Device Investors Showing Some Spine

This clearly isn’t the go-go period of spine in the mid-2000s, but venture capitalists can’t ignore the enormous opportunities for companies able to treat low back pain. But they can keep a lid on any irrational exuberance.

By Mary Stuart

- Spine start-ups might have had their pick of investors years ago when new implants and technologies looked to offer relief for back pain sufferers.
- But economics came into the equation as payors in certain categories of spinal fusion began balking at the prices they had to pay without first having clear-cut clinical evidence of success.
- Still, chronic low back pain continues to constitute an enormous patient population — at least 12 million patients — that needs more treatment options between the extremes of conservative care and spinal fusion.
- New findings about the interaction of muscles, nerves, and the skeletal system are driving new minimally invasive treatments that might someday satisfy payors’ demands for inexpensive but effective treatments.

The age of spine — roughly 2003 to 2007 — was a heady time for venture investors and spine entrepreneurs. Everyone involved knew the sector was getting too much attention from investors, but in their investment mind’s eye the other 300 or so spine start-ups would be the ones to pay the price. As things turned out, when the reality cops came to bust up the party few escaped unscathed.

The first pressure came from insurers who began requiring more clinical proof that spine devices could improve care without over-inflating costs. Then, the recession drained the capital pool causing several high profile start-ups to simply run out of funds.

Today, VCs profess to getting a chill down their spine at the mere mention of a spine deal. In truth, however, things aren’t so bad.

Elsevier’s Strategic Transactions shows that just in the last year, 26 companies operating in spine and low back pain received private funding. (See Exhibit 1.) To be sure, many were small rounds, some were funded with debt, and some were insider rounds trying to keep companies moving forward. Still, venture investors showed excitement in a select number of start-ups including Mainstay Medical Ltd., which raised $20 million in an oversubscribed Series B round for a novel neurostimulation approach to low back pain, Cerapedics Inc., with a new bone graft material, Relevant Medsystems Inc., which is developing a percutaneous back pain intervention, and Zyga Technology Inc., with devices for two joints that largely lack minimally invasive treatment options — the sacroiliac and the facet joints.

The climate clearly is different than five or six years ago, but spine isn’t alone. The entire medical device industry faces the headwinds coming from health care reform with its focus on cost reduction and comparative effectiveness, the continuing decline of venture capital for medical device companies, and pricing pressures.

But spine start-ups face unique challenges, particularly in pricing. Spine surgeons — along with other orthopedic surgeons - increasingly are signing on as hospital employees, at least partially forfeiting their exclusive reign over purchasing decisions, ceding some of the decision to cost-conscious administrators. Hospitals – and even surgeons – have little choice as payors continue to push back. In 2011, several private insurers changed their coverage policies, becoming stricter in their reimbursement of lumbar spine fusion surgeries. Several said that they would no longer cover vertebral fusions in the lumbar spine to treat degenerative disc disease or initial primary laminectomy or discectomy for nerve root decompression or spinal stenosis (unless there is documented spondylolisthesis). Degenerative disc disease previously accounted for 20% of lumbar fusions.

The required level of evidence for coverage is rising. The Centers for Medicare and Medicaid Services recently issued a non-coverage decision for intradiscal electrothermal therapy for the treatment of discogenic back pain. Surgeons complain that coverage has been denied for procedures that ought to be covered because they didn’t provide the proper documentation, or the prerequisite course of conservative care was not followed or documented properly. The effectiveness of minimally invasive treatments for vertebral compression fractures has come into question since the publication of a controversial study in the New England Journal of Medicine in 2010 (See “Vertebral Compression Fracture Treatments Under Pressure” — IN VIVO, December 2010). All new spine companies face hurdles higher than ever before in proving that their technologies actually work, and they’re pursuing a tricky endpoint: freedom from pain, with its psychosocial and other confounding issues.
### Recent Private Financings Of Spine Companies

