, such as a decrease of at least 25%, at least 50%, at least 75%, at least 90%, or at least 95% as compared to an amount prior to treatment. Detection of cardiolipin IgM antibodies can also be used to detect or diagnose congenital syphilis.

DETD In some examples, the method includes detecting cardiolipin IgG antibodies quantitatively. Such a method can be used as a confirmatory test, for example to confirm the results of a qualitative assay. Detection of cardiolipin IgG antibodies can be used to monitor the efficacy of treatment. For examples, levels of IgG antibodies in some examples. . . least 50%, at least 75%, at least 90%, or at least 95% as compared to an amount prior to treatment. Detection of IgG antibodies can also be used to determine the stages of syphilis.

DETD Oxidation of Mixtures of Cardiolipin and Lecithin

DETD This example describes the oxidation of mixtures of cardiolipin and lecithin, and demonstrates that oxidized mixtures of cardiolipin and lecithin perform at least as well as oxidized cardiolipin alone in the assays described in Examples 4-7.

DETD Cardiolipin and lecithin were mixed together in ratios of 1:1, 1:3, and 1:5 cardiolipin to lecithin by weight. The mixtures were then oxidized as described in Example 1. As shown in FIG. 8, lane A, a mixture of unmodified cardiolipin and unmodified lecithin resolves into two spots on a TLC strip. Unmodified cardiolipin migrates to the top of the TLC strip, as indicated by the dark spot furthest from the point of origin (see also, FIG. 2, lane A). Unmodified lecithin migrates somewhat more slowly on the TLC place and is shown as the dark spot approximately halfway between the cardiolipin. . .

DETD . . . acid side chains, and introduces carboxyl groups into one or more of the fatty acid side chains of cardiolipin and lecithin. Carboxyl groups present in oxidized molecules interact more strongly with the silica substrate of a TLC strip, which retards the migration of the oxidized forms along the strip. Hence, in oxidized mixtures of cardiolipin and lecithin, a pronounced smear in the direction of migration is observed (see FIG. 8, lanes B and C). In addition, oxidative. . . represented by a white spot (due to dye exclusion), which is coextensive with the point of origin. Following oxidation of cardiolipin/lecithin mixtures as described in this example, oxidized forms of cardiolipin were found predominantly in the t-butanol phase (shown in FIG.. . .

DETD A. BSA and KLH Conjugation of Oxidized Cardiolipin/Lecithin Mixtures

DETD Oxidized mixtures of cardiolipin and lecithin were conjugated to either BSA or KLH, as described in Method 3 of Example 2. The BSA- or KLH-conjugated cardiolipin/lecithin preparations are described in Table 5.

DETD

TABLE 5

Cardiolipin/Lecithin Mixtures

Cardiolipin (CL)			Amount of Attachment
Lecithin (L) Prep. No.	CL:L Ratio (by weight)	Attachment Molecule	Molecule Per Reaction (mg)
C/L 1	1:1	BSA	5
C/L 2	1:1	BSA	2
C/L. . .			

DETD B. RPR Inhibition Test of Oxidized Cardiolipin/Lecithin Mixtures

DETD The antigenicities of the cardiolipin/lecithin preparations described in Table 5 were tested in the RPR Inhibition Test, as described in Example 3. As shown in Table 6, each of the cardiolipin/lecithin preparations completely inhibited the reactivity of syphilitic serum in the traditional RPR test.

DETD

TABLE 6

RPR Inhibition Test Results for Cardiolipin/Lecithin Mixtures

Cardiolipin/Lecithin Prep. Used for Serum	Serum (Lot 50L) Dilution 1:1	1:2	1:4	1:8	1:16	1:32
None (i.e., Control)	R	R	R.sub.(-) Rm. . .			

DETD This result demonstrates that the oxidized cardiolipin/lecithin mixtures very efficiently strip (i.e., remove) anti-lipoidal antibodies

from the syphilitic serum, so that such serum is non-reactive in the. . .

DETD C. Immunodot Testing of Oxidized Cardiolipin/Lecithin Mixtures

DETD . . . (BioRad) with a goat anti-human IgG alkaline-phosphatase conjugate in accordance with the manufacturer's instructions. As shown in FIG. 10, oxidized cardiolipin/lecithin mixtures in the range 375 ng to 21 μg per dot reacted with syphilitic serum (Lot 94265; 1:50 dilution). In comparison, none of the tested amounts of the oxidized cardiolipin/lecithin preparations showed any significant reaction with normal, human serum (i.e., non-syphilitic serum).

DETD The preparations where cardiolipin and lecithin were oxidized in a 1:1 ratio (by weight) and then conjugated to either BSA or KLH (i.e., 1:1 BSA and. . .

DETD . . . for example, gold-labeled oxidized cardiolipin-BSA, or gold-labeled oxidized cardiolipin-KLH conjugate, or a gold-labeled, BSA-conjugated mixture of oxidized cardiolipin and oxidized lecithin, or a gold-labeled, KLH-conjugated mixture of oxidized cardiolipin and oxidized lecithin.

CLM What is claimed is:
18. A method for diagnosing syphilis, comprising: contacting a biological sample from a subject with the multi-well plate of claim 1; and detecting formation of a complex among an anti-lipoidal IgG, IgA, or IgM antibody in the biological sample and the oxidized cardiolipin on the solid support, wherein detection of the complex diagnoses syphilis.

CLM What is claimed is:
25. A method for diagnosing syphilis, comprising: contacting a biological sample from a subject with the multi-well plate of claim 15; detecting formation of a complex among an anti-lipoidal antibody in the biological sample and the oxidized cardiolipin; and detecting formation of a complex among an anti-treponemal antibody in the biological sample and the treponemal antigen, wherein detection of the complexes diagnoses syphilis.

L6 ANSWER 15 OF 39 CA COPYRIGHT 2022 ACS on STN DUPLICATE 4
ACCESSION NUMBER: 166:303848 CA Full-text
TITLE: Method for detecting syphilis using synthetic antigens
INVENTOR(S): Castro, Arnold R.
PATENT ASSIGNEE(S): The United States of America as Represented by the Secretary of the Department of Health and Human Services, Centers for Disease Control and Preventio, USA
SOURCE: U. S. Reissue, No pp. given
CODEN: UUXXA2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.		DATE
US 43914	E1	20130108	US 2011-13333849		20111221
WO 2000075666	A1	20001214	WO 2000-US15828		20000608
US 6815173	B1	20041109	US 2001-9698		20011205
PRIORITY APPLN. INFO.:			US 1999-60138192	P	19990609
			WO 2000-US15828	W	20000608
			US 2001-9698	E	20011205

PATENT STATUS PATENT INFORMATION:

PATENT NO.	KIND	STATUS	STATUS DATE
WO 2000075666	A1	Dead	20201106
US 6815173	B1	Dead	20201106

ASSIGNMENT HISTORY FOR US PATENT AVAILABLE IN LSUS DISPLAY FORMAT
OS.CITING REF COUNT: 1 THERE ARE 1 CAPLUS RECORDS THAT CITE THIS RECORD (1 CITINGS)

AB . . . of antibodies to Treponema pallidum and the diagnosis of syphilis are described. The antigen compn. contains synthetic cardiolipin and synthetic lecithin. The antigen compn. may addnl. contain cholesterol and an alc. The antigen compn. is useful as an immunoreagent in

immunoassays for the detection of antibodies assocd. with. . .
ST syphilis diagnosis synthetic antigen immunoassay; Treponema antibody detection synthetic antigen; cardiolipin lecithin synthetic syphilis antibody reagent
IT Cardiolipins
Phosphatidylcholines
RL: ARG (Analytical reagent use); THU (Therapeutic use); ANST (Analytical study); BIOL (Biological study); USES (Uses)
(synthetic, in antigen compn.; method for detecting syphilis using synthetic antigens)
IT Cardiolipins
RL: ARG (Analytical reagent use); THU (Therapeutic use); ANST (Analytical study); BIOL (Biological study); USES (Uses)
(tetramyristoyl-; method for detecting syphilis using synthetic antigens)

L6 ANSWER 16 OF 39 USPATFULL on STN
ACCESSION NUMBER: 2012:212975 USPATFULL Full-text
TITLE: METHODS, IMMUNOASSAYS AND DEVICES FOR DETECTION OF ANTI-LIPOIDAL ANTIBODIES
INVENTOR(S): Castro, Arnold R., Atlanta, GA, UNITED STATES
George, Robert W., Conyers, GA, UNITED STATES
PATENT ASSIGNEE(S): Department of Health and Human Services (U.S. corporation)
The Government of the United States of America as represented by the Secretary of the (U.S. corporation)

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 20120190041	A1	20120726
	US 8389229	B2	20130305
APPLICATION INFO.:	US 2012-13421681	A1	20120315 (13)

RELATED APPLN. INFO.: Continuation of Ser. No. US 2008-993213, filed on 11 Jan 2008, ABANDONED A 371 of International Ser. No. WO 2006-US24117, filed on 20 Jun 2006

	NUMBER	DATE
PRIORITY INFORMATION:	US 2005-60693120	20050621 (60)

DOCUMENT TYPE: Utility
FILE SEGMENT: APPLICATION
NUMBER OF CLAIMS: 39
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 5 Drawing Page(s)
LINE COUNT: 2811
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB Compositions, methods and devices for the detection of anti-lipoidal antibodies and the diagnosis of disease, for example, syphilis, are described. In particular, a method for immobilizing a lipoidal antigen, comprising cardiolipin, lecithin, and cholesterol, on a solid support (such as a nitrocellulose membrane) is described. The ability to immobilize a lipoidal antigen on a membrane satisfies a long-felt need for membrane-based assay for the detection of anti-lipoidal antibodies. Also described are immunoassay devices for concurrently performing treponemal and non-treponemal tests for syphilis.
SUMM Tests for anti-lipoidal antibodies (often called "non-treponemal tests") are typically based on an antigen composed of naturally occurring cardiolipin, cholesterol and lethicin. The widely used non-treponemal tests (e.g., Venereal Disease Research Laboratory (VDRL) test and Rapid Plasma Reagin (RPR) test). . .
SUMM . . . an approach for reliably attaching lipoidal antigens (which are made up of, at least, cardiolipin, phosphatidylcholine (also referred to as "lecithin"), and cholesterol) to a solid substrate (such as, a microporous membrane) while maintaining the antigenicity and specificity of the antigen for anti-lipoidal. . .
SUMM In one particular example, a lipoidal antigen comprising cardiolipin, lecithin and cholesterol is contacted with a population of Fab fragments specific for the lipoidal antigen to provide a lipoidal antigen-Fab complex, which. . .
DETD . . . is specifically bound by the anchor antibody and is thereby anchored to the substrate. The lipoidal antigen component includes

cardiolipin, lecithin and cholesterol and can be specifically bound by anti-lipoidal antibodies (such as reagin antibodies present in T. pallidum-infected subjects).

DETD . . . method involving (a) contacting the lipoidal antigen with one or more anchor antibodies specific for at least one of cardiolipin, lecithin, or cholesterol to form the lipoidal antigen-anchor antibody complex; and (b) applying the lipoidal antigen-anchor antibody complex to the membrane. In more. . . immobilized on the membrane by a method involving (i) immobilizing an anchor antibody specific for at least one of cardiolipin, lecithin, or cholesterol on the membrane; (ii) blocking non-specific binding sites on the membrane; (iii) contacting the immobilized anchor antibody with lipoidal antigen. . .

DETD . . . provide an anchor antibody bound to an epitope naturally occurring in a component of the lipoidal antigen (e.g., cardiolipin or cholesterol) and not to a derivative group introduced into the antigen for the purposes of providing a binding site for the. . . antibody. For example, the anchor antibody does not bind to a biotinylated component of the lipoidal antigen (such as biotinylated lecithin or cardiolipin).

DETD The disclosed immunoassay devices (e.g., flow-through or lateral-flow device) can be used in methods for detecting anti-lipoidal antibodies and/or diagnosing syphilis in a subject by applying a biological sample (such as, blood, serum, skin ulcer exudate, urine, saliva, or sputum) from. . . complex among the anti-lipoidal antibody, the anchor antibody-lipoidal antigen complex, and an anti-lipoidal antibody detector reagent in the capture area. Detection of the formation of the complex in the capture area detects an anti-lipoidal antibody associated with T. pallidum infection or the disease syphilis. In those embodiments in which the device includes a conjugate pad in the path of flow from the sample application area to the cardiolipin capture area, the detected complex includes the mobile or mobilizable detector. In other embodiments in which the detector reagent is. . .

DETD . . . exemplary methods for immobilizing immunoreactive cardiolipin on a solid support, involve (a) immobilizing one or more antibodies specific for cardiolipin, lecithin and/or cholesterol on a solid support; (b) blocking non-specific binding sites on the solid support; (c) applying a lipoidal antigen, comprising immunoreactive cardiolipin, lecithin and/or cholesterol, to the solid support to form lipoidal antigen-immobilized antibody complexes; and (d) washing the solid support to remove any lipoidal. . .

DETD Lipoidal Antigen: An antigen including (but not limited to) cardiolipin, lecithin and cholesterol that is capable of being specifically bound by anti-lipoidal antibodies. The nature of cardiolipin, lecithin and cholesterol as contemplated by the term "lipoidal antigen" is discussed in detail elsewhere in the specification.

DETD A lipoidal antigen is any antigen containing (without limitation) cardiolipin, lecithin and cholesterol, which antigen is capable of specifically binding an anti-lipoidal antibody. In some examples, a lipoidal antigen specifically binds an anti-lipoidal antibody (e.g., an anti-cardiolipin antibody) present in a T. pallidum-infected subject (such as, a human). Lipoidal antigens comprising cardiolipin (CL), lecithin (L) and cholesterol (Ch) have long been used in solution assays to detect anti-lipoidal antibodies in serum (see, e.g., prior discussion of "non-treponemal tests" for syphilis diagnosis). Specific exemplary CL/L/Ch-containing lipoidal antigens previously used in solution assays include the commonly known VDRL, RPR, and USR antigens. . . been a long-felt (but previously unmet) need to provide membrane-based assays (such as, flow-through or lateral flow immunoassay devices) for detection of anti-lipoidal antibodies, for instance, in biological samples. Such immunoassay devices would revolutionize, for example, point-of-care diagnosis of syphilis and other diseases characterized by the presence of anti-lipoidal antibodies. This disclosure describes, among other things, a method for immobilizing. . .

DETD . . . discussed above, methods and compositions described herein contemplate a lipoidal antigen that includes (e.g., comprises or consists essentially of) cardiolipin, cholesterol and lecithin. These exemplary components of a lipoidal antigen are described in more detail below.

DETD Lecithin is the common name for phosphatidylcholine. Phosphatidylcholine is a glycerophospholipid, which is usually the most abundant phospholipid in animal and. . . also the principal

phospholipid circulating in the plasma. Phosphatidylcholine contains two fatty acid side chains. As used herein, the term "lecithin" contemplates phosphatidylcholine having any distribution of fatty acid side chains. Thus, the two fatty acid side chains of cardiolipin can. . . about 4 double bonds, or from completely saturated to having about 2 double bonds). Exemplary fatty acid side chains of lecithin, as contemplated herein, independently include myristoyl (14:0); palmitoyl (16:0); stearoyl (18:0); oleoyl (18:1); myristoleoyl (14:1); palmitoleoyl (16:1); petroselinoyl (18:1); linoleoyl. . .

DETD In some embodiments, lecithin is a naturally occurring form of lecithin. The fatty acid composition of naturally occurring lecithin includes palmitoyl (16:0), palmitoleoyl (16:1), linoleoyl (18:2), stearoyl (18:0), arachidonoyl (20:4), myristoyl (14:0), oleoyl (18:1), and linolenoyl (18:3). The relative percentages of fatty acids in naturally occurring lecithin vary depending upon the source of the lecithin (e.g., Balint et al., J. Lipid Res., 6(1):96, 1965). For example, lecithin in human gallbladder bile is reported to be about 45% 16:0, 4% 16:1, 4% 18:0, 16% 18:1, 23% 18:2, 4% 20:4 with traces of 18:3 and 14:0; and lecithin in human plasma is reported to be about 35% 16:0, 1% 16:1, 14% 18:0, 17% 18:1, 17% 18:2, 14% 20:4 with traces of 18:3 and 14:0. In other embodiments, lecithin is a non-naturally occurring form (also referred to as "synthetic lecithin").

DETD Non-limiting examples of lecithin include, for example:

DETD Other particular lecithin examples include, without limitation, DL-α-dimyristoyl lecithin, L-α-dimyristoyl cephalin, L-α-dipalmitoyl lecithin, dipalmitoyl L-α-glycerophosphoric acid monocholine salt, L-α-dimyristoyl lecithin, D-α-dimyristoyl lecithin, L-α-distearoyl lecithin, stearoyl glycollecithin, 1,2-dioleoyl-sn-glycero-3-phosphocholine (18:1), 1,2-dilinoleoyl-sn-glycero-3-phosphocholine (18:2), 1,2-dimyristoyl-sn-glycero-3-phosphocholine (14:0), 1,2-dipentadecanoyl-sn-glycero-3-phosphocholine (15:0), 1,2-diphytanoyl-sn-glycero-3-phosphocholine (16:0), 1,2-dipalmitoyl-sn-glycero-3-phosphocholine (16:0), and 1-palmitoyl-2-oleoyl-sn-glycero-3-phosphocholine.

DETD C. Cholesterol

DETD Cholesterol is a steroid having, in one embodiment, the following structure:

DETD Cholesterol is known to interact with phospholipids (such as, cardiolipin and lecithin) in membranes or membrane-like structures (such as liposomes or micelles). In these circumstances, the cholesterol molecule is believed to be oriented parallel to the fatty acid chains of the phospholipids, and the cholesterol hydroxyl group interacts with the phospholipid head groups.

DETD In the formation of the lipoidal antigens disclosed herein, cholesterol is believed to stabilize the emulsion (e.g, micelle). Thus, for the purposes of this disclosure, the term "cholesterol"

includes any form of cholesterol or other cholesterol derivative that is capable of stabilizing an emulsion which contains a lipoidal antigen. In some examples, stabilizing a lipoidal-antigen-containing emulsion refers to extending the time an emulsified lipoidal antigen remains in solution. For example, addition of cholesterol to a lipoidal antigen may extend the time such an antigen remains dispersed in a continuous phase of an emulsion. . . an ethanolic solution) by 5%, 10%, 15% or 25% as compared to a comparable antigen containing relatively less or no cholesterol.

DETD Non-limiting examples of cholesterol derivatives include cholest-5-en-3 beta-yl-6-aminohexyl ether (AH-Chol; Zimmer et al., Eur. J. Pharm. Biopharm., 47(2):175-8, 1999); poly(ethylene glycol) cholesteryl ethers (PEG(n)-Chols; Baba et al., Traffic, 2(7):501-12, 2001; Ishiwata et al., Biochim. Biophys. Acta, 1359(2):123-35, 1997); a cationic cholesterol derivative with a hydroxyethyl amino head group described by Nakanishi and Noguchi (Adv. Drug Deliv. Rev., 52(3):197-207, 2001); cholesterol hemisuccinate (Meuillet et al., Eur. J. Pharmacol., 377(2-3):241-52, 1999; dehydroergosterol (DHE), which differs from cholesterol in having three additional double bonds and an extra methyl group (Mukherjee, Biophys. J., 75(4):1915-1925, 1998); cationic derivatives of cholesterol which contain a tertiary amino head group with a different spacer arm (Takeuchi et al., FEBS Lett., 397(2-3):207-9, 1996); cholesteryl-3beta-

carboxyamidoethylenedimethylamine. . . FEBS Lett., 433(1-2):169-173, 1998); and N-[tris [(beta-D-galactopyranosyloxy)methyl]methyl]-N alpha-[4-(5-cholesten-3 beta-yloxy)succinyl]glycinamide (Kempen et al., J. Medicin. Chem., 27:1306-1312, 1984). Further examples of cholesterol derivatives useful in the formation of membrane and membrane-like (e.g., liposomal or micellar) structures (like a disclosed lipoidal antigen) are. . .

DETD In CL/L/Ch lipoidal antigen embodiments, cardiolipin, lecithin and cholesterol can be combined in any proportion that forms an antigen capable of being specifically bound by an anti-lipoidal antibody (such. . . mixture will depend, for example, on the length and degree of saturation of the fatty acid chains of cardiolipin and lecithin, on the temperature, on the ionic composition of the aqueous medium, and on the mode of dispersal of the phospholipids. . .

DETD In some embodiments, a non-aqueous solution containing cardiolipin, lecithin and cholesterol (CL/L/Ch) is mixed with an aqueous solution to form an emulsion. Any non-aqueous solution in which cardiolipin, lecithin and cholesterol are each soluble (or partially soluble) can be used, including, for example, ethanol (such as absolute ethanol, 95% ethanol, or. . .

DETD . . . 0.05%, from about 0.01% to about 0.04%, or from about 0.025% to about 0.035%); from about 0.05% to about 0.5% lecithin (such as from about 0.07% to about 0.4%, from about 0.09% to about 0.3%, from about 0.1% to about 0.25%, or from about 0.14% to about 0.21%); and/or from about 0.2% to about 5% cholesterol (such as from about 0.4% to about 3%, from about 0.7% to about 2%, from about 0.8% to about 1%).. . . a CL/L/Ch solution useful for preparing a lipoidal antigen includes about 0.03% cardiolipin (such as, naturally occurring cardiolipin), about 0.21% lecithin (such as, naturally occurring lecithin), and about 0.9% cholesterol. In another example, a CL/L/Ch solution useful for preparing a lipoidal antigen includes about 0.03% tetramyristoyl cardiolipin, about 0.14% 1-palmitoyl-2-oleoyl-sn-glycero-3-phosphocholine and about 0.9% cholesterol.

DETD It is known that anti-lipoidal antibodies (e.g., reagin) in human serum will react with cardiolipin, lecithin and cholesterol-containing lipid antigens (such as, the RPR, VDRL, USR, or synthetic VDRL antigens). As discussed above, this knowledge formed the basis. . .

DETD . . . including, for example, anti-lipoidal antibodies from a T. pallidum-infected or T. pallidum-inoculated subject (such as, a human or a rabbit), anti-cholesterol antibodies, anti-cardiolipin antibodies, or anti-lecithin antibodies. As discussed in more detail below, antigen-binding fragments (such as, Fab fragments) of antibodies having the foregoing specificities can. . .

DETD Other exemplary anchor antibodies that can be used in the disclosed compositions and methods, include anti-cholesterol antibodies and anti-cardiolipin antibodies. Anti-cholesterol antibodies are present in human sera and can be isolated as described above for anti-lipoidal antibodies. Specific anti-cholesterol antibodies and/or protocols for producing and/or isolating anti-cholesterol antibodies can be found in Kruth et al. (J. Lipid Res., 42:1492-1500, 2001), Alving et al. (Biochem. Soc. Trans., 17:637-639,. . .

DETD . . . solid support by contacting in solution the lipoidal antigen with anchor antibodies specific for the lipoidal antigen (e.g., anti-lipoidal antibodies, anti-cholesterol antibodies, anti-lecithin antibodies, and/or anti-cardiolipin antibodies, and/or antigen-binding fragments of any of the foregoing) to form a lipoidal antigen-anchor antibody complex (or. . .

DETD . . . the purpose of serving as an epitope for an anchor antibody. Such examples do not exclude including derivatized cardiolipin, derivatized lecithin and/or derivatized cholesterol as components of a lipoidal antigen; however, in such examples, the derivative groups of such derivatized components do not serve. . .

DETD

Lipoidal Antigen	Anchor Antibody	Detector Reagent
CL/L/Ch	human, anti-lipoidal antigen-binding fragment (e.g., Fab)	Protein A, Protein G, or anti-human Ab(Fc)
CL/L/Ch	human, anti-cholesterol antigen-binding fragment (e.g., Fab)	Protein A, Protein G, or anti-human Ab(Fc)
CL/L/Ch	human, anti-cardiolipin antigen-binding	Protein A, Protein G, or

fragment (e.g., Fab) anti-human Ab(Fc)
CL/L/Ch non-human, anti-lipoidal full-length Ab anti-human Ab (any specificity)
CL/L/Ch non-human, anti-cholesterol full-length Ab anti-human Ab (any specificity)
CL/L/Ch non-human, anti-cardiolipin full-length Ab anti-human Ab (any specificity)
CL/L/Ch non-human (mammalian), anti-lipoidal Protein A, Protein G, anti-human
antigen-binding fragment (e.g., Fab) Ab (any specificity)
CL/L/Ch non-human (mammalian), anti-cholesterol Protein A, Protein G, anti-human
antigen-binding fragment (e.g., Fab) Ab (any specificity)
CL/L/Ch non-human (mammalian), anti-cardiolipin Protein A, Protein G, anti-human
. . .
DETD . . . to a 250 ml round, glass-stoppered bottle. Over a period of 40 to 60 seconds, 10 ml VDRL antigen (0.9% cholesterol, 0.03% bovine heart cardiolipin, and about 0.21% lethicin in ethanol) was added directly onto the buffered saline with continuous rotation. . .
CLM What is claimed is:
1. An immunoassay device comprising an anti-lipoidal antibody capture area, comprising: a microporous substrate; a lipoidal antigen, comprising cardiolipin, lecithin, and cholesterol, wherein the lipoidal antigen recognizes non-treponemal anti-lipoidal antibodies present in a patient infected with Treponema pallidum; and an anchor antibody fragment, wherein the anchor antibody fragment is (i) an Fab fragment specific for cardiolipin, lecithin, or cholesterol, or (ii) a plurality of Fab fragments produced from an immunoglobulin fraction from a subject infected with T. pallidum, wherein. . .
CLM What is claimed is:
. . . fragment, and which complex is immobilized on the membrane by the anchor antibody fragment; wherein the lipoidal antigen comprises cardiolipin, lecithin and cholesterol and recognizes non-treponemal anti-lipoidal antibodies present in a patient infected with Treponema pallidum, and wherein the anchor antibody fragment is. . .
CLM What is claimed is:
. . . An immunoassay device, comprising: a microporous substrate; an Fab fragment immobilized on the substrate; and a lipoidal antigen, comprising cardiolipin, lecithin, and cholesterol, wherein the lipoidal antigen recognizes non-treponemal anti-llipoidal antibodies present in a patient infected with Treponema pallidum, wherein the lipoidal antigen. . .
CLM What is claimed is:
37. The immunoassay device of claim 1, wherein the lipoidal antigen comprises: 0.001% to 0.1% cardiolipin; 0.05% to 0.5% lecithin; and 0.2% to 5% cholesterol.

CLM What is claimed is:
38. The immunoassay device of claim 1, wherein the lipoidal antigen comprises: 0.03% cardiolipin; 0.21% lecithin; and 0.9% cholesterol.

CLM What is claimed is:
39. The immunoassay device of claim 1, wherein the lipoidal antigen comprises: 0.03% tetramyristoyl cardiolipin, 0.14% 1-palmitoyl-2-oleoyl-sn-glycero-3-phosphocholine; and 0.9% cholesterol.

