

Neuropathic Pain Treatment Gives Avigen New Lease on Life and Neuromed Follows the Snail Trail

Wendy Wolfson

DOI 10.1016/j.chembiol.2007.04.003

Pain is one of the body's main warning systems, but when nerves malfunction, they may spontaneously amplify benign stimuli such as heat, cold, and light pressure, generating pain signals. This becomes a debilitating condition known as neuropathic pain, usually associated with nerve trauma or diseases such as diabetic neuropathy, multiple sclerosis, viral infections, or the course of cancer chemotherapy. It can also follow injury to the spinal cord or damage from a stroke. Recent studies suggest that the functional

from neuropathic pain have fewer options. First-line drugs such as anticonvulsants, local anesthetics, and some types of antidepressants are of limited effectiveness.

Treatment by Trial and Error

"In all those classes, the very best [patient] response rate is one in three," said Dr. Clifford Woolf, M.D., Ph.D., professor of anesthesia research, Department of Anesthesia and Critical Care at Massachusetts General Hospital and Harvard Medical School.

While a roster of drugs including opioids and nonsteroidal anti-inflammatories are deployed for the acute, inflammatory pain that occurs after injury or surgery, people who suffer from neuropathic pain have fewer options.

pain disorder fibromyalgia also has a neuropathic pain component.

Neuropathic pain can also emerge when "you lose a limb," said Allan Basbaum, Ph.D., professor and chair of the Department of Anatomy, University of California, San Francisco. "Everybody has a phantom. But in about 20% of people, the phantom doesn't disappear. Instead, patients are left with severe pain in the phantom limb. The pain arises from a combination of hyperactivity of the damaged nerves in the stump and a maladaptive alteration of nervous system circuits in the central nervous system (spinal cord and brain)." According to Basbaum, neuropathic pain may eventually resolve in some people, but it is often a chronic condition.

While a roster of drugs including opioids and nonsteroidal anti-inflammatories are deployed for the acute, inflammatory pain that occurs after injury or surgery, people who suffer

"We have no predictors of who comes into the office, who will respond. There is a big gap in our knowledge."

All the pharmaceutical companies and many biotech have discovery programs aimed at various pain targets including cation channels, neural transmission and signaling pathways (kinases). "In some cases, neuropathic pain may have a neurodegenerative component," Woolf said. "There are multiple mechanisms that operate. The solutions can be diverse as well." Research by Alameda, California-based Avigen (<http://www.avigen.com>) and Neuromed (<http://www.neuromed.com>) in Vancouver, British Columbia, may offer some novel alternatives in the near future.

Balancing the Immune and Neural Responses

Avigen estimates the chronic pain relief market in the U.S. and Europe to be worth about \$3 billion. The company

hopes its lead product, AV411, a small molecule oral drug for neuropathic pain, can take a share. AV411 attenuates the signaling function of the spine's glial cells. Its generic name is ibudilast (3-isobutyl-2-isopropylpyrazolo[1,5-a]pyridine). A nonselective phosphodiesterase (PDE) inhibitor approved in Japan for treatment of bronchial asthma and post-stroke dizziness, ibudilast (now off-patent) inhibits the production of pro-inflammatory cytokines, including tumor necrosis factor α and interleukin 1 β , and increases output of anti-inflammatory cytokine interleukin 10 (IL-10) as well as certain neurotrophic factors. Pro-inflammatory cytokines are a family of proteins released by activated immune cells that communicate with white blood cells. Another company, MediciNova, is testing ibudilast in Eastern Europe as a treatment for multiple sclerosis. AV411 is now in a phase II trial in Australia (which recognizes Japanese drug designations), and is undergoing a phase I trial in the U.S.

According to Dr. Linda Watkins, professor and researcher in the University of Colorado at Boulder's Psychology Department and Center for Neuroscience, some pain is simply not attributable to nerve damage. Moreover, some patients do not respond to opiates, which work directly on the pain centers in the brain. "We started with the idea that there was another player," said Watkins. Building upon research by Garrison and colleagues from the 1990s showing that astrocytes and microglia in the spinal cord were activated by damage to the sciatic nerve and caused neuropathic pain symptoms, Watkins's group found that pain triggers glial cells to release a cascade of pro-inflammatory cytokines [1].

According to Kirk Johnson, Ph.D., vice president of research and development at Avigen, stimulated glial cells produce pro-inflammatory cytokines and chemokines such as IL-1, IL-6, IL-8, and MCP-1. Natural counterbalances include IL-1 receptor antagonist and IL-10. An anti-inflammatory regulator for many of the pro-inflammatory cytokines, IL-10 reduces glial activation and attenuates chronic pain. Johnson's group looked for an oral pharmaceutical that would duplicate these effects and found it in ibudilast.

That Burning Sensation

Founded in 1992, Avigen, a public company, focused on gene therapy for its first decade but concluded that it wouldn't work fast enough to make the fortunes of a small company. In 2003, Avigen faced a crossroads. Ken Chahine, Ph.D., J.D., Avigen president and CEO, lobbied the board to divest itself of the gene therapy business before they burned through all of their cash. They sold their Parkinson's disease and hemophilia intellectual property to Genzyme for \$12 million in cash up front and milestone payments. To replace its pipeline, Avigen focused on acquiring small molecule and biological neurology products.