<table>
<thead>
<tr>
<th>(DATE)</th>
<th>COMPANY, AMOUNT RAISED, ROUND</th>
<th>BUSINESS/INVESTORS</th>
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<tr>
<td>(2/13)</td>
<td>Bone Therapeutics, €7.7 million ($10.4 million), Series D</td>
<td>Bone cell therapy. Lead product PREOB is in US clinical trials as enhanced bone graft for cervical spine applications./Nausicaa Ventures, BAM’s Angels Fund I, Life Science Research Partners, Orbimed, NGN Capital.</td>
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<tr>
<td>(2/13)</td>
<td>Osseon Therapeutics, $14 million</td>
<td>Addressing vertebral compression fractures with Osseoplasty system, steerable products for bone cement delivery, and a proprietary bone cement./Private investor.</td>
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<td>(1/13)</td>
<td>OsteoVantage, $150,000 Phase I SBIR grant</td>
<td>Selectively current-permeable osteogenic pedicle screw surface for vertebral fusion designed to form a robust, biomechanically sound intersegmental union and avoid pedicle screw loosening, a factor that contributes to the high failure rates of spinal fusion surgery.</td>
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<td>(12/12)</td>
<td>Ortho Kinematics, $2 million, Series B</td>
<td>Vertebral Motion Analysis technology received 510(k) clearance 1/12; now the KineGraph is undergoing limited launch.</td>
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<tr>
<td>(12/12)</td>
<td>Aurora Spine, $2 million</td>
<td>Minimally invasive regenerative technologies./Axcess Health Care Group.</td>
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<td>(12/12)</td>
<td>Cerapedics, $19 million, Series C</td>
<td>Ongoing IDE trial of i-FACTOR peptide-enhanced bone graft for cervical spine applications./MedImmune Ventures, CVF LLC, Orbimed, NGN Capital.</td>
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<td>(11/12)</td>
<td>Minimus Spine, $1 million of a planned $2 million financing</td>
<td>Ozone injection technology for disc herniations./19 Angel investors.</td>
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<tr>
<td>(10/12)</td>
<td>Intrinsic Therapeutics, $12.25 million of a $20 million offering</td>
<td>Lumbar discectomy with Barricaid Prosthesis. As of 12/12 had enrolled 300 patients for 400–650 patient study across Europe./11 investors.</td>
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<td>(10/12)</td>
<td>Spinal Restoration, $5 million, Series C</td>
<td>To fund biologic license application for Biostat, intradiscal biologic therapy for discogenic pain, which consists of a proprietary fibrin sealant and delivery device./$3 million in equity from Austin Ventures, Santé, MB Venture Partners and $2 million debt facility from Comerica Bank.</td>
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<tr>
<td>(10/12)</td>
<td>Lanx Inc., $8.7 million of planned $15 million offering</td>
<td>Minimally invasive fusion devices, including ASPEN for posterior spinal process fixation, TELLURIDE for less invasive pedicle screw fixation, and TIMBERLINE for lateral approach to interbody fusion.</td>
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<tr>
<td>(10/12)</td>
<td>Interventional Spine, $1.6 million debt out of targeted $4 million</td>
<td>Percutaneous spine treatments. PerX360° System including the Optiport access instrumentation and Opti- cage expandable interbody implant provide the capability to perform a lumbar interbody fusion via two incisions that are less than 15 mm each, at all levels of the lumbar spine from L2 to S1. The procedure can be performed in less than 40 minutes, including interbody placement and posterior stabilization.</td>
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<tr>
<td>(10/12)</td>
<td>Mainstay Medical, oversubscribed $20 million, Series B</td>
<td>Implant delivering electric stimulation to address chronic, non-specific low back pain./Fountain Healthcare Partners, Medtronic, Capricorn Venture Partners, Seventure Partners, SofinauroPartners, Twin City Angels.</td>
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<td>(9/12)</td>
<td>Ranier Technology, $5 million</td>
<td>Cadisc total disc replacements are single unit polymeric devices for cervical and lumbar spine./First Ventures, Alliance Trust Equity Partners.</td>
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<td>(9/12)</td>
<td>Illuminos, $28 million, Series C</td>
<td>Minimally invasive bone fracture repair (spine is among future applications). Photodynamic bone stabilization system through which a small flexible balloon catheter is inserted into the bone and the fracture is infused with a proprietary liquid monomer./TeKla Capital Management, Life Sciences Partners, Foundation Medical Partners, Mieza Capital, New Leaf Venture Partners, SR One, Excel Venture Management, Pappas Ventures, Slater Technology.</td>
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<td>(6/12)</td>
<td>Benvenue Medical, $25 million, Series D</td>
<td>The money will support worldwide commercialization activities for three products to treat vertebral compression fractures, and to introduce additional fusion and VCF devices in the US./DeNovo Ventures, Domain Associates, Technology Partners, Versant Ventures.</td>
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<td>(6/12)</td>
<td>Invuity Inc., $25 million, Series D</td>
<td>Has launched the illuminated Eigr Taylor Retractor System, which combines an optical waveguide and a fiber optic cable with a retractor or other surgical tool. The system guides and controls direct, uniform, and high-contrast illumination onto a target within a surgical incision, while remaining cool./Valence Advantage Life Sciences Fund II led the round and was joined by Kleiner Perkins Caufield &amp; Byers, InterWest Partners, and Wexford Capital.</td>
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<tr>
<td>(5/12)</td>
<td>Zyga Technology, $25 million, Series C</td>
<td>Funds will support commercialization activities for Simmetry sacroiliac joint fusion system and ongoing clinical development of the Glyder facet resurfacing device./Versant Ventures, Split Rock Partners, Domain Associates, MB Venture Partners.</td>
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<tr>
<td>(4/12)</td>
<td>LDR Holding, $15 million debt sale</td>
<td>Received FDA approvable letter in 2012 for two-level Mobi-C cervical disc.</td>
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As an investment category, spine is also jaundiced by past failures. In the early 2000s more than $1.5 billion were poured into four artificial disc companies that promised billion-dollar markets. Those markets haven’t materialized yet, particularly in the case of lumbar artificial discs, where studies showed outcomes no better than fusion, combined with the fact that early devices had a risk of displacement and component failure not easily addressed by revision surgery. CMS had a role to play in dampening that market, with an initial non-coverage decision issued in 2006, later reversing it but still restricting coverage. (Cervical disc replacements are a different case and this market is starting to grow.) (See “Motion Is Back In Spine Market” — Medtech Insight, December 2012.) Finally, although it is only natural that among 300 to 400 start-ups, there would be a large number of failures – and there were, including Applied Spine Technologies, Disc Dynamics Inc., Innovative Spinal Technologies, Vertebrofix, and Archus Orthopedics, to name a few – venture capitalists have become very cautious about the space.