L6 ANSWER 17 OF 39 USPATFULL on STN
ACCESSION NUMBER: 2012:206189 USPATFULL Full-text
TITLE: METHODS, IMMUNOASSAYS AND DEVICES FOR DETECTION OF ANTI-LIPOIDAL ANTIBODIES
INVENTOR(S): Castro, Arnold R., Atlanta, GA, UNITED STATES
PATENT ASSIGNEE(S): Department of Health and Human Services (U.S. corporation)
The Government of the United States of America as represented by the Secretary of the (U.S. corporation)

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 20120184049	A1	20120719

	US 8394600	B2	20130312
APPLICATION INFO.:	US 2012-13429183	A1	20120323 (13)

RELATED APPLN. INFO.: Division of Ser. No. US 2009-433626, filed on 30 Apr 2009, Pat. No. US 8148057 Continuation-in-part of Ser. No. US 2008-993213, filed on 11 Jan 2008, ABANDONED A 371 of International Ser. No. WO 2006-US24117, filed on 20 Jun 2006

	NUMBER	DATE
PRIORITY INFORMATION:	US 2005-60693120	20050621 (60)

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FILE SEGMENT: APPLICATION
NUMBER OF CLAIMS: 25
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 7 Drawing Page(s)
LINE COUNT: 3498
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB Compositions, methods and devices for the detection of anti-lipoidal antibodies and the diagnosis of disease, for example, syphilis, are described. In particular, a method for immobilizing a lipoidal antigen, comprising cardiolipin, lecithin, and cholesterol, on a solid support (such as a nitrocellulose membrane) is described. The ability to immobilize a lipoidal antigen on a membrane satisfies a long-felt need for a membrane-based assay for the detection of anti-lipoidal antibodies. Also described are immunoassay devices for concurrently performing treponemal and non-treponemal tests for syphilis.

SUMM Tests for anti-lipoidal antibodies (often called "non-treponemal tests") are typically based on an antigen composed of naturally occurring cardiolipin, cholesterol and lethicin. The widely used non-treponemal tests (e.g., Venereal Disease Research Laboratory (VDRL) test and Rapid Plasma Reagin (RPR) test). . .

SUMM . . . an approach for reliably attaching lipoidal antigens (which are made up of, at least, cardiolipin, phosphatidylcholine (also referred to as "lecithin"), and cholesterol) to a solid substrate (such as, a microporous membrane) while maintaining the antigenicity and specificity of the antigen for anti-lipoidal. . .

SUMM In one particular example, a lipoidal antigen including cardiolipin, lecithin and cholesterol is attached directly to a solid substrate (such as, a microporous membrane) without the use of an anchor component. The. . .

DETD . . . is specifically bound by the anchor antibody and is thereby anchored to the substrate. The lipoidal antigen component includes cardiolipin, lecithin and cholesterol and can be specifically bound by anti-lipoidal antibodies (such as reagin antibodies present in T. pallidum-infected subjects).

DETD . . . substrate. The lipoidal antigen includes a USR antigen, a RPR antigen, a VDRL antigen, a synthetic VRDL antigen or cardiolipin, lecithin and cholesterol. The lipoidal antigen micelle can be specifically bound by anti-lipoidal antibodies (such as reagin antibodies present in T. pallidum-infected subjects).

DETD . . . method involving (a) contacting the lipoidal antigen with one or more anchor antibodies specific for at least one of cardiolipin, lecithin, or cholesterol to form the lipoidal antigen-anchor antibody complex; and (b) applying the lipoidal antigen-anchor antibody complex to the membrane. In more. . . immobilized on the membrane by a method involving (i) immobilizing an anchor antibody specific for at least one of cardiolipin, lecithin, or cholesterol on the membrane; (ii) blocking non-specific binding sites on the membrane; (iii) contacting the immobilized anchor antibody with lipoidal antigen. . .

DETD . . . provide an anchor antibody bound to an epitope naturally occurring in a component of the lipoidal antigen (e.g., cardiolipin or cholesterol) and not to a derivative group introduced into the antigen for the purposes of providing a binding site for the. . . antibody. For example, the anchor antibody does not bind to a biotinylated component of the lipoidal antigen (such as biotinylated lecithin or cardiolipin).

DETD . . . exemplary methods for immobilizing immunoreactive cardiolipin on a solid support, involve (a) immobilizing one or more antibodies specific for cardiolipin, lecithin and/or cholesterol on a solid support; (b) blocking non-specific binding sites on the solid support; (c) applying a lipoidal antigen, including immunoreactive cardiolipin,

lecithin and/or cholesterol, to the solid support to form lipoidal antigen-immobilized antibody complexes; and (d) washing the solid support to remove any lipoidal. . .

DETD . . . another exemplary method for immobilizing immunoreactive cardiolipin on a solid support, involves (a) applying a lipoidal antigen, including immunoreactive cardiolipin, lecithin and cholesterol in the form of a micelle, to the solid support to form an immobilized lipoidal antigen micelle in a pore. . .

DETD Lipoidal Antigen: An antigen including (but not limited to) cardiolipin, lecithin and cholesterol that is capable of being specifically bound by anti-lipoidal antibodies. The nature of cardiolipin, lecithin and cholesterol as contemplated by the term "lipoidal antigen" is discussed in detail elsewhere in the specification.

DETD A lipoidal antigen is any antigen containing (without limitation) cardiolipin, lecithin and cholesterol, which antigen is capable of specifically binding an anti-lipoidal antibody. In some examples, a lipoidal antigen specifically binds an anti-lipoidal antibody (e.g., an anti-cardiolipin antibody) present in a T. pallidum-infected subject (such as, a human). Lipoidal antigens including cardiolipin (CL), lecithin (L) and cholesterol (Ch) have long been used in solution assays to detect anti-lipoidal antibodies in serum (see, e.g., prior discussion of "non-treponemal tests" for syphilis diagnosis). Specific exemplary CL/L/Ch-containing lipoidal antigens previously used in solution assays include the commonly known VDRL, RPR, and USR antigens. . . been a long-felt (but previously unmet) need to provide membrane-based assays (such as, flow-through or lateral flow immunoassay devices) for detection of anti-lipoidal antibodies, for instance, in biological samples. Such immunoassay devices would revolutionize, for example, point-of-care diagnosis of syphilis and other diseases characterized by the presence of anti-lipoidal antibodies. This disclosure describes, among other things, a method for immobilizing. . .

DETD . . . discussed above, methods and compositions described herein contemplate a lipoidal antigen that includes (e.g., comprises or consists essentially of) cardiolipin, cholesterol and lecithin. These exemplary components of a lipoidal antigen are described in more detail below.

DETD Lecithin is the common name for phosphatidylcholine. Phosphatidylcholine is a glycerophospholipid, which is usually the most abundant phospholipid in animal and. . . also the principal phospholipid circulating in the plasma. Phosphatidylcholine contains two fatty acid side chains. As used herein, the term "lecithin" contemplates phosphatidylcholine having any distribution of fatty acid side chains. Thus, the two fatty acid side chains of cardiolipin can. . . about 4 double bonds, or from completely saturated to having about 2 double bonds). Exemplary fatty acid side chains of lecithin, as contemplated herein, independently include myristoyl (14:0); palmitoyl (16:0); stearoyl (18:0); oleoyl (18:1); myristoleoyl (14:1); palmitoleoyl (16:1); petroselinoyl (18:1); linoleoyl. . .

DETD In some embodiments, lecithin is a naturally occurring form of lecithin. The fatty acid composition of naturally occurring lecithin includes palmitoyl (16:0), palmitoleoyl (16:1), linoleoyl (18:2), stearoyl (18:0), arachidonoyl (20:4), myristoyl (14:0), oleoyl (18:1), and linolenoyl (18:3). The relative percentages of fatty acids in naturally occurring lecithin vary depending upon the source of the lecithin (e.g., Balint et al., J. Lipid Res., 6(1):96, 1965). For example, lecithin in human gallbladder bile is reported to be about 45% 16:0, 4% 16:1, 4% 18:0, 16% 18:1, 23% 18:2, 4% 20:4 with traces of 18:3 and 14:0; and lecithin in human plasma is reported to be about 35% 16:0, 1% 16:1, 14% 18:0, 17% 18:1, 17% 18:2, 14% 20:4 with traces of 18:3 and 14:0. In other embodiments, lecithin is a non-naturally occurring form (also referred to as "synthetic lecithin").

DETD Non-limiting examples of lecithin include, for example:

DETD Other particular lecithin examples include, without limitation, DL-α-dimyristoyl lecithin, L-α-dimyristoyl cephalin, L-α-dipalmitoyl lecithin, dipalmitoyl L-α-glycerophosphoric acid monocholine salt, L-α-dimyristoyl lecithin, D-α-dimyristoyl lecithin, L-α-distearoyl lecithin, stearoyl glycollecithin, 1,2-dioleoyl-sn-glycero-3-phosphocholine (18:1), 1,2-dilinoleoyl-sn-glycero-3-phosphocholine (18:2), 1,2-dimyristoyl-sn-glycero-3-phosphocholine (14:0),

1,2-dipentadecanoyl-sn-glycero-3-phosphocholine (15:0), 1,2-diphytanoyl-sn-glycero-3-phosphocholine (16:0), 1,2-dipalmitoyl-sn-glycero-3-phosphocholine (16:0), and 1-palmitoyl-2-oleoyl-sn-glycero-3-phosphocholine.

DETD C. Cholesterol

DETD Cholesterol is a steroid having, in one embodiment, the following structure:

DETD Cholesterol is known to interact with phospholipids (such as, cardiolipin and lecithin) in membranes or membrane-like structures (such as liposomes or micelles). In these circumstances, the cholesterol molecule is believed to be oriented parallel to the fatty acid chains of the phospholipids, and the cholesterol hydroxyl group interacts with the phospholipid head groups.

DETD In the formation of the lipoidal antigens disclosed herein, cholesterol is believed to stabilize the emulsion (e.g., micelle). Thus, for the purposes of this disclosure, the term "cholesterol" includes any form of cholesterol or other cholesterol derivative that is capable of stabilizing an emulsion which contains a lipoidal antigen. In some examples, stabilizing a lipoidal-antigen-containing

emulsion refers to extending the time an emulsified lipoidal antigen remains in solution. For example, addition of cholesterol to a lipoidal antigen may extend the time such an antigen remains dispersed in a continuous phase of an emulsion. . . an ethanolic solution) by 5%, 10%, 15% or 25% as compared to a comparable antigen containing relatively less or no cholesterol.

DETD Non-limiting examples of cholesterol derivatives include cholest-5-en-3 beta-yl-6-aminohexyl ether (AH-Chol; Zimmer et al., Eur. J. Phatm. Biopharm., 47(2):175-8, 1999); poly(ethylene glycol) cholesteryl ethers (PEG(n)-Chols; Baba et al., Traffic, 2(7):501-12, 2001; Ishiwata et al., Biochim. Biophys. Acta, 1359(2):123-35, 1997); a cationic cholesterol derivative with a hydroxyethyl amino head group described by Nakanishi and Noguchi (Adv. Drug Deliv. Rev., 52(3):197-207, 2001); cholesterol hemisuccinate (Meuillet et al., Eur. J. Pharmacol., 377(2-3):241-52, 1999; dehydroergosterol (DHE), which differs from cholesterol in having three additional double bonds and an extra methyl group (Mukherjee, Biophys. J., 75(4):1915-1925, 1998); cationic derivatives of cholesterol which contain a tertiary amino head group with a different spacer arm (Takeuchi et al., FEBS Lett., 397(2-3):207-9, 1996); cholesteryl-3beta-carboxyamidoethylenedimethylamine. . . FEBS Lett., 433(1-2):169-173, 1998); and N-[tris [(beta-D-galactopyranosyloxy)methyl]methyl]-N alpha-[4-(5-cholesten-3 beta-yloxy)succinyl]glycinamide (Kempen et al., J. Medicin. Chem., 27:1306-1312, 1984). Further examples of cholesterol derivatives useful in the formation of membrane and membrane-like (e.g., liposomal or micellar) structures (like a disclosed lipoidal antigen) are. . .

DETD In CL/L/Ch lipoidal antigen embodiments, cardiolipin, lecithin and cholesterol can be combined in any proportion that forms an antigen capable of being specifically bound by an anti-lipoidal antibody (such. . . mixture will depend, for example, on the length and degree of saturation of the fatty acid chains of cardiolipin and lecithin, on the temperature, on the ionic composition of the aqueous medium, and on the mode of dispersal of the phospholipids. . .

DETD In some embodiments, a non-aqueous solution containing cardiolipin, lecithin and cholesterol (CL/L/Ch) is mixed with an aqueous solution to form an emulsion (e.g., micelle). Any non-aqueous solution in which cardiolipin, lecithin and cholesterol are each soluble (or partially soluble) can be used, including, for example, ethanol (such as absolute ethanol, 95% ethanol, or. . .

DETD . . . 0.05%, from about 0.01% to about 0.04%, or from about 0.025% to about 0.035%); from about 0.05% to about 0.5% lecithin (such as from about 0.07% to about 0.4%, from about 0.09% to about 0.3%, from about 0.1% to about 0.25%, or from about 0.14% to about 0.21%); and/or from about 0.2% to about 5% cholesterol (such as from about 0.4% to about 3%, from about 0.7% to about 2%, from about 0.8% to about 1%).. . . a CL/L/Ch solution useful for preparing a lipoidal antigen includes about 0.03% cardiolipin (such as, naturally occurring cardiolipin), about 0.21% lecithin (such as, naturally occurring lecithin), and about 0.9% cholesterol. In another example, a CL/L/Ch solution useful for preparing a lipoidal antigen includes about 0.03% tetramyristoyl cardiolipin, about 0.14% 1-palmitoyl-2-oleoyl-sn-glycero-3-

phosphocholine and about 0.9% cholesterol.

DETD It is known that anti-lipoidal antibodies (e.g., reagin) in human serum will react with cardiolipin, lecithin and cholesterol-containing lipid antigens (such as, the RPR, VDRL, USR, or synthetic VDRL antigens). As discussed above, this knowledge formed the basis. . .

DETD . . . including, for example, anti-lipoidal antibodies from a T. pallidum-infected or T. pallidum-inoculated subject (such as, a human or a rabbit), anti-cholesterol antibodies, anti-cardiolipin antibodies, or anti-lecithin antibodies. As discussed in more detail below, antigen-binding fragments (such as, Fab fragments) of antibodies having the foregoing specificities can. . .

DETD Other exemplary anchor antibodies that can be used in the disclosed compositions and methods, include anti-cholesterol antibodies and anti-cardiolipin antibodies. Anti-cholesterol antibodies are present in human sera and can be isolated as described above for anti-lipoidal antibodies. Specific anti-cholesterol antibodies and/or protocols for producing and/or isolating anti-cholesterol antibodies can be found in Kruth et al. (J. Lipid Res., 42:1492-1500, 2001), Alving et al. (Biochem. Soc. Trans., 17:637-639,. . .

DETD . . . solid support by contacting in solution the lipoidal antigen with anchor antibodies specific for the lipoidal antigen (e.g., anti-lipoidal antibodies, anti-cholesterol antibodies, anti-lecithin antibodies, and/or anti-cardiolipin antibodies, and/or antigen-binding fragments of any of the foregoing) to form a lipoidal antigen-anchor antibody complex. In. . .

DETD . . . the purpose of serving as an epitope for an anchor antibody. Such examples do not exclude including derivatized cardiolipin, derivatized lecithin and/or derivatized cholesterol as components of a lipoidal antigen; however, in such examples, the derivative groups of such derivatized components do not serve. . .

DETD In some embodiments, a non-aqueous solution containing cardiolipin, lecithin and cholesterol (CL/L/Ch) is mixed with an aqueous solution to form a micelle. Any non-aqueous solution in which cardiolipin, lecithin and cholesterol are each soluble (or partially soluble) can be used, including, for example, ethanol (such as absolute ethanol, 95% ethanol, or. . .

DETD . . . 0.05%, from about 0.01% to about 0.04%, or from about 0.025% to about 0.035%); from about 0.05% to about 0.5% lecithin (such as from about 0.07% to about 0.4%, from about 0.09% to about 0.3%, from about 0.1% to about 0.25%, or from about 0.14% to about 0.21%); and/or from about 0.2% to about 5% cholesterol (such as from about 0.4% to about 3%, from about 0.7% to about 2%, from about 0.8% to about 1%).. . . a CL/L/Ch solution useful for preparing a lipoidal antigen includes about 0.03% cardiolipin (such as, naturally occurring cardiolipin), about 0.21% lecithin (such as, naturally occurring lecithin), and about 0.9% cholesterol. In another example, a CL/L/Ch non-aqueous solution useful for preparing a lipoidal antigen includes about 0.03% tetramyristoyl cardiolipin, about 0.14% 1-palmitoyl-2-oleoyl-sn-glycero-3-phosphocholine and about 0.9% cholesterol.

DETD . . . support. In particular examples, the lipoidal antigen is a USR antigen, a VDRL antigen, a synthetic VDRL antigen or cardiolipin, lecithin and cholesterol.

DETD

Lipoidal Antigen	Anchor Antibody	Detector Reagent
CL/L/Ch	human, anti-lipoidal antigen-binding fragment (e.g., Fab)	Protein A, Protein G, or anti-human Ab(Fc)
CL/L/Ch	human, anti-cholesterol antigen-binding fragment (e.g., Fab)	Protein A, Protein G, or anti-human Ab(Fc)
CL/L/Ch	human, anti-cardiolipin antigen-binding fragment (e.g., Fab)	Protein A, Protein G, or anti-human Ab(Fc)
CL/L/Ch	non-human, anti-lipoidal full-length Ab	anti-human Ab (any specificity)
CL/L/Ch	non-human, anti-cholesterol full-length Ab	anti-human Ab (any specificity)
CL/L/Ch	non-human, anti-cardiolipin full-length Ab	anti-human Ab (any specificity)
CL/L/Ch	non-human (mammalian), anti-lipoidal antigen-binding	Protein A, Protein G, anti-human Ab (any

fragment (e.g., Fab) specificity)
CL/L/Ch non-human (mammalian), Protein A, Protein G,
anti-cholesterol antigen-binding anti-human Ab (any
fragment (e.g., Fab) specificity)
CL/L/Ch non-human (mammalian), Protein A, Protein G,
anti-cardiolipin antigen-binding anti-human Ab (any
fragment. . .
DETD . . . to a 250 ml round, glass-stoppered bottle. Over a period of 40 to 60 seconds, 10 ml VDRL antigen (0.9% cholesterol, 0.03% bovine heart cardiolipin, and about 0.21% lethicin in ethanol) was added directly onto the VDRL buffered saline with continuous. . .
DETD . . . a 2 liter round, glass-stoppered bottle. Over a period of approximately 60 seconds, 100 ml of synthetic VDRL antigen (0:9% cholesterol, 0.03% bovine heart cardiolipin, and about 0.21% lethicin in ethanol) was added slowly directly onto the VDRL buffered saline while. . .
DETD . . . a 2 liter round, glass-stoppered bottle. Over a period of approximately 60 seconds, 100 ml of synthetic VDRL antigen (0.9% cholesterol, 0.03% bovine heart cardiolipin, and about 0.21% lethicin in ethanol) was added slowly directly onto the buffered saline while the. . .
CLM What is claimed is:
. . . of claim 1, wherein the lipoidal antigen comprises a USR antigen, a VDRL antigen, a synthetic VDRL antigen or cardiolipin, lecithin and cholesterol.

CLM What is claimed is:
. . . claim 1, wherein the lipoidal antigen comprises from about 0.001% to about 0.1% cardiolipin; from about 0.05% to about 0.5% lecithin; and/or from about 0.2% to about 5% cholesterol.

CLM What is claimed is:
9. The method of claim 1, wherein the lipoidal antigen comprises cardiolipin, lecithin and cholesterol.

L6 ANSWER 18 OF 39 USPATFULL on STN
ACCESSION NUMBER: 2011:152901 USPATFULL Full-text
TITLE: MODIFIED CARDIOLIPIN AND USES THEREFOR
INVENTOR(S): Castro, Arnold R., Monroe, GA, UNITED STATES
Wang, Huiying, Lake Oswego, OR, UNITED STATES
PATENT ASSIGNEE(S): The Government of the United States of America, as represented by the Secretary of the Department of (U.S. corporation)

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 20110136143	A1	20110609
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APPLICATION INFO.:	US 2011-13027224	A1	20110214 (13)

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DOCUMENT TYPE: Utility
FILE SEGMENT: APPLICATION
NUMBER OF CLAIMS: 20
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 9 Drawing Page(s)
LINE COUNT: 2675
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB Compositions, methods and devices for the detection of anti-lipoidal antibodies and the diagnosis of disease, for example, syphilis, are described. In particular, oxidized cardiolipins, which may be conjugated with a variety of attachment molecules, such as BSA, KLH, biotin, synthetic protein MAPS, IgY, streptavidin, or avidin, are described. Such oxidized cardiolipin, alone or complexed with one or more attachment molecules, are useful to detect anti-lipoidal antibodies

in subjects, for example, when. . .

SUMM This disclosure relates to modified cardiolipin compositions and uses therefor; in particular, to methods of immobilizing modified cardiolipin to a solid support, and related immunoassays (such as ELISA) and immunoassay devices (such as test strips, flow-through devices, or lateral flow devices), which assays and devices are useful, for example, for detection of anti-lipoidal antibodies and/or diagnosis of disease (such as syphilis).

SUMM Tests for anti-lipoidal antibodies (often called "non-treponemal tests") are typically based on an antigen composed of naturally occurring cardiolipin, cholesterol and lecithin. The widely used non-treponemal tests (e.g., Venereal Disease Research Laboratory (VDRL) test and Rapid Plasma Reagin (RPR) test) monitor, either. . .

SUMM . . . an approach for reliably attaching cardiolipin (or lipoidal antigens comprising cardiolipin modified as described herein, phosphatidylcholine (also referred to as "lecithin"), and cholesterol) to a solid substrate (such as a microporous membrane or multi-well plate) while maintaining the antigenicity and specificity of the. . .

DRWD FIG. 8 shows a digital image of a thin-layer chromatograph of an oxidized cardiolipin-lecithin mixture. (A) A mixture of unmodified cardiolipin and unmodified lecithin in t-butanol; (B) an oxidized cardiolipin/lecithin mixture; (C) the upper, t-butanol phase following the oxidation of a cardiolipin/lecithin mixture; and (D) the lower, aqueous phase following the oxidation of a cardiolipin/lecithin mixture. The direction of migration of each sample is shown by an arrow.

DRWD FIG. 9 shows the chemical structures of four representative naturally occurring phosphatidylcholine (lecithin) molecules. For L-α-phosphatidylcholine (heart, bovine), the molecular formula is C.sub.42H.sub.80NO.sub.8P, the molecular weight is 758.07, the molecular weight (isotope) is. . .

DRWD FIG. 10 shows a digital image of a dot blot assay used to determine the antigenicity of six oxidized cardiolipin/lecithin-BSA or -KLH conjugates. The amounts of the respective antigens applied to each dot in the assay are given in the. . .

DETD The disclosed immunoassay devices can be used in methods for diagnosing syphilis in a subject by analyzing a biological sample from the subject, by applying the biological sample to the device and detecting formation of a complex among the anti-lipoidal antibody, the oxidized cardiolipin, and a detector reagent in the capture area. Detection of the formation of the complex in the capture area detects an anti-lipoidal antibody associated with infection with syphilis. In those embodiments in which the device includes a conjugate pad in the path of flow from the sample application area to the cardiolipin capture area, the detected complex includes the mobile or mobilizable detector reagent. In other embodiments in which the detector reagent. . .

DETD . . . to disease states, such as infection by T. pallidum. Naturally occurring cardiolipin has traditionally been used, often in combination with cholesterol and lecithin, in flocculation tests to detect anti-lipoidal antibodies, for example, in the serum of T. pallidum-infected patients.

DETD Lecithin (a.k.a., phosphatidylcholine): Lecithin is the common name for phosphatidylcholine. Phosphatidylcholine is a glycerophospholipid, which is usually the most abundant phospholipid in animal and. . .

DETD As used herein, the term "lecithin" includes both naturally occurring lecithins and any modified synthetic lecithin that has structural similarity to naturally occurring lecithin. For example, the fatty acids of synthetic lecithins may include the following:

DETD D. Cardiolipin/Lecithin Mixtures

DETD Mixtures of cardiolipin and lecithin may be oxidized by the same methods described above for cardiolipin alone; the only difference being that the starting material is a mixture of cardiolipin and lecithin. In the initial oxidation reaction, cardiolipin and lecithin are mixed together in a weight ratio (cardiolipin:lecithin) between about 20:1 to about 1:1, or between about 1:1 to about 1:10, or between about 10:1 to about 1:10,. . . between about 5:1 to about 1:5, or between about 1:1 to about 1:5. In particular examples, the weight ratio of cardiolipin:lecithin includes about 20:1, about 10:1, about 5:1, about 2:1, about 1:1, about 1:2, about 1:3, about 1:5, or about 1:10.

DETD The discovery herein of a method to oxidize cardiolipin and prepare cardiolipin-attachment molecule conjugates, which can be immobilized

on a solid support (such as a microporous membrane, like nitrocellulose, nylon or PVDF) enables solid-surface-based immunoassays (such as, EIA, ELISA, flow-through devices, dipsticks, and lateral flow devices) for the detection of cardiolipin-binding analytes (such as anti-lipoidal antibodies in biological samples from T. pallidum-infected subjects). In some examples, a disclosed immunoassay permits detection of the presence (or absence) of anti-lipoidal antibodies in a biological sample for diagnosis of syphilis.

DETD . . . antigens (e.g., oxidized cardiolipin-attachment molecule complex) and other antigens specific for anti-lipoidal antibody; for example, immobilized lipoidal antigen comprising cardiolipin, lecithin and cholesterol. Immobilization of lipoidal antigen is described in detail in PCT/US2006/024117, which is incorporated herein in its entirety by reference. In one example, a lipoidal antigen comprising cardiolipin (e.g., naturally occurring or synthetic cardiolipin), lecithin and cholesterol is contacted with a population of Fab fragments specific for the lipoidal antigen to provide a lipoidal antigen-Fab complex, which. . .

DETD Oxidation of Mixtures of Cardiolipin and Lecithin

DETD This example describes the oxidation of mixtures of cardiolipin and lecithin, and demonstrates that oxidized mixtures of cardiolipin and lecithin perform at least as well as oxidized cardiolipin alone in the assays described in Examples 4-7.

DETD Cardiolipin and lecithin were mixed together in ratios of 1:1, 1:3, and 1:5 cardiolipin to lecithin by weight. The mixtures were then oxidized as described in Example 1. As shown in FIG. 8, lane A, a mixture of unmodified cardiolipin and unmodified lecithin resolves into two spots on a TLC strip. Unmodified cardiolipin migrates to the top of the TLC strip, as indicated by the dark spot furthest from the point of origin (see also, FIG. 2, lane A). Unmodified lecithin migrates somewhat more slowly on the TLC place and is shown as the dark spot approximately halfway between the cardiolipin. . .

