Peptide leads new class of chronic pain drugs

For the past 40 years, there has been no major addition to the repertoire of drugs for treating severe, chronic pain. Nonsteroidal anti-inflammatory drugs, including COX-2 inhibitors, or opioids have been the treatments of choice. Now, two drugs with a completely different mechanism of action, targeting N-type calcium channels, namely Elan's peptide ziconotide (Prialt) and Pfizer's small molecule pregabalin (Lyrica), are making their market debuts in the US and Europe—milestones that have received remarkably little attention. Although these drugs may change the way pain is treated, several competing companies are at work to develop orally available small molecules that promise, in particular, fewer side effects than ziconotide.

On February 22, the European Commission approved the first peptide, ziconotide, a month after its US debut. Ziconotide's approval for chronic pain "paves the way for the next generation of pain killers," says Joseph McGivern, principal scientist at Amgen of Thousand Oaks, California. A peptide derived from the venom of a fish-hunting Pacific Ocean cone snail, ziconotide was isolated by Salt Lake City-based University of Utah scientists in 1979 but never patented. The biotech company Neurex in Menlo Park, California, which was acquired by Irish biopharmaceutical company Elan of Dublin in 1998, developed a synthetic version and brought it to the clinic.

Ziconotide's approval "is probably the ultimate proof of concept of a new mechanism of action for targeting neuropathic and chronic pain," says Terrance Snutch, CSO at Canadian pain therapeutics company Neuromed in Vancouver, British Columbia. Neuropathic pain—which is arising from nerve injury—affects over a million North Americans, and no good treatment exists. (Morphine and other opioids are usually ineffective.) Chronic, inflammatory pain affects millions more. Ziconotide, approved for severe chronic pain resistant to other treatments, specifically targets N-type calcium channels, which are crucial for transmitting pain signals from sensory neurons to the spinal cord and then to the brain. A thousand times more potent than morphine, ziconotide works by preventing neurotransmitter release at the synapse, thus blocking pain sensation.

Although ziconotide is likely to bridge a gap in the pain market segment, other players should eventually supersede this new biotech drug because of its delivery system—a pump implanted in the patient's spinal cord. Because of this restriction, Elan estimates peak sales for ziconotide at only $150–250 million per year. By comparison, the new neuropathic pain treatment pregabalin (Lyrica), which was approved for post-herpetic neuralgia and diabetic neuropathy, has the potential to reach $2.7 billion in sales. That's what blockbuster epilepsy drug gabapentin (Neurontin), a less potent version of pregabalin developed by New York-based Pfizer, achieved in 2003, before going off-patent. Both target N-type calcium channels but work differently from Elan's peptide.

Already companies are aggressively developing competing products (see **Table 1**). Elan biochemist and research fellow George Miljanich in S. San Francisco, California, who conceived the idea of using the original snail toxin to treat pain, predicts that ziconotide is destined for replacement by future small molecules offering "a quantum leap in improvement." McGivern agrees: "All the companies are in a race to identify the small molecule drug that would make it to the market first". Orally bioavailable small molecules should be superior painkillers, he adds. With the most advanced small molecule N-type calcium channel blocker in phase 1, however, products are still many years away.

Pacific Ocean cone snail whose venom was the basis for the new pain drug ziconotide

One of the strategies competitors could adopt is to try and reduce the toxicity of ziconotide. Indeed, though it lacks morphine's addictive potential and tendency to depress breathing, ziconotide can have some severe side effects, mainly neuropsychiatric disturbances, as well as confusion, nausea and dizziness. That's mainly because the drug sits on calcium channels, blocking not only pain transmission but also other nerve functions. In theory, small molecule N-type calcium channel blockers should avoid the worst of these side effects, because they're 'state-dependent'—they act only on nerves that are firing in response to painful stimuli.

Another target of interest is the voltage-gated sodium channel known as Nav1.8. Unlike a calcium channel block, which stops the pain signal at the synapse, blocking Nav1.8 prevents the nerve from firing to begin with. "If you can get sufficiently selective and potent blockers, you should be able to knock out the pain signal with out getting any of the side effects that are often associated with sodium channel block," says Iain James, director of drug discovery at Ionix Pharmaceuticals in Cambridge, UK. Barry Berkowitz, CEO of Scion Pharmaceuticals in Medford, Massachusetts, fully expects ion channel blockers to provide "the next generation of compounds" for pain.

Ken Garber, Ann Arbor, Michigan

Table 1 Companies targeting N-type calcium channels for pain

Company	Compound	Stage
Elan	Prialt (ziconotide; synthetic conopeptide)	Approved, Dec. 2004
Pfizer	Lyrica (pregabalin; alpha2-delta ligand)	Approved, Dec. 2004
Amrad (Melbourne, Australia)	AM-336 (synthetic conopeptide)	Phase 2[b]
Neuromed	NMED-1600, small molecule	Phase 1
Ionix	IX-2000, small molecule	Preclinical
Scion	SCI-860, small molecule	Preclinical
Astra-Zeneca[a] (London)	Small molecule	Undisclosed
Merck[a] (Whitehouse Station, New Jersey)	Small molecule	Undisclosed

[a]Compound patents and/or patent applications recorded, but programs unconfirmed. [b]Suspended since 2003, up for licensing.