

News Analysis

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Who'll stop the pain?

The race is on to find the next blockbuster pain-relief drug, with VCs investing more in the pain segment last year than they have in the past 10 years

If there's one guy who really understands pain, it is Dr. **James Campbell**. He's a professor of neurosurgery at Johns Hopkins, founder of two startups developing pain treatments and one of the early investigators of capsaicin.

Capsaicin, if you're lucky enough not to know, is the active ingredient in chili peppers, and it reduces the effects of chronic pain by burning off nerve endings. Just getting this pain-relief treatment can be so painful that it is typically given only after a liberal dose of lidocaine, the local anesthetic applied by dentists before they pull a tooth.

Campbell used his capsaicin research as the basis for his first startup, **AlgoRx Pharmaceuticals**. AlgoRx raised \$97 million from **InterWest Partners**, **Index Ventures**, **Sofinnova** and others before selling to **Corgentech** for \$130 million in December 2005.

Today, Campbell is chief executive of another pain-relief company, **Arcion Therapeutics**, which raised \$8.8 million in Series A financing in January from **CMEA Ventures** and InterWest. Arcion is part of a growing wave of companies trying to ease pain. Investment peaked last year, with VCs investing more than \$720 million in 49 companies addressing pain, the largest amount they've invested in at least 10 years, according to **Thomson Reuters** (publisher of *VCJ*). Startups developing pain-relieving drugs make up the bulk of the fundings (21 such companies attracted more than \$400 million last year), with device makers and others rounding out the total.

The payoff could be huge for any one of these pain-relief companies, but it promises to come only after a long and arduous development process. The efficacy of pain medication is notoriously difficult to measure, clinical trials require carefully considered set up and even the most successful drugs can take more than a decade to reach commercialization.

Market researchers, including various arms of the U.S. government, estimate that between one-sixth and one-third of all Americans experience chronic pain at some point in their lives. It's big business. Just one pain treatment, **Merck's** anti-inflammatory Vioxx medication, contributed \$2.5 billion to the company's top line before it was pulled in 2004 because of concerns that it increased the risk of heart attacks and strokes. Wall Street analysts estimate that **Johnson & Johnson** sold \$1.16 billion worth of patch-based pain reliever Duragesic in 2007. And **Pfizer** reports that sales of osteo-arthritis drug Celebrex hit \$2.29 billion last year.

The Baby Boomer demographic is helping drive the market, as are improvements in other fields of medicine. Diseases that once killed people are now treated as chronic illnesses. Patients living with cancer or HIV are patients living with pain.

"That's one of the negative side effects of living longer with disease," says **Dan Janney**, managing director of **Alta Partners** and a prolific investor in pain management companies. "When you look at the demographics in this country, with its aging population, you see there's going to be a lot of opportunity [for pain management companies]."

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Managing Director
Alta Partners

Alta Partners has backed six companies focused on pain management, but only one, U.K.-based **Vernalis**, has a product on the market. That's not particularly strange, either. It takes an average of 15 years to go from drug discovery to final approval according to research by the Government Accountability Office, the non-partisan research group that reports to the U.S. Congress. There's no reason to believe that new pain medications would take any less time.

"It's tough biology," Janney says. "Outside of the age-old molecules, there's not a lot of novel pain therapy."

Even if you find a new therapy, proving that it works can be a nightmare. "Trying to do a pain trial sounds easy, but you would not believe how hard it is," says **Arnold Oronsky**, a general partner at InterWest. Pain is such a subjective experience that it's difficult to quantify from person to person. People in pain will generally do whatever it takes to get into a clinical study and typically end up inflating their reports of pain just to be included, says Campbell.

Pain is also one of the conditions most-prone to the placebo effect. Some 30% to 40% of patients in double-blind trials that get fake treatments for their pain report feeling better, Oronsky says.

And there's little room for error. A clinical study for a pain medication might cost \$5,000 to \$10,000 per person to implement and might include more than 1,000 people, Oronsky notes.

Finding someone who can plan out these difficult and complicated clinical trials effectively can be the difference between failure and success for a venture-backed pain-relief company.