DETD . . . acid side chains, and introduces carboxyl groups into one or more of the fatty acid side chains of cardiolipin and lecithin. Carboxyl groups present in oxidized molecules interact more strongly with the silica substrate of a TLC strip, which retards the migration of the oxidized forms along the strip. Hence, in oxidized mixtures of cardiolipin and lecithin, a pronounced smear in the direction of migration is observed (see FIG. 8, lanes B and C). In addition, oxidative. . . represented by a white spot (due to dye exclusion), which is coextensive with the point of origin. Following oxidation of cardiolipin/lecithin mixtures as described in this example, oxidized forms of cardiolipin were found predominantly in the t-butanol phase (shown in FIG.. . .

DETD A. BSA and KLH Conjugation of Oxidized Cardiolipin/Lecithin Mixtures

DETD Oxidized mixtures of cardiolipin and lecithin were conjugated to either BSA or KLH, as described in Method 3 of Example 2. The BSA- or KLH-conjugated cardiolipin/lecithin preparations are described in Table 5.

DETD

TABLE 5

Cardiolipin/Lecithin Mixtures

Cardiolipin (CL) Lecithin (L) Prep. No.	CL:L Ratio (by weight)	Attachment Molecule	Amount of Attachment Molecule Per Reaction (mg)
C/L 1	1:1	BSA	5
C/L 2	1:1	BSA. . .	

DETD B. RPR Inhibition Test of Oxidized Cardiolipin/Lecithin Mixtures

DETD The antigenicities of the cardiolipin/lecithin preparations described in Table 5 were tested in the RPR Inhibition Test, as described in Example 3. As shown in Table 6, each of the cardiolipin/lecithin preparations completely inhibited the reactivity of syphilitic serum in the traditional RPR test.

DETD

TABLE 6

RPR Inhibition Test Results

for Cardiolipin/Lecithin Mixtures
Cardiolipin/Lecithin
Prep. Used for Serum Serum (Lot 50L) Dilution
Preincubation 1:1 1:2 1:4 1:8 1:16 1:32

None (i.e., Control) R. . .
DETD This result demonstrates that the oxidized cardiolipin/lecithin mixtures very efficiently strip (i.e., remove) anti-lipoidal antibodies from the syphilitic serum, so that such serum is non-reactive in the. . .
DETD C. Immunodot Testing of Oxidized Cardiolipin/Lecithin Mixtures
DETD . . . (BioRad) with a goat anti-human IgG alkaline-phosphatase conjugate in accordance with the manufacturer's instructions. As shown in FIG. 10, oxidized cardiolipin/lecithin mixtures in the range 375 ng to 21 μg per dot reacted with syphilitic serum (Lot 94265; 1:50 dilution). In comparison, none of the tested amounts of the oxidized cardiolipin/lecithin preparations showed any significant reaction with normal, human serum (i.e., non-syphilitic serum).
DETD The preparations where cardiolipin and lecithin were oxidized in a 1:1 ratio (by weight) and then conjugated to either BSA or KLH (i.e., 1:1 BSA and. . .
DETD . . . for example, gold-labeled oxidized cardiolipin-BSA, or gold-labeled oxidized cardiolipin-KLH conjugate, or a gold-labeled, BSA-conjugated mixture of oxidized cardiolipin and oxidized lecithin, or a gold-labeled, KLH-conjugated mixture of oxidized cardiolipin and oxidized lecithin.
CLM What is claimed is:
17. A method for diagnosing syphilis, comprising: applying a biological sample from a subject to the solid support of claim 1; and detecting formation of a complex among an anti-lipoidal antibody in the biological sample and the oxidized cardiolipin, wherein detection of the complex diagnoses syphilis.

CLM What is claimed is:
19. A method for diagnosing syphilis, comprising: applying a biological sample from a subject to the solid support of claim 15; detecting formation of a complex among an anti-lipoidal antibody in the biological sample and the oxidized cardiolipin; and detecting formation of a complex among an anti-treponemal antibody in the biological sample and the treponemal antigen, wherein detection of the complexes diagnoses syphilis.

L6 ANSWER 19 OF 39 USPATFULL on STN
ACCESSION NUMBER: 2010:249296 USPATFULL Full-text
TITLE: METHODS, IMMUNOASSAYS AND DEVICES FOR DETECTION OF ANTI-LIPOIDAL ANTIBODIES
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LEGAL REPRESENTATIVE: KLARQUIST SPARKMAN, LLP, 121 S.W. SALMON STREET, SUITE 1600, PORTLAND, OR, 97204, US
NUMBER OF CLAIMS: 44
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 10 Drawing Page(s)
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CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB Compositions, methods and devices for the detection of anti-lipoidal

antibodies and the diagnosis of disease, for example, syphilis, are described. In particular, a method for immobilizing a lipoidal antigen, comprising cardiolipin, lecithin, and cholesterol, on a solid support (such as a nitrocellulose membrane) is described. The ability to immobilize a lipoidal antigen on a membrane satisfies a long-felt need for membrane-based assay for the detection of anti-lipoidal antibodies. Also described are immunoassay devices for concurrently performing treponemal and non-treponemal tests for syphilis.

SUMM Tests for anti-lipoidal antibodies (often called "non-treponemal tests") are typically based on an antigen composed of naturally occurring cardiolipin, cholesterol and lethicin. The widely used non-treponemal tests (e.g., Venereal Disease Research Laboratory (VDRL) test and Rapid Plasma Reagin (RPR) test). . .

SUMM . . . an approach for reliably attaching lipoidal antigens (which are made up of, at least, cardiolipin, phosphatidylcholine (also referred to as "lecithin"), and cholesterol) to a solid substrate (such as, a microporous membrane) while maintaining the antigenicity and specificity of the antigen for anti-lipoidal. . .

SUMM In one particular example, a lipoidal antigen comprising cardiolipin, lecithin and cholesterol is contacted with a population of Fab fragments specific for the lipoidal antigen to provide a lipoidal antigen-Fab complex, which. . .

DETD . . . is specifically bound by the anchor antibody and is thereby anchored to the substrate. The lipoidal antigen component includes cardiolipin, lecithin and cholesterol and can be specifically bound by anti-lipoidal antibodies (such as reagin antibodies present in T. pallidum-infected subjects).

DETD . . . method involving (a) contacting the lipoidal antigen with one or more anchor antibodies specific for at least one of cardiolipin, lecithin, or cholesterol to form the lipoidal antigen-anchor antibody complex; and (b) applying the lipoidal antigen-anchor antibody complex to the membrane. In more. . . immobilized on the membrane by a method involving (i) immobilizing an anchor antibody specific for at least one of cardiolipin, lecithin, or cholesterol on the membrane; (ii) blocking non-specific binding sites on the membrane; (iii) contacting the immobilized anchor antibody with lipoidal antigen. . .

DETD . . . provide an anchor antibody bound to an epitope naturally occurring in a component of the lipoidal antigen (e.g., cardiolipin or cholesterol) and not to a derivative group introduced into the antigen for the purposes of providing a binding site for the. . . antibody. For example, the anchor antibody does not bind to a biotinylated component of the lipoidal antigen (such as biotinylated lecithin or cardiolipin).

DETD The disclosed immunoassay devices (e.g., flow-through or lateral-flow device) can be used in methods for detecting anti-lipoidal antibodies and/or diagnosing syphilis in a subject by applying a biological sample (such as, blood, serum, skin ulcer exudate, urine, saliva, or sputum) from. . . complex among the anti-lipoidal antibody, the anchor antibody-lipoidal antigen complex, and an anti-lipoidal antibody detector reagent in the capture area. Detection of the formation of the complex in the capture area detects an anti-lipoidal antibody associated with T. pallidum infection or the disease syphilis. In those embodiments in which the device includes a conjugate pad in the path of flow from the sample application area to the cardiolipin capture area, the detected complex includes the mobile or mobilizable detector. In other embodiments in which the detector reagent is. . .

DETD . . . exemplary methods for immobilizing immunoreactive cardiolipin on a solid support, involve (a) immobilizing one or more antibodies specific for cardiolipin, lecithin and/or cholesterol on a solid support; (b) blocking non-specific binding sites on the solid support; (c) applying a lipoidal antigen, comprising immunoreactive cardiolipin, lecithin and/or cholesterol, to the solid support to form lipoidal antigen-immobilized antibody complexes; and (d) washing the solid support to remove any lipoidal. . .

DETD Lipoidal Antigen: An antigen including (but not limited to) cardiolipin, lecithin and cholesterol that is capable of being specifically bound by anti-lipoidal antibodies. The nature of cardiolipin, lecithin and cholesterol as contemplated by the term "lipoidal antigen" is discussed in detail elsewhere in the specification.

DETD A lipoidal antigen is any antigen containing (without limitation) cardiolipin, lecithin and cholesterol, which antigen is capable of specifically binding an anti-lipoidal antibody. In some examples, a

lipoidal antigen specifically binds an anti-lipoidal antibody (e.g., an anti-cardiolipin antibody) present in a T. pallidum-infected subject (such as, a human). Lipoidal antigens comprising cardiolipin (CL), lecithin (L) and cholesterol (Ch) have long been used in solution assays to detect anti-lipoidal antibodies in serum (see, e.g., prior discussion of "non-treponemal tests" for syphilis diagnosis). Specific exemplary CL/L/Ch-containing lipoidal antigens previously used in solution assays include the commonly known VDRL, RPR, and USR antigens. . . been a long-felt (but previously unmet) need to provide membrane-based assays (such as, flow-through or lateral flow immunoassay devices) for detection of anti-lipoidal antibodies, for instance, in biological samples. Such immunoassay devices would revolutionize, for example, point-of-care diagnosis of syphilis and other diseases characterized by the presence of anti-lipoidal antibodies. This disclosure describes, among other things, a method for immobilizing. . .

DETD . . . discussed above, methods and compositions described herein contemplate a lipoidal antigen that includes (e.g., comprises or consists essentially of) cardiolipin, cholesterol and lecithin. These exemplary components of a lipoidal antigen are described in more detail below.

DETD Lecithin is the common name for phosphatidylcholine. Phosphatidylcholine is a glycerophospholipid, which is usually the most abundant phospholipid in animal and. . . also the principal phospholipid circulating in the plasma. Phosphatidylcholine contains two fatty acid side chains. As used herein, the term "lecithin" contemplates phosphatidylcholine having any distribution of fatty acid side chains. Thus, the two fatty acid side chains of cardiolipin can. . . about 4 double bonds, or from completely saturated to having about 2 double bonds). Exemplary fatty acid side chains of lecithin, as contemplated herein, independently include myristoyl (14:0); palmitoyl (16:0); stearoyl (18:0); oleoyl (18:1); myristoleoyl (14:1); palmitoleoyl (16:1); petroselinoyl (18:1); linoleoyl. . .

DETD In some embodiments, lecithin is a naturally occurring form of lecithin. The fatty acid composition of naturally occurring lecithin includes palmitoyl (16:0), palmitoleoyl (16:1), linoleoyl (18:2), stearoyl (18:0), arachidonoyl (20:4), myristoyl (14:0), oleoyl (18:1), and linolenoyl (18:3). The relative percentages of fatty acids in naturally occurring lecithin vary depending upon the source of the lecithin (e.g., Balint et al., J. Lipid Res., 6(1):96, 1965). For example, lecithin in human gallbladder bile is reported to be about 45% 16:0, 4% 16:1, 4% 18:0, 16% 18:1, 23% 18:2, 4% 20:4 with traces of 18:3 and 14:0; and lecithin in human plasma is reported to be about 35% 16:0, 1% 16:1, 14% 18:0, 17% 18:1, 17% 18:2, 14% 20:4 with traces of 18:3 and 14:0. In other embodiments, lecithin is a non-naturally occurring form (also referred to as "synthetic lecithin").

DETD Non-limiting examples of lecithin include, for example:

DETD Other particular lecithin examples include, without limitation, DL-a-dimyristoyl lecithin, L-a-dimyristoyl cephalin, L-a-dipalmitoyl lecithin, dipalmitoyl L-a-glycerophosphoric acid monocholine salt, L-a-dimyristoyl lecithin, D-a-dimyristoyl lecithin, L-a-distearoyl lecithin, stearoyl glycollecithin, 1,2-dioleoyl-sn-glycero-3-phosphocholine (18:1), 1,2-dilino1eoyl-sn-glycero-3-phosphocholine (18:2), 1,2-dimyristoyl-sn-glycero-3-phosphocholine (14:0), 1,2-dipentadecanoyl-sn-glycero-3-phosphocholine (15:0), 1,2-diphytanoyl-sn-glycero-3-phosphocholine (16:0), 1,2-dipalmitoyl-sn-glycero-3-phosphocholine (16:0), and 1-palmitoyl-2-oleoyl-sn-glycero-3-phosphocholine.

DETD C. Cholesterol

DETD Cholesterol is a steroid having, in one embodiment, the following structure:

DETD Cholesterol is known to interact with phospholipids (such as, cardiolipin and lecithin) in membranes or membrane-like structures (such as liposomes or micelles). In these circumstances, the cholesterol molecule is believed to be oriented parallel to the fatty acid chains of the phospholipids, and the cholesterol hydroxyl group interacts with the phospholipid head groups.

DETD In the formation of the lipoidal antigens disclosed herein, cholesterol is believed to stabilize the emulsion (e.g, micelle). Thus, for the purposes of this disclosure, the term "cholesterol"

includes any form of cholesterol or other cholesterol derivative that is capable of stabilizing an emulsion which contains a lipoidal

antigen. In some examples, stabilizing a lipoidal-antigen-containing emulsion refers to extending the time an emulsified lipoidal antigen remains in solution. For example, addition of cholesterol to a lipoidal antigen may extend the time such an antigen remains dispersed in a continuous phase of an emulsion. . . an ethanolic solution) by 5%, 10%, 15% or 25% as compared to a comparable antigen containing relatively less or no cholesterol.

DETD Non-limiting examples of cholesterol derivatives include cholest-5-en-3 beta-yl-6-aminohexyl ether (AH-Chol; Zimmer et al., Eur. J. Pharm. Biopharm., 47(2):175-8, 1999); poly(ethylene glycol) cholesteryl ethers (PEG(n)-Chols; Baba et al., Traffic, 2(7):501-12, 2001; Ishiwata et al., Biochim. Biophys. Acta, 1359(2):123-35, 1997); a cationic cholesterol derivative with a hydroxyethyl amino head group described by Nakanishi and Noguchi (Adv. Drug Deliv. Rev., 52(3):197-207, 2001); cholesterol hemisuccinate (Meuillet et al., Eur. J. Pharmacol., 377(2-3):241-52, 1999; dehydroergosterol (DHE), which differs from cholesterol in having three additional double bonds and an extra methyl group (Mukherjee, Biophys. J., 75(4):1915-1925, 1998); cationic derivatives of cholesterol which contain a tertiary amino head group with a different spacer arm (Takeuchi et al., FEBS Lett., 397(2-3):207-9, 1996); cholesteryl-3. . . FEBS Lett., 433(1-2):169-173, 1998); and N-[tris [(beta-D-galactopyranosyloxy)methyl]methyl]-N alpha-[4-(5-cholesten-3 beta-yloxy)succinyl]glycinamide (Kempen et al., J. Medicin. Chem., 27:1306-1312, 1984). Further examples of cholesterol derivatives useful in the formation of membrane and membrane-like (e.g., liposomal or micellar) structures (like a disclosed lipoidal antigen) are. . .

DETD In CL/L/Ch lipoidal antigen embodiments, cardiolipin, lecithin and cholesterol can be combined in any proportion that forms an antigen capable of being specifically bound by an anti-lipoidal antibody (such. . . mixture will depend, for example, on the length and degree of saturation of the fatty acid chains of cardiolipin and lecithin, on the temperature, on the ionic composition of the aqueous medium, and on the mode of dispersal of the phospholipids. . .

DETD In some embodiments, a non-aqueous solution containing cardiolipin, lecithin and cholesterol (CL/L/Ch) is mixed with an aqueous solution to form an emulsion. Any non-aqueous solution in which cardiolipin, lecithin and cholesterol are each soluble (or partially soluble) can be used, including, for example, ethanol (such as absolute ethanol, 95% ethanol, or. . .

DETD . . . 0.05%, from about 0.01% to about 0.04%, or from about 0.025% to about 0.035%); from about 0.05% to about 0.5% lecithin (such as from about 0.07% to about 0.4%, from about 0.09% to about 0.3%, from about 0.1% to about 0.25%, or from about 0.14% to about 0.21%); and/or from about 0.2% to about 5% cholesterol (such as from about 0.4% to about 3%, from about 0.7% to about 2%, from about 0.8% to about 1%).. . . a CL/L/Ch solution useful for preparing a lipoidal antigen includes about 0.03% cardiolipin (such as, naturally occurring cardiolipin), about 0.21% lecithin (such as, naturally occurring lecithin), and about 0.9% cholesterol. In another example, a CL/L/Ch solution useful for preparing a lipoidal antigen includes about 0.03% tetramyristoyl cardiolipin, about 0.14% 1-palmitoyl-2-oleoyl-sn-glycero-3-phosphocholine and about 0.9% cholesterol.

DETD It is known that anti-lipoidal antibodies (e.g., reagin) in human serum will react with cardiolipin, lecithin and cholesterol-containing lipid antigens (such as, the RPR, VDRL, USR, or synthetic VDRL antigens). As discussed above, this knowledge formed the basis. . .

DETD . . . including, for example, anti-lipoidal antibodies from a T. pallidum-infected or T. pallidum-inoculated subject (such as, a human or a rabbit), anti-cholesterol antibodies, anti-cardiolipin antibodies, or anti-lecithin antibodies. As discussed in more detail below, antigen-binding fragments (such as, Fab fragments) of antibodies having the foregoing specificities can. . .

DETD Other exemplary anchor antibodies that can be used in the disclosed compositions and methods, include anti-cholesterol antibodies and anti-cardiolipin antibodies. Anti-cholesterol antibodies are present in human sera and can be isolated as described above for anti-lipoidal antibodies. Specific anti-cholesterol antibodies and/or protocols for producing and/or isolating anti-cholesterol antibodies can be found in

Kruth et al. (J. Lipid Res., 42:1492-1500, 2001), Alving et al. (Biochem. Soc. Trans., 17:637-639,. . .

DETD . . . solid support by contacting in solution the lipoidal antigen with anchor antibodies specific for the lipoidal antigen (e.g., anti-lipoidal antibodies, anti-cholesterol antibodies, anti-lecithin antibodies, and/or anti-cardiolipin antibodies, and/or antigen-binding fragments of any of the foregoing) to form a lipoidal antigen-anchor antibody complex (or. . .

DETD . . . the purpose of serving as an epitope for an anchor antibody. Such examples do not exclude including derivatized cardiolipin, derivatized lecithin and/or derivatized cholesterol as components of a lipoidal antigen; however, in such examples, the derivative groups of such derivatized components do not serve. . .

DETD

Lipoidal Antigen	Anchor Antibody	Detector Reagent
CL/L/Ch	human, anti-lipoidal antigen-binding fragment (e.g., Fab)	Protein A, Protein G, or anti-human Ab(Fc)
CL/L/Ch	human, anti-cholesterol antigen-binding fragment (e.g., Fab)	Protein A, Protein G, or anti-human Ab(Fc)
CL/L/Ch	human, anti-cardiolipin antigen-binding fragment (e.g., Fab)	Protein A, Protein G, or anti-human Ab(Fc)
CL/L/Ch	non-human, anti-lipoidal full-length Ab	anti-human Ab (any specificity)
CL/L/Ch	non-human, anti-cholesterol full-length Ab	anti-human Ab (any specificity)
CL/L/Ch	non-human, anti-cardiolipin full-length Ab	anti-human Ab (any specificity)
CL/L/Ch	non-human (mammalian), anti-lipoidal antigen-binding fragment (e.g., Fab)	Protein A, Protein G, anti-human Ab (any specificity)
CL/L/Ch	non-human (mammalian), anti-cholesterol antigen-binding fragment (e.g., Fab)	Protein A, Protein G, anti-human Ab (any specificity)
CL/L/Ch	non-human (mammalian), anti-cardiolipin antigen-binding fragment. . .	Protein A, Protein G, anti-human Ab (any specificity)

DETD . . . to a 250 ml round, glass-stoppered bottle. Over a period of 40 to 60 seconds, 10 ml VDRL antigen (0.9% cholesterol, 0.03% bovine heart cardiolipin, and about 0.21% lethicin in ethanol) was added directly onto the buffered saline with continuous rotation. . .

CLM What is claimed is:

. . . anti-lipoidal antibody capture area, comprising: (a) an anchor antibody immobilized on the substrate; and (b) a lipoidal antigen, comprising cardiolipin, lecithin, and cholesterol, wherein the immobilized anchor antibody is specifically bound to one or more of the cardiolipin, lecithin or cholesterol components of the lipoidal antigen thereby forming an immobilized anchor antibody-lipoidal antigen complex.

CLM What is claimed is:

. . . claim 1, wherein the anchor antibody does not specifically bind an exogenous epitope in one or more of the cardiolipin, lecithin or cholesterol components of the lipoidal antigen.

CLM What is claimed is:

. . . a method comprising: contacting the lipoidal antigen with one or more anchor antibodies specific for at least one of cardiolipin, lecithin, or cholesterol to form the lipoidal antigen-anchor antibody complex; and applying the lipoidal antigen-anchor antibody complex to the substrate.

CLM What is claimed is:

. . . is immobilized on the substrate by a method, comprising: immobilizing an anchor antibody specific for at least one of cardiolipin, lecithin, or cholesterol on the substrate; blocking non-specific binding sites

on the substrate; contacting the immobilized anchor antibody with a lipoidal antigen to. . .

CLM What is claimed is:

. . . anchor antibody, and which complex is immobilized on the membrane by the anchor antibody; wherein the lipoidal antigen comprises cardiolipin, lecithin and cholesterol; and a flow path from the sample application area to the anti-lipoidal antibody capture area; wherein the presence and/or amount. . .

CLM What is claimed is:

42. The method of claim 36, comprising: contacting a lipoidal antigen, comprising immunoreactive cardiolipin, lecithin, and cholesterol, with an antibody fragment specific for cardiolipin, lecithin, or cholesterol to form a lipoidal antigen-antibody complex; wherein the antibody fragment does not substantially react with Protein A, Fc-specific Protein G,. . .

CLM What is claimed is:

. . . The method of claim 42, comprising contacting a lipoidal antigen, comprising immunoreactive cardiolipin, with a Fab fragment specific for cardiolipin, lecithin, or cholesterol to form a lipoidal antigen-Fab complex; wherein the lipoidal antigen is a USR antigen, a VDRL antigen, or a synthetic. . .

CLM What is claimed is:

. . . immunoreactive cardiolipin on a substrate, the method comprising: immobilizing one or more antibodies specific for at least one of cardiolipin, lecithin or cholesterol on a substrate; blocking non-specific binding sites on the substrate; applying a lipoidal antigen, comprising at least one immunoreactive cardiolipin, lecithin or cholesterol, to the substrate to form lipoidal antigen-immobilized antibody complexes; and washing the substrate to remove any lipoidal antigen that is. . .

L6 ANSWER 20 OF 39 CA COPYRIGHT 2022 ACS on STN DUPLICATE 5
ACCESSION NUMBER: 151:446105 CA Full-text
TITLE: Immunoassays and devices for detection of anti-lipoidal antibodies in syphilis diagnosis
INVENTOR(S): Castro, Arnold R.
PATENT ASSIGNEE(S): United States Dept. of Health and Human Services, USA
SOURCE: U.S. Pat. Appl. Publ., 43 pp., Cont.-in-part of U.S. Ser. No. 993,213.
CODEN: USXXCO
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
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US 20090263825	A1	20091022	US 2009-433626	20090430
US 8148057	B2	20120403		
WO 2007002178	A2	20070104	WO 2006-US24117	20060620
WO 2007002178	A3	20070510		
US 20100221740	A1	20100902	US 2008-993213	20080111
US 20120184049	A1	20120719	US 2012-13429183	20120323
US 8394600	B2	20130312		

PRIORITY APPLN. INFO.:

US 2005-60693120	P	20050621
WO 2006-US24117	W	20060620
US 2008-993213	A2	20080111
US 2009-433626	A3	20090430

PATENT STATUS PATENT INFORMATION:

PATENT NO.	KIND	STATUS	STATUS DATE
US 20090263825	A1	Alive	20201120
US 8148057	B2	Alive	20201121
WO 2007002178	A2	Dead	20201202
WO 2007002178	A3	Dead	20201201
US 20100221740	A1	Dead	20201120
US 20120184049	A1	Alive	20201121
US 8394600	B2	Alive	20201121

ASSIGNMENT HISTORY FOR US PATENT AVAILABLE IN LSUS DISPLAY FORMAT
AB . . . and the diagnosis of syphilis are disclosed.. In particular, a method is disclosed for immobilizing a lipoidal antigen, comprising

cardiolipin, lecithin, and cholesterol, on a solid support (e.g., a nitrocellulose membrane). In one example, an anti-lipoidal antibody Fab fragment comprise the immobilization method.. . .

IT Micelles
(complexes with cardiolipin and cholesterol; immobilization on microporous membranes for detection of anti-lipoidal antibodies in diagnosis of syphilis)

IT Phosphatidylcholines
RL: ARG (Analytical reagent use); DGN (Diagnostic use); ANST (Analytical study); BIOL (Biological study); USES (Uses)
(micellar complexes with cardiolipin and cholesterol ; detection of anti-lipoidal antibodies for diagnosis of syphilis)

IT Cardiolipins
RL: ARG (Analytical reagent use); DGN (Diagnostic use); ANST (Analytical study); BIOL (Biological study); USES (Uses)
(micellar complexes with lecithin and cholesterol; detection of anti-lipoidal antibodies for diagnosis of syphilis)

IT 57-88-5D, Cholesterol, micellar complexes with lecithin and cardiolipin
RL: ARG (Analytical reagent use); DGN (Diagnostic use); ANST (Analytical study); BIOL (Biological study); USES (Uses)
(detection of anti-lipoidal antibodies for diagnosis of syphilis)

L6 ANSWER 21 OF 39 USPATFULL on STN

ACCESSION NUMBER:	2008:354768 USPATFULL Full-text			
TITLE:	Modified Cardiolipin and Uses Therefor			
INVENTOR(S):	Castro, Arnold R., Monroe, GA, UNITED STATES Wang, Huiying, Lake Oswego, OR, UNITED STATES			
	NUMBER	KIND	DATE	
PATENT INFORMATION:	US 20080311597	A1	20081218	
	US 7888043	B2	20110215	
APPLICATION INFO.:	US 2008-94144	A1	20061117	(12)
	WO 2006-US44572		20061117	
			20080516	PCT 371 date
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PRIORITY INFORMATION:	US 2005-60737901		20051118 (60)	
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LEGAL REPRESENTATIVE:	KLARQUIST SPARKMAN, LLP, 121 S.W. SALMON STREET, SUITE 1600, PORTLAND, OR, 97204, US			
NUMBER OF CLAIMS:	46			
EXEMPLARY CLAIM:	1			
NUMBER OF DRAWINGS:	9 Drawing Page(s)			
LINE COUNT:	2866			

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB Compositions, methods and devices for the detection of anti-lipoidal antibodies and the diagnosis of disease, for example, syphilis, are described. In particular, oxidized cardiolipins, which may be conjugated with a variety of attachment molecules, such as BSA, KLH, biotin, synthetic protein MAPS, IgY, streptavidin, or avidin, are described. Such oxidized cardiolipin, alone or complexed with one or more attachment molecules, are useful to detect anti-lipoidal antibodies in subjects, for example, when. . .

