Selective Phospholipase A2 Inhibitors of Neurological Diseases

Tech ID: 19964 / UC Case 2009-298-0

BACKGROUND

The past two decades has resulted in a marked increase in our knowledge about phospholipase A_2 (PLA_2) enzymes. The PLA_2 superfamily of enzymes has been divided into four main types: secreted sPLA_2s, cytosolic cPLA_2s, calcium-independent iPLA_2s, and lipoprotein-associated/PAF acetyl hydrolase LpPLA_2s.

The association of the different types of PLA_2s with diverse indications has justified pharma's interest in developing selective inhibitors to the specific types. Undeveloped indications exist in the central nervous system (CNS) and the ability to target these underserved indications would enable a new means for targeting the underlying inflammatory causes of numerous diseases.

TECHNOLOGY DESCRIPTION

Researchers at UC San Diego and their international collaborators have developed a portfolio of issued and pending patents disclosing composition of matter and methods for selectively inhibiting s, i, and cPLA_2s. Compositions span three, distinct chemical classes (amides, oxoamides, and fluoroketones) and proprietary methods claim treatment of various neurological illnesses, including hyperalgesia, multiple sclerosis (MS), and spinal cord injury. More detailed, non-confidential information is available in the Detailed Description.

ADVANTAGES

Proof of concept and IP is available for compositions of matter, target enzymes, and disease applications for novel relatively unexplored targets for a variety of neurological diseases for which good treatment options do not exist.

STATE OF DEVELOPMENT

In vitro and in vivo experiments validate a suite of potent inhibitors of PLA_2, with differential specificity for the sPLA_2, cPLA_2, and iPLA_2. Specifically, sPLA_2 inhibitors markedly improve functional recovery and enhance tissue protection and axon regeneration in the mouse spinal-cord contusion injury model, while cPLA_2 and iPLA_2 inhibitors reduce the severity of disease in a widely used animal model of MS (experimental autoimmune encephalomyelitis, or EAE) and iPLA_2 inhibitors protect in rat models of hyperalgesia.

INTELLECTUAL PROPERTY INFO

Issued and pending U.S. patents include: 7,745,489, 5,464,754, WO/2009/009449, and WO/2008/122119.

Numerous foreign issued patents are available online and unpublished applications are available under confidentiality. See also WO/2010/011686, *Amides as Inhibitors of Human Secreted Phospholipase A2*.

OTHER INFORMATION

See related case SD1998-078 as described in U.S. patent number 7,294,496.

RELATED MATERIALS

- See the inventor's Web site at http://cobra.ucsd.edu.
- Barbayianni E, Stephens D, Grkovich A, Magrioti V, Hsu YH, Dolatzas P, Kalogiannidis D, Dennis EA, Kokotos G. (2009) 2-Oxoamide inhibitors of phospholipase A_2 activity and cellular arachidonate release based on dipeptides and pseudodipeptides. *Bioorg Med Chem* 17(13):4833-43.

CONTACT

University of California, San Diego
Office of Innovation and Commercialization
innovation@ucsd.edu
tel: 858.534.5815.

INVENTORS

- Dennis, Edward A.

OTHER INFORMATION

KEYWORDS

phospholipase A2, PLA2, calcium-independent, cytosolic, secretory, lipoprotein-associated, PAF acetyl hydrolase, inhibitor, inhibition, inflammation, demyelination, multiple sclerosis, spinal cord injury, hyperalgesia, neurogenic disease,, amides, dipeptides, oxoamides, pseudodipeptides, fluroketones, prostaglandins, eicosanoids

CATEGORIZED AS

- **Medical**
  - Disease: Autoimmune and Inflammation
  - Disease: Central Nervous System
  - New Chemical Entities, Drug Leads

RELATED CASES

2009-298-0, 2009-002-1, 2009-002-2, 2007-146-1, 2007-146-2, 2007-145-1, 2007-145-2, 2002-133-1, 2002-133-2, 2002-133-3, 2002-133-4, 1991-A95-1, 1998-078-2

▶ Baskakis C., V. Magrioti, N. Cotton, D. Stephens, V. Constantinou-Kokotou, E.A. Dennis, and G. Kokotos. (2008) Synthesis of Polyfluoro Ketones for Selective Inhibition of Human Phospholipase A_2 Enzymes. *J Med Chem*., 51 (24), 8027-8037.

▶ Lucas KK, Svensson CI, Hua XY, Yaksh TL, Dennis EA. (2005) Spinal phospholipase A_2 in inflammatory hyperalgesia: role of group IVA cPLA_2. *Br J Pharmacol* 144(7):940-52.

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▶ Stephens D., E. Barbayianni, V. Constantinou-Kokotou, A. Peristeraki, D.A. Six,J. Cooper, R. Harkewicz, R.A. Deems, E.A. Dennis, and G. Kokotos. (2006) Differential Inhibition of Group IVA and Group VIA Phospholipases A_2 by 2-Oxoamides, *J Med Chem*, 49 (9), 2821-2828.

▶ Yaksh TL, Kokotos G, Svensson CI, Stephens D, Kokotos CG, Fitzsimmons B, Hadjipavlou-Litina D, Hua XY, Dennis EA. (2006) Systemic and intrathecal effects of a novel series of phospholipase A_2 inhibitors on hyperalgesia and spinal prostaglandin E2 release. *J Pharmacol Exp Ther* 316(1):466-75.

▶ V. Magrioti, G. Kokotos. (2010) Phospholipase A_2 inhibitors as potential therapeutic agents for the treatment of inflammatory diseases, Exp Opin Ther Pat, 20 (1), 1-18.

PATENT STATUS

Country	Type	Number	Dated	Case
United States Of America	Issued Patent	8,580,852	11/12/2013	2009-298

RELATED TECHNOLOGIES

▶ Amide Inhibitors of Human Secreted Phospholipase A2

ADDITIONAL TECHNOLOGIES BY THESE INVENTORS

▶ Amide Inhibitors of Human Secreted Phospholipase A2

University of California, San Diego
Office of Innovation and Commercialization
9500 Gilman Drive, MC 0910, ,
La Jolla,CA 92093-0910

Tel: 858.534.5815
innovation@ucsd.edu
https://innovation.ucsd.edu
Fax: 858.534.7345