That's exactly why people such as Campbell are in high demand. With AlgoRx and decades of clinical research under his belt, the good doctor knows a thing or two about working efficiently with pain trials. His new startup, Arcion, is streamlined to minimize costs by picking up the rights to a promising chemical compound that didn't quite make it through clinical trials. Arcion was built from the ashes of **Curatek Pharmaceuticals**, a company that had licensed Campbell's research findings almost a decade ago to develop a treatment for neuropathic pain.

Neuropathic pain comes from damage done to neurons, nerve cells that transmit electrical messages from the extremities to the brain. Diabetics suffer from it because heightened glucose levels in their blood hurt neurons that lead to their extremities.

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Dr. James Campbell
CEO

Arcion Therapeutics

Campbell came up with an interesting approach to treating neuropathic pain, repurposing a drug called clonidine. The drug was originally used to decrease the withdrawal symptoms faced by drug addicts, specifically their high blood pressure. Using a drug designed for one thing for something completely different isn't quite like trying to use engine oil to wash your windshield. It happens all the time. Clonidine, for example, is also used to treat Tourette syndrome.

"We're taking advantage of the fact that some of the pain signaling is coming at the level of the skin," Campbell says. "This is something that's gradually being understood by academics."

Neuropathic pain is particularly difficult to work with because you can't always see what's causing the pain. But if you can point to where it hurts, Campbell's innovation may help by giving you localized relief.

"It avoids the adverse effects of systemic dosing," he explains. Rubbing clonidine onto your leg won't upset your stomach, for example. "If the drug works at the level of the skin, why not apply it there?"

Sounds great, but the **Food and Drug Administration** hasn't had a clear set of rules and procedures for clinical trials associated with drugs to treat neuropathic pain.

Setting up a clinical trial for measuring the effect of acute pain—pain caused by a direct injury—is comparatively easy. There's what's known as the "third molar trial," which, as CMEA Managing Director **David Collier** describes it, is "essentially a bunch of college kids getting their wisdom teeth out." The pain level is well understood, its cause clear, its duration predictable. "Neuropathic pain doesn't have this standard model," Collier says.

That's what tripped up Curatek (the precursor to Arcion). It spent a bunch of money pushing its Clonidine treatment for neuropathic pain through clinical trials, but it stalled out just short of its goal. "It's pretty convincing that the trial probably was successful, but based on the statistical plan they had laid out with the FDA, it fell short of statistical significance," Collier says of Curatek's drug trials.

The difficulty of getting good drugs to market irritates Campbell. "There's zero question in my mind that promising drugs have been passed over because the trial design wasn't right," he says. It is difficult for a number of reasons, each of which Campbell can speak to at length. The biggest problem with drug trials for neuropathic pain, he says, is the lack of partnership between companies and researchers. When it comes to designing good trials "everybody's passing the buck," he says.

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David Collier
Managing Director
CMEA Ventures

Campbell hopes that by picking up where Curatek left off that Arcion will have enough of a head start to cross the finish line. Arcion bought Curatek's patent license, hired former Curatek employees as part-time consultants and is off and running in its own clinical trials. "The intent is to run it in a very lean fashion," Collier says. "If it fails, the amount of money lost will be small, but if it succeeds, the return will be very attractive."

Researchers-slash-entrepreneurs like Campbell are few and far between. His journey into startups was born of frustration. He wanted his work to matter to people, literally to take their pain away. He needed an outlet to flex his creativity and compassion and found it starting companies. "Despite the fact that there's been an explosion in understanding of the neurobiology of pain, very little has been translated into patient care," he says.

"Coming up with ideas is one thing, getting those ideas published and funded through the NIH [**National Institutes of Health**] is one level of activity," Campbell says. "But to really make your ideas count, these ideas have to be translated into practice." The best way he figured he could do that was as an inventor and entrepreneur.

Venture investors have yet to walk away with billions from any one pain management startup. Given the trying nature of the pharmaceutical business, it'll be a rare drug company that does—despite the huge potential market and opportunities of unmet need. Reducing costs by picking up abandoned work or streamlining trials can help. So can working with compounds that have been approved for other uses, or finding motivated people like Campbell.

But venture capitalists that get into this sector should be motivated to improve patient care, not just put money to work. No matter who you get to work on your company, the process of going through trials and bringing a drug to market will still be a pain.