SUMM This disclosure relates to modified cardiolipin compositions and uses therefor; in particular, to methods of immobilizing modified cardiolipin to a solid support, and related immunoassays (such as ELISA) and immunoassay devices (such as test strips, flow-through devices, or lateral flow devices), which assays and devices are useful, for example, for detection of anti-lipoidal antibodies and/or diagnosis of disease (such as syphilis).

SUMM Tests for anti-lipoidal antibodies (often called "non-treponemal tests") are typically based on an antigen composed of naturally occurring cardiolipin, cholesterol and lecithin. The widely used non-treponemal tests (e.g., Venereal Disease Research Laboratory (VDRL)

test and Rapid Plasma Reagin (RPR) test) monitor, either. . .

SUMM . . . an approach for reliably attaching cardiolipin (or lipoidal antigens comprising cardiolipin modified as described herein, phosphatidylcholine (also referred to as "lecithin"), and cholesterol) to a solid substrate (such as a microporous membrane or multi-well plate) while maintaining the antigenicity and specificity of the. . .

DRWD FIG. 8 shows a digital image of a thin-layer chromatograph of an oxidized cardiolipin-lecithin mixture. (A) A mixture of unmodified cardiolipin and unmodified lecithin in t-butanol; (B) an oxidized cardiolipin/lecithin mixture; (C) the upper, t-butanol phase following the oxidation of a cardiolipin/lecithin mixture; and (D) the lower, aqueous phase following the oxidation of a cardiolipin/lecithin mixture. The direction of migration of each sample is shown by an arrow.

DRWD FIG. 9 shows the chemical structures of four representative naturally occurring phosphatidylcholine (lecithin) molecules. For L-α-phosphatidylcholine (heart, bovine), the molecular formula is C.sub.42H.sub.80NO.sub.8P, the molecular weight is 758.07, the molecular weight (isotope) is. . .

DRWD FIG. 10 shows a digital image of a dot blot assay used to determine the antigenicity of six oxidized cardiolipin/lecithin-BSA or -KLH conjugates. The amounts of the respective antigens applied to each dot in the assay are given in the. . .

DETD The disclosed immunoassay devices can be used in methods for diagnosing syphilis in a subject by analyzing a biological sample from the subject, by applying the biological sample to the device and detecting formation of a complex among the anti-lipoidal antibody, the oxidized cardiolipin, and a detector reagent in the capture area. Detection of the formation of the complex in the capture area detects an anti-lipoidal antibody associated with infection with syphilis. In those embodiments in which the device includes a conjugate pad in the path of flow from the sample application area to the cardiolipin capture area, the detected complex includes the mobile or mobilizable detector reagent. In other embodiments in which the detector reagent. . .

DETD . . . to disease states, such as infection by T. pallidum. Naturally occurring cardiolipin has traditionally been used, often in combination with cholesterol and lecithin, in flocculation tests to detect anti-lipoidal antibodies, for example, in the serum of T. pallidum-infected patients.

DETD Lecithin (a.k.a., phosphatidylcholine): Lecithin is the common name for phosphatidylcholine. Phosphatidylcholine is a glycerophospholipid, which is usually the most abundant phospholipid in animal and. . .

DETD As used herein, the term "lecithin" includes both naturally occurring lecithins and any modified synthetic lecithin that has structural similarity to naturally occurring lecithin. For example, the fatty acids of synthetic lecithins may include the following:

DETD D. Cardiolipin/Lecithin Mixtures

DETD Mixtures of cardiolipin and lecithin may be oxidized by the same methods described above for cardiolipin alone; the only difference being that the starting material is a mixture of cardiolipin and lecithin. In the initial oxidation reaction, cardiolipin and lecithin are mixed together in a weight ratio (cardiolipin:lecithin) between about 20:1 to about 1:1, or between about 1:1 to about 1:10, or between about 10:1 to about 1:10,. . . between about 5:1 to about 1:5, or between about 1:1 to about 1:5. In particular examples, the weight ratio of cardiolipin:lecithin includes about 20:1, about 10:1, about 5:1, about 2:1, about 1:1, about 1:2, about 1:3, about 1:5, or about 1:10.

DETD The discovery herein of a method to oxidize cardiolipin and prepare cardiolipin-attachment molecule conjugates, which can be immobilized on a solid support (such as a microporous membrane, like nitrocellulose, nylon or PVDF) enables solid-surface-based immunoassays (such as, EIA, ELISA, flow-through devices, dipsticks, and lateral flow devices) for the detection of cardiolipin-binding analytes (such as anti-lipoidal antibodies in biological samples from T. pallidum-infected subjects). In some examples, a disclosed immunoassay permits detection of the presence (or absence) of anti-lipoidal antibodies in a biological sample for diagnosis of syphilis.

DETD . . . antigens (e.g., oxidized cardiolipin-attachment molecule complex) and other antigens specific for anti-lipoidal antibody; for example, immobilized lipoidal antigen comprising cardiolipin, lecithin and cholesterol. Immobilization of lipoidal antigen is described in

detail in PCT/US2006/024117, which is incorporated herein in its entirety by reference. In one example, a lipoidal antigen comprising cardiolipin (e.g., naturally occurring or synthetic cardiolipin), lecithin and cholesterol is contacted with a population of Fab fragments specific for the lipoidal antigen to provide a lipoidal antigen-Fab complex, which. . .

DETD Oxidation of Mixtures of Cardiolipin and Lecithin

DETD This example describes the oxidation of mixtures of cardiolipin and lecithin, and demonstrates that oxidized mixtures of cardiolipin and lecithin perform at least as well as oxidized cardiolipin alone in the assays described in Examples 4-7.

DETD Cardiolipin and lecithin were mixed together in ratios of 1:1, 1:3, and 1:5 cardiolipin to lecithin by weight. The mixtures were then oxidized as described in Example 1. As shown in FIG. 8, lane A, a mixture of unmodified cardiolipin and unmodified lecithin resolves into two spots on a TLC strip. Unmodified cardiolipin migrates to the top of the TLC strip, as indicated by the dark spot furthest from the point of origin (see also, FIG. 2, lane A). Unmodified lecithin migrates somewhat more slowly on the TLC place and is shown as the dark spot approximately halfway between the cardiolipin. . .

DETD . . . acid side chains, and introduces carboxyl groups into one or more of the fatty acid side chains of cardiolipin and lecithin. Carboxyl groups present in oxidized molecules interact more strongly with the silica substrate of a TLC strip, which retards the migration of the oxidized forms along the strip. Hence, in oxidized mixtures of cardiolipin and lecithin, a pronounced smear in the direction of migration is observed (see FIG. 8, lanes B and C). In addition, oxidative. . . represented by a white spot (due to dye exclusion), which is coextensive with the point of origin. Following oxidation of cardiolipin/lecithin mixtures as described in this example, oxidized forms of cardiolipin were found predominantly in the t-butanol phase (shown in FIG.. . .

DETD A. BSA and KLH Conjugation of Oxidized Cardiolipin/Lecithin Mixtures

DETD Oxidized mixtures of cardiolipin and lecithin were conjugated to either BSA or KLH, as described in Method 3 of Example 2. The BSA- or KLH-conjugated cardiolipin/lecithin preparations are described in Table 5.

DETD

TABLE 5

Cardiolipin/Lecithin Mixtures

Cardiolipin (CL) Lecithin (L) Prep. No.	CL:L Ratio (by weight)	Attachment Molecule	Amount of Attachment Molecule Per Reaction (mg)
C/L 1	1:1	BSA	5
C/L 2	1:1	BSA	2
C/L 3	1:1	KLH	2

C/L. . .

DETD B. RPR Inhibition Test of Oxidized Cardiolipin/Lecithin Mixtures

DETD The antigenicities of the cardiolipin/lecithin preparations described in Table 5 were tested in the RPR Inhibition Test, as described in Example 3. As shown in Table 6, each of the cardiolipin/lecithin preparations completely inhibited the reactivity of syphilitic serum in the traditional RPR test.

DETD

TABLE 6

RPR Inhibition Test Results for Cardiolipin/Lecithin Mixtures

Cardiolipin/Lecithin Prep. Used for Preincubation	Serum (Lot 50 L) Dilution 1:1	1:2	1:4	1:8	1:16	1:32
None (i.e., Control)	R	R	R.sub.(-). . .			

DETD This result demonstrates that the oxidized cardiolipin/lecithin mixtures very efficiently strip (i.e., remove) anti-lipoidal antibodies from the syphilitic serum, so that such serum is non-reactive in the. . .

DETD C. Immunodot Testing of Oxidized Cardiolipin/Lecithin Mixtures
DETD . . . (BioRad) with a goat anti-human IgG alkaline-phosphatase conjugate in accordance with the manufacturer's instructions. As shown in FIG. 10, oxidized cardiolipin/lecithin mixtures in the range 375 ng to 21 µg per dot reacted with syphilitic serum (Lot 94265; 1:50 dilution). In comparison, none of the tested amounts of the oxidized cardiolipin/lecithin preparations showed any significant reaction with normal, human serum (i.e., non-syphilitic serum).
DETD The preparations where cardiolipin and lecithin were oxidized in a 1:1 ratio (by weight) and then conjugated to either BSA or KLH (i.e., 1:1 BSA and. . .
DETD . . . for example, gold-labeled oxidized cardiolipin-BSA, or gold-labeled oxidized cardiolipin-KLH conjugate, or a gold-labeled, BSA-conjugated mixture of oxidized cardiolipin and oxidized lecithin, or a gold-labeled, KLH-conjugated mixture of oxidized cardiolipin and oxidized lecithin.
CLM What is claimed is:
35. A method for diagnosing syphilis by analyzing a biological sample from a subject, comprising: applying the biological sample to the device of claim 27; and detecting the formation of a complex among the anti-lipoidal antibody, the oxidized cardiolipin, and a detector reagent in the capture area, wherein detection of the formation of the complex in the capture area. . .
CLM What is claimed is:
. . . through the primary and secondary capture areas; detecting the formation of a first complex among the anti-lipoidal antibody, the oxidized cardiolipin, and at least one detector reagent in the primary capture area; and detecting the formation of a second complex among the treponemal antibody, the second immobilized binding partner, and at least one detector reagent in the secondary capture area; wherein detection of the formation of the first complex and the second complex diagnoses syphilis in the patient.

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ABEN
Compositions, methods and devices for the detection of anti-lipoidal antibodies and the diagnosis of disease, for example, syphilis, are described. In particular, oxidized cardiolipins, which may be conjugated with a variety of attachment molecules, such as BSA, KLH, biotin, synthetic protein MAPS, IgY, streptavidin, or avidin, are described. Such oxidized cardiolipin, alone or complexed with one or more attachment molecules, are useful to detect anti-lipoidal antibodies in subjects, for example, when. . .

ABFR
La presente invention concerne des compositions, procedes et dispositifs de detection d'anticorps anti-lipoidaux et le diagnostic de maladies telles que la syphilis. Il s'agit en particulier de cardiolipines oxydees, qui peuvent etre conjuguees a une variete de molecules de liaison, telles que l'ASB, la KLH, la biotine, la proteine synthetique MAPS, IgY, la streptavidine ou l'avidine. Cette cardiolipine oxydee, seule ou en complexe avec une ou plusieurs molecules de liaison, est utile pour detecter les anticorps anti-lipoidaux chez. . .

DETDEN
[0003] This disclosure relates to modified cardiolipin compositions and uses therefor; in particular, to methods of immobilizing modified cardiolipin to a solid support, and related immunoassays (such as ELISA) and immunoassay devices (such as test strips, flow-through devices, or lateral flow devices), which assays and devices are useful, for example, for detection of anti-lipoidal antibodies and/or diagnosis of disease (such as syphilis).

DETDEN . . .
[00010] Tests for anti-lipoidal antibodies (often called "non-treponemal tests") are typically based on an antigen composed of naturally occurring cardiolipin, cholesterol and lecithin. The widely used non-treponemal tests (e.g., Venereal Disease Research Laboratory (VDRL) test and Rapid Plasma Reagin (RPR) test) monitor, either. . .

DETDEN . . .
an approach for reliably attaching cardiolipin (or lipoidal antigens comprising cardiolipin modified as described herein, phosphatidylcholine (also referred to as "lecithin"), and cholesterol) to a solid substrate (such as a microporous membrane or multi-well plate) while maintaining the antigenicity and specificity of the. . .

DETDEN
[0026] FIG. 8 shows a digital image of a thin-layer chromatograph of an oxidized cardiolipin-lecithin mixture. (A) A mixture of unmodified cardiolipin and unmodified lecithin in t-butanol; (B) an oxidized cardiolipin/lecithin mixture; (C) the upper, t-butanol phase following the oxidation of a cardiolipin/lecithin mixture; and (D) the lower, aqueous phase following the oxidation of a cardiolipin/lecithin mixture. The direction of migration of each sample is shown by an arrow.

DETDEN
[0027] FIG. 9 shows the chemical structures of four representative naturally occurring phosphatidylcholine (lecithin) molecules. For L-a-phosphatidylcholine (heart, bovine), the molecular formula is C42H80NO8P, the molecular weight is 758.07, the molecular weight (isotope). . .

DETDEN . . .
[0028] FIG. 10 shows a digital image of a dot blot assay used to determine the antigenicity of six oxidized cardiolipin/lecithin-BSA or -KLH conjugates. The amounts of the respective antigens applied to each dot in the assay are given in the. . .

DETDEN

[0037] The disclosed immunoassay devices can be used in methods for diagnosing syphilis in a subject by analyzing a biological sample from the subject, by applying the biological sample to the device and detecting formation of a complex among the anti-lipoidal antibody, the oxidized cardiolipin, and a detector reagent in the capture area.

DETDEN
Detection of the formation of the complex in the capture area detects an anti-lipoidal antibody associated with infection with syphilis. In those embodiments in which the device includes a conjugate pad in the path of flow from the sample application area to the cardiolipin capture area, the detected complex includes the mobile or mobilizable detector reagent. In other embodiments in which the detector reagent. . .

DETDEN
pallidum. Naturally occurring cardiolipin has traditionally been used, often in combination with cholesterol and lecithin, in flocculation tests to detect anti-lipoidal antibodies, for example, in the serum of T. pallidum-infected patients.

DETDEN
[0075] Lecithin (a.k.a., phosphatidylcholine): Lecithin is the common name for phosphatidylcholine. Phosphatidylcholine is a glycerophospholipid, which is usually the most abundant phospholipid in animal and. . .

DETDEN
[0076] As used herein, the term "lecithin" includes both naturally occurring lecithins and any modified synthetic lecithin that has structural similarity to naturally occurring lecithin. For example, the fatty acids of synthetic lecithins may include the following:

DETDEN . . .
(see, e.g., Example 4). As shown in Example 4 (below), methods of oxidizing cardiolipin described herein maintain cardiolipin antigenicity. D. Cardiolipin/Lecithin Mixtures

DETDEN
[00112] Mixtures of cardiolipin and lecithin may be oxidized by the same methods described above for cardiolipin alone; the only difference being that the starting material is a mixture of cardiolipin and lecithin. In the initial oxidation reaction, cardiolipin and lecithin are mixed together in a weight ratio (cardiolipin:lecithin) between about 20:1 to about 1:1, or between about 1:1 to about 1:10, or between about 10:1 to about 1:10,. . . about 5:1 to about 1:5, or between about 1:1 to about 1:5. In particular examples, the weight ratio of cardiolipin: lecithin includes about 20:1, about 10:1, about 5:1, about 2:1, about 1:1, about 1:2, about 1:3, about 1:5, or about 1:10.

DETDEN
[00123] The discovery herein of a method to oxidize cardiolipin and prepare cardiolipin-attachment molecule conjugates, which can be immobilized on a solid support (such as a microporous membrane, like nitrocellulose, nylon or PYDF) enables solid-surface-based immunoassays (such as, EIA, ELISA, flow-through devices, dipsticks, and lateral flow devices) for the detection of cardiolipin-binding analytes (such as anti-lipoidal antibodies in biological samples from T. pallidum-mfQQXQd subjects). In some examples, a disclosed immunoassay permits detection of the presence (or absence) of anti-lipoidal antibodies in a biological sample for diagnosis of syphilis.

DETDEN . . .
antigens (e.g., oxidized cardiolipin-attachment molecule complex) and other antigens specific for anti-lipoidal antibody; for example, immobilized lipoidal antigen comprising cardiolipin, lecithin and cholesterol. Immobilization of lipoidal antigen is described in detail in PCT/US2006/024117, which is incorporated herein in its entirety by reference. In one example, a lipoidal antigen comprising cardiolipin (e.g., naturally occurring or synthetic cardiolipin), lecithin and cholesterol is contacted with a population of Fab fragments specific for the lipoidal antigen to provide a lipoidal antigen-Fab complex, which. . .

DETDEN
OXIDATION OF MIXTURES OF CARDIOLIPIN AND LECITHIN.

DETDEN
[00216] This example describes the oxidation of mixtures of cardiolipin and lecithin, and demonstrates that oxidized mixtures of cardiolipin and lecithin perform at least as well as oxidized cardiolipin alone in the assays described in Examples 4-7.

DETDEN
[00217] Cardiolipin and lecithin were mixed together in ratios of 1:1, 1:3, and 1:5 cardiolipin to lecithin by weight. The mixtures were then oxidized as described in Example 1. As shown in FIG. 8, lane A, a mixture of unmodified cardiolipin and unmodified lecithin resolves into two spots on a TLC strip. Unmodified cardiolipin migrates to the top of the TLC strip, as indicated by the dark spot furthest from the point of origin (see also, FIG. 2, lane A). Unmodified lecithin migrates somewhat more slowly on the TLC place and is shown as the dark spot approximately halfway between the cardiolipin. . .

DETDEN . . .
acid side chains, and introduces carboxyl groups into one or more of the fatty acid side chains of cardiolipin and lecithin. Carboxyl groups present in oxidized molecules interact more strongly with the silica substrate of a TLC strip, which retards the migration of the oxidized forms along the strip. Hence, in oxidized mixtures of cardiolipin and lecithin, a pronounced smear in the direction of migration is observed (see FIG. 8, lanes B and C). In addition, oxidative. . . represented by a white spot (due to dye exclusion), which is coextensive with the point of origin. Following oxidation of cardiolipin/lecithin mixtures as described in this example, oxidized forms of cardiolipin were found predominantly in the t-butanol phase

(shown in FIG.. . .

DETDEN
A. BSA AND KLH CONJUGATION OF OXIDIZED CARDIOLIPIN/LECITHIN MIXTURES.

DETDEN
[00219] Oxidized mixtures of cardiolipin and lecithin were conjugated to either BSA or KLH, as described in Method 3 of Example 2. The BSA- or KLH-conjugated cardiolipin/lecithin preparations are described in Table 5.

DETDEN
Table 5. Cardiolipin/Lecithin Mixtures Cardiolipin (CL) Lecithin (L) Prep. No. CL:L Ratio (by weight) Attachment Molecule Amount of Attachment Molecule Per Reaction (mg) C/L 1 1:1 BSA. . .

DETDEN
B. RPR INHIBITION TEST OF OXIDIZED CARDIOLIPIN/LECITHIN MIXTURES.

DETDEN
[00220] The antigenicities of the cardiolipin/lecithin preparations described in Table 5 were tested in the RPR Inhibition Test, as described in Example 3. As shown in Table 6, each of the cardiolipin/lecithin preparations completely inhibited the reactivity of syphilitic serum in the traditional RPR test.

DETDEN
Table6. RPR Inhibition Test Results for Cardiolipin/Lecithin Mixtures Cardiolipin/Lecithin Serum (Lot 50L) Dilution Prep. Used for Serum Preincubation 1:1 1:2 1:4 1:8 1:16 1:32 None (i.e., Control) R R. . .

DETDEN
[00221] This result demonstrates that the oxidized cardiolipin/lecithin mixtures very efficiently strip (i.e., remove) anti-lipoidal antibodies from the syphilitic serum, so that such serum is non-reactive in the. . .

DETDEN
C. Immunodot Testing of Oxidized Cardiolipin/Lecithin Mixtures

DETDEN . . .
(BioRad) with a goat anti-human IgG alkaline-phosphatase conjugate in accordance with the manufacturer's instructions. As shown in FIG. 10, oxidized cardiolipin/lecithin mixtures in the range 375 ng to 21 pg per dot

reacted with syphilitic serum (Lot 94265; 1:50 dilution).

DETDEN
In comparison, none of the tested amounts of the oxidized cardiolipin/lecithin preparations showed any significant reaction with normal, human serum (i.e., non-syphilitic serum).

DETDEN
[00223] The preparations where cardiolipin and lecithin were oxidized in a 1:1 ratio (by weight) and then conjugated to either BSA or KLH (i.e., 1:1 BSA and. . .

DETDEN . . .
for example, gold-labeled oxidized cardiolipin-BSA, or gold-labeled oxidized cardiolipin-KLH conjugate, or a gold-labeled, BSA-conjugated mixture of oxidized cardiolipin and oxidized lecithin, or a gold-labeled, KLH-conjugated mixture of oxidized cardiolipin and oxidized lecithin.

CLMEN
35. A method for diagnosing syphilis by analyzing a biological sample from a subject, comprising: applying the biological sample to the device of claim 27 ; and detecting the formation of a complex among the anti-lipoidal antibody, the oxidized cardiolipin, and a detector reagent in the capture area, wherein detection of the formation of the complex in the capture area. . .

CLMEN. . .
through the primary and secondary capture areas; detecting the formation of a first complex among the anti-lipoidal antibody, the oxidized cardiolipin, and at least one detector reagent in the primary capture area; and detecting the formation of a second complex among the treponemal antibody, the second immobilized binding partner, and at least one detector reagent in the secondary capture area; wherein detection of the formation of the first complex and the second complex diagnoses syphilis in the patient.

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TITLE (ENGLISH): METHODS, IMMUNOASSAYS AND DEVICES FOR DETECTION OF ANTI-LIPOIDAL ANTIBODIES
TITLE (FRENCH): PROCEDES, IMMUNODOSAGES ET DISPOSITIFS POUR LA DETECTION D'ANTICORPS ANTI-LIPOIDAUX
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PATENT APPLICANT(S): THE GOVERNMENT OF THE UNITED STATES OF AMERICA AS REPRESENTED BY THE SECRETARY OF THE DEPARTMENT OF HEALTH AND HUMAN SERVICES, CENTERS FOR DISEASE CONTROL AND PREVENTION, TECHNOLOGY TRANSFER OFFER, 4770 Buford Highway (k79), Atlanta, GA 30341, US, [NAT: US, RES: US], for all designated states except US
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RW (EAPO): AM AZ BY KG KZ MD RU TJ TM
RW (EPO): AT BE BG CH CY CZ DE DK EE ES FI FR GB GR HU IE IS IT
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ABEN
Compositions, methods and devices for the detection of anti-lipoidal antibodies and the diagnosis of disease, for example, syphilis, are described. In particular, a method for immobilizing a lipoidal antigen, comprising cardiolipin, lecithin, and cholesterol, on a solid support (such as a nitrocellulose membrane) is described. The ability to immobilize a lipoidal antigen on a membrane satisfies a long-felt need for membrane-based assay for the detection of anti-lipoidal antibodies. Also described are immunoassay devices for concurrently performing treponemal and non-treponemal tests for syphilis.

ABFR
Compositions, procedes et dispositifs pour la detection d'anticorps anti-lipoidaux et le diagnostic de maladies, par exemple la syphilis, et en particulier procede d'immobilisation d'antigene lipoidal, comprenant de la cardiolipine, de la lecithine et du cholesterol, sur un support solide (du type membrane nitrocellulosique). La capacite a immobiliser un antigene lipoidal sur une membrane repond au besoin, existant de longue date, en dosage a base de membrane pour la detection d'anticorps anti-lipoidaux. Dispositifs d'immunodosage pour la conduite simultanee d'essais de type treponemal et non treponemal en liaison avec la syphilis.

DETDEN . . .
[010] Tests for anti-lipoidal antibodies (often called "non-treponemal tests") are typically based on an antigen composed of naturally occurring cardiolipin, cholesterol and lethicin. The widely used non-treponemal tests (e.g., Venereal Disease Research Laboratory (VDRL) test and Rapid Plasma Reagin (RPR) test). . .

DETDEN . . .
an approach for reliably attaching lipoidal antigens (which are made up of, at least, cardiolipin, phosphatidylcholine (also referred to as "lecithin"), and cholesterol) to a solid substrate (such as, a microporous membrane) while maintaining the antigenicity and specificity of the antigen for anti-lipoidal. . .

DETDEN
[017] In one particular example, a lipoidal antigen comprising cardiolipin, lecithin and cholesterol is contacted with a population of Fab fragments specific for the lipoidal antigen to provide a lipoidal antigen-Fab complex, which. . .

DETDEN . . .
is specifically bound by the anchor antibody and is thereby anchored to the substrate. The lipoidal antigen component includes cardiolipin, lecithin and cholesterol and can be specifically bound by anti-lipoidal antibodies (such as reagin antibodies present in T. pallidum-infected, subjects).

DETDEN . . .
method involving (a) contacting the lipoidal antigen with one or more anchor antibodies specific for at least one of cardiolipin, lecithin, or cholesterol to form the lipoidal antigen-anchor antibody complex; and (b) applying the lipoidal antigen-anchor antibody complex to the membrane. In more. . . immobilized on the membrane by a method involving (i) immobilizing an anchor antibody specific for at least one of cardiolipin, lecithin, or cholesterol on the membrane; (ii) blocking non-specific binding sites on the membrane; (iii) contacting the immobilized anchor antibody with lipoidal antigen. . .

DETDEN . . .
provide an anchor antibody bound to an epitope naturally occurring in a component of the lipoidal antigen (e.g., cardiolipin or cholesterol) and not to a derivative group introduced into the antigen for the purposes of providing a binding site for the. . . antibody. For example, the anchor antibody does not bind to a biotinylated component of the lipoidal antigen (such as biotinylated lecithin or cardiolipin).

DETDEN
Detection of the formation of the complex in the capture area detects an anti-lipoidal antibody associated with T. pallidum infection or the disease syphilis. In those embodiments in which the device includes a conjugate pad in the path of flow from the sample application area to the cardiolipin capture area, the detected complex includes the mobile or mobilizable detector. In other embodiments in which the detector reagent is. . .

