

Device Investors Look for Gains in Pain

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Summary: In 2009, investors quietly invested in seven different start-ups developing devices for pain. Why the sudden interest? Interventional pain is on the rise as a specialty, large numbers of patients with chronic pain need better therapies, and relative to other emerging device sectors, pain offers large markets but lower clinical, regulatory and market risks.

Further Analysis:	Title	Magazine	Issue	Article ID
	Vertos Medical's Blue Ocean Opportunity	<i>IN VIVO</i>	Dec. 2009	<u>2009800223</u>

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Device Investors Look for Gains in Pain

Interventional pain is on the rise as a specialty and it's presenting investors with an attractive large market offering unmet needs, and, relative to other emerging medical device opportunities, a lower degree of risk.

by Mary Stuart

Last year investors demonstrated their interest in pain, funding seven device start-ups working in chronic pain.

Devices could play a crucial role in fighting chronic pain, especially for certain conditions where drugs are ineffective or pose unacceptable side effects. This is especially true for the elderly, the population that suffers the most from chronic pain.

Large device companies selling neurostimulation devices and implantable drug pumps have demonstrated that pain is a substantial market, offering double-digit growth in revenues.

For venture investors, this established revenue path opens doors to potential customers and lowers regulatory and reimbursement risks, with small and manageable clinical trial populations and shorter follow-up periods.

Venture capitalists have endured their fair share of pain over recent years, at least in a financial sense. But their discomfort completely pales in comparison to those millions of people across the globe who must endure the misery of chronic pain or suffer from the side effects of the drugs they take to relieve it. So it's fitting that venture device investors might find relief from their own fiscal and regulatory misery by investing in companies that someday might help those people forced to live with the real thing.

Venture capitalists clearly see huge potential. In the past year, according to Elsevier's *Strategic Transactions*, 20 pharmaceutical companies and seven medical device companies with products that promise some pain relief raised money from private investors. (See Exhibits 1 and 2.) No doubt, most investors have firsthand knowledge of someone dealing with pain, and the pain population is growing as the general population ages. In the US, 75 million people suffer from chronic pain, defined as pain that last for more than three months. Back pain caused by injury or degenerative disease is common, as is neuropathic pain that follows the incidence of diabetes. Post-surgical pain, long-term pain following limb amputation, tunnel syndromes (like carpal tunnel), and cancer are other conditions causing intractable pain. Enormous numbers of patients suffer from chronic pain and many of them are not well served by existing drug or device treatments. This treatment regimen for pain is riddled with gaps and holes that venture capital-backed start-ups can address. "One, pain is chronically undertreated, and we're looking for ways to successfully treat patients," says Casey J. O'Donnell, DO, a physiatrist and board-certified pain physician at the NEA Interventional Pain Management Center in Warwick, RI. "Two, we're finding out more about current medications, their side effects and how they interact with each other, and in particular, as patients get older, they are more sensitive to opioids and anti-inflammatory drugs, which can affect multiple organ systems. Three, a lot of patients don't want to take medications all the time. They want to function without taking a pill bottle wherever they go." Finally, some pain indications are notoriously difficult to treat with oral medications; failed back or neck surgeries, complex regional pain syndrome, phantom pain from an amputation and severe peripheral neuropathy from diabetes or chemotherapy, to name just a few, and that creates an opening for interventional approaches, O'Donnell says.