Constraints call for creativity and many of the newer companies see in the pressure placed on spine a fusion a need for less invasive, less expensive, and perhaps more targeted alternatives, and that’s what has driven a number of the companies profiled below. Tony Recupero, president and CEO of Baxano Inc., says, “As payors become more restrictive on certification for fusion, we want to put more tools into the hands of surgeons so they will have more ways at their disposal to address disease states.” K Spine Inc. has staked out scoliosis as an area still waiting for a less invasive alternative to an invasive surgery, as has Zyga Technology, in addressing the facet and sacroiliac joints. Two companies, Mainstay Medical and Relievant Medsystems, believe they’ll address the back pain that plagues patients without putting them through long surgeries and lengthy rehabilitation periods. Baxano redefines minimally invasive, with an open incision but an over-the-wire delivery platform to minimize the damage to tissue that’s in the way of the surgical site. In this field, the drive to minimally invasive procedures has as much to do with sparing the spine’s underlying anatomy – the interaction of muscle, nerve, and bone – as it does with the size of the incision, and that’s the idea behind many of the lateral fusion approaches being developed by companies like NuVasive Inc. and Lanx Inc.

Investors picked these companies because they have the right value proposition: the ability to improve patient health at a lower cost than the current system of care. According to an article in the September 1, 2012 issue of Spine (by Matthew A. Davis, DC) expenditures for the treatment of back and neck problems in the US nearly doubled between 1999 and 2008. Adjusted for inflation, annual medical spending for spinal care per patient increased by 95% during that period. Back pain is the second most common reason for visits to physicians’ offices (after upper respiratory infections), with 13.6 million visits annually for the diagnosis of a back or neck condition. Degenerative disc disease will only grow as the number of people over the age of 65 continues to increase.

According to the prospectus for the 2012 IPO of spine company Globus Medical Inc., the only medical device company to successfully go public (on a US stock exchange) in 2012, the $10 billion worldwide spine market consists of the $5.9 billion spinal fusion market and the $4.1 billion disruptive technologies market. The start-ups interviewed here hope to get their share of the latter.

**TREATING MUSCLE DYSFUNCTION IN CHRONIC LOW BACK PAIN**

As we’ve established, spine isn’t as popular with investors as it used to be. Peter Crosby, CEO of new company Mainstay Medical Inc., says these days a company working in back pain has to fulfill three requirements in order to pique the interest of investors: “It has to be different, the science needs to make sense, and it needs to work.” Mainstay Medical, founded in 2008, is well on the way to demonstrating all three of those properties. It has at least done well enough to convince investors to pitch in on a $20 million Series B round in September 2012. Fountain Healthcare Partners, Medtronic Inc., Capricorn Venture Partners, and Seventure Partners joined returning shareholders Sofinnova Partners and Twin City Angels.

Founder Danny Sachs, MD, an emergency physician with an MBA from Harvard Business School and a former venture capital partner with Spray Venture Partners and Investor Growth Capital, founded Mainstay. Sachs has a reputation for doing things a bit differently. He previously founded Respiscardia Inc., the rare company focusing on central sleep apnea (rather than obstructive sleep apnea), a condition the company treats with an implantable electri-
can be seen on MRI or X-ray scans. This type of back pain is character-
chronic, non-specific low back pain, which is back pain that has lasted
and cause movement, and keep the spine stable, he says.

It was in the process of studying back surgery for his scoliosis
start-up K Spine that Sachs observed surgeons stripping muscles
off the spinal column in order to access the
spine. Sachs wondered about that; those mus-
cles are there for a reason, he supposed. This
led him down a path of inquiry about the func-
tion of the muscles in stabilizing the back.

CEO Crosby explains that the spinal column is not unlike a mast on a sailboat, which
is held up by guy wires (the wires that hold the
mast). “The spinal column is fundamentally
unstable. The muscles act like stays around it
to keep it stable.” Those muscles get activated
by the brain in response to movements: walk-
ing, sitting, bending over and tying your shoe laces. They initiate
cause movement, and keep the spine stable, he says.

Patients with chronic low back pain often experience dysfunction
of the lumbar stabilizer muscles. Mainstay is specifically targeting
chronic, non-specific low back pain, which is back pain that has lasted
for more than three months and for which no obvious structural cause
can be seen on MRI or X-ray scans. This type of back pain is character-
ized by waxing and waning; people live with a low level of continuous
pain that they can usually tolerate, but occasionally, as many people
put it, “their back goes out,” and they’re laid low for a period of time.

Back pain often begins with an initial injury – a bad golf swing,
bending down to pick up a child, hefting a heavy wheelbarrow
while gardening – but the pain becomes chronic because the fun-
damental instability that comes with muscle dysfunction allows
reinjury. “Even if the pain goes away, many people are unable to
activate their muscles voluntarily,” Crosby explains.