SIDEBAR: PUBLIC PAIN

The public markets have been a real headache for venture-backed pain companies. At least four have gone public through various means in the past several years, but none is trading above its IPO price.

Take **NeurogesX** (Nasdaq: NGSX), which makes a capsaicin-related compound to knock-out over-active nerves. It collected \$95 million from VCs such as Alta Partners, **ARCH Venture Partners**, **SV Life Sciences** and **Walden International** before going public on May 2, 2007. It priced at \$11 per share, fell to \$10.65 at the end of the day and dropped all the way to \$8.10 by the end of that month.

NeurogesX put \$25 million into R&D last year and leaned "Trying to do a pain trial sounds easy, but you would not believe how hard it is." on its VCs for a PIPE in January, collecting \$25 million to Arnold Oronsky continue development of its pain treatments. But without General Partner revenue, it can't convince Wall Street to value its shares InterWest Partners above \$3.50.

Anesiva (Nasdaq: ANSV) has had a similarly painful experience on the Nasdaq. Anesiva came to life after **Corgentech** acquired VC-backed **AlgoRx Pharmaceuticals** for \$130 million in December 2005. It was a good deal for AlgoRx's backers (including **InterWest Partners**, **Index Ventures**, **Sofinnova** and others), who had invested \$97 million in the company, which was developing therapies based on capsaicin. Public investors haven't fared so well: Anesiva's stock is currently trading below \$3.50 per share, down from Corgentech's 2004 IPO price of \$16 per share.

Then there is **Cadence Pharmaceuticals** (Nasdaq: CADX), which makes drugs for hospital settings, including a pain drug that is currently in Phase III trials. After raising \$128 million from **Domain Associates**, **Proquest Investments**, **CDIB Venture Management** and others, Cadence priced at \$9 per share in October 2006. Today its shares are trading around \$6.50.

Pain Therapeutics (Nasdaq: PTIE) has done a little better. The company is working on a non-addictive form of opioid drugs that it hopes will hit the market soon. It raised \$28.6 million from **TVM Capital** and others before going public in 2000. The company hit it big when **King Pharmaceuticals** offered it \$150 million to co-develop its abuse-resistant drug in December 2005. Last year, Pain Therapeutics earned \$20.3 million on \$42.7 million in revenue collected from King for work on its product.

Still, at \$7.76 per share, Pain Therapeutics is quite a bit off its \$12 IPO price and a long ways off its first-day run up to nearly \$22 per share.

Despite the lackluster performance of Pain Therapeutics and the others, VCs remain optimistic that the public markets will be receptive to their pain management startups.

"Pain is something that everyone, including investors, has experienced in one form or another," says **Lou Bock** of **Scale Venture Partners**. "It's more tangible than other diseases that only affect a smaller number of people."

Scale is an investor in **Zogenix Inc.**, one of three VC-backed pain-management companies that have registered to go public.

Zogenix, which is working on drugs for central nervous system disorders and pain, filed registration papers in March and has not yet set the terms of its offering. To date, it has raised \$78.8 million in venture backing. Its largest venture shareholders are **Domain Associates** (with a 23.2% stake), **Clarus Lifesciences** (23.1%), **Scale Venture Partners** (15.4%), **Thomas, McNerney & Partners** (13.2%) and **Abingworth Bioventures** (10%).

The other two VC-backed pain companies in registration are **Omeros Corp.** and **Xanodyne Pharmaceuticals Inc.** Neither has set the terms of its offering.

Omeros makes anti-inflammation and CNS drugs for inflammation and pain associated with medical procedures. It has raised about \$79 million in venture backing and **Arch Venture Partners** is its largest VC shareholder, with 5.1% of its stock. (None of its other VCs held enough shares to be listed in its prospectus.)

Xanodyne is developing pain medication for women. It has raised more than \$230 million in VC and private equity to date. **Apax Partners** is its largest venture shareholder, with a 23.2% stake, followed by **MPM Capital** (21.3%), **Essex Woodlands Health Ventures** (10.7%), **HealthCare Ventures** (10.3%), **Perseus-Soros Biopharmaceutical Fund** (9.5%) and **Blue Chip Venture Co.** (7.8%) — *Alexander Haislip with additional reporting by Lawrence Aragon*

By Alexander Haislip, Senior Writer

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