Exhibit 1

Recent Private Financings of Pain Pharmaceutical Companies

COMPANY FINANCING DATE AND AMOUNT RAISED	DESCRIPTION/INVESTORS
Wax Pharmaceuticals (01/10) Raised \$31.9mm from rights offering	Developing candidates for pain and drug addiction including tetrodotoxins for cancer pain and chemotherapy-induced neuropathic pain
Afferent Pharmaceuticals (12/09) Raised \$23mm in Series A	P2X3 antagonists (P2X3 receptors are expressed specifically in C-fiber afferent neurons) licensed from Roche/Third Rock Ventures, Pappas Ventures, Domain Associates, New Leaf Venture Partners
Zogenix (12/09) Closed second tranche of Series B, total raised is \$71mm	Specialty pharma improving upon existing CNS and pain drugs; ZX002 is a novel controlled-release formulation of hydrocodone for chronic pain
NeuroAxon (12/09) Raised \$8.75mm from convertible debt financing	Neuronal nitric oxide synthase inhibitors for pain/Delphi, OrbiMed, Ventures West Capital, HIG Ventures, BDC Venture Capital, NeuroVentures Fund, and NeuroAxon's CEO Lawrence Block
SantoSolve AS (11/09) Raised \$5.5mm from Series C	Topical analgesics based on non-radioactive strontium for pain/Teknovest, InnovationsKapital, Investinor
AcelRx (11/09) Raised \$14.8mm in Series C	NanoTab is drug formulation for transmucosal drug delivery system used with pre-programmed handheld device that provides patient-controlled analgesia; lead candidates are ARX01 for acute postoperative pain and ARX02 for breakthrough cancer pain/Eight undisclosed investors (Three Arch, Alta, Skyline Ventures, Kaiser Permanente Ventures and Pinnacle Ventures participated in Series A and B)
GRxPharma (11/09) Raised \$20.2mm from rights issue and private placement	Developing combinations of existing products for CNS disorders including MoxDuo IR, an immediate-release version of oxycodone and morphine for acute pain
Labopharm (11/09) Raised \$24mm under SEDA (standby equity distribution agreement).	Specialty pharma improving on existing formulations of pain and other CNS drugs
Xanodyne Pharmaceuticals (10/09) Raised \$87.8mm	Fast-acting diclofenac pain treatment Zipsor (NSAID) and XP20B (opioid)/25 investors lead by MPM Capital and existing backers AIG Investments, Aising Capital, Blue Chip Venture, Essex Woodlands, HealthCare Ventures, Union Springs
Javelin Pharmaceuticals (10/09) Raised \$3.8mm from registered direct offering to one investor	Reformulates existing drugs for the treatment of pain
KemPharm (09/09) Raised \$3.9mm from Series B	Ligand Activated Therapy improves upon existing pain drugs/DeWay Investment Partners and individuals
Durect (09/09) Raised \$10mm from private placement	Oral, transdermal and injectable pain drug delivery systems/Venrock Healthcare Capital Partners and VHCP Co-Investment Holdings
China Axon Pharmaceutical (08/09) Raised \$5mm	Manufactures opioids
GW Pharmaceuticals (08/09) Nets \$10.7mm from private placement	Cannabinoid-based therapies for cancer pain/Great Point Partners, M&G Investment Management
Limerick BioPharma (07/09) Raised \$15mm from Series C	Adjunctive drugs for the mitigation of opiate side effects/OVP Venture Partners, ARCH Venture Partners, Sevin Rosen Funds, Altitude Funds
Origin BioMed (04/09) Raised \$3.3mm in Series C	OTC natural products including <i>Neuragen</i> , a topical pain reliever for pain associated with fibromyalgia, diabetic neuropathy and post-shingles nerve pain
Vernalis (04/09) Raised \$29.4mm from open offer to qualified investors	V3381 for neuropathic pain has dual action (NMDA antagonist and MAO-A inhibitor) that modulates pain at both central and peripheral sites, and V158866 (Fatty Acid Amide Hydrolase) for chronic pain
Orthocon (04/09) Raised \$25mm from B round	Implantable devices designed to deliver therapeutics to bone to stop bleeding and relieve pain/ProQuest Investments, Canaan Partners, BB Biotech Ventures
Ikano Therapeutics (03/09) Raised \$9mm from Series B	Nasal delivery platform focused on seizures and pain/SV Life Sciences, Burnil & Co., Tullis-Dickerson, Fidelity Biosciences, Apjohn Ventures, Fort Washington Capital, Commonwealth Seed Capital, Kentucky-Co-Investment Partners
Hydra Biosciences (01/09) Raised \$22mm in Series D	Ion channel therapeutics for pain, inflammation and pulmonary diseases/MedImmune Ventures, Advanced Technology Ventures, Abingworth, Polaris, BioVentures, Biogen Idec New Ventures, Lilly Ventures