Mainstay has developed an implantable neurostimulator of the
muscles that stabilize the back. (Crosby doesn’t want to name the
target muscles yet for IP reasons.) “We try to fix the cause of back pain
in our target patient population, which is a motor control disorder,” he
says. Crosby notes that activation of these muscles is involuntary, so it
is very difficult to train them through physical therapy, which at any
rate is long, expensive, and relies on patient compliance. The company
envisions a long-term implant, because the patients it treats tend
to be susceptible to reinjury: “If bending down and tying your shoe lace
can send you into an episode of back pain, it is probably going to happen
again because you are still going to tie your shoelaces,” Crosby
says, noting that the device can remain dormant (or turned off) until
it is needed, and some patients might benefit from maintenance doses.

The company, which was founded in Minneapolis but is now based
in Dublin, began its feasibility study in Europe in 2011 using off-the-
shelf neurostimulation components. “We found that it worked well,
in fact better than we expected,” according to Crosby. Meanwhile, the
company is developing its own implantable pulse generator and lead
and is getting close to starting human trials with its own device.

Again, being deliberately vague, Crosby notes that “in develop-
our product, we have done a lot of work on understanding the
anatomy of the area we are targeting, which was not well under-
stood. We have worked out how to place electrodes quickly and
easily and in exactly the right spot to achieve the intended effect.”

He says Mainstay might offer an outpatient procedure or perhaps a
day surgery depending upon the physician group. “The procedure
is fairly straightforward and patients will go home fairly quickly.”

It is still early for Mainstay and it has challenges ahead. Crosby
notes that although the company got a pretty strong signal from its
feasibility study, this is a field in which studies have to be designed carefully to rule out the pla-
placebo effect, and the company has planned for a study to do that. Many of the other customary
start-up risks have been mitigated. This is Cros-
by’s sixth company (he was CEO of Ventracor, Ischemia Technologies, CardioComm Solutions,
NeoVision Corp. and Ausonics) and he says that
if you define risks in five ways—product, market,
clinical, financing, and people—the company has
an attractive risk-benefit profile. “The therapy
is likely to work. We had good outcomes in our
feasibility study so a lot of the clinical risk has been scrubbed.” The
product risk is low, Crosby says. Implantable stimulators are used for
many applications in the body. The market for people with chronic,
non-specific low back pain is enormous, and these people have noth-
ing to help them beyond physical therapy and pain medications. The
company conservatively estimates that there are 2 million people in
the US with the type of muscle control dysfunction that can be
addressed by its therapy.

Mainstay still faces reimbursement and financing risk. “There is
always a risk on how much we can get paid, and we are probably
going to end up with pricing similar to other implantable devices,
but I think we are going to be able to show that the incremental
cost-effectiveness of the therapy will easily justify the pricing,”
says Crosby. Finally, he notes that in Ireland and Minneapolis, “We
have great people on two continents and can get more done with
less capital. Financing is always a risk, but we have good investors
and provided we continue to meet our milestones, I think we will
continue to be supportive of the company.”

**MINIMALLY INVASIVE SPINAL SURGERY FROM THE INSIDE OUT**
The drive toward minimally invasive procedures in spine is just as
compelling as it has been in other specialties of medicine, for the
ability to produce lower complication rates, shorter healing times,
reduced length of stays in the hospital, and a quicker return to an
active life compared with open, invasive surgeries. These advant-
ages are more desirable than ever, since they reduce costs and
translate into cost-effective care. However, minimally invasive in
spine doesn’t quite mean the same thing as it does in other organs.

Tony Recupero, president and CEO of Baxano Inc., who began
his medical device career more than 20 years ago at United States
Surgical, the pioneer of laparoscopic surgery, points out that gen-
eral surgeons and thoracic surgeons work inside cavities of the body
where there is space to move instruments and anatomical structures
around. Spinal anatomy, on the other hand, can be extremely diffi-
cult to access, covered as it is with muscle tissue and bony stabilizing
structures. Thus, the goal of a minimally invasive spine procedure is
not to simply minimize the size of the incision through the skin, but
Jeffery Bleich, MD, an anesthesiologist at Stanford University Medical Center, founded Baxano in 2005 with venture funding from Prospect Venture Partners and Three Arch Partners (which came in later). As a board-certified pain management physician, Bleich saw lots of patients who still had pain after decompression procedures and often required additional surgeries including spinal fusion. These decompression surgeries treat spinal stenosis, a condition where the spinal nerve root in the lower back becomes compressed and sends pain into the low back, buttocks and legs. He surmised that much of the ongoing pain was coming from the healthy tissue that was either being destroyed simply to get to the area where the nerve was impinged, or the tissue impinging on the nerve root.

Since it was possible to put a needle into the spine to deliver an epidural anesthetic or steroid injection, Bleich wondered if there might not also be a way to pull through a wire steroid injection, Bleich wondered if there might not also be a way to pull through a wire to the spine to deliver an epidural anesthetic or on the nerve root. Once the surgeon knows that the nerve was impinged, or the tissue impinging from the healthy tissue that was either being targeted decompression with minimal tissue trauma on their way there. Recupero emphasizes that the procedure is not percutaneous, as many often think it is because of the over-the-wire access.

