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Declarations under Rule 4.17:

- as to applicant's entitlement to apply for and be granted a patent (Rule 4.17(ii))
- as to the applicant's entitlement to claim the priority of the earlier application (Rule 4.17(iii))

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- with international search report (Art. 21(3))
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(54) **Title:** COMPOSITIONS AND METHODS UTILIZING PHOSPHODIESTERASE INHIBITORS TO TREAT BLAST-INDUCED TINNITUS AND/OR HEARING LOSS

(57) **Abstract:** The present disclosure provides compositions and methods utilizing phosphodiesterase inhibitors to treat blast-induced tinnitus and/or hearing loss. The compositions include phosphodiesterase inhibitors such as sildenafil.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 14/34569

A. CLASSIFICATION OF SUBJECT MATTER
 IPC(8) - C12N 9/00 (2014.01)
 CPC - C 12N 9/93, A 61K 38/00, A 61K 39/00, C 12N 9/00, A 61K 48/00
 According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED
 Minimum documentation searched (classification system followed by classification symbols)
 USPC- 435/183

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
 IPC(8)- C12N 9/00 (2014.01)
 USPC- 435/336; CPC-C 12N 9/93, A 61K 38/00, A 61K 39/00, C 12N 9/00, A 61K 48/00

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
 PatBase (PGPB, USPT, USOC, EPAB, JPAB, DWPI, TDBD), FreePatentsOnline (US Pat, PgPub, EPO, JPO, WIPO, NPL),
 GoogleScholar (PL, NPL); search terms: treating high-frequency blast-induced tinnitus phosphodiesterase inhibitor Compositions method
 utilizing treat hearing loss

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US 2010/0184769 A1 (Sandner) 22 July 2010 (22.07.2010) Abstract, para [0001], [0028]-[0036], Table 1	1-14, 17-19
Y	Zhang et al., Auditory Cortex Electrical Stimulation Suppresses Tinnitus in Rats, JARO 12: 185-201 (2011) abstract, pg 185, col 1, para 1; pg 191, col 2, para 4; pg 193, col 1, para 1; pg.197, col 2, para 2	1-14, 17-19
Y	WO 2012/106654 A1 (Kopke et al.) 09 August 2012 (09.08.2012) Abstract, para [0003]-[0008], [0042], [0049], [0065]	1-14, 17-19
Y	Mazurek et al., Evaluation of vardenafil for the treatment of subjective tinnitus: a controlled pilot study, Journal of Negative Results in BioMedicine, 2009, 8:3, 1-12 (17 February 2009) abstract. pg 4, col 2, para 2, pg 6, col 2, para 5	1-14, 17-19
Y	Coleman et al., Pharmacological rescue of noise induced hearing loss using N-acetylcysteine and acetyl-L-carnitine, Hearing Research 226, 104-113 (2007) abstract, pg 106, col 1, para 2.1, 2.1.1; col 2, para 2.1.2.2. pg 107, col 1, para 3.1	1-14, 17-19
Y	Elgoyhen, Pharmacological approaches to the treatment of tinnitus, Drug Discovery Today, Volume 15, Numbers 7/8, 300-305 (April 2010) abstract, pg 301, col 1, para 2; col 2, box 1	1-14, 17-19
Y	Zhang, Parallel Human and Animal Models of Blast- and Concussion-Induced Tinnitus and Related Traumatic Brain Injury (TBI), Annual Report, Wayne State University, Detroit, MI 48201, pp 1-206 (January 2013), available at: http://www.ntis.gov/search/product.aspx?ABBR=ADA599905 ; accessed on 06 October 2014 (06.10.2014) pg 1, para 1 to pg 3, para 1b	1-14, 17-19

Further documents are listed in the continuation of Box C.

* Special categories of cited documents:	
"A" document defining the general state of the art which is not considered to be of particular relevance	"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"E" earlier application or patent but published on or after the international filing date	"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"O" document referring to an oral disclosure, use, exhibition or other means	"&" document member of the same patent family
"P" document published prior to the international filing date but later than the priority date claimed	

Date of the actual completion of the international search 06 October 2014 (06.10.2014)	Date of mailing of the international search report 07 NOV 2014
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Name and mailing address of the ISA/US Mail Stop PCT, Attn: ISA/US, Commissioner for Patents P.O. Box 1450, Alexandria, Virginia 22313-1450 Facsimile No. 571-273-3201	Authorized officer: Lee W. Young PCT Helpdesk: 571-272-4300 PCT OSP: 571-272-7774
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INTERNATIONAL SEARCH REPORT

International application No.