SOURCE: Medtech Insight; Elsevier's *Strategic Transactions*

Exhibit 2

Recent Private Financings of Pain Device Companies

COMPANY FINANCING DATE AND AMOUNT RAISED	DESCRIPTION/INVESTORS
Spinal Modulation (11/09) Raised \$27.4mm in Series C	Next-generation spinal cord stimulator for chronic pain/Johnson & Johnson Development Corp., DFJ InCube, Raffle Venture Partners, De Novo, DFJ ePlanet, Kleiner Perkins Caufield & Byers and MedVenture Associates
Neuros Medical (08/09) Raised \$1.3mm in Series A	Peripheral nerve stimulation, initial application is residual limb pain/North Coast Angel Fund, Glengary Ohio Tech Angel Fund, Queen City Angels First Fund III and individuals
Current Solutions (08/09) Raised \$4.1mm in Series A	Established in July 2009 to acquire Koalaty products; wholesale distributor of electrotherapy devices including TENS and EMS./Advantage Capital, Texas Certified Capital, Focus Strategies Investment Banking and individuals
Relieva Medsystems (07/09) Raised \$20mm in Series C	Minimally invasive radiofrequency device for chronic back pain/Morgenthaler, Emergent Medical Partners, Canaan Partners, Onset Ventures
Palyon Medical (04/09) Raised \$24mm in Series A	Programmable implantable intrathecal drug delivery device based on IP licensed from Fresenius/Baird Venture Partners, Hambrecht & Quist Capital Management, Fountain Healthcare Partners, BB Biotech Ventures, Cross Atlantic Partners, Arcus Ventures, Nextech Venture
MicroTransponder (03/09) Raised \$2.2mm in Series A	Minimally-invasive, wireless peripheral nerve stimulation for chronic pain has implants small enough to be placed anywhere in the body
ReGear Life Sciences (03/09) Raised \$2.5mm in Series A	ReBound is small portable warming system licensed from the US Navy that incorporates radiofrequency to generate heat deep within tissue for osteoarthritis pain, fibromyalgia, carpal tunnel syndrome, wounds, back pain, and chronic pain/Stonewood Capital Management, individual investors (Innovation Works and Pittsburgh Life Sciences Greenhouse invested prior to Series A)
Nervo Corp. (10/08) Raised \$22mm in Series A	Formerly NEI Development; undisclosed implantable neuromodulation device/Accuitive, Aberdare, Bay City Capital, Mayo Clinic, MPM Capital, Three Arch Partners

SOURCE: Medtech Insight; Elsevier's Strategic Transactions

It's clear that pharmaceuticals aren't providing the ideal solution. Yet, people suffering with pain are always steered toward medication first, initially over-the-counter non-steroidal anti-inflammatory drugs (aspirin and ibuprofen, for example). These first-line medications bear gastrointestinal, renal and cardiovascular side effects, or, in the case of acetaminophen, the risk of liver toxicity. If pain continues to defy management, then patients are prescribed stronger drugs from the opioid class, high doses of which can lead to respiratory depression and death. Opioids can also cause cognitive impairment, nausea, and constipation, and of course, are highly addictive. Yet even with those potentially dangerous and certainly uncomfortable side effects, the pain relief market is a huge, multi-billion dollar opportunity. This explains the high level of interest of pharmaceutical companies in finding novel targets and novel drugs.

Device investors see the prevention of side effects as a clear opportunity. The device market for pain relief products is already huge. In fiscal 2009, **Medtronic Inc.**, selling both spinal cord stimulators and pumps for intrathecal (inside the spinal canal) drug delivery, reported more than \$1.1 billion in revenues for its neuro-implantables division, encompassing pain management and movement disorders, a 7% increase over last year. **St. Jude Medical Inc.**, which entered the neurostimulation market with its acquisition of Advanced Neuromodulation Systems, chalked up \$331 million in sales of spinal cord stimulation devices for chronic pain in 2009, a 30% increase over the prior year. [W#200510185] **Boston Scientific Corp.**, selling neurostimulation devices for pain it acquired as part of **Advanced Bionics Corp.**, sold \$245 million in spinal cord stimulators in 2008, up 20% from the previous year. [W#200410130]

In the area of radiofrequency nerve ablation, a minimally invasive option for chronic pain, **Smith & Nephew PLC** and **Stryker Corp.** have established themselves with interventional pain physicians, and now **Kimberly-Clark Corp.** joins them. In 2009, Kimberly-Clark purchased the pain management business of **Baylis Medical Co. Inc.**, a manufacturer of radiofrequency ablation systems for chronic pain, a transaction that serves the company's interest in "the higher-growth, higher-margin medical device market," the company said in a press release. [W#200910121]

Devices Move Up the Treatment Continuum

As always, medical device investors think they've found technology and tools that can do the job better. On the whole, the recently funded ventures hope to make payors happy, with new devices that aim to improve

upon the efficacy of existing categories of devices, including neurostimulators and pain pumps. But device investors and start-ups hope to do more than improve on existing treatments. Instead of serving as a last line of treatment for patients failed by drugs and surgeries, many of the devices under development could become options for early intervention. **Relieva Medsystems Inc.** hopes to avoid or delay surgery for patients suffering from back pain. Its nerve ablation therapy in development can be delivered via a needle to a novel pain target in the vertebral bodies. The company hopes the low degree of invasiveness of its therapy may even bump it up to a major therapeutic option, after NSAIDs and before opioids, and delay or even obviate the need for other spine procedures. Operating in peripheral nerve stimulation, **Neuros Medical Inc.** and **MicroTransponder Inc.** believe that smaller, less invasive devices may also get to play a role in early intervention for chronic pain.