DETDEN . . .
exemplary methods for immobilizing immunoreactive cardiolipin on a solid support, involve (a) immobilizing one or more antibodies specific for cardiolipin, lecithin and/or cholesterol on a solid support; (b) blocking non-specific binding sites on the solid support; (c) applying a lipoidal antigen, comprising immunoreactive cardiolipin, lecithin and/or cholesterol, to the solid support to form lipoidal antigen-immobilized antibody complexes; and (d) washing the solid support to remove any lipoidal. . .

DETDEN
[068] Lipoidal Antigen: An antigen including (but not limited to) cardiolipin, lecithin and cholesterol that is capable of being specifically bound by anti-lipoidal antibodies. The nature of cardiolipin, lecithin and cholesterol as contemplated by the term "lipoidal antigen" is discussed in detail elsewhere in the specification.

DETDEN
[075] A lipoidal antigen is any antigen containing (without limitation) cardiolipin, lecithin and cholesterol, which antigen is capable of specifically binding an anti-lipoidal antibody. In some examples, a lipoidal antigen specifically binds an anti-lipoidal antibody (e.g., an anti-cardiolipin antibody) present in a T. pallidum-infected subject (such as, a human). Lipoidal antigens comprising cardiolipin (CL), lecithin (L) and cholesterol (Ch) have long been used in solution assays to detect anti-lipoidal antibodies in serum (see, e.g., prior discussion of "non-treponemal tests" for syphilis diagnosis). Specific exemplary CL/L/Ch-containing lipoidal antigens previously used in solution assays include the commonly known VDRL, RPR, and USR antigens. . .

DETDEN . . .
discussed above, methods and compositions described herein contemplate a lipoidal antigen that includes (e.g., comprises or consists essentially of) cardiolipin, cholesterol and lecithin. These exemplary components of a lipoidal antigen are described in more detail below.

DETDEN
[080] Lecithin is the common name for phosphatidylcholine.

DETDEN . . .
also the principal phospholipid circulating in the plasma. Phosphatidylcholine contains two fatty acid side chains. As used herein, the term "lecithin" contemplates phosphatidylcholine having any distribution of fatty acid side chains. Thus, the two fatty acid side chains of cardiolipin can. . .

DETDEN
Exemplary fatty acid side chains of lecithin, as contemplated herein, independently include myristoyl (14:0); palmitoyl (16:0); stearoyl (18:0); oleoyl (18:1); myristoleoyl (14:1); palmitoleoyl (16:1); petroselinoyl (18.T)QUO linoleoyl. . .

DETDEN
[081] In some embodiments, lecithin is a naturally occurring form of

lecithin.

DETDEN
The fatty acid composition of naturally occurring lecithin includes palmitoyl (16:0), palmitoleoyl (16:1), linoleoyl (18:2), stearoyl (18:0), arachidonoyl (20:4), myristoyl (14:0), oleoyl (18:1), and linolenoyl (18:3). The relative percentages of fatty acids in naturally occurring lecithin vary depending upon the source of the lecithin (e.g., Balint et a.scriptl.., J. Lipid Res., 6(1):96, 1965). For example, lecithin in human gallbladder bile is reported to be about 45% 16:0,4% 16:1, 4% 18:0,16% 18:1, 23% 18:2, 4% 20:4 with traces of 18:3 and 14:0; and lecithin in human plasma is reported to be about 35% 16:0,1% 16:1, 14% 18:0, 17% 18:1,17% 18:2,14% 20:4 with traces of 18:3 and 14:0. In other embodiments, lecithin is a non-naturally occurring form (also referred to as "synthetic lecithin").

DETDEN
[082] Non-limiting examples of lecithin include, for example: Carbon Number 1-Acyl 2-Acyl 14:0-14:0 Myristoyl Myristoyl 14:0-16:0 Myristoyl Palmitoyl 14:0-18:0 Myristoyl Stearoyl 16:0-14:0 Palmitoyl Myristoyl 16:0-16:0. . .

DETDEN
[083] Other particular lecithin examples include, without limitation, DL-adimyristoyl lecithin, L-a-dimyristoyl cephalin, L-a-dipalmitoyl lecithin, dipalmitoyl L-aglycerophosphoric acid monocholine salt, L-a-dimyristoyl lecithin, D-a-dimyristoyl lecithin, L-a-distearoyl lecithin, stearoyl glycollecithin,

DETDEN
C. Cholesterol

DETDEN
[084] Cholesterol is a steroid having, in one embodiment, the following structure:

DETDEN
Cholesterol is known to interact with phospholipids (such as, cardiolipin and lecithin) in membranes or membrane-like structures (such as liposomes

or micelles). In these circumstances, the cholesterol molecule is believed to be oriented parallel to the fatty acid chains of the phospholipids, and the cholesterol hydroxyl group interacts with the phospholipid head groups.

DETDEN
[085] In the formation of the lipoidal antigens disclosed herein, cholesterol is believed to stabilize the emulsion (e.g, micelle). Thus, for the purposes of this disclosure, the term "cholesterol" includes any form of cholesterol or other cholesterol derivative that is capable of stabilizing an emulsion which contains a lipoidal antigen. In some examples, stabilizing a lipoidal-antigen-containing emulsion refers to extending the time an emulsified lipoidal antigen remains in solution. For example, addition of cholesterol to a lipoidal antigen may extend the time such an antigen remains dispersed in a continuous phase of an

DETDEN . . .
an ethanolic solution) by 5%, 10%, 15% or 25% as compared to a comparable antigen containing relatively less or no cholesterol.

DETDEN
[086] Non-limiting examples of cholesterol derivatives include cholest-5-en-3 beta-yl-6-aminohexyl ether (AH-Chol; Zimmer et a.scriptl.., Eur. J. Pharm. Biopharm., 47(2): 175-8, 1999); poly(ethylene glycol) cholesteryl ethers (PEG(n)-Chols; Baba et a.scriptl.., Traffic, 2(7):501-12, 2001; Ishiwata et a.scriptl.., Biochim. Biophys. Acta, 1359(2): 123-35, 1997); a cationic cholesterol derivative with a hydroxyethyl amino head group described by Nakanishi and Noguchi (Adv. DrugDeliv. Rev., 52(3): 197-207, 2001); cholesterol hemisuccinate (Meuillet et a.scriptl.., Eur. J. Pharmacol., 377(2-3):241-52, 1999;

DETDEN
dehydroergosterol (DHE), which differs from cholesterol in having three additional double bonds and an extra methyl group (Mukheijee, Biophys. J.,

75(4): 1915-1925,1998); cationic derivatives of cholesterol which contain a tertiary amino head group with a different spacer arm (Takeuchi et α.scriptl.., FEBSLett., 397(2-3):207-9, 1996); cholesteryl-3betacarboxyamidoethylenedimethylamine (Noguchi. . .

DETDEN
Further examples of cholesterol derivatives useful in the formation of membrane and membrane-like (e.g., liposomal or micellar) structures (like a disclosed lipoidal antigen) are. . .

DETDEN
[087] In CL/L/Ch lipoidal antigen embodiments, cardiolipin, lecithin and cholesterol can be combined in any proportion that forms an antigen capable of being specifically bound by an anti-lipoidal antibody (such. . . mixture will depend, for example, on the length and degree of saturation of the fatty acid chains of cardiolipin and lecithin, on the temperature, on the ionic composition of the aqueous medium, and on the mode of dispersal of the phospholipids. . .

DETDEN
[089] In some embodiments, a non-aqueous solution containing cardiolipin, lecithin and cholesterol (CL/L/Ch) is mixed with an aqueous solution to form an emulsion.

DETDEN
Any non-aqueous solution in which cardiolipin, lecithin and cholesterol are each soluble (or partially soluble) can be used, including, for example, ethanol (such as absolute ethanol, 95% ethanol, or. . .

DETDEN . . .
0.05%, from about 0.01% to about 0.04%, or from about 0.025% to about 0.035%); from about 0.05% to about 0.5% lecithin (such as from about 0.07% to about 0.4%, from about 0.09% to about 0.3%, from about 0.1% to about 0.25%, or from about 0.14% to about 0.21%); and/or from about 0.2% to about 5% cholesterol (such as from about 0.4% to about 3%, from about 0.7% to about 2%, from about 0.8% to about 1%).. . . a CL/L/Ch solution useful for preparing a lipoidal antigen includes about 0.03% cardiolipin (such as, naturally occurring cardiolipin), about 0.21% lecithin (such as, naturally occurring lecithin), and about 0.9% cholesterol. In another example, a CL/L/Ch solution useful for preparing a lipoidal antigen includes about 0.03% tetramyristoyl cardiolipin, about 0.14% 1-palmitoyl-2-oleoyl-sM-glycero-3-phosphocholine and about 0.9% cholesterol.

DETDEN
[093] It is known that anti-lipoidal antibodies (e.g., reagin) in human serum will react with cardiolipin, lecithin and cholesterol-containing lipid antigens (such as, the RPR, VDRL, USR, or synthetic VDRL antigens). As discussed above, this knowledge formed the basis. . .

DETDEN . . .
antigen, including, for example, anti-lipoidal antibodies from a T. pallidum-infected or T. pallidum-subject (such as, a human or a rabbit), anti-cholesterol antibodies, anti-cardiolipin antibodies, or anti-lecithin antibodies. As discussed in more detail below, antigen-binding fragments (such as, Fab fragments) of antibodies having the foregoing specificities can. . .

DETDEN
[097] Other exemplary anchor antibodies that can be used in the disclosed compositions and methods, include anti-cholesterol antibodies and anti-cardiolipin antibodies. Anti-cholesterol antibodies are present in human sera and can be isolated as described above for anti-lipoidal antibodies. Specific anti-cholesterol antibodies and/or protocols for producing and/or isolating anti-cholesterol antibodies can be found in Kruth et α.scriptl.. (J. Lipid Res., 42:1492-1500, 2001), Alving et α.scriptl.. (.Biochem. Soc. Trans., 11:631-639,. . .

DETDEN . . .
solid support by contacting in solution the lipoidal antigen with anchor antibodies specific for the lipoidal antigen (e.g., anti-lipoidal antibodies, anti-cholesterol antibodies, anti-lecithin antibodies, and/or anti-cardiolipin antibodies, and/or antigen-binding fragments of any of the

foregoing) to form a lipoidal antigen-anchor antibody complex (or. . .

DETDEN . . .
the purpose of serving as an epitope for an anchor antibody. Such examples do not exclude including derivatized cardiolipin, derivatized lecithin and/or derivatized cholesterol as components of a lipoidal antigen; however, in such examples, the derivative groups of such derivatized components do not serve. . .

DETDEN . . .
Anchor Antibody Detector Reagent CL/L/Ch human, anti-lipoidal antigen-binding fragment (e.g., Fab) Protein A, Protein G, or anti-human Ab(Fc) CL/L/Ch human, anti-cholesterol antigen-binding fragment (e.g., Fah) Protein A, Protein G, or anti-human Ab(Fc) CL/L/Ch human, anti-cardiolipin antigen-binding fragment (e.g., Fab) Protein A, Protein G, or anti-human Ab(Fc) CL/L/Ch non-human, anti-lipoidal full-length Ab anti-human Ab (any specificity) CL/L/Ch non-human, anti-cholesterol full-length Ab anti-human Ab (any specificity) CL/L/Ch non-human, anti-cardiolipin full-length Ab anti-human Ab (any specificity) CL/L/Ch non-human (mammalian), anti-lipoidal antigen-binding fragment (e.g., Fab) Protein A, Protein G, anti-human Ab (any specificity) CL/L/Ch non-human (mammalian), anti-cholesterol antigen-binding fragment (e.g., Fab) Protein A, Protein G, anti-human Ab (any specificity) CL/L/Ch non-human (mammalian), anti-cardiolipin antigen-binding fragment (e.g., Fab). . .

DETDEN . . .
to a 250 ml round, glass-stoppered bottle. Over a period of 40 to 60 seconds, 10 ml VDRL antigen (0.9% cholesterol, 0.03% bovine heart cardiolipin, and about 0.21% lethicin in ethanol) was added directly onto the buffered saline with continuous rotation. . .

CLMEN. . .
anti-lipoidal antibody capture area, comprising: (a) an anchor antibody immobilized on the substrate; and (b) a lipoidal antigen, comprising cardiolipin, lecithin, and cholesterol, wherein the immobilized anchor antibody is specifically bound to one or more of the cardiolipin, lecithin or cholesterol components of the lipoidal antigen thereby forming an immobilized anchor antibody-lipoidal antigen complex.

CLMEN. . .
1 , wherein the anchor antibody does not specifically bind an exogenous epitope in one or more of the cardiolipin, lecithin or cholesterol components of the lipoidal antigen.

CLMEN. . .
a method comprising: contacting the lipoidal antigen with one or more anchor antibodies specific for at least one of cardiolipin, lecithin, or cholesterol to form the lipoidal antigen-anchor antibody complex; and applying the lipoidal antigen-anchor antibody complex to the substrate.

CLMEN. . .
is immobilized on the substrate by a method, comprising: immobilizing an anchor antibody specific for at least one of cardiolipin, lecithin, or cholesterol on the substrate; blocking non-specific binding sites on the substrate; contacting the immobilized anchor antibody with a lipoidal antigen to. . .

CLMEN. . .
anchor antibody, and which complex is immobilized on the membrane by the anchor antibody; wherein the lipoidal antigen comprises cardiolipin, lecithin and cholesterol; and a flow path from the sample application area to the anti-lipoidal antibody capture area; wherein the presence and/or amount. . .

CLMEN
42. The method of claim 36 , comprising: contacting a lipoidal antigen, comprising immunoreactive cardiolipin, lecithin, and cholesterol, with an antibody fragment specific for cardiolipin, lecithin, or cholesterol to form a lipoidal antigen-antibody complex; wherein the antibody fragment does not substantially react with Protein A, Fc-specific Protein G,. . .

CLMEN. . .

method of claim 42 , comprising contacting a lipoidal antigen, comprising immunoreactive cardiolipin, with a Fab fragment specific for cardiolipin, lecithin, or cholesterol to form a lipoidal antigen-Fab complex; wherein the lipoidal antigen is a USR antigen, a VDRL antigen, or a synthetic. . .

CLMEN. . .
immunoreactive cardiolipin on a substrate, the method comprising: immobilizing one or more antibodies specific for at least one of cardiolipin, lecithin or cholesterol on a substrate; blocking non-specific binding sites on the substrate; applying a lipoidal antigen, comprising at least one immunoreactive cardiolipin, lecithin or cholesterol, to the substrate to form lipoidal antigen-immobilized antibody complexes; and washing the substrate to remove any lipoidal antigen that is. . .

L6 ANSWER 24 OF 39 USPATFULL on STN
ACCESSION NUMBER: 2004:282666 USPATFULL Full-text
TITLE: Method for detecting syphilis using synthetic antigents
INVENTOR(S): Pope, Victoria, Atlanta, GA, United States
Castro, Arnold R., Atlanta, GA, United States
Morrill, William E., Snellville, GA, United States
PATENT ASSIGNEE(S): The United States of America as represented by the Department of Health and Human Services, Washington, DC, United States (U.S. government)
Centers for Disease Control & Prevention, Atlanta, GA, United States (U.S. corporation)

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 6815173	B1	20041109
	WO 2000075666		20001214
APPLICATION INFO.:	US 2001-9698		20011205 (10)
	WO 2000-US15828		20000608

	NUMBER	DATE
PRIORITY INFORMATION:	US 1999-60138192	19990609 (60)

DOCUMENT TYPE: Utility
FILE SEGMENT: GRANTED
PRIMARY EXAMINER: Swartz, Rodney P
ASSISTANT EXAMINER: Shahnan-Shah, Khatol
LEGAL REPRESENTATIVE: Klarquist Sparkman, LLP
NUMBER OF CLAIMS: 23
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 0 Drawing Figure(s); 0 Drawing Page(s)
LINE COUNT: 807
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB An antigen composition and method for the detection of antibodies to Treponema pallidum and the diagnosis of syphilis are described. The antigen composition contains synthetic cardiolipin and synthetic lecithin. The antigen composition may additionally contain cholesterol and an alcohol. The antigen composition is useful as an immunoreagent in immunoassays for the detection of antibodies associated with. . .
SUMM The present invention relates to the fields of microbiology and immunology and more specifically relates to compositions and methods for detecting, diagnosing and monitoring the treatment of syphilis. In particular, the invention pertains to synthetic cardiolipin and lecithin antigen compositions and their use in immunoassays.
SUMM For these reasons, most cases of syphilis are first diagnosed serologically using non-treponemal assays. Non-treponemal tests detect substances, such as antibodies, that are produced in the presence of a T. pallidum infection. The currently available non-treponemal assays most often used to detect evidence of a syphilis infection air the Venereal Disease Research Laboratory (VDRL) test and the rapid plasma reagin (RPR) test. The VDRL test employs. . . naturally-occurring sources, to detect anti-lipoidal antibodies that are generated upon infection by T. pallidum. These antibodies are generated against the cardiolipin of the T. pallidum organism by the immune system of the individual infected with T. pallidum and may be found. . .
SUMM . . . malaria, acute bacterial and viral infections, and autoimmune disease can cause false positive test results in presently available

tests for syphilis. For example, intravenous drug use or autoimmune disease causes tissue damage, which results in the release of cardiolipin and the production of anti-cardiolipin antibodies. Detection of these anti-cardiolipin antibodies in a non-treponemal test would therefore produce a false positive result. Successful diagnosis is particularly problematic for the detection. . .

SUMM An antigen composition and method for detecting Treponema pallidum infection and thereby diagnosing syphilis are provided. The antigen composition contains a combination or mixture of synthetic cardiolipin and synthetic lecithin. The preferred antigen composition also contains a cholesterol. The preferred antigen composition further includes an alcohol. The alcohol solubilizes the lipids in the antigen composition to form a. . .

SUMM The more preferred antigen composition contains purified, synthetic cardiolipin, synthetic lecithin, natural or non-synthetic cholesterol, and an alcohol. The optimal purity of the synthetic cardiolipin and lecithin in the composition is 99% or greater. The optimal purity of the cholesterol is 98% or greater, or is ash free. Most preferably, the antigen composition contains tetramyristoyl cardiolipin, 1-palmitoyl-2-oleoyl-sn-glycero-3-phosphocholine, cholesterol, and absolute (100%) ethanol. The preferred concentration by volume of synthetic cardiolipin in the composition is between about 0.01-0.05%, or between approximately 0.02-0.04%, or more preferably 0.03%. The preferred concentration by volume of synthetic lecithin in the composition is between approximately 0.11-0.16%, more preferably 0.14%. The preferred concentration by volume of cholesterol in the composition is approximately 0.9%, and the remainder of the composition is the alcohol.

SUMM . . . a sufficient amount of time under conditions that facilitate the binding of anti-lipoidal antibodies in the sample to a synthetic cardiolipin-lecithin matrix, to form an antibody-antigen complex. This complex is then detected using methods well known to those skilled in the. . .

DETD . . . method for the detection of Treponema pallidum are described herein. The antigen composition contains a mixture or combination of synthetic cardiolipin and synthetic lecithin. Cardiolipin is a 1,3-bis(phophatidyl)glycerol having antigenic properties. Lecithin is a phospholipid. The antigen composition preferably also includes a non-synthetic (natural) cholesterol. An alcohol is also a component of the preferred antigen composition. The alcohol solubilizes the lipids, thereby forming a suspension. The synthetic cardiolipin and lecithin have an optimal purity of 99% or greater. The cholesterol has an optimal purity of 98% or greater, or is ash free. The antigen composition is useful as a reagent. . . antibodies associated with T. pallidum infection in a biological sample. Preferably, the antigen composition is an immunoassay reagent for the detection or measurement of antibodies generated in a patient infected with T. pallidum, which is diagnostic or prognostic for the occurrence or recurrence of syphilis.

DETD . . . antigenicity or antigenic determinants. The term "antigen composition" as used herein refers to a composition containing synthetic cardiolipin and synthetic lecithin. "Antigenic determinant," as used herein, refers to a region of an antigen that is recognized by an antibody.

DETD The composition provided herein contains a combination, suspension or physical mixture of one or more synthetic cardiolipins and lecithins. A preferred composition contains synthetic cardiolipin, synthetic lecithin, and synthetic or non-synthetic (naturally occurring) cholesterol. The more preferred composition contains synthetic cardiolipin, synthetic lecithin, natural cholesterol, and an alcohol.

DETD . . . 0.01-0.05% by volume, or between approximately 0.02-0.04% by volume, or more preferably 0.03% by volume. The preferred concentration of synthetic lecithin in the composition is between approximately 0.11 and 0.16% by volume, more preferably 14% by volume. The preferred concentration of natural cholesterol in the composition is approximately 0.9% by volume, and the remainder of the composition is alcohol, preferably ethanol, most preferably. . .

DETD The synthetic lecithin may be derived from soybeans or egg. In a preferred embodiment, the lecithin is a 16:0, 18:1 lecithin also described as 1-palmitoyl-2-oleoyl-sn-glycero-3-phosphocholine or 3-sn-phosphatidylcholine (sn means stereospecifically numbered), which is also available commercially from sources such as Avanti. . .

DETD In a most preferred embodiment, the composition is a suspension

containing approximately 0.03% tetramyristoyl cardiolipin, 0.11-0.16% 1-palmitoyl-2-oleoyl-sn-glycero-3-phosphocholine, and 0.9% natural cholesterol in absolute ethanol. The cholesterol is also available from commercial sources such as Avanti Polar Lipids (Alabaster, Ala.). The alcohol can be purchased from chemical. . .

DETD When combined together with the alcohol, the cardiolipin, lecithin, and cholesterol form a lipid matrix or micelle. As described in more detail below, antibodies associated with the presence of a human T. pallidum infection, referred to herein as anti-cardiolipin antibodies, bind to these lipid micelles and form antibody-antigen complexes. Therefore, the detection or measurement of these antibody-antigen complexes can. . . diagnose a T. pallidum infection. Although not wishing to be bound by the following hypothesis, it is believed that the anti-cardiolipin matrix antibodies bind to the synthetic antigen composition described herein with greater specificity and higher avidity than they bind to naturally occurring cardiolipin and lecithin. The synthetic antigen composition thereby provides a more efficient, more sensitive, and more specific means to detect antibodies associated with a syphilis infection.

DETD . . . concentration by volume ranging from about 0.01-0.05%, or 0.02 to 0.04%, or more preferably 0.03%. An ethanolic solution of synthetic lecithin having a concentration by volume of approximately 0.11 to 0.16%, more preferably 0.14%, and an ethanolic solution of natural cholesterol of 0.9% are added to the cardiolipin solution. The components are added in the following sequence: cardiolipin, lecithin, cholesterol, and ethanol to volume. The antigen is solubilized and stored at room temperature overnight before testing.

DETD . . . quantify antibodies capable of binding to the antigen composition described above. These methods permit detection of circulating antibodies to the cardiohpin-lecithin matrix in order to indicate the presence of T. pallidum infection and thereby diagnose infection or monitor the progress of. . .

DETD A kit for diagnosing or otherwise evaluating a syphilis infection by detecting the presence or quantity of anti-cardiolipin antibodies is also provided. The kit can be in any configuration well known to those of ordinary skill in the art and is useful for performing one or more of the methods described herein for the detection of anti-cardiolipin-lecithin matrix antibodies in biological samples or for the detection or monitoring of T. pallidum infection in a patient or carrier.. . . are convenient in that they supply many if not all of the essential reagents for conducting an assay for the detection of syphilis antibodies in a biological sample. The reagents may be

pre-measured and contained in a stable form in vessels or on. . .

DETD . . . which can be used for the detection of cardiolipin antibodies associated with T. pallidum infection. The kit also preferably contains cholesterol and can additionally contain the appropriate reagents that aid in detecting antibody-antigen complexes. The kit may additionally contain equipment for. . .

DETD Preparation of a Synthetic Cardiolipin and Lecithin Composition

DETD Lecithin (1-palmitoyl-2-oleoyl-sn-glycero-phosphocholine) powder, purified by silica gel chromatography to a purity of approximately 99%, was also obtained from Avanti Polar Lipids. The lecithin was originally isolated from soybeans.

DETD A 1.2% solution of cholesterol (Avanti Polar Lipids) in absolute ethanol was prepared and filtered with alcohol-rinsed filter paper #560. The cholesterol was originally derived from wool grease and purified by re-crystallization, and the crystals were stored at -20° C.

DETD An antigen composition was prepared by combining the synthetic cardiolipin with the synthetic lecithin, the cholesterol solution and the ethanol, in that order. The final concentration of synthetic cardiolipin was 0.02-0.03% by volume. The final concentration of synthetic lecithin was 0.11-0.16% by volume. The final concentration of cholesterol was 0.9% by volume and the remainder of the antigen composition was the ethanol.

DETD The sensitivity of the VDRL slide assay using the synthetic cardiolipin and lecithin composition described in Example 1 was compared with the sensitivity of the conventional VDRL slide assay as described in A. .

.

DETD . . . antigen composition was more sensitive than the test using the standard VDRL antigen, which was made using natural cardiolipin and lecithin.

DETD The sensitivities of the VDRL slide assay using the synthetic cardiolipin and lecithin antigen composition described in Example 1 and the conventional VDRL slide assay were also compared against the conventional RPR slide. . .

CLM What is claimed is:
2. The antigen composition of claim 1, further comprising cholesterol.

CLM What is claimed is:
3. The composition of claim 2, wherein the concentration of cholesterol is 0.9%.

CLM What is claimed is:
11. The method of claim 10, wherein the composition further comprises cholesterol and an alcohol.

CLM What is claimed is:
12. The method of claim 11, wherein the concentration of cholesterol in the composition is 0.9%.

CLM What is claimed is:
19. An antigen composition comprising between 0.02 and 0.04% tetramyristoyl cardiolipin, between 0.11 and 0.16% 1-palmitoyl-2-oleoyl-sn-glycero-3-phosphocholine, 0.9% cholesterol, and ethanol to volume.

CLM What is claimed is:
20. An antigen composition comprising 0.03% tetramyristoyl cardiolipin, between 0.11 and 0.16% 1-palmitoyl-2-oleoyl-sn-glycero-3-phosphocholine, and 0.9% natural cholesterol in absolute ethanol to volume.

CLM What is claimed is:
. . . combining the biological sample with a composition comprising between 0.02 and 0.04% tetramyristoyl cardiolipin, between 0.11 and 0.16% 1-palmitoyl-2-oleoyl-sn-glycero-3-phosphocholine, 0.9% cholesterol, and ethanol to volume; and (c) detecting an immunocomplex formed between an antibody in the biological sample and the composition.
. . .

