



Conotoxins for Pharmaceutical Development

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Field

Biomedical Applications
Drug Discovery
Research Tools and
Instruments

**Patent/Patent Application
Number:**
6,307,014

The recent withdrawal of several COX-2 inhibitors from the marketplace coupled with evidence that even over-the counter analgesics taken in high doses may contribute to cardiovascular disease brings urgency to the need for new pharmaceutical compounds to alleviate pain. One approach exemplified by companies such as Cognetix and Metabolic Pharmaceuticals is the development of peptide toxins that bind to nerve cell receptors originally isolated from snails.

We offer sequence information on several patented conotoxins (U.S. Patent #6,307,014) as well as unpublished sequence information on a number of non-patented toxins as potential lead compounds for pharmaceutical development. While application as analgesics is of particular interest, other uses applications as anti-convulsants and neuroprotectives are possible. We seek to provide an option to license our proprietary compounds to a partner who will examine their usefulness as pharmaceutical lead compounds. In return we would grant an option to license the compounds.

TECHNOLOGY

This information emanates from a research program of Bruce and Barbara Furie at the Marine Biological Laboratory in Woods Hole, MA. Well known for their research in hemostasis and thrombosis at a major Boston teaching hospital, the Furies interest in snail toxins containing gamma-carboxyglutamic acid arises as an offshoot of their studies on vitamin K dependent metabolic pathways. The Marine Biological Laboratory provides excellent access to a variety of marine organisms for this research. The conotoxins of interest all contain α -carboxyglutamic acid (Gla) residues and fall within the definition of conantokins. All are peptides that are small enough for production by chemical synthesis. There is some evidence that at least one residue of Gla is required for their toxic action. The conotoxins inhibit both pre- and post-synaptic current in a cholinergic synapse, most likely by inhibiting calcium ion transport. There is good evidence that this class of conotoxins act as antagonists of the NMDA receptor. Among the patented compounds available are peptides with the following sequences:

Asp-Val-Pro-X1-Ile-Val-Leu-X2-Phe-Met-Cys-Pro-Val-Ile-Cys-Gly-Asn-Gly-Phe-Gly-X3-Glu-Tyr-Cys-Asn-Cys-Thr

Ser-Cys-Asp-Ser-X4-Phe-Ser-Ser-X5-Phe-Cys-X6-Arg-Pro-X7-X8-Ser-Cys-Ser-Cys-Ser-Thr-His-Thr-Cys-Cys-His-Trp-Ala-Arg-Arg-Asp-Gln-Cys-Met-Lys-Pro-Gln-Arg-Cys-Ile-Ser-Ala-Gln-Lys-Gly-Asn

Arg-X9-X10-Cys-Cys-Ser-Asp-Pro-Arg-Cys-Asn-Ser-Ser-His-Pro-X11-Leu-Cys-Gly Gly-Cys-Asn-Asn-Ser-Cys-Gln-X12-His-Ser-Asp-Cys-X13-Ser-Hys-Cys-Ile-Cys-Thr-Phe-Arg-Gly-Cys-Gly-Ala-Val-Asn

Cys-Ile-Pro-Gal-Gly-Ser-Ser-Cys-Ser-Ser-Ser-Gly-Ser-Cys-Cys-His-Lys-Ser-Cys-Cys-Arg-Trp-Thr-Cys-Asn-Gln-Pro-Cys-Leu

Gly-Met-X14-Gly-X15-Cys-Lys-Asp-Gly-Leu-Thr-Thr-Cys-Leu-Ala-X16-Ser-
X17-Cys-Cys-Ser- X18-Asp-Cys-X19-Gly-Ser-Cys-Thr-Met-X20

X21-Cys-Cys-X22-Asp-Gly-X23-Cys-Cys-Thr-Ala-Ala-X24

Ser-Cys-Ser-Asp-Asp-Trp-Gln-Tyr-Cys-Gla-Ser-X25-Thr-Asp-Cys-Cys-Ser-
X26-Asp-Cys-Asp-Val-Val- Cys-Ser

Ala-X27-Cys-His-X28-Cys-X29-Phe-Gla-Tyr

Asn-Cys-Ser-Asp-Asp-Trp-Gln-Tyr-Cys-Gla-Ser-X30-Ser-Asp-Cys-Cys-Ser-
X31-Asp-Cys-Asp-Val-Val-Cys-Ser

Leu-Cys-X32-Asp-Tyr-Thr-X33-X34-Cys-Ser-His-Ala-His-X35-Cys-Cys-Ser-
X36-Asn-Cys-Tyr-Asn-Gly-His-Cys-Thr-Gly

Where at least one X in each peptide is Gla.

INVENTOR(S):

Furie, Bruce; Furie, Barbara C.; Stenflo, Johan; Rigby, Alan C.; Roepstorff, Peter