Spinal Modulation Inc. and **Palyon Medical Corp.** both aim to take advantage of existing markets. Spinal Modulation has a plan to address many of the shortcomings of current spinal cord stimulators. Palyon has staked out intrathecal drug delivery, a market in which today there is really only one player which is offering, Palyon says, a technology that is basically ten years old, despite its incremental improvements over the years. With a platform in-licensed from giant infusion expert **Fresenius Medical Care AG** (a division of **Fresenius SE**), Palyon will take on Medtronic. Michael Liang, PhD, a principal with Palyon's investor Baird Venture Partners says that with a new product with an improved feature set, Palyon will be in a good position to take a share of a market that brought Medtronic \$375 million last year from one product.

Lower Clinical Risk, Growing Specialty

Investors may have turned to pain in 2009 because of its relative attractiveness compared to more risky medical device applications. In the pain pump market, for example, Palyon's clinical trial endpoints are not complicated. The company will simply need to demonstrate safety, and that it delivers the proper dose of morphine. Investors are skittish in the current investment environment. "Right now we don't want to take on large studies with undefined endpoints that could be moving, or where it's hard to triangulate what subset of patients is going to hit those endpoints," Liang says. "That makes things more complex and introduces a high degree of variability as to whether you are going to hit those endpoints or not." Liang says he has confidence that Palyon will be able to hit its fairly straightforward endpoints. David Wood, CEO of Spinal Modulation says he saw in chronic pain an opportunity that connected all the dots. "Is there a big clinical need? Is there a novel, proprietary technology? Is there a pathway through the regulatory agency, and at the end of the day do you think you can get reimbursement?" In chronic pain, he says, Spinal Modulation can check all the "yes" boxes.

Pain device companies might also benefit from a growing interventional pain specialty that could offer a clear-cut call point for sales representatives. Such practices provide a variety of pain management techniques, including the implantation of spinal cord stimulators, epidural injections, nerve ablation procedures, drug pump implantation procedures, and in some cases, even kyphoplasty and vertebroplasty spine procedures. Today a sub-specialty populated by anesthesiologists, physiatrists, and to a lesser degree, interventional radiologists, neurosurgeons and orthopedic or spine surgeons, the American Board of Pain Medicine is actively campaigning to designate pain medicine as a primary medical specialty. The field is growing; at the most recent meeting of the American Society of Interventional Pain Physicians, 450 physicians were in attendance. Thus, while patients with chronic pain are found in a variety of medical specialties, for example, orthopedics, oncology, endocrinology and surgery, ultimately there is a cohesive group of treating physicians for companies to target with their sales and marketing efforts, and companies like Medtronic, St. Jude Medical, Boston Scientific, Smith & Nephew, and Stryker have already created the pathway. From the clinical standpoint, Dr. O'Donnell, the physiatrist and board-certified pain physician at the NEA Interventional Pain Management Center, says the emergence of this specialty will help get patients with chronic pain into treatment earlier. Referring doctors, he says, "are beginning to understand that pain is complex and that there are more and more treatment options available, which require the input of pain management specialists. This is good, because the earlier we see the patient, the more likely they are to have a successful outcome with the treatment." O'Donnell adds that there are now numerous options to help avoid the overuse and misuse of

opioids, and that's where devices can play a crucial role.

Improving Upon Spinal Cord Stimulation

As noted, spinal cord stimulation for chronic pain has become a successful product area for Medtronic, St. Jude Medical, and Boston Scientific, which together are producing more than \$1 billion in revenues from these implantable devices in a market that's growing by 15-20% a year, as they serve patients at the end of their rope after failing back surgery and pain medications.

Spinal cord stimulation (SCS) has been around for some 40 years. The therapy works by blocking the transmission of pain through sensory nerves. SCS devices have several components: electrodes that deliver electrical stimulation to tissue (which are placed via epidural access on the dorsal column by anesthesiologists, physiatrists, neurosurgeons and other pain physicians in interventional pain practices); small electrical impulse generators, usually implanted in the abdomen, posterior gluteal area or the left chest; leads that connect the electrodes and the generator, and an external controller that allows patients to control the device. SCS is indicated for intractable pain of the trunk or limbs. As the electrical stimulation therapy interrupts pain signals going to the brain, patients feel a tingling sensation, known as paresthesia, instead of pain.

Although the SCS category is successful, spinal cord stimulation devices still have drawbacks, which Spinal Modulation has set out to address.

Spinal Modulation President & CEO David Wood says that SCS is life-changing in patients for whom it works. Chronic pain can create a high degree of disability—sleeplessness, anxiety, depression, and lost days of work leading to \$100 billion in costs related to loss of productivity and litigation, according to estimates by Boston Scientific. For many patients, SCS can restore a good quality of life to patients in whom nothing else has worked. But not as many as one would like. Overall success rates for SCS are 25-30%, if one considers the pool of patients who are originally candidates for SCS and the long-term success rates.