The surgeon makes a small incision at the mid-line or just off the mid-line of the lumbar spine through the muscle down to the lamina of the spine. After the surgeon gains access through the lamina, an introducer probe delivers a nitinol wire with a hitch on the end to the surgical site, then an EMG-enabled device sends out an electrical signal that allows the surgeon to know where he is in relationship to the nerve root. Once the surgeon knows that he is in the correct plane, he brings through a thin flexible shaver and reciprocates it to remove tissue locally.

From 2006 through 2008 Baxano received 510(k) clearances for the iO-Flex components, which are classified as tools that enable existing procedures, rather than as a new procedure (an example of which was kyphoplasty). Thus its products fit within existing reimbursement codes. The company conducted a limited launch at centers of excellence and went to full launch in January 2011.

“For us, the challenge was not how to get a new code, but how to demonstrate for the hospitals how improved clinical outcomes translate into cost-effectiveness for this device,” says Recupero. The company is gathering that data now with a post-market clinical trial. The company’s iO-Flex study enrolled 59 patients with one- or two-level lumbar spinal stenosis and will look at reduction in pain and symptoms. The company will also gather data on operating room times, length of stay, complication rates, and reoperation rates. Baxano has submitted data for publication out to one year, and although the details aren’t published yet, Recupero says the study shows improvements in patient-reported outcomes and cost-effectiveness for decompression of lumbar spinal stenosis. “We think this is due to the fact that the devices enable the surgeons to decompress from the inside out, rather than having to remove a lot of healthy tissue to get to where the impingement is.” He says the devices also enable a far lateral decompression, which is very difficult to reach with traditional techniques. “We believe the maintenance of the healthy structural tissue that the surgeon usually takes down plays a role in the patient’s post-op course and the morbidity associated with the procedure.”

The company is continuing its commercial ramp. Its revenues were $3.9 million in 2011 and $9.4 million in 2012. Approximately 900 surgeons have been trained in iO-Flex and Baxano has approvals at more than 300 hospitals.

Baxano has raised $58 million up through its series C round from a group of investors that includes Prospect Venture Partners, Three Arch Partners, Kearny Venture Partners, CMEA Capital, Kaiser Permanente Ventures, Affinity Capital Management, and Athenian Ventures, and it is fundraising for its next round.

Recupero notes that in about 70% of the iO-Flex procedures the device is used for straightforward decompressions for spinal stenosis or stable grade I spondylolisthesis, and 30% of the time it is used to enable a minimally invasive fusion. As payors become more restrictive on certifications for fusion and other procedures, Recupero says, “We want to put more tools into the hands of surgeons so that they have more ways to address disease states. We want our devices to help surgeons gain better outcomes whether as a stand-alone decompression or to facilitate a minimally invasive fusion.”

**CARVING OUT UNSOLVED SPINE PROBLEMS**

Degeneration of just two joint systems – the facet joints and the sacroiliac joints – is responsible for 50% of low back pain, yet these conditions have largely lacked surgical solutions. Patients with pain from these sources tend to undergo routine steroidal or analgesic injections, rhizotomies or chiropractic manipulations, which don’t address the underlying problem of joint degeneration. Zyga Technology Inc. was founded in 2008 by Robert Assell, vice president of research and development at Trans1 Inc. (a successful company treating degenerative conditions of the lumbar spine with a range of fusion products), to deliberately solve the problems of facetogenic and sacroiliac joint pain.

Pain due to the degeneration of facet joints is responsible for 22% to 30% of low back pain cases, according to various estimates. Facet joints are located on the back of the spinal column, with one pair (one on each side of the spine) between each pair of vertebrae. The alignment of the facet joints allows freedom of movement as you bend forward and backward but prevents over-twisting. Surface cartilage helps the joints operate smoothly. Because of injury
or the thinning of the vertebral disc that comes with age, articular cartilage on the facet joints can wear down over time and when bone meets bone, pain can result.

In the first wave of motion preservation in spine, such a common problem prompted the development of total facet replacement devices. These devices have been in development for a decade now, but are not yet commercially available. Facet Solutions has been at it since 2003, and had completed pilot studies in Brazil, Europe, and the US on Acadia, an unconstrained pedicle-screw-based total facet replacement system, when it was acquired by Globus Medical Inc. in 2011. Globus is still enrolling for the Acadia pivotal clinical trial, which began in 2006, and the trial is expected to be completed in late 2013. Archus Orthopedics was likewise going after a total facet joint replacement, but after raising some $63 million and in the midst of a 450-patient clinical trial it filed for bankruptcy. Its assets were acquired by Facet Solutions in 2009. (See “Archus: Using Old Principles to Open a New Market in Spine” — IN VIVO, July 2008.)

Few companies facing such an arduous undertaking are able to attract venture capital funding these days, but Zyga Technology has a different value proposition. With a minimally invasive and tissue-sparing solution for patients suffering from facetogenic pain and sacroiliac joint dysfunction, Zyga was able to raise a $25 million Series C round in May 2012 led by Versant Ventures with returning shareholders Domain Associates, MB Venture Partners, and Split Rock Partners.