L6 ANSWER 25 OF 39 CA COPYRIGHT 2022 ACS on STN DUPLICATE 6
ACCESSION NUMBER: 134:41088 CA Full-text
TITLE: Method for detecting syphilis using synthetic antigens
INVENTOR(S): Pope, Victoria; Castro, Arnold R.; Morrill, William E.
PATENT ASSIGNEE(S): Government of the United States of America, Represented by the Secretary, Department of Health and Human Services, USA
SOURCE: PCT Int. Appl., 34 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.		DATE
WO 2000075666	A1	20001214	WO 2000-US15828		20000608
CA 2375448	A1	20001214	CA 2000-2375448		20000608
CA 2375448	C	20090407			
AU 2000054756	A	20001228	AU 2000-54756		20000608
AU 771548	B2	20040325			
EP 1185872	A1	20020313	EP 2000-939708		20000608
EP 1185872	B1	20060118			
BR 2000011449	A	20020319	BR 2000-11449		20000608
BR 2000011449	B1	20131203			
JP 2003501662	T	20030114	JP 2001-501890		20000608
JP 4531314	B2	20100825			
RU 2244933	C2	20050120	RU 2001-135795		20000608
CN 1195986	C	20050406	CN 2000-808540		20000608
AT 316245	T	20060215	AT 2000-939708		20000608
US 6815173	B1	20041109	US 2001-9698		20011205
US 43914	E1	20130108	US 2011-13333849		20111221
PRIORITY APPLN. INFO.:			US 1999-60138192	P	19990609

	WO 2000-US15828	W	20000608
	US 2001-9698	E	20011205

PATENT STATUS PATENT INFORMATION:

PATENT NO.	KIND	STATUS	STATUS DATE
WO 2000075666	A1	Dead	20201106
CA 2375448	A1	Dead	20201106
CA 2375448	C	Dead	20201107
AU 2000054756	A	Dead	20201107
AU 771548	B2	Dead	20201106
EP 1185872	A1	Dead	20201107
EP 1185872	B1	Dead	20201106
BR 2000011449	A	Dead	20210610
BR 2000011449	B1	Dead	20210610
JP 4531314	B2	Dead	20201106
RU 2244933	C2	Dead	20201106
CN 1195986	C	Dead	20201107
AT 316245	T	Dead	20201107
US 6815173	B1	Dead	20201106

ASSIGNMENT HISTORY FOR US PATENT AVAILABLE IN LSUS DISPLAY FORMAT
OTHER SOURCE(S): CASFORMULTNS 2000:881429
OS.CITING REF COUNT: 3 THERE ARE 3 CAPLUS RECORDS THAT CITE THIS RECORD (3 CITINGS)
REFERENCE COUNT: 6 THERE ARE 6 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

AB . . . of antibodies to Treponema pallidum and the diagnosis of syphilis are described. The antigen compn. contains synthetic cardiolipin and synthetic lecithin . The antigen compn. may addnl. contain cholesterol and an alc. The antigen compn. is useful as an immunoreagent in immunoassays for the detection of antibodies assocd. with. . .

ST syphilis diagnosis synthetic antigen immunoassay; Treponema antibody detection synthetic antigen; cardiolipin lecithin synthetic syphilis antibody reagent

IT Cardiolipins
Phosphatidylcholines, biological studies
RL: ARG (Analytical reagent use); THU (Therapeutic use); ANST (Analytical study); BIOL (Biological study); USES (Uses)
(synthetic, in antigen compn.; method for detecting syphilis using synthetic antigens)

IT Cardiolipins
RL: ARG (Analytical reagent use); THU (Therapeutic use); ANST (Analytical study); BIOL (Biological study); USES (Uses)
(tetramyristoyl-; method for detecting syphilis using synthetic antigens)

IT 57-88-5, Cholesterol, biological studies 26853-31-6, 1-Palmitoyl-2-oleoyl-sn-glycero-3-phosphocholine
RL: ARG (Analytical reagent use); THU (Therapeutic use); ANST (Analytical study); BIOL (Biological study); USES (Uses)
(method for detecting syphilis using synthetic antigens)

L6 ANSWER 26 OF 39 MEDLINE ® on STN DUPLICATE 7
ACCESSION NUMBER: 2000425594 MEDLINE Full-text
DOCUMENT NUMBER: PubMed ID: 10882668
TITLE: Use of synthetic cardiolipin and lecithin in the antigen used by the venereal disease research laboratory test for serodiagnosis of syphilis.
AUTHOR: Castro A R
CORPORATE SOURCE: Division of AIDS, STD, and TB Laboratory Research, Centers for Disease Control and Prevention, Atlanta, Georgia 30333, USA. ajc5@cdc.gov
AUTHOR: Morrill W E; Shaw W A; Gale D C; Park M M; Peregrino-Ferreira L A; Bazzo M L; Pope V
SOURCE: Clinical and diagnostic laboratory immunology, (2000 Jul) Vol. 7, No. 4, pp. 658-61.
Journal code: 9421292. ISSN: 1071-412X. L-ISSN: 1071-412X.
Report No.: PMC-PMC95930.
DIGITAL OBJECT ID: http://dx.doi.org/10.1128/CDLI.7.4.658-661.2000
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: MEDLINE; Priority Journals

FILE SEGMENT: Print
ENTRY MONTH: 200009
ENTRY DATE: Entered STN: 22 Sep 2000
Last Updated on STN: 22 Sep 2000
Entered Medline: 12 Sep 2000
MEDLINE REFERENCE COUNT: 8 There are 8 cited references available in MEDLINE for this document.
TI Use of synthetic cardiolipin and lecithin in the antigen used by the venereal disease research laboratory test for serodiagnosis of syphilis.
AB The Venereal Disease Research Laboratory (VDRL) test is a microflocculation test for syphilis that uses an antigen containing cardiolipin, lecithin, and cholesterol. For more than 50 years, the preparation of natural cardiolipin and lecithin for this test has been based on the Pangborn method which involves isolating and purifying these components from beef hearts.. . . time-consuming and results in a variable purity range. In our studies, we found that a VDRL antigen using synthetic tetramyristoyl cardiolipin and synthetic 1-palmitoyl-2-oleoyl-sn-glycero-3-phosphocholine (lecithin) was as specific in detecting syphilis as a VDRL antigen made with natural components. In 85% of the cases, we obtained an endpoint titer of 1/2. . .

L6 ANSWER 27 OF 39 CA COPYRIGHT 2022 ACS on STN DUPLICATE 8
ACCESSION NUMBER: 129:257361 CA Full-text
ORIGINAL REFERENCE NO.: 129:52351a,52354a
TITLE: Manufacture of reagents for measuring phospholipid antibodies
INVENTOR(S): Oota, Tetsuya; Yoshikawa, Katsumi
PATENT ASSIGNEE(S): Sekisui Chemical Co. Ltd., Japan
SOURCE: Jpn. Kokai Tokkyo Koho, 5 pp.
CODEN: JKXXAF
DOCUMENT TYPE: Patent
LANGUAGE: Japanese
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
JP 10239315	A	19980911	JP 1997-175797	19970701
JP 3647210	B2	20050511		

PRIORITY APPLN. INFO.: JP 1996-347987 A 19961226
PATENT STATUS PATENT INFORMATION:

PATENT NO.	KIND	STATUS	STATUS DATE
JP 10239315	A	Dead	20201107
JP 3647210	B2	Dead	20201107

AB . . . is prepd. for measuring phospholipid antibody that may be used for detection of syphilis. The lipid antigen consists of cardiolipin, lecithin, and cholesterol, and the antigen is bound to an insol. carrier. The relative amts. of the antigen components are cardiolipin 0.01-1.0 μg, lecithin 3-15 fold of cardiolipin, and cholesterol 0-5 fold of cardiolipin against 10 μg of the insol. carrier. The reaction temp. is 30-55°, and the reaction time. . .
IT Cardiolipins
Lecithins
RL: ARG (Analytical reagent use); ANST (Analytical study); USES (Uses) (in reagents for measuring phospholipid antibodies for syphilis detection)
IT 57-88-5, Cholesterol, uses
RL: ARG (Analytical reagent use); ANST (Analytical study); USES (Uses) (in reagents for measuring phospholipid antibodies for syphilis detection)

L6 ANSWER 28 OF 39 USPATFULL on STN
ACCESSION NUMBER: 97:106984 USPATFULL Full-text
TITLE: Stabilized microspheres and methods of preparation
INVENTOR(S): Malick, Adrien, Granite, MD, United States
Feindt, Hans H., Parkton, MD, United States
Hahn, Gerald D., Severn, MD, United States
PATENT ASSIGNEE(S): Becton, Dickinson and Company, Franklin Lakes, NJ,

United States (U.S. corporation)

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 5688697		19971118
APPLICATION INFO.:	US 1996-642373		19960503 (8)

RELATED APPLN. INFO.: Division of Ser. No. US 1994-343305, filed on 22 Nov 1994, now patented, Pat. No. US 5580735 which is a division of Ser. No. US 1993-1907, filed on 4 Jan 1993, now patented, Pat. No. US 5393527
DOCUMENT TYPE: Utility
FILE SEGMENT: Granted
PRIMARY EXAMINER: Green, Lora M.
LEGAL REPRESENTATIVE: Fugit, Donna R.
NUMBER OF CLAIMS: 15
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: No Drawings
LINE COUNT: 744
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
SUMM . . . be included in the mixture of stabilizing amphiphiles which comprises the coating on the surface of the droplet. For example, cardiolipin, a four-chain phospholipid, is a suitable amphiphile for preparation of the microemulsions and is also useful as an antigen ligand for syphilis serology testing. Microparticles which include cardiolipin on their surfaces can be used in agglutination immunoassays for detection of anti-syphilis antibodies.
SUMM Cholesterol may be included with the amphiphiles but is generally not required as it is for liposomes because the amphiphiles form a monolayer on the microdroplet rather than a collection of bilayers as in liposomes. As the function of cholesterol in liposome membranes is to intercalate in and stabilize the liposome bilayers, it is optional in the present invention. Preferably, cholesterol is not included when the microparticles are used as tracers, as its presence may increase background staining and baseline levels. . .
DETD Commercially available VDRL antigen (Difco Laboratories, Detroit, Mich.) contains 0.03% cardiolipin, 0.21% lecithin and 0.9% cholesterol in ethanol. This ethanol solution was added to formaldehyde buffered saline, forming a colloidal suspension. The suspension was centrifuged and. . .

L6 ANSWER 29 OF 39 USPATFULL on STN
ACCESSION NUMBER: 97:47266 USPATFULL Full-text
TITLE: Stabilized microspheres and methods of preparation
INVENTOR(S): Malick, Adrien, Granite, MD, United States
Feindt, Hans H., Parkton, MD, United States
PATENT ASSIGNEE(S): Becton, Dickinson and Company, Franklin Lakes, NJ, United States (U.S. corporation)

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 5635357		19970603
APPLICATION INFO.:	US 1994-343313		19941122 (8)

RELATED APPLN. INFO.: Continuation of Ser. No. US 1993-1907, filed on 4 Jan 1993, now patented, Pat. No. US 5393527
DOCUMENT TYPE: Utility
FILE SEGMENT: Granted
PRIMARY EXAMINER: Cunningham, Thomas M.
LEGAL REPRESENTATIVE: Fugit, Donna R.
NUMBER OF CLAIMS: 7
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: No Drawings
LINE COUNT: 704
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
SUMM . . . be included in the mixture of stabilizing amphiphiles which comprises the coating on the surface of the droplet. For example, cardiolipin, a four-chain phospholipid, is a suitable amphiphile for preparation of the microemulsions and is also useful as an antigen ligand for syphilis setology testing. Microparticles which include cardiolipin on their surfaces can be used in agglutination immunoassays for detection of anti-syphilis antibodies.
SUMM Cholesterol may be included with the amphiphiles but is generally not

required as it is for liposomes because the amphiphiles form a monolayer on the microdroplet rather than a collection of bilayers as in liposomes. As the function of cholesterol in liposome membranes is to intercalate in and stabilize the liposome bilayers, it is optional in the present invention. Preferably, cholesterol is not included when the microparticles are used as tracers, as its presence may increase background staining and baseline levels. . .

DETD Commercially available VDRL antigen (Difco Laboratories, Detroit, Mich.) contains 0.03% cardiolipin, 0.21% lecithin and 0.9% cholesterol in ethanol. This ethanol solution was added to formaldehyde buffered saline, forming a colloidal suspension. The suspension was centrifuged and. . .

L6 ANSWER 30 OF 39 USPATFULL on STN

ACCESSION NUMBER:	97:31625 USPATFULL Full-text		
TITLE:	Stabilized microspheres and methods of preparation		
INVENTOR(S):	Malick, Adrien, Granite, MD, United States Feindt, Hans H., Parkton, MD, United States Hahn, Gerald D., Severn, MD, United States		
PATENT ASSIGNEE(S):	Becton, Dickinson and Company, Franklin Lakes, NJ, United States (U.S. corporation)		
	NUMBER	KIND	DATE
PATENT INFORMATION:	US 5620903		19970415
APPLICATION INFO.:	US 1995-374001		19950118 (8)
RELATED APPLN. INFO.:	Continuation-in-part of Ser. No. US 1993-1907, filed on 4 Jan 1993, now patented, Pat. No. US 5393527, issued on 28 Feb 1995		
DOCUMENT TYPE:	Utility		
FILE SEGMENT:	Granted		
PRIMARY EXAMINER:	Scheiner, Toni R.		
ASSISTANT EXAMINER:	Huff, Sheela J.		
LEGAL REPRESENTATIVE:	Fugit, Donna R.		
NUMBER OF CLAIMS:	14		
EXEMPLARY CLAIM:	1		
NUMBER OF DRAWINGS:	No Drawings		
LINE COUNT:	935		

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

SUMM . . . be included in the mixture of stabilizing amphiphiles which comprises the coating on the surface of the droplet. For example, cardiolipin, a four-chain phospholipid, is a suitable amphiphile for preparation of the microemulsions and is also useful as an antigen ligand for syphilis serology testing. Microparticles which include cardiolipin on their surfaces can be used in agglutination immunoassays for detection of anti-syphilis antibodies.

SUMM Cholesterol may be included with the amphiphiles but is generally not required as it is for liposomes because the amphiphiles form a monolayer on the microdroplet rather than a collection of bilayers as in liposomes. As the function of cholesterol in liposome membranes is to intercalate in and stabilize the liposome bilayers, it is optional in the present invention. Preferably, cholesterol is not included when the microparticles are used as tracers, as its presence may increase background staining and baseline levels. . .

DETD Commercially available VDRL antigen (Difco Laboratories, Detroit, Mich.) contains 0.03% cardiolipin, 0.21% lecithin and 0.9% cholesterol in ethanol. This ethanol solution was added to formaldehyde buffered saline, forming a colloidal suspension. The suspension was centrifuged and. . .

DETD . . . system at an ethanol concentration of 25% and a rate of formation of 2.5 mL/sec. Particles were made both with cholesterol (50 mg.) and without cholesterol. The microparticles were dialyzed into water and used as a replacement for charcoal ("mock charcoal") in the RPR agglutination assay.. . .

DETD TABLE

Microemulsion Components

DSPC/
DSPG Cholesterol
Cardiolipin
Continuous Phase

A	Yes	Yes	No	Water
B	Yes	No	No	Water
E	Yes	Yes	No	Form./Saline
F	Yes	No	No	Form./Saline
X	VDRL. . .			

L6 ANSWER 31 OF 39 USPATFULL on STN
ACCESSION NUMBER: 97:3692 USPATFULL Full-text
TITLE: Stabilized microspheres and methods of preparation
INVENTOR(S): Malick, Adrien, Granite, MD, United States
Feindt, Hans H., Parkton, MD, United States
PATENT ASSIGNEE(S): Becton, Dickinson and Company, Franklin Lakes, NJ, United States (U.S. corporation)

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 5593843		19970114
APPLICATION INFO.:	US 1994-343795		19941122 (8)

RELATED APPLN. INFO.: Division of Ser. No. US 1993-1907, filed on 4 Jan 1993, now patented, Pat. No. US 5393527, issued on 28 Feb 1995
DOCUMENT TYPE: Utility
FILE SEGMENT: Granted
PRIMARY EXAMINER: Scheiner, Toni R.
ASSISTANT EXAMINER: Huff, Sheela J.
LEGAL REPRESENTATIVE: Fugit, Donna R.
NUMBER OF CLAIMS: 9
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: No Drawings
LINE COUNT: 758
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
DETD . . . be included in the mixture of stabilizing amphiphiles which comprises the coating on the surface of the droplet. For example, cardiolipin, a four-chain phospholipid, is a suitable amphiphile for preparation of the microemulsions and is also useful as an antigen ligand for syphilis serology testing. Microparticles which include cardiolipin on their surfaces can be used in agglutination immunoassays for detection of anti-syphilis antibodies.
DETD Cholesterol may be included with the amphiphiles but is generally not required as it is for liposomes because the amphiphiles form a monolayer on the microdroplet rather than a collection of bilayers as in liposomes. As the function of cholesterol in liposome membranes is to intercalate in and stabilize the liposome bilayers, it is optional in the present invention. Preferably, cholesterol is not included when the microparticles are used as tracers, as its presence may increase background staining and baseline levels. . .
DETD Commercially available VDRL antigen (Difco Laboratories, Detroit, Mich.) contains 0.03% cardiolipin, 0.21% lecithin and 0.9% cholesterol in ethanol. This ethanol solution was added to formaldehyde buffered saline, forming a colloidal suspension. The suspension was centrifuged and. . .

L6 ANSWER 32 OF 39 USPATFULL on STN
ACCESSION NUMBER: 96:113849 USPATFULL Full-text
TITLE: Determination and detection of antibody and its immunoglobulin class
INVENTOR(S): Ito, Michio, Yokohama, Japan
Ogura, Minoru, Yokohama, Japan
Kohno, Hideki, Kawasaki, Japan
PATENT ASSIGNEE(S): Mitsubishi Kasei Corporation, Tokyo, Japan (non-U.S. corporation)

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 5583054		19961210
APPLICATION INFO.:	US 1994-312431		19940926 (8)

RELATED APPLN. INFO.: Continuation of Ser. No. US 1993-64370, filed on 19 May 1993, now abandoned which is a continuation of Ser. No. US 1990-557390, filed on 24 Jul 1990, now abandoned

	NUMBER	DATE
PRIORITY INFORMATION:	JP 1989-195968	19890728
	JP 1990-162056	19900620

DOCUMENT TYPE: Utility
FILE SEGMENT: Granted
PRIMARY EXAMINER: Feisee, Lila
ASSISTANT EXAMINER: Wolski, Susan C.
LEGAL REPRESENTATIVE: Conlin, David G., Resnick, David S.Dike, Bronstein, Roberts & Cushman, LLP
NUMBER OF CLAIMS: 19
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 3 Drawing Figure(s); 3 Drawing Page(s)
LINE COUNT: 734
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

DETD . . . sedimented by centrifugation and the supernatant was removed. Then, 4 ml of ethanol solution containing 0.03% of cardiolipin, 0.03% of lecithin and 0.9% of cholesterol was added to the sediment followed by dispersion, and the dispersion was further stirred for 30 minutes to homogenize it.

DETD . . . same sensitivity as or more sensitivity than a commercially available product as a reagent for RPR method (a method of detecting anti-cardiolipin antibody by a visual inspection of carbon powder agglomeration), which is one of the assays for syphilis.

DETD Each of syphilis patient serum, which is positive (detection limit dilution: 16-fold) by the RPR method, and normal serum, which is negative by the same methol, was diluted with. . . was apportioned to two wells in 96-hole microplate with an amount of 100 μl. After each 50 μl of the cardiolipin antigen-carrying carbon powder suspension diluted to 2-fold with the tris buffer solution was apportioned thereto, and immediately a side of. . .

L6 ANSWER 33 OF 39 USPATFULL on STN
ACCESSION NUMBER: 96:111326 USPATFULL Full-text
TITLE: Stabilized microspheres and methods of preparation
INVENTOR(S): Malick, Adrien, Granite, MD, United States
Feindt, Hans H., Parkton, MD, United States
Hahn, Gerald D., Severn, MD, United States
PATENT ASSIGNEE(S): Becton, Dickinson and Company, Franklin Lakes, NJ, United States (U.S. corporation)

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 5580735		19961203
APPLICATION INFO.:	US 1994-343305		19941122 (8)

RELATED APPLN. INFO.: Division of Ser. No. US 1993-1907, filed on 4 Jan 1993, now patented, Pat. No. US 5393527
DOCUMENT TYPE: Utility
FILE SEGMENT: Granted
PRIMARY EXAMINER: Chan, Christina Y.
ASSISTANT EXAMINER: Green, Lora M.
LEGAL REPRESENTATIVE: Fugit, Donna R.
NUMBER OF CLAIMS: 5
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: No Drawings
LINE COUNT: 711
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

DETD . . . be included in the mixture of stabilizing amphiphiles which comprises the coating on the surface of the droplet. For example, cardiolipin, a four-chain phospholipid, is a suitable amphiphile for preparation of the microemulsions and is also useful as an antigen ligand for syphilis serology testing. Microparticles which include cardiolipin on their surfaces can be used in agglutination immunoassays for detection of anti-syphilis antibodies.

DETD Cholesterol may be included with the amphiphiles but is generally not required as it is for liposomes because the amphiphiles form a monolayer on the microdroplet rather than a collection of bilayers as in liposomes. As the function of cholesterol in liposome membranes is to intercalate in and stabilize the liposome bilayers, it is optional in the present invention. Preferably, cholesterol is not included when

the microparticles are used as tracers, as its presence may increase background staining and baseline levels. . .

DETD Commercially available VDRL antigen (Difco Laboratories, Detroit, Mich.) contains 0.03% cardiolipin, 0.21% lecithin and 0.9% cholesterol in ethanol. This ethanol solution was added to formaldehyde buffered saline, forming a colloidal suspension. The suspension was centrifuged and. . .

L6 ANSWER 34 OF 39 USPATFULL on STN

ACCESSION NUMBER: 95:18200 USPATFULL Full-text
TITLE: Stabilized microspheres and methods of preparation
INVENTOR(S): Malick, Adrien, Granite, MD, United States
Feindt, Hans H., Parkton, MD, United States
PATENT ASSIGNEE(S): Becton, Dickinson and Company, Franklin Lakes, NJ, United States (U.S. corporation)

	NUMBER	KIND	DATE	
PATENT INFORMATION:	US 5393527		19950228	
APPLICATION INFO.:	US 1993-1907		19930104	(8)

DOCUMENT TYPE: Utility
FILE SEGMENT: Granted
PRIMARY EXAMINER: Wax, Robert A.
ASSISTANT EXAMINER: Schmickel, David
LEGAL REPRESENTATIVE: Fugit, Donna R.
NUMBER OF CLAIMS: 11
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: No Drawings
LINE COUNT: 730
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

SUMM . . . be included in the mixture of stabilizing amphiphiles which comprises the coating on the surface of the droplet. For example, cardiolipin, a four-chain phospholipid, is a suitable amphiphile for preparation of the microemulsions and is also useful as an antigen ligand for syphilis serology testing. Microparticles which include cardiolipin on their surfaces can be used in agglutination immunoassays for detection of anti-syphilis antibodies.

SUMM Cholesterol may be included with the amphiphiles but is generally not required as it is for liposomes because the amphiphiles form a monolayer on the microdroplet rather than a collection of bilayers as in liposomes. As the function of cholesterol in liposome membranes is to intercalate in and stabilize the liposome bilayers, it is optional in the present invention. Preferably, cholesterol is not included when the microparticles are used as tracers, as its presence may increase background staining and baseline levels. . .

DETD Commercially available VDRL antigen (Difco Laboratories, Detroit, Mich.) contains 0.03% cardiolipin, 0.21% lecithin and 0.9% cholesterol in ethanol. This ethanol solution was added to formaldehyde buffered saline, forming a colloidal suspension. The suspension was centrifuged and. . .

L6 ANSWER 35 OF 39 CA COPYRIGHT 2022 ACS on STN DUPLICATE 9

ACCESSION NUMBER: 120:161621 CA Full-text
ORIGINAL REFERENCE NO.: 120:28489a,28492a
TITLE: Immunoassay with solid phase-immobilized lipid antigen and magnetic particle-conjugated anti-human IgG or IgM antibody
INVENTOR(S): Tamai, Toyohiro
PATENT ASSIGNEE(S): Olympus Optical Co, Japan
SOURCE: Jpn. Kokai Tokkyo Koho, 6 pp.
CODEN: JKXXAF
DOCUMENT TYPE: Patent
LANGUAGE: Japanese
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
JP 05312808	A	19931126	JP 1992-117674	19920511
PRIORITY APPLN. INFO.:			JP 1992-117674	19920511

PATENT STATUS PATENT INFORMATION:

PATENT NO.	KIND	STATUS	STATUS DATE
JP 05312808	A	Dead	20201106

AB . . . are detd. by an immunoassay using solid phase-immobilized lipid antigens and magnetic particle-conjugated anti-human IgG or IgM antibodies. Thus, for syphilis diagnosis or anti-Treponema pallidum antibody detection in patients, a mixt. of cardiolipin, lecithin and cholesterol was immobilized on a microtiter plate, contacted with sample serum, treated with anti-human IgG-sensitized magnetic particles, and examd. for the. . .

IT Lecithins
RL: BIOL (Biological study)
(solid phase-immobilized cardiolipin and cholesterol and, anti-human IgG or IgM-sensitized magnetic particles and, for immunoassay of human antibodies)

IT Cardiolipins
RL: BIOL (Biological study)
(solid phase-immobilized cholesterol and lecithin and, anti-human IgG or IgM-sensitized magnetic particles and, for immunoassay of human antibodies)

IT 57-88-5, Cholesterol, uses
RL: USES (Uses)
(solid phase-immobilized cardiolipin and lecithin and, anti-human IgG or IgM-sensitized magnetic particles and, for immunoassay of human antibodies)

L6 ANSWER 36 OF 39 CA COPYRIGHT 2022 ACS on STN DUPLICATE 10
ACCESSION NUMBER: 107:234644 CA Full-text
ORIGINAL REFERENCE NO.: 107:37695a,37698a
TITLE: Reaginic agglutination test for syphilis-associated antibodies using cardiolipin coupled to latex particles
INVENTOR(S): Yabusaki, Kenichi Ken
PATENT ASSIGNEE(S): Advanced Polymer Systems, Inc., USA
SOURCE: PCT Int. Appl., 23 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 8703692	A1	19870618	WO 1986-US2592	19861202
US 4738932	A	19880419	US 1985-804059	19851203
EP 249627	A1	19871223	EP 1987-900452	19861202
JP 63501902	T	19880728	JP 1987-500194	19861202
ZA 8609137	A	19870826	ZA 1986-9137	19861203

PRIORITY APPLN. INFO.: US 1985-804059 A 19851203
WO 1986-US2592 W 19861202

PATENT STATUS PATENT INFORMATION:

PATENT NO.	KIND	STATUS	STATUS DATE
WO 8703692	A1	Dead	20201106
US 4738932	A	Dead	20201106
EP 249627	A1	Dead	20201107

ASSIGNMENT HISTORY FOR US PATENT AVAILABLE IN LSUS DISPLAY FORMAT
OS.CITING REF COUNT: 4 THERE ARE 4 CAPLUS RECORDS THAT CITE THIS RECORD (4 CITINGS)
REFERENCE COUNT: 5 THERE ARE 5 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

AB . . . saline soln., incubated for 2 h at 37° and overnight at 4°, and washed. An EtOH soln. contg. cardiolipin 0.03, lecithin 0.21, and cholesterol 0.9% was added and the suspension was stored at 4° and pH 6.0. This suspension 0.02 was mixed with nonheated. . .