Built into the SCS paradigm is an initial screening step to determine which patients might benefit. Before a patient is permitted to have surgery, he or she first undergoes a one week trial with percutaneous leads attached to an external device to make sure that spinal cord stimulation will result in pain relief. This step helps avoid \$30,000 in costs (for the implanted devices and the procedure) for patients unlikely to benefit, which makes payors happy. At that initial screening, approximately 50% of patients drop out. Of the 50% who continue on to the surgical implantation of the therapy, 50% of those fail over the long-term, according to Wood, a success rate that could stand some improvement.

Spinal Modulation was founded in 2004 by Daniel Kim, MD, a neurosurgeon at **Stanford University**, and Mir Imran, founder of medical device incubator InCube Labs and more than 20 life science companies. Initially funded by De Novo Ventures, DFJ ePlanet, Kleiner Perkins Caufield & Byers and MedVenture Associates, in 2009 Spinal Modulation raised a \$27.4 million Series C financing round from original investors and new investors Johnson & Johnson Development Corp., DFJ InCube Ventures and Raffles Ventures Partners. [W#200930596] Although the Series C round readies the company for clinical trials, it is still in stealth mode. Wood says he can't talk about the specifics, but he outlines the areas where current spinal cord stimulators have problems that Spinal Modulation aims to solve.

There are a number of reasons why spinal cord stimulation fails, according to Wood. It can be difficult to place the leads in such a way as to target specific anatomy with the goal of stimulating sensory, but not motor fibers. Also, leads can migrate. "There are millions of sensory fibers within the spinal cord and you are trying to pick out the ones associated with the pain. It is a very challenging targeting process," Wood says, relying on the accurate placement of leads and programming combinations of electrodes to fire on specific nerves. "If your knee hurts, and the lead is not placed precisely, you can create paresthesia [numbness or tingling] over the entire leg or both legs which can be an undesirable side effect." An even worse problem can occur when

electrodes stimulate not just sensory nerves, but motor nerves that control muscles and movement. Inaccurate targeting of SCS can cause unwanted limb movement or twitching. However, targeting isn't as simple as it sounds, because it depends upon posture. Wood explains, "When you have an electrode running along the spinal cord, if you bend over, turn or twist, the relative position of the electrodes to the nerves that you are trying to target can change. As a result, you can get changes in the location of the paresthesia or unwanted motor activation."

Spinal Modulation plans on addressing another drawback of current SCS systems: the very large amounts of energy required to compensate for the fact that the spinal canal is an energy sink, since it's filled with cerebral fluid or, in other words, conductive salt water. Wood says, "You place electrodes on the outside of the spinal cord because you are trying to drive electrical energy through the cerebral spinal fluid to hit the sensory nerves, but most of that energy is lost." Therefore, the amount of energy required to deliver therapy is high, he says, and from a medical device perspective, that translates into a product that either requires a very large battery, or small rechargeable batteries that require frequent recharging.

Last but not least on the list of drawbacks, are parts of the body that Woods says are simply difficult to target with spinal cord stimulation—for example, pain that radiates axially up the back, foot pain, or diabetic neuropathies. "There are large groups of patients for whom SCS doesn't work well simply because of anatomy." Adding all that up accounts for the rather disappointing overall results of SCS, Wood says.

Without disclosing the technical approach of Spinal Modulation, Wood says "Let's just say that if you go through that list of problems with SCS from the inability to target precisely, frequent muscle stimulation, and high energy requirements, there is a significant need for improvement."

Spinal Modulation is entering the chronic pain market at a good time in its evolution. For years dominated by Medtronic, in 2001 Advanced Neuromodulation Systems came in and was followed in 2004 by Advanced Bionics. These companies have increased the visibility of SCS and, as noted, have grown the overall market.

Peripheral Nerve Stimulation Plays Early Role in Pain Intervention

Because there are regions of the body and types of chronic pain that spinal cord stimulation just can't help—for example, chronic post surgical pain following an amputation, thoracotomy, hernia or mastectomy, or the occipital nerve implicated in chronic headaches--Jon Snyder, a former CEO-in-residence at BioEnterprise (a regional incubator in Cleveland, OH) started up Neuros Medical in 2008 to create a platform suitable for peripheral nerve block stimulation.

Snyder had a great deal of familiarity with the neurostimulation markets, having served as a sales and marketing executive at **Cyberonics Inc.** (Most recently Snyder was head of marketing for the surgical instrumentation division of Cardinal Health.)