PCT/US 14/34569

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

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

- 1. Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

- 2. Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

- 3. Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:
See supplemental box

- 1. As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
- 2. As all searchable claims could be searched without effort justifying additional fees, this Authority did not invite payment of additional fees.
- 3. As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
- 4. No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:
1-14, 17-19

- Remark on Protest**
- The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.
 - The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.
 - No protest accompanied the payment of additional search fees.

Continuation of Box III, lack of unity

This application contains the following inventions or groups of inventions which are not so linked as to form a single general inventive concept under PCT Rule 13.1.

Group I, claims 1-9, 10-14 (in part), 17-18, and 19 (in part), directed to a method of treating a high-frequency blast-induced tinnitus in subject having 26-28 kHz blast-induced tinnitus by reducing in the subject 26-28 kHz blast-induced tinnitus 3-6 weeks following exposure to the blast.

Group II, claims 10-14 (in part), 15-16, and 19 (in part), directed to a method of treating a high-frequency blast-induced tinnitus in subject in need thereof, reducing 18-20 kHz blast-induced tinnitus 3-6 weeks following exposure to the blast.

Group III, claims 20-38, directed to a method of treating hearing loss in a subject in need thereof.

Group IV, claims 39-66, directed to a method of treating a condition of hearing loss together with tinnitus in a subject in need thereof.

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

Special Technical Features (Distinct Technical Features):

The special technical feature of Group I is a treating a high-frequency blast-induced tinnitus in a subject in need thereof, having 26-28 kHz blast-induced tinnitus 3-6 weeks following exposure to the blast, not required in any other group.

The special technical feature of Group II is a method of treating a high-frequency blast-induced tinnitus in a subject in need thereof, having 18-20 kHz blast-induced tinnitus 3-6 weeks following exposure to the blast, not required in any other group.

The special technical feature of Group III is a method of treating a high-frequency blast-induced hearing loss in a subject in need thereof, not required in any other group.

The special technical feature of Group IV is a method of treating a high-frequency blast-induced condition (hearing impairment) comprising hearing loss and tinnitus in a subject in need thereof, not required in any other group.

Common Technical Features (Features Do Not Make a Contribution Over the Prior Art):

Groups I-IV share the technical feature of a method of treating high-frequency blast-induced condition in a subject in need thereof comprising administering to the subject a therapeutically effective amount of a phosphodiesterase inhibitor (PDE-I) within a time period associated with exposure to a blast thereby providing a therapeutic treatment by reducing in the subject the blast-induced condition following the time period associated with exposure to the blast. However, this common technical feature cannot be considered as a unifying technical feature, because it is anticipated by US 2010/0184769 A1 (Sandner). Sandner discloses treatment of hearing loss and tinnitus (Abstract) comprising administering to the subject in need thereof a therapeutically effective amount of a pharmaceutical composition of a PDE-5 (= PDE-I) inhibitors verdanafil (para [0036]-[0037]) and sildanafil (para [0029], [0031]), within a time period associated with exposure to a blast (para [0036]) thereby providing a therapeutic treatment by reducing in the subject the blast-induced condition following the time period associated with exposure to the blast (para [0036]).

Therefore, Groups I-IV lack unity under PCT Rule 13.

Note:

Claims 19 and 39 are unclear as written.

Claim 39 is unclear due to improper Markush group, because a subject cannot be exposed to a blast of 6-8 kHz, 14-16 kHz, 18-20 kHz, and 26-28 kHz at once or simultaneously. Although a subject can have perfect hearing while suffering from tinnitus, it is also possible that both conditions can manifest in a subject. Thus, separate treatments of tinnitus in a subject and hearing loss in a subject are different from the treatment of tinnitus combined with hearing loss (aka hearing impairment) in a subject. Therefore, for the purpose of this lack of unity draft, claim 39 has been assumed as follows for this opinion:

39. A method of treating high-frequency blast-induced tinnitus and hearing loss in a subject in need thereof comprising administering to the subject a therapeutically effective amount of a phosphodiesterase inhibitor (PDE-I) within a time period associated with exposure to a blast thereby providing a therapeutic treatment by reducing in the subject:

- (i) 26-28 kHz blast-induced tinnitus 3-6 weeks following exposure to the blast;
- (ii) 18-20 kHz [[and/]]or 26-28 kHz blast induced tinnitus 3-4 weeks following exposure to the blast; [[and]] or
- (iii) 6-8 kHz hearing loss 0-2 weeks following exposure to the blast; 14-16 kHz hearing loss 0-4 weeks following exposure to the blast [[and/]]or 18-20 kHz hearing loss 0-2 weeks [[and/]]or 4-6 weeks following exposure to the blast.

Similarly, claim 19 has been assumed as follows:

19. A method of claim 10 wherein the therapeutic treatment reduces 18-20 kHz [[and]] or 26-28 kHz blast-induced tinnitus in the subject 3-4 weeks following exposure to the blast.