IT Syphilis
(diagnosis of, antibody detection with cardiolipin -coated latex particles in)

IT Cardiolipins

RL: BIOL (Biological study)
(latex particles coated with, for antibody detection in syphilis diagnosis)
IT Latex
(particles, cardiolipin-coated, for antibody detection in syphilis diagnosis)
IT Blood analysis
(syphilis-assocd. antibodies detection in, by agglutination test with cardiolipin-coated latex particles)
IT Antibodies and Immunoglobulins
RL: BIOL (Biological study)
(syphilis-assocd., detection of, with cardiolipin-coated latex particles)
IT Immunochemical analysis
(agglutination test, syphilis-assocd. antibodies detection by, with cardiolipin-coated latex particles)

L6 ANSWER 37 OF 39 MEDLINE ® on STN DUPLICATE 11
ACCESSION NUMBER: 1986252390 MEDLINE Full-text
DOCUMENT NUMBER: PubMed ID: 3722824
TITLE: Large liposome agglutination technique for the serological detection of syphilis.
AUTHOR: Kung V T; Vollmer Y P; Martin F J
SOURCE: Journal of immunological methods, (1986 Jun 24) Vol. 90, No. 2, pp. 189-96.
Journal code: 1305440. ISSN: 0022-1759. L-ISSN: 0022-1759.
DIGITAL OBJECT ID: http://dx.doi.org/10.1016/0022-1759(86)90075-x
PUB. COUNTRY: Netherlands
DOCUMENT TYPE: (COMPARATIVE STUDY)
Journal; Article; (JOURNAL ARTICLE)
(RESEARCH SUPPORT, NON-U.S. GOV'T)
LANGUAGE: English
FILE SEGMENT: MEDLINE; Priority Journals
FILE SEGMENT: Print
ENTRY MONTH: 198607
ENTRY DATE: Entered STN: 21 Mar 1990
Last Updated on STN: 6 Feb 1998
Entered Medline: 29 Jul 1986
OS.CITING REF COUNT: 1 There are 1 MEDLINE records that cite this record
AB . . . an antibody complex, called reagin, appears in the serum of the syphilitic patients. Reagin has the ability to combine with cardiolipin, therefore, cardiolipin has traditionally been used as the antigen in different test configurations for the serological detection of syphilis: the VDRL (Venereal Disease Research Laboratory) flocculation test and the RPR (rapid plasma reagin) test. Here we introduce a liposome preparation composed of cardiolipin, lecithin and cholesterol and containing a colored dye which upon mixing with syphilitic serum on a slide or a plastic card results in. . .

L6 ANSWER 38 OF 39 CA COPYRIGHT 2022 ACS on STN DUPLICATE 12
ACCESSION NUMBER: 97:37437 CA Full-text
ORIGINAL REFERENCE NO.: 97:6399a,6402a
TITLE: Serologic test reagents for syphilis diagnosis
PATENT ASSIGNEE(S): Eiken Chemical Co., Ltd., Japan
SOURCE: Jpn. Kokai Tokkyo Koho, 3 pp.
CODEN: JKXXAF
DOCUMENT TYPE: Patent
LANGUAGE: Japanese
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
JP 57048659	A	19820320	JP 1980-124171	19800908

PRIORITY APPLN. INFO.: JP 1980-124171 19800908
PATENT STATUS PATENT INFORMATION:

PATENT NO.	KIND	STATUS	STATUS DATE
JP 57048659	A	Dead	20201107

AB A lipid antigen, prepd. from bovine cardiolipin plus lecithin and cholesterol as a sensitizer, is treated with Sudan Black and immobilized on kaolin particles to produce an immunol. test reagent for. . . high sensitivity and forms large aggregates which can be obsd. visually. Thus, 100 mL of a mixt. (contg. cardiolipin 66.15, lecithin 486.0, cholesterol 200, Sudan Black 165 mg, and EtOH to 100 mL) and 80 mL of a buffer (contg. Na2HPO4 2.82, KH2PO4. . .

IT Blood analysis
(antibodies to cardiolipin-contg. antigen detection in, of human by agglutination test, in syphilis diagnosis)

IT Cardiolipins
RL: BIOL (Biological study)
(antibodies to, detection of, in human blood serum in syphilis diagnosis)

IT Lecithins
RL: BIOL (Biological study)
(reagent contg., for syphilis diagnosis in humans)

IT Antibodies
RL: ANT (Analyte); ANST (Analytical study)
(reaginic, detection of, in human blood serum in syphilis diagnosis, artificial cardiolipin antigen for)

L6 ANSWER 39 OF 39 MEDLINE ® on STN DUPLICATE 13
ACCESSION NUMBER: 1977142642 MEDLINE Full-text
DOCUMENT NUMBER: PubMed ID: 321698
TITLE: Immune lysis of spin label loaded liposomes incorporating cardiolipin; a new sensitive method for detecting anticardiolipin antibodies in syphilis serology.
AUTHOR: Rosenqvist E; Vistnes A I
SOURCE: Journal of immunological methods, (1977) Vol. 15, No. 2, pp. 147-55.
Journal code: 1305440. ISSN: 0022-1759. L-ISSN: 0022-1759.
DIGITAL OBJECT ID: http://dx.doi.org/10.1016/0022-1759(77)90025-4
PUB. COUNTRY: Netherlands
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: MEDLINE; Priority Journals
FILE SEGMENT: Print
ENTRY MONTH: 197705
ENTRY DATE: Entered STN: 13 Mar 1990
Last Updated on STN: 13 Mar 1990
Entered Medline: 25 May 1977
OS.CITING REF COUNT: 1 There are 1 MEDLINE records that cite this record

TI Immune lysis of spin label loaded liposomes incorporating cardiolipin; a new sensitive method for detecting anticardiolipin antibodies in syphilis serology.

AB Liposomes prepared from a mixture of the pure lipids cholesterol, lecithin and cardiolipin (molar ratio 50/45/5), are able to bind antibodies directed against Treponema pallidum. When the liposomes are loaded with. . .

=> e kaul rav?/au

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E1            6     KAUL RAUF UR RASHID/AU
E2            1     KAUL RAUF UR RASHID DR/AU
E3            0 --> KAUL RAV?/AU
E4          148     KAUL RAVI/AU
E5           12     KAUL RAVINDER/AU
E6            4     KAUL RAVINDER N/AU
E7           31     KAUL RAVINDERNATH/AU
E8            3     KAUL RAVINDERNATH DR/AU
E9            2     KAUL REBECCA L/AU
E10           2     KAUL REBECCA LYNN/AU
E11           2     KAUL RENE/AU
E12          38     KAUL RENUKA/AU
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=> s e4

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L7         148 "KAUL RAVI"/AU

=> s l7 and syphilis

L8           9 L7 AND SYPHILIS

=> dup rem l8

PROCESSING COMPLETED FOR L8
L9            7 DUP REM L8 (2 DUPLICATES REMOVED)

=> d ibib ab 1-7


L9     ANSWER 1 OF 7 PCTFULL COPYRIGHT 2022 LNU on STN
ACCESSION NUMBER:       2022020234   PCTFULL Full-text
ENTRY DATE:             20220131
UPDATE DATE:            20220404
ENTRY DATE (FULLTEXT):  20220404
DATA ENTRY DATE:        20220315
DATA UPDATE DATE:       20220329
TITLE (ENGLISH):        IMMUNOASSAY FOR SARS-COV-2 NEUTRALIZING ANTIBODIES AND
                        MATERIALS THEREFOR
TITLE (FRENCH):         DOSAGE IMMUNOLOGIQUE POUR ANTICORPS NEUTRALISANT LE
                        SARS-COV-2 ET MATERIAUX CORRESPONDANTS
INVENTOR(S):            GAO, Qian, C/O BIO-RAD LABORATORIES, INC., 1000 Alfred
                        Nobel Drive, Hercules, CA 94547, US, for all designated
                        states
                        KAUL, Ravi, C/O BIO-RAD LABORATORIES, INC., 1000
                        Alfred Nobel Drive, Hercules, CA 94547, US, for all
                        designated states
                        ZHOU, Shuxia, C/O BIO-RAD LABORATORIES, INC., 1000
                        Alfred Nobel Drive, Hercules, CA 94547, US, for all
                        designated states
                        WALKER, Roger, P., C/O BIO-RAD LABORATORIES, INC., 1000
                        Alfred Nobel Drive, Hercules, CA 94547, US, for all
                        designated states
PATENT APPLICANT(S):    BIO-RAD LABORATORIES, INC., 1000 Alfred Nobel Drive,
                        Hercules, CA 94547, US, [NAT: US, RES: US], for all
                        designated states
AGENT:                  ESENSCHENK, Frank, C. et al., Saliwanchik, Lloyd &
                        Eisenschenk, P.O. BOX 142950, Gainesville, FL
                        32614-2950, US
LANGUAGE OF FILING:     English
LANGUAGE OF PUBL.:      English
DOCUMENT TYPE:          Patent; (Fulltext)
PATENT INFORMATION:     WO 2022020234 A2   20220127
DESIGNATED STATES:
        W:              AE AG AL AM AO AT AU AZ BA BB BG BH BN BR BW BY BZ CA
                        CH CL CN CO CR CU CZ DE DJ DK DM DO DZ EC EE EG ES FI
                        GB GD GE GH GM GT HN HR HU ID IL IN IR IS IT JO JP KE
                        KG KH KN KP KR KW KZ LA LC LK LR LS LU LY MA MD ME MG
                        MK MN MW MX MY MZ NA NG NI NO NZ OM PA PE PG PH PL PT
                        QA RO RS RU RW SA SC SD SE SG SK SL ST SV SY TH TJ TM
                        TN TR TT TZ UA UG US UZ VC VN WS ZA ZM ZW
        RW (ARIPO):     BW GH GM KE LR LS MW MZ NA RW SD SL ST SZ TZ UG ZM ZW
        RW (EAPO):      AM AZ BY KG KZ RU TJ TM
        RW (EPO):       AL AT BE BG CH CY CZ DE DK EE ES FI FR GB GR HR HU IE
                        IS IT LT LU LV MC MK MT NL NO PL PT RO RS SE SI SK SM
                        TR
        RW (OAPI):      BF BJ CF CG CI CM GA GN GQ GW KM ML MR NE SN TD TG
APPLICATION INFO.:      WO 2021-US42170        20210719
PRIORITY INFO.:         US 2020-63053888       20200720
                        US 2020-63088195       20201006
                        US 2020-63114685       20201117

ABEN
  The present invention relates to the development of novel immunoassays for
  the detection of neutralizing antibodies and/or high avidity neutralizing
  antibodies to SARS- CoV -2 spike protein variants or fragments thereof and.
  optionally, one or more cytokine in patient samples. Novel multiplex and
```

singieplex immunoassays for the detection of neutralizing antibodies and/or high avidity neutralizing antibodies to SARS-CoV-2 spike protein variants or fragments thereof and, optionally, one or more cytokine in patient samples are also provided.

ABFR
La presente invention concerne le developpement de nouveaux dosages immunologiques pour la detection d'anticorps neutralisants et/ou d'anticorps neutralisants a avidite elevee diriges contre des variants de proteine spicule de SARS-CoV-2 ou des fragments de ceux-ci et, de maniere facultative, une ou plusieurs cytokines dans des echantillons de patient. L'invention concerne egalement de nouveaux dosages immunologiques multiplex et monoplex pour la detection d'anticorps neutralisants et/ou d'anticorps neutralisants a avidite elevee diriges contre des variants de proteine spicule de SARS-CoV-2 ou des fragments de ceux-ci et, de maniere facultative, une ou plusieurs cytokines dans des echantillons de patient.

L9 ANSWER 2 OF 7 USPATFULL on STN

ACCESSION NUMBER:	2022:21860 USPATFULL Full-text		
TITLE:	IMMUNOASSAY FOR SARS-COV-2 NEUTRALIZING ANTIBODIES AND MATERIALS THEREFOR		
INVENTOR(S):	GAO, QIAN, CONCORD, CA, UNITED STATES KAUL, RAVI, DAVIS, CA, UNITED STATES ZHOU, SHUXIA, BENICIA, CA, UNITED STATES WALKER, ROGER P., BENICIA, CA, UNITED STATES		
APPLICANT(S):	BIO-RAD LABORATORIES, INC., Hercules, CA, UNITED STATES		
	NUMBER	KIND	DATE
PATENT INFORMATION:	US 20220018838	A1	20220120
APPLICATION INFO.:	US 2021-17379193	A1	20210719 (17)
	NUMBER		DATE
PRIORITY INFORMATION:	US 2020-63053888		20200720 (63)
	US 2020-63088195		20201006 (63)
	US 2020-63114685		20201117 (63)
DOCUMENT TYPE:	Utility		
FILE SEGMENT:	APPLICATION		
NUMBER OF CLAIMS:	21		
EXEMPLARY CLAIM:	1		
NUMBER OF DRAWINGS:	8 Drawing Page(s)		
LINE COUNT:	3080		

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB The present invention relates to the development of novel immunoassays for the detection of neutralizing antibodies and/or high avidity neutralizing antibodies to SARS-CoV-2 spike protein variants or fragments thereof and, optionally, one or more cytokine in patient samples. Novel multiplex and singleplex immunoassays for the detection of neutralizing antibodies and/or high avidity neutralizing antibodies to SARS-CoV-2 spike protein variants or fragments thereof and, optionally, one or more cytokine in patient samples are also provided.

L9 ANSWER 3 OF 7 USPATFULL on STN

ACCESSION NUMBER:	2021:181550 USPATFULL Full-text		
TITLE:	COMBINATION TREPONEMAL AND NON-TREPONEMAL SYPHILIS TEST		
INVENTOR(S):	Kaul, Ravi, Davis, CA, UNITED STATES Zheng, Weiming, Emeryville, CA, UNITED STATES Walker, Roger, Benicia, CA, UNITED STATES		
APPLICANT(S):	Bio-Rad Laboratories, Inc., Hercules, CA, UNITED STATES		
	NUMBER	KIND	DATE
PATENT INFORMATION:	US 20210156859	A1	20210527
APPLICATION INFO.:	US 2021-17170577	A1	20210208 (17)
RELATED APPLN. INFO.:	Continuation of Ser. No. US 2020-16832608, filed on 27 Mar 2020, Pat. No. US 10942182 Division of Ser. No. US 2019-16405588, filed on 7 May 2019, Pat. No. US 10648981 Continuation of Ser. No. US 2017-15701272, filed on 11 Sep 2017, Pat. No. US 10324091 Continuation		

of Ser. No. WO 2016-US21379, filed on 8 Mar 2016, PENDING

	NUMBER	DATE
PRIORITY INFORMATION:	US 2015-62181685	20150618 (62)
	US 2015-62131062	20150310 (62)

DOCUMENT TYPE: Utility
FILE SEGMENT: APPLICATION
NUMBER OF CLAIMS: 20
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 2 Drawing Page(s)
LINE COUNT: 1199
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB Provided herein are multiplex assays for detecting antibodies indicative of presence and stage of syphilis infection in an individual. Individuals infected with syphilis produce antibodies directed to syphilis components and the lipid cellular debris associated with the infection. The present disclosure represents the first combination of these diverse antibody targets in a single assay.

L9 ANSWER 4 OF 7 USPATFULL on STN
ACCESSION NUMBER: 2020:258223 USPATFULL Full-text
TITLE: COMBINATION TREPONEMAL AND NON-TREPONEMAL SYPHILIS TEST
INVENTOR(S): Kaul, Ravi, Davis, CA, UNITED STATES
Zheng, Weiming, Emeryville, CA, UNITED STATES
Walker, Roger, Benicia, CA, UNITED STATES
APPLICANT(S): Bio-Rad Laboratories, Inc., Hercules, CA, UNITED STATES

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 20200225230	A1	20200716
	US 10942182	B2	20210309
APPLICATION INFO.:	US 2020-16832608	A1	20200327 (16)

RELATED APPLN. INFO.: Division of Ser. No. US 2019-16405588, filed on 7 May 2019, Pat. No. US 10648981 Continuation of Ser. No. US 2017-15701272, filed on 11 Sep 2017, Pat. No. US 10324091 Continuation of Ser. No. WO 2016-US21379, filed on 8 Mar 2016, PENDING

	NUMBER	DATE
PRIORITY INFORMATION:	US 2015-62181685	20150618 (62)
	US 2015-62131062	20150310 (62)

DOCUMENT TYPE: Utility
FILE SEGMENT: APPLICATION
NUMBER OF CLAIMS: 20
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 2 Drawing Page(s)
LINE COUNT: 1164
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB Provided herein are multiplex assays for detecting antibodies indicative of presence and stage of syphilis infection in an individual. Individuals infected with syphilis produce antibodies directed to syphilis components and the lipid cellular debris associated with the infection. The present disclosure represents the first combination of these diverse antibody targets in a single assay.

L9 ANSWER 5 OF 7 USPATFULL on STN
ACCESSION NUMBER: 2019:303731 USPATFULL Full-text
TITLE: COMBINATION TREPONEMAL AND NON-TREPONEMAL SYPHILIS TEST
INVENTOR(S): Kaul, Ravi, Davis, CA, UNITED STATES
Zheng, Weiming, Emeryville, CA, UNITED STATES
Walker, Roger, Benicia, CA, UNITED STATES
APPLICANT(S): Bio-Rad Laboratories, Inc., Hercules, CA, UNITED STATES

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 20190265240	A1	20190829
	US 10648981	B2	20200512

APPLICATION INFO.: US 2019-16405588 A1 20190507 (16)
RELATED APPLN. INFO.: Continuation of Ser. No. US 2017-15701272, filed on 11 Sep 2017, Pat. No. US 10324091 Continuation of Ser. No. WO 2016-US21379, filed on 8 Mar 2016, PENDING

	NUMBER	DATE
PRIORITY INFORMATION:	US 2015-62181685	20150618 (62)
	US 2015-62131062	20150310 (62)

DOCUMENT TYPE: Utility
FILE SEGMENT: APPLICATION
NUMBER OF CLAIMS: 9
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 2 Drawing Page(s)
LINE COUNT: 1152
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB Provided herein are multiplex assays for detecting antibodies indicative of presence and stage of syphilis infection in an individual. Individuals infected with syphilis produce antibodies directed to syphilis components and the lipid cellular debris associated with the infection. The present disclosure represents the first combination of these diverse antibody targets in a single assay.

L9 ANSWER 6 OF 7 USPATFULL on STN
ACCESSION NUMBER: 2017:426008 USPATFULL Full-text
TITLE: COMBINATION TREPONEMAL AND NON-TREPONEMAL SYPHILIS TEST
INVENTOR(S): Kaul, Ravi, Davis, CA, UNITED STATES
Zheng, Weiming, Emeryville, CA, UNITED STATES
Walker, Roger, Benicia, CA, UNITED STATES
APPLICANT(S): Bio-Rad Laboratories, Inc., Hercules, CA, UNITED STATES

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 20170370931	A1	20171228
	US 10324091	B2	20190618
APPLICATION INFO.:	US 2017-15701272	A1	20170911 (15)

RELATED APPLN. INFO.: Continuation of Ser. No. WO 2016-US21379, filed on 8 Mar 2016, PENDING

	NUMBER	DATE
PRIORITY INFORMATION:	US 2015-62181685	20150618 (62)
	US 2015-62131062	20150310 (62)

DOCUMENT TYPE: Utility
FILE SEGMENT: APPLICATION
NUMBER OF CLAIMS: 20
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 2 Drawing Page(s)
LINE COUNT: 1203
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB Provided herein are multiplex assays for detecting antibodies indicative of presence and stage of syphilis infection in an individual. Individuals infected with syphilis produce antibodies directed to syphilis components and the lipid cellular debris associated with the infection. The present disclosure represents the first combination of these diverse antibody targets in a single assay.

L9 ANSWER 7 OF 7 CA COPYRIGHT 2022 ACS on STN DUPLICATE 1
ACCESSION NUMBER: 165:361510 CA Full-text
TITLE: Combination treponemal and non-treponemal antigens for syphilis test and kit
INVENTOR(S): Kaul, Ravi; Zheng, Weiming; Walker, Roger
PATENT ASSIGNEE(S): Bio-Rad Laboratories, Inc., USA
SOURCE: PCT Int. Appl., 36pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2016144962	A1	20160915	WO 2016-US21379	20160308
CN 107533060	A	20180102	CN 2016-80027067	20160308
CN 107533060	B	20191105		
EP 3268743	A1	20180117	EP 2016-762346	20160308
EP 3268743	B1	20200902		
BR 112017019236	A2	20180424	BR 2017-112017019236	20160308
ES 2834880	T3	20210621	ES 2016-762346	20160308
US 20170370931	A1	20171228	US 2017-15701272	20170911
US 10324091	B2	20190618		
US 20190265240	A1	20190829	US 2019-16405588	20190507
US 10648981	B2	20200512		
US 20200225230	A1	20200716	US 2020-16832608	20200327
US 10942182	B2	20210309		
US 20210156859	A1	20210527	US 2021-17170577	20210208

PRIORITY APPLN. INFO.:

US 2015-62131062	P	20150310
US 2015-62181685	P	20150618
WO 2016-US21379	W	20160308
US 2017-15701272	A1	20170911
US 2019-16405588	A3	20190507
US 2020-16832608	A1	20200327

PATENT STATUS PATENT INFORMATION:

PATENT NO.	KIND	STATUS	STATUS DATE
WO 2016144962	A1	Dead	20201201
CN 107533060	A	Alive	20201121
CN 107533060	B	Alive	20201121
EP 3268743	A1	Indeterminate	20201107
EP 3268743	B1	Indeterminate	20201107
BR 112017019236	A2	Alive	20201121
ES 2834880	T3	Alive	20210701
US 20170370931	A1	Alive	20201120
US 10324091	B2	Alive	20201121
US 20190265240	A1	Alive	20201121
US 10648981	B2	Alive	20201121
US 20200225230	A1	Alive	20201121
US 10942182	B2	Alive	20210318
US 20210156859	A1	Alive	20210604

ASSIGNMENT HISTORY FOR US PATENT AVAILABLE IN LSUS DISPLAY FORMAT

AB Provided herein are kits and multiplex assays for detecting antibodies indicative of presence and stage of syphilis infection in an individual. Individuals infected with syphilis produce antibodies directed to syphilis components and the lipid cellular debris assocd. with the infection. The present disclosure represents the first combination of these diverse antibody targets in a single assay.

REFERENCE COUNT: 4 THERE ARE 4 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

=> e zheng weimin?/au

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L10        376 "ZHENG WEIMING"/AU

=> s l10 and syphilis

L11          7 L10 AND SYPHILIS

=> dup rem l11

PROCESSING COMPLETED FOR L11
L12           5 DUP REM L11 (2 DUPLICATES REMOVED)

=> d ibib ab 1-5


L12  ANSWER 1 OF 5  USPATFULL on STN
ACCESSION NUMBER:       2021:181550  USPATFULL Full-text
TITLE:                  COMBINATION TREPONEMAL AND NON-TREPONEMAL SYPHILIS TEST
INVENTOR(S):            Kaul, Ravi, Davis, CA, UNITED STATES
                        Zheng, Weiming, Emeryville, CA, UNITED STATES
                        Walker, Roger, Benicia, CA, UNITED STATES
APPLICANT(S):           Bio-Rad Laboratories, Inc., Hercules, CA, UNITED STATES

                             NUMBER       KIND    DATE
                        ---------------- ------ --------
PATENT INFORMATION:     US 20210156859     A1   20210527
APPLICATION INFO.:      US 2021-17170577   A1   20210208  (17)
RELATED APPLN. INFO.:   Continuation of Ser. No. US 2020-16832608, filed on 27
                        Mar 2020, Pat. No. US 10942182 Division of Ser. No. US
                        2019-16405588, filed on 7 May 2019, Pat. No. US
                        10648981 Continuation of Ser. No. US 2017-15701272,
                        filed on 11 Sep 2017, Pat. No. US 10324091 Continuation
                        of Ser. No. WO 2016-US21379, filed on 8 Mar 2016,
                        PENDING

                               NUMBER             DATE
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PRIORITY INFORMATION:   US 2015-62181685         20150618 (62)
                        US 2015-62131062         20150310 (62)
DOCUMENT TYPE:          Utility
FILE SEGMENT:           APPLICATION
NUMBER OF CLAIMS:       20
EXEMPLARY CLAIM:        1
NUMBER OF DRAWINGS:     2 Drawing Page(s)
LINE COUNT:             1199
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB     Provided herein are multiplex assays for detecting antibodies indicative
       of presence and stage of syphilis infection in an individual.
       Individuals infected with syphilis produce antibodies directed to
       syphilis components and the lipid cellular debris associated with the
       infection. The present disclosure represents the first combination of
       these diverse antibody targets in a single assay.


L12  ANSWER 2 OF 5  USPATFULL on STN
ACCESSION NUMBER:       2020:258223  USPATFULL Full-text
TITLE:                  COMBINATION TREPONEMAL AND NON-TREPONEMAL SYPHILIS TEST
INVENTOR(S):            Kaul, Ravi, Davis, CA, UNITED STATES
                        Zheng, Weiming, Emeryville, CA, UNITED STATES
                        Walker, Roger, Benicia, CA, UNITED STATES
APPLICANT(S):           Bio-Rad Laboratories, Inc., Hercules, CA, UNITED STATES
```

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 20200225230	A1	20200716
	US 10942182	B2	20210309
APPLICATION INFO.:	US 2020-16832608	A1	20200327 (16)

RELATED APPLN. INFO.: Division of Ser. No. US 2019-16405588, filed on 7 May 2019, Pat. No. US 10648981 Continuation of Ser. No. US 2017-15701272, filed on 11 Sep 2017, Pat. No. US 10324091 Continuation of Ser. No. WO 2016-US21379, filed on 8 Mar 2016, PENDING

	NUMBER	DATE
PRIORITY INFORMATION:	US 2015-62181685	20150618 (62)
	US 2015-62131062	20150310 (62)

DOCUMENT TYPE: Utility
FILE SEGMENT: APPLICATION
NUMBER OF CLAIMS: 20
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 2 Drawing Page(s)
LINE COUNT: 1164
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB Provided herein are multiplex assays for detecting antibodies indicative of presence and stage of syphilis infection in an individual. Individuals infected with syphilis produce antibodies directed to syphilis components and the lipid cellular debris associated with the infection. The present disclosure represents the first combination of these diverse antibody targets in a single assay.