Snyder didn't need to look far for the company's core technology. At BioEnterprise, he happened to be right across the street from **Case Western Reserve University**, where Kevin Kilgore, PhD, and Niloy Bhadra, MD, PhD, both with the department of biomedical engineering, were developing a neurostimulation device called *Nerve Block*, to treat pain that originates in the peripheral nervous system. Neuros gained an exclusive license to that IP from Case Western Reserve University, and in 2009 raised a series A round of \$1.8 million from North Coast Angel Fund, Glengary Ohio Tech Angel Fund, Queen City Angels First Fund III and individual investors. [W#200930570]

Neuros is developing a device that consists of an electrode, which is attached at one end to a particular nerve in the peripheral nervous system and at the other to a small pacemaker-sized stimulator that can be placed in the lower leg, the outer thigh, the chest pocket or the abdomen, depending upon the particular pain application.

According to Snyder, Neuros is offering something very different from spinal cord stimulation. "We stimulate at a much higher frequency. Spinal cord stimulation fires at about 30-100 herz. We stimulate at about 5,000 herz, and as a result, block nerve activity at the focal point in the peripheral nervous system where the pain originates." Snyder explains that in contrast, SCS doesn't stop the pain signal in its tracks; instead, it masks it, creating a feeling of tingling along the spinal column.

Neuros plans to first enter the market with a focus on residual limb pain, for patients that continue to feel pain at the stump post-amputation. (This is distinct from phantom limb pain, where patients' pain seems to originate from the place where the limb used to be.) There are almost one million patients with intractable residual limb pain, according Snyder, which can arise when small benign tumors called neuromas develop on the tip of cut nerves. Only 30% of patients with residual limb pain respond to currently available treatments.

To increase its odds for success in the clinic and with payors, Neuros has adopted the model of SCS, screening patients to determine which can benefit from *Nerve Block* before the implantation procedure. Before the surgery, the pain physician will inject lidocaine or another short-acting local anesthetic into the treatment area. If the patient experiences pain relief, he or she will be a good candidate for the Neuros technology.

Snyder notes that in contrast to other companies working in neurostimulation, Neuros knows the mechanism of action of its therapy. "We are blocking the action potential of a particular nerve. Knowing the mechanism of action, then showing that it works in a clinical study, will be helpful in gaining adoption," he says.

Future large potential markets for the Neuros peripheral nerve blocking technology include post-surgical patients with chronic pain, of which there are 500,000, occipital neuralgia, perhaps chronic migraine, which afflicts 25-30 million patients in the US, and facial pain caused by trigeminal neuralgia. Neuros plans to begin clinical trials in 2010 and hopes to be on the market by 2012.

Both because the company can predict which patients might benefit from its treatment and because that treatment is easily reversible (simply by turning it off) Snyder believes that *Nerve Block* has the potential to move up in the treatment continuum, before opioid use. Of course, with a device in the \$15,000-\$16,000 range cost is an issue, but Snyder says in chronic pain, he thinks use of the device will yield an ROI in three years in terms of the medications a patient would have otherwise used in that time frame. In addition, lost days of work and the financial impact to the overall economy are hidden costs due to poorly managed pain, he says.

Neurostimulation Enters the Wireless Age

MicroTransponder Inc. believes that it, too, will have a place in early intervention for chronic pain. The start-up is working on a neurostimulation platform with an implantable component that is so small that it could be implanted with a needle in a 15-minute procedure. The company has a lot of work to do before it gets to that point; it's in preclinical studies now and hasn't yet finalized its clinical prototype, but that's the goal.

The device that MicroTransponder is advancing toward the clinic was the product of two inventive minds: Larry Cauller, PhD, a renowned neuroscientist at the University of Texas who was attempting to develop a neural interface for a prosthetic hand, and Richard Weiner, MD, a neurosurgeon in Dallas who was frustrated by currently available neurostimulation technology as he tried to block occipital nerves to treat migraine pain. Will Rosellini, a neuroscientist in the laboratory of professor Cauller, was the link between the two. Knowing both men, Rosellini saw in Cauller's wireless neural interface the makings of a platform for the wireless stimulation of peripheral nerves. In 2007 MicroTransponder obtained from the university an exclusive license to the technology and was off and running.

MicroTransponder's product embodies two novel approaches to neurostimulation: one, a novel target for stimulation, whereby the stimulation doesn't actually touch the nerve but instead the fat tissue surrounding it, and the second, the use of wireless technology to minimize the size of the implant.

The *MicroStim Pain Management System* consists of a handheld controller, an external coil worn on the arm, and an implant called *SAINT (Subcutaneous Arrangement of Injectable Neural Transponders)*, designed to be injected under the skin into the peripheral nerves via a 12-gauge needle.