In February 2013, Zyga completed enrollment for a 40-patient clinical trial in Europe testing its minimally invasive Glyder facet resurfacing system, which delivers through a small incision two PEEK (a type of polymer) wafers that work with the native cartilage of the facet to resurface the joints. The Glyder implants are inserted in the facet and maintain position with a proprietary fixation surface. There is no drilling, no hardware, and it is a very quick procedure, according to president and CEO Jim Bullock. In Europe, he notes, surgeons are treating both facets in a procedure that can be completed within a half hour.

The company aims to use the results from this first trial as a foundation for its DUET clinical trial in Europe and a mid-2013 IDE submission to the FDA. Bullock says the initial patients treated are now reaching two years post-surgery and are experiencing sustained pain relief. Based on 10 million steroidal injections that patients are getting each year for facet pain (with patients receiving two or three injections per year) Bullock estimates a US market of about $4 billion.

Zyga has also developed a product for treatment of the sacroiliac (SI) joint. Over the past five or six years, treatment of the SI joint has emerged as an important treatment target. First-mover SI-Bone Inc., which has been in the market for three years now with a minimally invasive alternative to a morbid surgery, deserves credit for developing a new market that still has room for product alternatives.

Traditional surgical fusion of the SI joint requires an anterior approach that involves pushing aside organs and muscles to access and partially decorticate both sides of the SI, then stabilizing it with bone graft and screws to induce healing. Invasive fusions of the sacroiliac joint decreased for a time during the adoption of spinal fusion and other procedures for degenerative disc disease, but over time, as these procedures failed to completely address pain, and as the interventions themselves resulted in adjacent level joint degeneration, the SI joint has re-emerged as a potential pain-generator. The L5–S1 fusion is the most common level fusion in the lumbar spine, Bullock points out, and the SI joint is immediately adjacent. “If L4-L5 isn’t the pain generator, the SI joint should be considered,” says Bullock.

“Three years after a fusion, the surgeon may end up injecting an anesthetic into the SI joint only to discover that it is the source of the pain.” Indeed, 35% of back pain following lumbar fusion originates in the SI joint, according to Bullock.

As noted, in the sacroiliac joint treatment space, SI-Bone leads the way with its FDA-cleared, CE-marked iFuse, a titanium implant coated with a porous plasma spray that can be delivered through a small incision. The porous coat facilitates bone in-growth, according to SI-Bone, and minimizes movement of the implant. In December 2012, SI-Bone noted that it had treated 5,000 patients. (SI-Bone has raised approximately $26.6 million in venture capital from Montreux Equity Partners, Skyline Ventures, and 19 investors.)

Zyga’s product for sacroiliac joint conditions is called Symmetry. It also uses minimally invasive techniques to access the joint through a small incision. Symmetry uses a unique set of instruments to collect autologous bone and to partially decorticate the joint on both the sacral and ilial sides down to bleeding bone. The joint is then packed with bone graft and two titanium threaded implants are placed across the joint to create what Bullock describes as “the environment for true arthrodesis.” Once the bone is in a bleeding state, Bullock notes, it is ready to heal. “We make sure that the joint achieves true, long-term fusion through bone growth and doesn’t rely only on rods or screws.” Pain relief has been immediate, anecdotally at least. Whether Symmetry will result in long-term pain relief remains to be seen and the company is in the process of designing its clinical trial. Meanwhile, Zyga already has 510(k) clearance for Symmetry and its 10-person sales force is out selling in the US. According to Bullock, the company has trained almost 80 surgeons so far. Many of its potential patients will be found in the 3,500 pain clinics served by 6,000 board-certified pain specialists in the US, Bullock believes. “There is a huge pent up demand among these patients. Once long-term results of this product are out, this is going to be a very large market and the strategies are going to have to pay attention to it.”

**FIRST IN SPINAL DENERVATION**

In 2012, Relievant Medsystems Inc. drew in $30 million in a series D financing round led by New Enterprise Associates with returning shareholders Canaan Partners, Emergent Medical Partners, Morgenthaler Ventures, and Onset Ventures. It was the year that in cardiology renal denervation start-ups attracted the attention of investors and strategics in a big way, and perhaps Relievant’s investors wanted to be in on the first spinal denervation company. (See “The Renal Denervation Buzz: Separating Fact From Myth” — “The Gray Sheet,” July 9, 2012.) More likely though, the company’s investors, which have put in $38 million since the company’s founding in 2004, liked the company’s nerve ablation technology.
because it addresses the largest market in low back pain – chronic, axial low back pain – with a minimally invasive intervention that addresses the pain directly. Justin Klein, MD, a partner at lead investor NEA says, “In addition to the huge market opportunity, we saw the chance to invest in an experienced team who is bringing forth a highly disruptive, cost-effective approach to a condition where so many other alternatives have fallen short.”

