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- (71) Applicants (for all designated States except US): **CHILDREN'S MEDICAL CENTER CORPORATION** [US/US]; 55 Shattuck Street, Boston, MA 02214 (US). **MASACHUSETTS INSTITUTE OF TECHNOLOGY** [US/US]; 77 Massachusetts Avenue, Cambridge, MA 02139 (US).

- (72) Inventors; and
- (75) Inventors/Applicants (for US only): **KOHANE, Daniel, S.** [US/US]; 41 Leslie Rd., Newton, MA 02466 (US). **SAGIE, Itay** [US/IL]; 85 Shvedia Street, 34980 Haifa (IL). **SIMONS, Emmanuel, J.** [US/US]; 250 Mercer Street, Apt.C-403, New York, NY 10012 (US).
- (74) Agents: **PABST, Patrea, L.** et al.; Pabst Patent Group LLP, 1545 Peachtree Street, N.E., Suite 320, Atlanta, GA 30309 (US).
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[Continued on next page]

(54) Title: CHEMICAL PERMEATION ENHANCERS ENHANCE NERVE BLOCKADE BY TOXINS

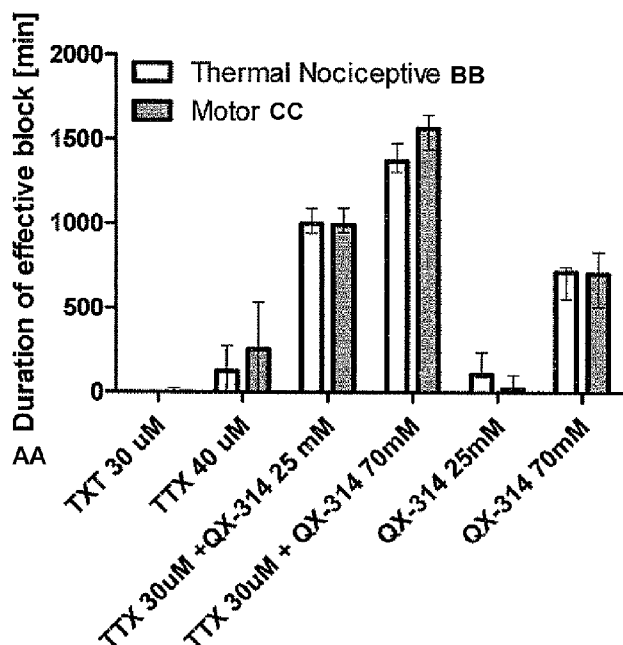


FIGURE 5B

(57) Abstract: Chemical permeation enhancers (CPEs) improve access of local anesthetics to the nerve, thereby improving their performance. Surfactants, representing three CPE sub-groups: anionic, cationic, and nonionic surfactants, were co-injected with tetrodotoxin (TTX) or bupivacaine at the sciatic nerve of Sprague-Dawley rats. All enhancers produced marked concentration-dependent improvements in the frequency and duration of block with TTX but not bupivacaine. An *in vitro* toxicity assay showed a wide range of CPE myotoxicity, but *in vivo* histological assessment showed no signs of muscle or nerve damage at concentrations of CPEs that produced a half-maximal increase in the duration of block of TTX. There was no systematic relationship between the enhancers' charge or hydrophobicity and their enhancement of block duration or potency. Thus, CPEs can provide marked prolongation of nerve blockade from TTX, without apparent local tissue toxicity, and therefore enhance the clinical applicability of TTX for prolonged-duration local anesthesia.



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GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

— *before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments (Rule 48.2(h))*

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**INTERNATIONAL SEARCH REPORT**

International application No  
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**A. CLASSIFICATION OF SUBJECT MATTER**

INV. A61K31/519 A61K47/10 A61K47/18 A61K47/20 A61K47/26  
A61K45/06

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)  
A61K

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

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

EPO-Internal, WPI Data

**C. DOCUMENTS CONSIDERED TO BE RELEVANT**

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X,P	SIMONS EMMANUEL J ET AL: "Effect of chemical permeation enhancers on nerve blockade." 23 December 2008 (2008-12-23), MOLECULAR PHARMACEUTICS 2009 JAN-FEB LNKD-PUBMED:19105721, VOL. 6, NR. 1, PAGE(S) 265 - 273 , XP002607655 ISSN: 1543-8384 See abstract, figures 1-5, tables 1-3 results and discussion: chemical permeation enhancers (the same used in the present application) enhance nerve blockade induced by tetrodotoxine (the preferred site I sodium channel of the present application). ----- -/--	1-18

Further documents are listed in the continuation of Box C.

See patent family annex.

\* Special categories of cited documents :

- "A" document defining the general state of the art which is not considered to be of particular relevance
- "E" earlier document but published on or after the international filing date
- "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- "O" document referring to an oral disclosure, use, exhibition or other means
- "P" document published prior to the international filing date but later than the priority date claimed

- "T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- "X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- "Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- "&" document member of the same patent family

Date of the actual completion of the international search

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28/01/2011

Name and mailing address of the ISA/

European Patent Office, P.B. 5818 Patentlaan 2  
NL - 2280 HV Rijswijk  
Tel. (+31-70) 340-2040,  
Fax: (+31-70) 340-3016

Authorized officer

Veronese, Andrea

# INTERNATIONAL SEARCH REPORT

International application No.  
PCT/US2009/044548

## 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:

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.:

see annex

### 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.

1. **Claims** : 1-18

method for enhancing the nerve blockade without significant toxicity, comprising the administration of a combination of a site I channel local anesthetic and a permeation enhancer as defined in claim 1, and compositions for use in such method.