The implanted micro-coils are powered by the external controller. To illustrate how it works, Rosellini uses the analogy of the "E-Z Pass" on toll roads. "On the outside of the body, you have a small device like an iPod which houses an external battery and circuitry. This generates a wireless magnetic field, just as the tollgate does. The implant—the little coil and the electrode—is like the toll tag that you hang on your windshield. The external device generates wireless energy that powers the wireless implant and then sends electricity out through the electrodes and onto the nerves."

The implants are so tiny that it will be feasible to place them anywhere in the body, Rosellini says. Because they're light, the company also bets they'll float on the tissue so they won't migrate like the leads and electrodes of other neurostimulation systems, which require revision over time to reposition electrodes. MicroTransponder's founders hope that less micromotion will result in less scar tissue and a reduced need to reprogram and reposition implants over time.

Cauler's invention allows nerve stimulation in a way that requires on the order of 25 times less power than conventional neurostimulators, according to Rosellini. "We aren't necessarily able to get more power into an implant, we are just better at utilizing it." That's because, Rosellini says, the company's technology is optimized for the capacitive nature of the nerve membrane and not the resistive surrounding tissue. .

MicroTransponder will ultimately seek FDA approval of its platform for chronic pain of the trunk and limb. But one of the initial trials the company has planned is for refractory tunnel syndromes—carpal tunnel or tarsal tunnel. Many patients with these conditions undergo surgery to free up compressed nerves. Success rates are 95%, but if revisions are required, the success rates drop to 25-50%. The company will see what it can do to help those patients deal with chronic pain.

Rosellini notes that tunnel syndromes provide a model for use of the MicroTransponder technology in many other chronic pain conditions caused by peripheral nerves, including but not limited to neuropathies due to crush injury, bone fracture or other mechanical severance or puncture injury, and post-surgical trauma caused, for example, by tumor resection, injections, or nerve grafts. There are more than 250 million people worldwide with peripheral nerve pain, according to Rosellini, who believes that MicroTransponder might be able to help refractory patients who have failed to benefit from any other treatment. The company's second market will be in craniofacial pain, where it believes it will be able to target the occipital nerve with far more precision than Dr. Weiner was able to do in his earlier peripheral nerve stimulation studies.

As noted, the company is at the preclinical stage, and hopes to be ready to begin clinical trials at the end of 2010. Rosellini believes the MicroTransponder device will follow the 510(k) route to approval based on a couple of predicates the company has identified in peripheral nerve stimulation, but that remains to be ironed out with the FDA.

Initial funding for MicroTransponder came from angel investors and the state of Texas' Emergent Technology Fund, which provided an award of \$1.38 million. MicroTransponder has also been supported by a number of Small Business Innovation Research grants from the National Institutes of Health. The company raised its Series A round in 2009, bringing in \$2.2 million to get to proof-of-principle and a prototype. [W#200930106] The company is now putting together its B round to help it meet clinical and regulatory endpoints.

Relievent Offers *Band-Aid* Treatment for Back Pain

Back pain is the second most common reason that patients consult physicians, after headaches. In fact, each year, 12 million new patients show up at physicians' offices with back pain. For 10 million of them, the pain will resolve on its own. But two million patients will continue to suffer.

It's frustrating and puzzling, but for those chronic pain sufferers who go on to have back surgery, including discectomies, laminectomies, facet joint injections or ablations, and the ultimate stabilization procedure, fusion surgery, a whopping 40% will achieve little or no pain relief. This would lead one to believe that something else in the spine is causing this back pain. Michael Heggeness, MD, PhD, professor of orthopedic surgery at **Baylor University's Baylor College of Medicine**, conducted a detailed histological analysis of the vertebral body and discovered an abundance of nerves on the end plates, the vertebra's surfaces that come into contact with the disc. Heggeness identified a nerve that originates in the center of the vertebral body and within the bone, and extends its branches toward the end plates at the top and bottom of the vertebrae. He posited that these nerves are a major culprit in axial back pain.

Heggeness patented his findings, which were subsequently licensed to **Johnson & Johnson's Depuy Spine Inc.** In 2006, a small group of engineers acquired the technology from Depuy, licensed some additional patents from **University of California, San Francisco**, and raised \$10 million in funding from Canaan Partners and ONSET Ventures. That was the genesis of Relievent Medsystems Inc.