Alex DiNello, who joined Relievant as president and CEO in 2011, has spent 20 years in the spine industry, as a vice president and general manager for Medtronic Kyphon and as head of research and development for many of the industry’s giants, including Abbott Spine, and DePuy Spine. DiNello has recruited talent from Kyphon, which had a similar experience in building a new category of therapy.

“It’s a frustrating fact of spine care, but even after injections, discectomies, laminectomies, and spinal fusions, large numbers of patients continue to suffer from pain. DiNello says, “Having been on the hardware side, we have seen very good results in addressing structural issues, but we still fall short on patient outcomes as they relate to pain.” Relievant intends to intervene directly at the sources of back pain by ablating the nerve that transmits pain signals emanating from the endplates of vertebral bodies.

The intellectual property behind Relievant was created by Michael Heggeness, MD, the past president of the North American Spine Society (NASS) while he was professor and chair of orthopedic surgery at Baylor College of Medicine. In the mid-90s, while many researchers were focusing their work exclusively on the disc, Heggeness was conducting anatomical studies of human vertebrae. He identified the basivertebral nerve, which enters the vertebral body from the posterior wall and traverses to the center of the vertebral body, subsequently branching out to the endplates of the vertebral body that interface with the disc and was the first to identify an abundance of nociceptors (which relay pain signals) within the vertebral endplates.

Relievant has developed a percutaneous ablation therapy called Intracpect, which delivers radiofrequency energy into the vertebral body of the affected spinal level to ablate the basivertebral nerve. Using a trocar and stylette, under fluoroscopic guidance the surgeon accesses the pedicle in a procedure familiar to anyone that has been trained on kyphoplasty. Based on easily identified anatomic landmarks, the surgeon targets the nerve in the vertebral body and ablates with an RF probe. After the ablation, the instruments are removed and the incision can be closed with a few stitches.

Investigators reported on results of the company’s 16-person pilot study at the annual North American Spine Society meeting in 2011. Immediate relief was experienced by 13 of 16 patients. At one year, there was a significant improvement in pain relief as measured by a reduction in the Oswestry Disability Index (ODI) of 28 points. DiNello says, “To give you some perspective, a 10-point improvement is clinically significant. We saw nearly three times that.”

DiNello believes Relievant has already alleviated many startup risks. The pilot study validated the science by establishing the linkage between the basivertebral nerve and pain. Today the company is executing on larger scale clinical development. Down the road, the learning curve for Intracpect will not be high since it will leverage existing skills in the community of more than 5,000 operators worldwide who have already been trained on kyphoplasty for the treatment of vertebral compression fractures. The economics of Intracpect are attractive compared with $30,000 for surgeries for spine fusion or to implant spinal cord stimulators for pain relief. Intracpect is a relatively short procedure, whereas those other procedures require a minimum of two hours in the OR. Recovery and follow-up should also be much shorter for Intracpect. From the customer side, patients have few options between conservative care and spinal fusion, so Intracpect may be extremely attractive. “It is a very different approach,” DiNello says.

Intracpect has gained 510(k) clearance as a soft-tissue ablation device, but Relievant knows that it needs to back up a brand-new therapy and a novel mechanism of action with high quality clinical data. Pain relief is a complicated endpoint with psychosocial and other confounding factors, and the proof of Intracpect’s efficacy lies in clinical studies. To get that solid proof, the company sponsored a clinical trial called SMART (Surgical Multi-Center Assessment of RF Ablation for the Treatment of Vertebragenic Back Pain) under an IDE with the FDA.

SMART is a randomized, sham-controlled double-blind study of 200 patients at up to 20 US medical centers designed to generate Level I evidence of the safety and effectiveness of the implant. The company enrolled its first patient in October 2011 and expects to complete enrollment by the end of this year. The trial was rigorously designed with specific inclusion and exclusion criteria. SMART is recruiting only patients who have not had surgery before, who have pure, chronic, axial low pain without any stenosis or symptoms of radiating leg or buttock pain. The patients must also have failed conservative care for at least six months. The study is “a landmark randomized, sham-controlled, double-blind trial in spine and a focused way to show a linkage between chronic axial low back pain and the role played by the basivertebral nerve in transmitting pain,” says DiNello.

Intracpect’s initial indications for use will be based on this clinical trial population, but DiNello notes that the company’s end markets may ultimately extend into other groups of patients based on additional planned studies. “Patients who need stabilization for the spine also tend to suffer from concomitant pain, or longer term, people who get treatments for structural issues who still have pain might be candidates.” DiNello says Intracpect might be chosen for patients who have degenerative disc disease in cases where payors will not pay for fusion (as is increasingly the case), with the limitation that the therapy addresses only patients in whom pain is coming from the vertebral body. For example, clinicians might have to take care to rule out facet pain or a herniated disc.

Relievant’s target patients see a variety of clinicians: spine surgeons, interventional radiologists, and pain specialists. In the US, each year 12 million people consult physicians for chronic low back pain. Twenty percent of them may become surgical candidates, leav-
ing 10 million patients in the non-specific back pain category. Within that group, approximately 4 million will be classified with vertebral or discogenic pain, the group that is Relievant’s target market.

Once Relievant establishes its new therapy, will this space become like renal denervation, inviting a flood of competitors? DiNello says, “We have watched what has happened in renal denervation, and we have confidence in our robust global IP portfolio, which has early priority dates.”