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2. **Claims** : 19-22

methods for providing local anesthesia comprising the administration of site I sodium channel blocker and a local anesthetic as defined in claim 19, and compositions for use in such method.

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## INTERNATIONAL SEARCH REPORT

International application No

PCT/US2009/044548

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	<p>WO 02/41915 A1 (NANNING MAPLE LEAF PHARMACEUTI [CN]; KANG YUHONG [CN]; SHUM FRANK HAYK) 30 May 2002 (2002-05-30)            See page 4, lines 25-27; claims 1, 14, examples: compositions comprising tetrodotoxin and a permeation enhancer selected among a glycol, oleic acid and an alkyl amine. See also examples comprising tetrodotoxin and propylene glycol, i.e. a permeation enhancer</p> <p style="text-align: center;">-----</p>	1-3,6, 10-15
X	<p>US 6 326 020 B1 (KOHANE DANIEL S [US] ET AL) 4 December 2001 (2001-12-04)            cited in the application            See column 1, lines 9-15, column 2, lines 30-37, figures 2, 9, column 5, lines 45-52, column 7, lines 15-21; claims 1, 2, 17: combinations of site 1 sodium channel inhibitors (e.g. tetrodotoxin and saxitoxin) and local anesthetics (bivucaine, dibucaine etc.)            See figures 9, 10; column 5, lines 4-12; column 8, lines 15-24; ample 4, claims 1, 2, 10, 17, 23: combinations of site 1 sodium channel inhibitors and surfactants (e.g. tween) which are penetration enhancers            See claims 1, 2, 17: combinations of sodim 1 channel inhibitors and vasoconstrictors</p> <p style="text-align: center;">-----</p>	1-6, 10-15
X	<p>DATABASE WPI Week 200627            Thomson Scientific, London, GB; AN            2006-263478            XP002607656            &amp; WO 2006/034624 A1 (HUANG Z)            6 April 2006 (2006-04-06)            See abstract: anesthetic compositions comprising tetrodotoxin and surfactants and amphiphilic lipids, i.e. penetration enhancers</p> <p style="text-align: center;">-----</p>	1-3
Y	<p>AKERMAN B ET AL: "PENETRATION ENHANCERS AND OTHER FACTORS GOVERNING PERCUTANEOUS LOCAL ANAESTHESIA WITH LIDOCAINE"            ACTA PHARMACOLOGICA ET TOXICOLOGICA,            MUNKSGAARD, DK,            vol. 45, no. 1, 1 July 1979 (1979-07-01),            pages 58-65, XP001070299            ISSN: 0001-6683            Dimethylformamide and dimethylacetamide are penetration enhancers which enhance the anesthetic effect of lidocaine</p> <p style="text-align: center;">-----</p> <p style="text-align: center;">-/--</p>	1-18

## INTERNATIONAL SEARCH REPORT

International application No

PCT/US2009/044548

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	FANG ET AL: "Synergistically enhanced transdermal permeation and topical analgesia of tetracaine gel containing menthol and ethanol in experimental and clinical studies" EUROPEAN JOURNAL OF PHARMACEUTICS AND BIOPHARMACEUTICS, ELSEVIER SCIENCE PUBLISHERS B.V., AMSTERDAM, NL LNKD-DOI:10.1016/J.EJPB.2007.02.007, vol. 68, no. 3, 1 March 2008 (2008-03-01), pages 735-740, XP022518690 ISSN: 0939-6411	1-3,6, 10-15
Y	Mentol and ethanol are penetration enhancers which enhance percutaneous penetration and skin analgesia induced by tetracaine	1-18
Y	----- WO 01/41550 A2 (COMPOUNDINGPHARMACIES COM INC [US]; WEPFER SCOTT [US] TRANSDERMATECH I) 14 June 2001 (2001-06-14) See claims, table I and examples: anesthetic compositions comprising an anesthetic agent and a permeation enhancers (e.g. propylene glycol).	1-18
Y	----- WO 93/11798 A1 (ALZA CORP [US]) 24 June 1993 (1993-06-24) See claims and examples 7 and 8: compositions comprising penetration enhancers and anesthetic agents	1-18
E	----- WO 2009/143174 A2 (CHILDRENS MEDICAL CENTER [US]; MASSACHUSETTS INST TECHNOLOGY [US]; KOH) 26 November 2009 (2009-11-26) the whole document	1-18
E	----- WO 2009/143175 A2 (CHILDRENS MEDICAL CENTER [US]; MASSACHUSETTS INST TECHNOLOGY [US]; KOH) 26 November 2009 (2009-11-26) the whole document	1-18
T	----- SAGIE ITAY ET AL: "Prolonged sensory-selective nerve blockade." 23 February 2010 (2010-02-23), PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF THE UNITED STATES OF AMERICA 23 FEB 2010 LNKD- PUBMED:20133669, VOL. 107, NR. 8, PAGE(S) 3740 - 3745 , XP002607657 ISSN: 1091-6490 the whole document	

# INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/US2009/044548

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
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WO 2009143174	A2	26-11-2009	NONE
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WO 2009143175	A2	26-11-2009	NONE
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