Relievent's President and CEO Paul Goeld says the company's technology fills the considerable void that exists between failed conservative treatment and invasive spine surgery. The Relievent treatment, called

Intracept, uses a needle to deliver radiofrequency energy in a 45-minute procedure done under fluoroscopy to ablate the nerve in the vertebral body. With the patient lying prone, a surgeon places a needle through the skin, where it is advanced through the pedicle of the vertebra and guided to the nerve target. The needle is then replaced with a radiofrequency probe, which heats up and destroys the pain-emitting nerve. "We ablate this nerve right at the stalk of the pain tree," says Goeld, who reports that in a pilot study of 17 patients, the treatment was "fast, appeared to be safe and easy, and most importantly, resulted in dramatic pain relief for most patients."

It's Relievant's hypothesis that the nerves on the end plates of the vertebral body are responsible for a great deal of this chronic, unremitting pain. Goeld points out that of all the interventions physicians undertake to address back pain, none directly addresses this painful nerve in the vertebral body. Goeld goes so far as to say, "Treating the disc for back pain is like treating a hammer after you've smashed your finger with it." The disc may stimulate the pain, he explains, but pain is being emitted from the throbbing nerve inside the vertebral body. "There's a difference between the cause of the pain and the origin of the pain," Goeld says. "Many interventions treat the disc, but it has no blood vessels or nerves. We shouldn't be surprised that so often there is so little pain relief."

Relievant is about to begin a large-scale, randomized pivotal trial, for which it will recruit patients with pure axial back pain. "Our targeted patient would ordinarily be diagnosed with degenerative disc disease, but we address the pain by treating the painful nerve instead of the disc."

There are many precedents for obtaining pain relief by ablating inflamed nerves to alleviate pain, the most classic of which is a root canal. Nerves are also ablated in the facet joints but Goeld points out that no product deliberately ablates Relievant's targeted nerve. Kyphoplasty and vertebroplasty procedures, which are designed to treat vertebral compression fractures, deactivate this nerve as a by-product of bone cement injected into the vertebral body. Goeld says, "It is very possible that the pain relief that results from kyphoplasty and vertebroplasty is due to the ablation of the nerve that we target." He also points out that the market for vertebral compression fractures is relatively small when compared to axial back pain.

Goeld expects the Relievant *Intracept* treatment to be priced comparably to kyphoplasty. Because it employs a similar technique, *Intracept* should be easily adopted by surgeons who currently perform vertebroplasty or place pedicle screws under fluoroscopic guidance. "We project it will be a \$10,000 procedure, which includes the cost of the facility, the surgeon, and our device. This represents a huge potential savings for payors, who may be able to postpone or avoid paying for a \$50,000 to \$60,000 fusion procedure."

The company has already received 510(k) clearance, but is about to undertake a 200-patient study in 15 centers around the US to prove the benefits of this treatment in a controlled, randomized trial. The proposed endpoint is a reduction in pain at six months. Because the operative techniques are similar, surgeons familiar with kyphoplasty and vertebroplasty seem to be especially enamored with the Relievant procedure, according to Goeld, but interestingly enough, the selection of investigators won't be limited to spine surgeons. Some interventional pain practices already offer vertebroplasty and kyphoplasty and because they see so many patients with back pain, certain pain specialists may also be included in Relievant's trial. (In addressing spinal stenosis, **Vertos Medical Inc.** is following a similar path in targeting interventional pain physicians ahead of surgeons.) (See "*Vertos Medical's Blue Ocean Opportunity*," IN VIVO, December 2009 [A#2009800223]).

In a difficult financing environment, Relievant raised \$20 million in July 2009. New investors Morgenthaler Ventures and Emergent Medical Ventures came in on the Series C round, joining the company's original investors. [W#200930291] Goeld says Relievant's approach resonates with both private equity and strategic players. "We have a low cost, therapeutic device in a huge, growing market with an approved 510(k). Payors recognize the enormous potential our treatment has to dramatically reduce their spending on more expensive and perhaps less effective interventions."

Goeld points out that while the large orthopedic players like Johnson & Johnson, Smith & Nephew, Biomet Inc., Medtronic and **Zimmer Holdings Inc.** have billions of dollars invested in hardware, they have few products for these earlier and larger segments of the treatment continuum. "A proprietary product that addresses such a large group of patients with a minimally invasive, low intensity treatment should be an attractive opportunity," Goeld believes.

Perhaps it's ironic that it is in pain that device investors find relief, but the market potential is huge. At a time when investors are grappling with increasing levels of risk surrounding all aspects of device development—health care reform, financing risk, regulatory uncertainties and high reimbursement hurdles, devices for pain offer investors the potential for returns from large, untapped medical markets that have a reduced risk profile compared to other device areas. For device companies operating in interventional pain, markets and reimbursement pathways have already been blazed by large companies, and these are showing excellent growth in their pain management product segments.