ANATOMY-SPARING SCOLIOSIS SURGERY

It’s a tried and true formula in the medical device industry: take an invasive, morbid surgery and create a device that permits it to be done with a lower degree of invasiveness. That’s what the founders of K Spine Inc., serial entrepreneur Dan Sachs, MD, and orthopedic spine surgeon Allen Carl, MD, aim to do for patients with scoliosis, an abnormal twisting and curvature of the spine.

Patients who undergo scoliosis surgeries are generally adolescent girls, who schedule these major procedures at the beginning of the summer so they can recuperate during the school break. Surgery is indicated for severe or rapidly progressing scoliosis when the curvature is greater than 40 degrees, as measured on a scale known as the Cobb angle. Any more than that and the spine deformity (curvature and rotation) is likely to progress in severity, which can lead to an unsightly rib hump and can impede the function of the lungs or the heart.

Current surgeries for scoliosis are generally performed from a posterior approach. A long incision is made along the length of the thoracic and lumbar spine and the muscles are stripped off the spine to allow the surgeon access to its bony elements. The bony facets are removed along the length of the spinal column, and intervertebral ligaments may be cut to mobilize the spine. After a maneuver to correct the deformity, a surgeon attaches long metal rods to each side of the patient’s spine with pedicle screws inserted into each of the vertebral bodies – in some girls, eight to 12 levels of fusion are done. Finally, the spine is fused with a bone graft, either autograft taken from the patient’s ribs or hip, or allograft from cadavers. It’s a long procedure, notes Sachs, six hours or so. Pedicle screws are placed by fluoroscopy, so a young person and the surgeon are exposed to a fair amount of radiation, and each time a pedicle screw is inserted, there is always the risk, however slight, of penetrating the spinal canal and causing harm.

Sachs and Carl looked at current scoliosis surgery to see if they could come up with something that would better preserve native anatomy (avoid stripping muscles and destroying facet joints) and avoid fusing as many levels. By reducing the number of fused vertebral motion segments, the K Spine device preserves trunk growth and height potential in patients, many of whom have not yet reached skeletal maturity. Other areas the two wanted to improve upon were reducing the number of pedicle screws needed and the risks associated with their insertion. The founders believed their device could shorten OR time, reduce post-operative recovery time (patients are in the hospital for a week after the conventional surgery), and reduce the convalescence period prior to a return to unrestricted physical activity.

Sachs doesn’t wish to disclose the details of the device’s operation, although the company has completed animal studies, human feasibility studies and a pilot study with long-term follow-up. The device gained a CE mark in Europe. According to Sachs, the device achieves a three-dimensional correction (translation and de-rotation) similar to the existing procedure, without the need for a “full metal jacket” of hardware typical of current pedicle screw constructs. K Spine is also reducing the number of levels that are fused and is preserving the native anatomy and function, he says.

The company plans to launch its device in Europe in 2014, which it can accomplish as a small company because it’s working with a focused group of clinicians known as deformity surgeons. Seventy percent of scoliosis surgeries are done by 250 surgeons, Sachs notes. “Our clinical investigators in Europe have been motivated to implant our system because of the clinical benefits it offers their patients. They enrolled their clinical study patients on schedule and are eager for us to proceed to the commercial phase so that they can offer our device as a less morbid alternative to their current practice.” Unlike some other surgical specialties, deformity surgeons develop long-term relationships with their patients, who are children. They follow them over time, seeing them periodically over the years to check the Cobb angle for disease progression. Sachs says, “Their patient relationships are like that of primary care doctors.”

K Spine’s initial market is adolescent idiopathic scoliosis (AIS). Annually, 38,000 invasive long fusion procedures are done to treat AIS. Deformity correction is a $1 billion market in young children, adolescents and adults, according to Sachs. “It’s not as huge a market as some other crowded sectors in spine surgery, but it’s an unmet need with clear patient selection criteria, objective short-term efficacy endpoints [a measurement of the Cobb angle] and no major technology improvements since the introduction of pedicle screw constructs in the late 1990s. I think there is an opportunity to reduce the morbidity and costs of scoliosis surgery.”

K Spine has raised $16 million to date. VC backers include Dave Stassen from Split Rock Partners (previously the CEO of Spine-Tech) and Tim Haines from Abingworth (previously CEO of Axiom Therapeutics and two divisions of Datascapes Corp.) K Spine’s CEO and chairman is Ross Longhini, the former VP of research and development for Zimmer Spine and once COO and interim CEO of American Medical Systems.

K SPINE INC.

Founded: 2007
Clinical Focus: Spinal Deformity
Target Market: $1 billion Worldwide
Funds Raised To Date: $16 million
Products: Anatomy-sparing alternative to traditional scoliosis surgery

Related Reading

“Vertebral Compression Fracture Treatments Under Pressure” — IN VIVO, December 2010 [A200108001999]

“Motion Is Back In Spine Market” — Medtech Insight, December 2012 [A20127000091]

“Archus: Using Old Principles to Open a New Market in Spine” — IN VIVO, July 2008 [A20127800118]


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