# 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 $sPLA_2$s, cytosolic $cPLA_2$s, calcium-independent $iPLA_2$s, and lipoprotein-associated/PAF acetyl hydrolase $LpPLA_2$s.

The association of the different types of $PLA_2$s 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 $cPLA_2$s. 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Numerous foreign issued patents are available online and unpublished applications are available under confidentiality.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

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