In 2006, the company in-licensed formulations of AV650, (tolperisone), a non-sedating drug approved in Europe for neuromuscular spasms and spasticity caused by spinal cord injury and multiple sclerosis, from Sanochemia. Avigen is developing the drug into a slow-release formulation, so that patients can sleep through the night without muscle spasms. So far, Avigen has conducted a 12 week phase I safety and efficacy trial. Broadening their pipeline, Avigen's AV513, a sulfated carbohydrate for hemophilia A and B, is entering clinical trials. The company intends to bring AV513 to phase II and then license it to a pharmaceutical company. AV333 is a preclinical, plasmid-based DNA therapy that when injected into the spinal cord induces production of IL-10. "It is not an insignificant candidate because its efficacy is substantial for intractable chronic pain," says Johnson.

Newly restyled, Avigen's burn rate of \$18 million in 2005 and 2006 is expected to rise to about \$20 million in 2007, due to the clinical trials the company is conducting. "A key thing is to make decisions when you still have money," said Chahine. "You need some runway." At the end of 2006, Avigen received another \$19 million from a private placement with investors, bringing the company to about \$70 million in cash in the bank, off-setting an accumulated deficit of \$195 million.

For Neuromed, Blocking Channels Is Blocking Pain

North of the border, Neuromed makes small molecule drugs based on what the company terms a selective calcium channel inhibitor. Neuromed looks at two of the five pharmacological classes of calcium channels found in the body for analgesia: N-type in the nervous system and T-type in the heart and nervous system.

Neuromed was launched in 1994, but the company's turning point was a major licensing deal with Merck in 2006 for its N-type channel inhibitors, consisting of \$25 million up front and a potential \$450 million in milestone payments, the largest such deal ever for a Canadian biotech. Neuromed's lead compound, NMED-160 (MK-6721), now in phase II development for the treatment of neuropathic pain, is not expected to hit the market before 2011. Neuromed is also internally developing T-type channel inhibitors.

According to Dr. Christopher Gallen, Neuromed president and CEO, drugs like Procardia (Nifedipine), a channel blocker taken for high blood pressure, were identified in the 1970s and 80s by serendipity, but because nobody knew how to design selective calcium channel blockers, there was not a second crop of follow-on molecules. The company's intellectual property is based on the work of Dr. Terrance Snutch, professor in the Departments of Zoology and Psychiatry and the Brain Research Centre at University of British Columbia and chief scientific officer at Neuromed. Snutch cloned the genes encoding the various calcium channels important in the brain and heart. Because the crystal struc-

tures of these channel proteins are unknown and the requirement for patch clamp electrophysiology assays made it impossible to do mass library screening, Snutch developed what became Neuromed's compounds by examining known inhibitors and finding a common pharmacophore. It took several years for Snutch to learn how to reverse engineer molecules to produce blockers selective for the N-type and the three T-type calcium channels.

Watch Out for That Snail

Ziconotide (Prialt), a painkiller marketed by Elan Pharmaceuticals, set the stage for developing channel blockers as analgesics. [2] Prialt's active ingredient is a synthetic version of a peptide derived from a conotoxin found in the venom of the *Conus magus* snail (see cover of this issue); it is the first N-type channel antagonist that worked powerfully against both neuropathic and inflammatory pain. However, as a large protein, Prialt needs to be injected into the spine with a pump. It also causes loss of muscular coordination, delirium, and psychosis in patients, as well as influencing blood pressure. To develop a small molecule, oral drug that would relieve pain with fewer side effects, Snutch designed a small molecule that selectively blocks the N-type calcium channel when it is in the configuration it assumes when highly stimulated by pain.

Neuromed was initially funded by local Vancouver venture capitalists and later involved U.S. venture capitalists in the Series C round led by MPM Capital. The company has undergone four rounds of financing for a total of U.S. \$74 million. The company currently has about \$50 million in the bank and remains privately held.

Pinpointing Where It Hurts

Over the next few decades, the real hope for treating neuropathic pain patients is the ability to determine which drugs will work for individuals. "One (issue) is to better understand the mechanisms of neuropathic pain, particularly the pathophysiology," said Dr. David Simpson, director, Clinical Neurophysiology Laboratories, Neuro-AIDS Program, Mount Sinai Medical

Center. “The other issue is to try to understand the particular disease state...whether we can identify or not the specific mechanism in neuropathic pain in a specific patient. There may be more than one mechanism in a disease or even in a given patient, but right now we don’t have those tools available to

identify those mechanisms that are operative in a given patient’s pain syndrome.” With the goal of treating every pain patient, not just one in three, companies like Avigen and Neuromed are exploring these questions, and pharma companies are lining up to invest in promising answers.

REFERENCES

1. Watkins, L., Milligan, E.D., and Maier, S.F. (2001). *Trends Neurosci.* 24, 450–455.
2. Snutch, T.P. (2005). *NeuroRx* 2, 662–670.

Wendy Wolfson (wendywolfson@nasw.org) is a California-based science and technology writer.