L12 ANSWER 3 OF 5 USPATFULL on STN
ACCESSION NUMBER: 2019:303731 USPATFULL Full-text
TITLE: COMBINATION TREPONEMAL AND NON-TREPONEMAL SYPHILIS TEST
INVENTOR(S): Kaul, Ravi, Davis, CA, UNITED STATES
Zheng, Weiming, Emeryville, CA, UNITED STATES
Walker, Roger, Benicia, CA, UNITED STATES
APPLICANT(S): Bio-Rad Laboratories, Inc., Hercules, CA, UNITED STATES

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 20190265240	A1	20190829
	US 10648981	B2	20200512
APPLICATION INFO.:	US 2019-16405588	A1	20190507 (16)

RELATED APPLN. INFO.: Continuation of Ser. No. US 2017-15701272, filed on 11 Sep 2017, Pat. No. US 10324091 Continuation of Ser. No. WO 2016-US21379, filed on 8 Mar 2016, PENDING

	NUMBER	DATE
PRIORITY INFORMATION:	US 2015-62181685	20150618 (62)
	US 2015-62131062	20150310 (62)

DOCUMENT TYPE: Utility
FILE SEGMENT: APPLICATION
NUMBER OF CLAIMS: 9
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 2 Drawing Page(s)
LINE COUNT: 1152
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB Provided herein are multiplex assays for detecting antibodies indicative of presence and stage of syphilis infection in an individual. Individuals infected with syphilis produce antibodies directed to syphilis components and the lipid cellular debris associated with the infection. The present disclosure represents the first combination of these diverse antibody targets in a single assay.

L12 ANSWER 4 OF 5 USPATFULL on STN
ACCESSION NUMBER: 2017:426008 USPATFULL Full-text
TITLE: COMBINATION TREPONEMAL AND NON-TREPONEMAL SYPHILIS TEST
INVENTOR(S): Kaul, Ravi, Davis, CA, UNITED STATES
Zheng, Weiming, Emeryville, CA, UNITED STATES

	Walker, Roger, Benicia, CA, UNITED STATES
APPLICANT(S):	Bio-Rad Laboratories, Inc., Hercules, CA, UNITED STATES

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 20170370931	A1	20171228
	US 10324091	B2	20190618
APPLICATION INFO.:	US 2017-15701272	A1	20170911 (15)

RELATED APPLN. INFO.: Continuation of Ser. No. WO 2016-US21379, filed on 8 Mar 2016, PENDING

	NUMBER	DATE
PRIORITY INFORMATION:	US 2015-62181685	20150618 (62)
	US 2015-62131062	20150310 (62)

DOCUMENT TYPE: Utility
FILE SEGMENT: APPLICATION
NUMBER OF CLAIMS: 20
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 2 Drawing Page(s)
LINE COUNT: 1203
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB Provided herein are multiplex assays for detecting antibodies indicative of presence and stage of syphilis infection in an individual. Individuals infected with syphilis produce antibodies directed to syphilis components and the lipid cellular debris associated with the infection. The present disclosure represents the first combination of these diverse antibody targets in a single assay.

L12 ANSWER 5 OF 5 CA COPYRIGHT 2022 ACS on STN DUPLICATE 1
ACCESSION NUMBER: 165:361510 CA Full-text
TITLE: Combination treponemal and non-treponemal antigens for syphilis test and kit
INVENTOR(S): Kaul, Ravi; Zheng, Weiming; Walker, Roger
PATENT ASSIGNEE(S): Bio-Rad Laboratories, Inc., USA
SOURCE: PCT Int. Appl., 36pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2016144962	A1	20160915	WO 2016-US21379	20160308
CN 107533060	A	20180102	CN 2016-80027067	20160308
CN 107533060	B	20191105		
EP 3268743	A1	20180117	EP 2016-762346	20160308
EP 3268743	B1	20200902		
BR 112017019236	A2	20180424	BR 2017-112017019236	20160308
ES 2834880	T3	20210621	ES 2016-762346	20160308
US 20170370931	A1	20171228	US 2017-15701272	20170911
US 10324091	B2	20190618		
US 20190265240	A1	20190829	US 2019-16405588	20190507
US 10648981	B2	20200512		
US 20200225230	A1	20200716	US 2020-16832608	20200327
US 10942182	B2	20210309		
US 20210156859	A1	20210527	US 2021-17170577	20210208

PRIORITY APPLN. INFO.:	US 2015-62131062	P	20150310
	US 2015-62181685	P	20150618
	WO 2016-US21379	W	20160308
	US 2017-15701272	A1	20170911
	US 2019-16405588	A3	20190507
	US 2020-16832608	A1	20200327

PATENT STATUS PATENT INFORMATION:

PATENT NO.	KIND	STATUS	STATUS DATE
WO 2016144962	A1	Dead	20201201
CN 107533060	A	Alive	20201121
CN 107533060	B	Alive	20201121
EP 3268743	A1	Indeterminate	20201107

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     EP 3268743           B1   Indeterminate   20201107
     BR 112017019236      A2   Alive           20201121
     ES 2834880           T3   Alive           20210701
     US 20170370931       A1   Alive           20201120
     US 10324091          B2   Alive           20201121
     US 20190265240       A1   Alive           20201121
     US 10648981          B2   Alive           20201121
     US 20200225230       A1   Alive           20201121
     US 10942182          B2   Alive           20210318
     US 20210156859       A1   Alive           20210604
ASSIGNMENT HISTORY FOR US PATENT AVAILABLE IN LSUS DISPLAY FORMAT
AB   Provided herein are kits and multiplex assays for detecting antibodies
     indicative of presence and stage of syphilis infection in an individual.
     Individuals infected with syphilis produce antibodies directed to
     syphilis components and the lipid cellular debris assocd. with the
     infection.  The present disclosure represents the first combination of
     these diverse antibody targets in a single assay.
REFERENCE COUNT:         4     THERE ARE 4 CITED REFERENCES AVAILABLE FOR THIS
                               RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT



=> e walker roge?/au

E1            2     WALKER RODRI O/AU
E2            1     WALKER ROE/AU
E3            0 --> WALKER ROGE?/AU
E4          178     WALKER ROGER/AU
E5            3     WALKER ROGER B/AU
E6            3     WALKER ROGER BOYD/AU
E7           24     WALKER ROGER C/AU
E8            4     WALKER ROGER C II/AU
E9           13     WALKER ROGER CLAYTON/AU
E10           4     WALKER ROGER D/AU
E11           1     WALKER ROGER DANIEL/AU
E12           6     WALKER ROGER E/AU

=> s e4

L13         178 "WALKER ROGER"/AU

=> s l13 and syphilis

L14           7 L13 AND SYPHILIS

=> dup rem l14

PROCESSING COMPLETED FOR L14
L15            5 DUP REM L14 (2 DUPLICATES REMOVED)

=> d ibib ab 1-5


L15  ANSWER 1 OF 5  USPATFULL on STN
ACCESSION NUMBER:       2021:181550  USPATFULL Full-text
TITLE:                  COMBINATION TREPONEMAL AND NON-TREPONEMAL SYPHILIS TEST
INVENTOR(S):            Kaul, Ravi, Davis, CA, UNITED STATES
                        Zheng, Weiming, Emeryville, CA, UNITED STATES
                        Walker, Roger, Benicia, CA, UNITED STATES
APPLICANT(S):           Bio-Rad Laboratories, Inc., Hercules, CA, UNITED STATES

                             NUMBER       KIND    DATE
                        ---------------- ------ --------
PATENT INFORMATION:     US 20210156859     A1   20210527
APPLICATION INFO.:      US 2021-17170577   A1   20210208  (17)
RELATED APPLN. INFO.:   Continuation of Ser. No. US 2020-16832608, filed on 27
                        Mar 2020, Pat. No. US 10942182 Division of Ser. No. US
                        2019-16405588, filed on 7 May 2019, Pat. No. US
                        10648981 Continuation of Ser. No. US 2017-15701272,
                        filed on 11 Sep 2017, Pat. No. US 10324091 Continuation
                        of Ser. No. WO 2016-US21379, filed on 8 Mar 2016,
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PENDING

	NUMBER	DATE
PRIORITY INFORMATION:	US 2015-62181685	20150618 (62)
	US 2015-62131062	20150310 (62)

DOCUMENT TYPE: Utility
FILE SEGMENT: APPLICATION
NUMBER OF CLAIMS: 20
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 2 Drawing Page(s)
LINE COUNT: 1199
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB Provided herein are multiplex assays for detecting antibodies indicative of presence and stage of syphilis infection in an individual. Individuals infected with syphilis produce antibodies directed to syphilis components and the lipid cellular debris associated with the infection. The present disclosure represents the first combination of these diverse antibody targets in a single assay.

L15 ANSWER 2 OF 5 USPATFULL on STN
ACCESSION NUMBER: 2020:258223 USPATFULL Full-text
TITLE: COMBINATION TREPONEMAL AND NON-TREPONEMAL SYPHILIS TEST
INVENTOR(S): Kaul, Ravi, Davis, CA, UNITED STATES
Zheng, Weiming, Emeryville, CA, UNITED STATES
Walker, Roger, Benicia, CA, UNITED STATES
APPLICANT(S): Bio-Rad Laboratories, Inc., Hercules, CA, UNITED STATES

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 20200225230	A1	20200716
	US 10942182	B2	20210309
APPLICATION INFO.:	US 2020-16832608	A1	20200327 (16)

RELATED APPLN. INFO.: Division of Ser. No. US 2019-16405588, filed on 7 May 2019, Pat. No. US 10648981 Continuation of Ser. No. US 2017-15701272, filed on 11 Sep 2017, Pat. No. US 10324091 Continuation of Ser. No. WO 2016-US21379, filed on 8 Mar 2016, PENDING

	NUMBER	DATE
PRIORITY INFORMATION:	US 2015-62181685	20150618 (62)
	US 2015-62131062	20150310 (62)

DOCUMENT TYPE: Utility
FILE SEGMENT: APPLICATION
NUMBER OF CLAIMS: 20
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 2 Drawing Page(s)
LINE COUNT: 1164
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB Provided herein are multiplex assays for detecting antibodies indicative of presence and stage of syphilis infection in an individual. Individuals infected with syphilis produce antibodies directed to syphilis components and the lipid cellular debris associated with the infection. The present disclosure represents the first combination of these diverse antibody targets in a single assay.

L15 ANSWER 3 OF 5 USPATFULL on STN
ACCESSION NUMBER: 2019:303731 USPATFULL Full-text
TITLE: COMBINATION TREPONEMAL AND NON-TREPONEMAL SYPHILIS TEST
INVENTOR(S): Kaul, Ravi, Davis, CA, UNITED STATES
Zheng, Weiming, Emeryville, CA, UNITED STATES
Walker, Roger, Benicia, CA, UNITED STATES
APPLICANT(S): Bio-Rad Laboratories, Inc., Hercules, CA, UNITED STATES

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 20190265240	A1	20190829
	US 10648981	B2	20200512
APPLICATION INFO.:	US 2019-16405588	A1	20190507 (16)

RELATED APPLN. INFO.: Continuation of Ser. No. US 2017-15701272, filed on 11 Sep 2017, Pat. No. US 10324091 Continuation of Ser. No. WO 2016-US21379, filed on 8 Mar 2016, PENDING

	NUMBER	DATE
PRIORITY INFORMATION:	US 2015-62181685	20150618 (62)
	US 2015-62131062	20150310 (62)

DOCUMENT TYPE: Utility
FILE SEGMENT: APPLICATION
NUMBER OF CLAIMS: 9
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 2 Drawing Page(s)
LINE COUNT: 1152
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB Provided herein are multiplex assays for detecting antibodies indicative of presence and stage of syphilis infection in an individual. Individuals infected with syphilis produce antibodies directed to syphilis components and the lipid cellular debris associated with the infection. The present disclosure represents the first combination of these diverse antibody targets in a single assay.

L15 ANSWER 4 OF 5 USPATFULL on STN
ACCESSION NUMBER: 2017:426008 USPATFULL Full-text
TITLE: COMBINATION TREPONEMAL AND NON-TREPONEMAL SYPHILIS TEST
INVENTOR(S): Kaul, Ravi, Davis, CA, UNITED STATES
Zheng, Weiming, Emeryville, CA, UNITED STATES
Walker, Roger, Benicia, CA, UNITED STATES
APPLICANT(S): Bio-Rad Laboratories, Inc., Hercules, CA, UNITED STATES

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 20170370931	A1	20171228
	US 10324091	B2	20190618
APPLICATION INFO.:	US 2017-15701272	A1	20170911 (15)

RELATED APPLN. INFO.: Continuation of Ser. No. WO 2016-US21379, filed on 8 Mar 2016, PENDING

	NUMBER	DATE
PRIORITY INFORMATION:	US 2015-62181685	20150618 (62)
	US 2015-62131062	20150310 (62)

DOCUMENT TYPE: Utility
FILE SEGMENT: APPLICATION
NUMBER OF CLAIMS: 20
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 2 Drawing Page(s)
LINE COUNT: 1203
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB Provided herein are multiplex assays for detecting antibodies indicative of presence and stage of syphilis infection in an individual. Individuals infected with syphilis produce antibodies directed to syphilis components and the lipid cellular debris associated with the infection. The present disclosure represents the first combination of these diverse antibody targets in a single assay.

L15 ANSWER 5 OF 5 CA COPYRIGHT 2022 ACS on STN DUPLICATE 1
ACCESSION NUMBER: 165:361510 CA Full-text
TITLE: Combination treponemal and non-treponemal antigens for syphilis test and kit
INVENTOR(S): Kaul, Ravi; Zheng, Weiming; Walker, Roger
PATENT ASSIGNEE(S): Bio-Rad Laboratories, Inc., USA
SOURCE: PCT Int. Appl., 36pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE

WO 2016144962	A1	20160915	WO 2016-US21379	20160308
CN 107533060	A	20180102	CN 2016-80027067	20160308
CN 107533060	B	20191105		
EP 3268743	A1	20180117	EP 2016-762346	20160308
EP 3268743	B1	20200902		
BR 112017019236	A2	20180424	BR 2017-112017019236	20160308
ES 2834880	T3	20210621	ES 2016-762346	20160308
US 20170370931	A1	20171228	US 2017-15701272	20170911
US 10324091	B2	20190618		
US 20190265240	A1	20190829	US 2019-16405588	20190507
US 10648981	B2	20200512		
US 20200225230	A1	20200716	US 2020-16832608	20200327
US 10942182	B2	20210309		
US 20210156859	A1	20210527	US 2021-17170577	20210208

PRIORITY APPLN. INFO.:

US 2015-62131062	P	20150310
US 2015-62181685	P	20150618
WO 2016-US21379	W	20160308
US 2017-15701272	A1	20170911
US 2019-16405588	A3	20190507
US 2020-16832608	A1	20200327

PATENT STATUS PATENT INFORMATION:

PATENT NO.	KIND	STATUS	STATUS DATE
WO 2016144962	A1	Dead	20201201
CN 107533060	A	Alive	20201121
CN 107533060	B	Alive	20201121
EP 3268743	A1	Indeterminate	20201107
EP 3268743	B1	Indeterminate	20201107
BR 112017019236	A2	Alive	20201121
ES 2834880	T3	Alive	20210701
US 20170370931	A1	Alive	20201120
US 10324091	B2	Alive	20201121
US 20190265240	A1	Alive	20201121
US 10648981	B2	Alive	20201121
US 20200225230	A1	Alive	20201121
US 10942182	B2	Alive	20210318
US 20210156859	A1	Alive	20210604

ASSIGNMENT HISTORY FOR US PATENT AVAILABLE IN LSUS DISPLAY FORMAT

AB Provided herein are kits and multiplex assays for detecting antibodies indicative of presence and stage of syphilis infection in an individual. Individuals infected with syphilis produce antibodies directed to syphilis components and the lipid cellular debris assocd. with the infection. The present disclosure represents the first combination of these diverse antibody targets in a single assay.

REFERENCE COUNT: 4 THERE ARE 4 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

=>

PART B - FEE(S) TRANSMITTAL

Complete and send this form, together with applicable fee(s), by mail or fax, or via EFS-Web.

By mail, send to: Mail Stop ISSUE FEE
Commissioner for Patents
P.O. Box 1450
Alexandria, Virginia 22313-1450

By fax, send to: (571)-273-2885

INSTRUCTIONS: This form should be used for transmitting the ISSUE FEE and PUBLICATION FEE (if required). Blocks 1 through 5 should be completed where appropriate. All further correspondence including the Patent, advance orders and notification of maintenance fees will be mailed to the current correspondence address as indicated unless corrected below or directed otherwise in Block 1, by (a) specifying a new correspondence address; and/or (b) indicating a separate "FEE ADDRESS" for maintenance fee notifications.

CURRENT CORRESPONDENCE ADDRESS (Note: Use Block 1 for any change of address)

23552 7590 03/13/2023

MERCHANT & GOULD P.C.
P.O. BOX 2903
MINNEAPOLIS, MN 55402-0903

Note: A certificate of mailing can only be used for domestic mailings of the Fee(s) Transmittal. This certificate cannot be used for any other accompanying papers. Each additional paper, such as an assignment or formal drawing, must have its own certificate of mailing or transmission.

Certificate of Mailing or Transmission

I hereby certify that this Fee(s) Transmittal is being deposited with the United States Postal Service with sufficient postage for first class mail in an envelope addressed to the Mail Stop ISSUE FEE address above, or being transmitted to the USPTO via EFS-Web or by facsimile to (571) 273-2885, on the date below.

(Typed or printed name)
(Signature)
(Date)

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
17/151,938	01/19/2021	Mark E. Deem	19264.0001USC8	1034

TITLE OF INVENTION: SYSTEMS AND METHODS FOR DELIVERY OF A THERAPEUTIC AGENT

APPLN. TYPE	ENTITY STATUS	ISSUE FEE DUE	PUBLICATION FEE DUE	PREV. PAID ISSUE FEE	TOTAL FEE(S) DUE	DATE DUE
nonprovisional	SMALL	$480	$0.00	$0.00	$480	06/13/2023

EXAMINER	ART UNIT	CLASS-SUBCLASS
NAVARRO, ALBERT MARK	1645	424-190100

1. Change of correspondence address or indication of "Fee Address" (37 CFR 1.363).

❑ Change of correspondence address (or Change of Correspondence Address form PTO/AIA/122 or PTO/SB/122) attached.

❑ "Fee Address" indication (or "Fee Address" Indication form PTO/AIA/47 or 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 Merchant & Gould P.C.
2
3

3. ASSIGNEE NAME AND RESIDENCE DATA TO BE PRINTED ON THE PATENT (print or type)

PLEASE NOTE: Unless an assignee is identified below, no assignee data will appear on the patent. If an assignee is identified below, the document must have been previously recorded, or filed for recordation, as set forth in 37 CFR 3.11 and 37 CFR 3.81(a). Completion of this form is NOT a substitute for filing an assignment.

(A) NAME OF ASSIGNEE: The Foundry, LLC

(B) RESIDENCE: (CITY and STATE OR COUNTRY): Menlo Park, California

Please check the appropriate assignee category or categories (will not be printed on the patent) : ❑ Individual ☒ Corporation or other private group entity ❑ Government

4a. Fees submitted: ☒ Issue Fee ❑ Publication Fee (if required) ❑ Advance Order - # of Copies _____

4b. Method of Payment: *(Please first reapply any previously paid fee shown above)*

☒ Electronic Payment via EFS-Web ❑ Enclosed check ❑ Non-electronic payment by credit card (Attach form PTO-2038)

☒ The Director is hereby authorized to charge the required fee(s), any deficiency, or credit any overpayment to Deposit Account No. 13-2725

5. **Change in Entity Status** (from status indicated above)

❑ Applicant certifying micro entity status. See 37 CFR 1.29

❑ Applicant asserting small entity status. See 37 CFR 1.27

❑ Applicant changing to regular undiscounted fee status.

NOTE: Absent a valid certification of Micro Entity Status (see forms PTO/SB/15A and 15B), issue fee payment in the micro entity amount will not be accepted at the risk of application abandonment.
NOTE: If the application was previously under micro entity status, checking this box will be taken to be a notification of loss of entitlement to micro entity status.
NOTE: Checking this box will be taken to be a notification of loss of entitlement to small or micro entity status, as applicable.

NOTE: This form must be signed in accordance with 37 CFR 1.31 and 1.33. See 37 CFR 1.4 for signature requirements and certifications.

Authorized Signature /Robert A. Kalinsky/ Date May 3, 2023

Typed or printed name Robert A. Kalinsky Registration No. 50,471

UNITED STATES
PATENT AND TRADEMARK OFFICE

P.O. Box 1450
Alexandria, VA 22313 - 1450
www.uspto.gov

ELECTRONIC PAYMENT RECEIPT

APPLICATION #	RECEIPT DATE / TIME	ATTORNEY DOCKET #
17/151,938	05/03/2023 01:13:24 PM ET	19264.0001USC8

Title of Invention

SYSTEMS AND METHODS FOR DELIVERY OF A THERAPEUTIC AGENT

Application Information

APPLICATION TYPE	Utility - Nonprovisional Application under 35 USC 111(a)	PATENT #	-
CONFIRMATION #	1034	FILED BY	Theresa Powless
PATENT CENTER #	62029819	AUTHORIZED BY	Robert Kalinsky
CUSTOMER #	23552	FILING DATE	01/19/2021
CORRESPONDENCE ADDRESS	-	FIRST NAMED INVENTOR	Mark E. Deem

Payment Information

PAYMENT METHOD	PAYMENT TRANSACTION ID	PAYMENT AUTHORIZED BY
CARD / 4938	E202353D15469059	Theresa Powless

PRE-AUTHORIZED ACCOUNT	PRE-AUTHORIZED CATEGORY
132725	37 CFR 1.16 (National application filing, search, and examination fees); 37 CFR 1.17 (Patent application and reexamination processing fees); 37 CFR 1.19 (Document supply fees); 37 CFR 1.20 (Post Issuance fees); 37 CFR 1.21 (Miscellaneous fees and charges)

FEE CODE	DESCRIPTION	ITEM PRICE($)	QUANTITY	ITEM TOTAL($)
2501	UTILITY ISSUE FEE	480.00	1	480.00
			TOTAL AMOUNT:	$480.00

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 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

P.O. Box 1450
Alexandria, VA 22313 - 1450
www.uspto.gov

ELECTRONIC ACKNOWLEDGEMENT RECEIPT

APPLICATION #	RECEIPT DATE / TIME	ATTORNEY DOCKET #
17/151,938	**05/03/2023 01:13:24 PM ET**	**19264.0001USC8**

Title of Invention

SYSTEMS AND METHODS FOR DELIVERY OF A THERAPEUTIC AGENT

Application Information

APPLICATION TYPE	Utility - Nonprovisional Application under 35 USC 111(a)	PATENT #	-
CONFIRMATION #	1034	FILED BY	Theresa Powless
PATENT CENTER #	62029819	FILING DATE	01/19/2021
CUSTOMER #	23552	FIRST NAMED INVENTOR	Mark E. Deem
CORRESPONDENCE ADDRESS	-	AUTHORIZED BY	Robert Kalinsky

Documents

TOTAL DOCUMENTS: 1

DOCUMENT	PAGES	DESCRIPTION	SIZE (KB)
2023-05-03--Issue Fee Xmtl--19264.0001USC8.PDF	1	Issue Fee Payment (PTO-85B)	145 KB

Digest

DOCUMENT	MESSAGE DIGEST(SHA-512)
2023-05-03--Issue Fee Xmtl--19264.0001USC8.PDF	BB2899F99054B6D542BC40B708855973791A150A35034343E7925ECDAF8A53C33E1D886C7C620107CCFE0C25EBEFE0FEC24458D1296C91A4DC6DE70EC7FD97D6

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 filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application

National Stage of an International Application under 35 U.S.C. 371

If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office

If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	ISSUE DATE	PATENT NO.	ATTORNEY DOCKET NO.	CONFIRMATION NO.
17/151,938	06/20/2023	11679077	19264.0001USC8	1034

23552 7590 05/31/2023

MERCHANT & GOULD P.C.
P.O. BOX 2903
MINNEAPOLIS, MN 55402-0903

ISSUE NOTIFICATION

The projected patent number and issue date are specified above. The patent will issue electronically. The electronically issued patent is the official patent grant pursuant to 35 U.S.C. § 153. The patent may be accessed on or after the issue date through Patent Center at https://patentcenter.uspto.gov/. The patent will be available in both the public and the private sides of Patent Center. Further assistance in electronically accessing the patent, or about Patent Center, is available by calling the Patent Electronic Business Center at 1-888-217-9197.

The USPTO is implementing electronic patent issuance with a transition period, during which period the USPTO will mail a ceremonial paper copy of the electronic patent grant to the correspondence address of record. Additional copies of the patent (i.e., certified and presentation copies) may be ordered for a fee from the USPTO's Certified Copy Center at https://certifiedcopycenter.uspto.gov/index.html. The Certified Copy Center may be reached at (800)972-6382.

Determination of Patent Term Adjustment under 35 U.S.C. 154 (b)
(application filed on or after May 29, 2000)

The Patent Term Adjustment is 0 day(s). Any patent to issue from the above-identified application will include an indication of the adjustment on the front page.

If a Continued Prosecution Application (CPA) was filed in the above-identified application, the filing date that determines Patent Term Adjustment is the filing date of the most recent CPA.

Applicant will be able to obtain more detailed information by accessing the Patent Application Information Retrieval (PAIR) WEB site (http://pair.uspto.gov).

Any questions regarding the Patent Term Extension or Adjustment determination should be directed to the Office of Patent Legal Administration at (571)-272-7702. Questions relating to issue and publication fee payments should be directed to the Application Assistance Unit (AAU) of the Office of Patents Stakeholder Experience (OPSE), Stakeholder Support Division (SSD) at (571)-272-4200.

INVENTOR(s) (Please see PAIR WEB site http://pair.uspto.gov for additional inventors):

Mark E. Deem, Mountain View, CA;
Hanson Gifford, Woodside, CA;

APPLICANT(s) (Please see PAIR WEB site http://pair.uspto.gov for additional applicants):

The Foundry, LLC, Menlo Park, CA

The United States represents the largest, most dynamic marketplace in the world and is an unparalleled location for business investment, innovation, and commercialization of new technologies. The USA offers tremendous resources and advantages for those who invest and manufacture goods here. Through SelectUSA, our nation works to encourage and facilitate business investment. To learn more about why the USA is the best country in the world to develop technology, manufacture products, and grow your business, visit SelectUSA.gov.

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, VA 22313-1450
www.uspto.gov

APPLICATION NO.	ISSUE DATE	PATENT NO.
17/151,938	20-JUN-23	11679077

MERCHANT & GOULD P.C.
P.O. BOX 2903
MINNEAPOLIS, MN 55402-0903

EGRANT NOTIFICATION

Your electronic patent grant (eGrant) is now available, which can be accessed via Patent Center at https://patentcenter.uspto.gov

The electronic patent grant is the official patent grant under 35 U.S.C. 153. For more information, please visit https://www.uspto.gov/electronicgrants