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MARKET TRACK

Global DES Market

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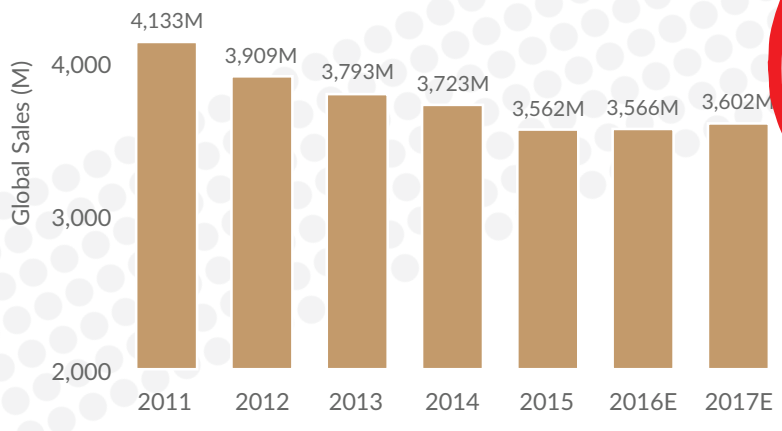

SetPoint Medical:
A Bioelectronic Therapy for the Largest Drug Market

SetPoint Medical has developed a bioelectronic medicine to treat chronic inflammation-mediated diseases of the immune system, such as rheumatoid arthritis and Crohn's disease. Unlike neuromodulation therapies that have come before, SetPoint elicits a molecular, rather than functional, reaction from the body, restoring the regulatory signal that tells the body to downregulate pro-inflammatory cytokines.

by
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YEAR FOUNDED

2007

WHO'S BEHIND IT

Kevin Tracey, MD, a neurosurgeon and researcher responsible for the discovery of the cholinergic anti-inflammatory pathway, now president, Feinstein Institute for Medical Research; Mike Faltys, CTO; Ralph Zitnik, CMO; and Anthony Arnold, CEO

UNMET CLINICAL NEED

A new treatment option for patients suffering from chronic inflammatory diseases such as Crohn's disease and rheumatoid arthritis, that is, an alternative to expensive, injectable or infused biologics for patients who don't want them, and for the large number of patients who don't respond to or suffer from adverse reactions to available drugs

SOLUTION

A bioelectronic medicine that stimulates the vagus nerve to produce a potent anti-inflammatory response at the molecular level

FUNDING TO DATE

$60 million in three rounds

In the recent investor presentations of major medical device companies, neuromodulation has been cast as a platform for growth into billion-dollar-plus markets currently dominated by pharmaceutical treatments. Today, the largest such market is the treatment of pain by spinal cord stimulation, which **St. Jude Medical Inc.** describes as a $1.6 billion-plus market worldwide. **LivaNova** has described neuromodulation for heart failure and sleep apnea each as having a potential market value of $1 billion. But that's only a drop in the bucket, compared to what's possible as device companies move into drug markets.

In going after rheumatoid arthritis (RA) and Crohn's disease with a neuromodulation platform, **SetPoint Medical Corp.** is targeting one of the largest opportunities: the $40 billion market for biologic drugs (such as **Amgen Inc.**'s *Enbrel* and **AbbVie**'s *Humira*). The company isn't out to displace these highly effective drugs, but aims to offer an alternative for large numbers of patients who don't respond to existing treatments or who eschew them because of potential side effects and high out-of-pocket costs (wholesale costs of *Enbrel* and *Humira* range from $3,700-$4,000 for a 30-day supply). Notes Anthony Arnold, CEO of SetPoint Medical, "The biologics market for rheumatoid arthritis and inflammatory bowel disease is $30 billion. Even if we only take 7-9% of the market, it's one of the largest medical device markets. It's right up there with cardiac pacemakers."

And that's just the beginning. While rheumatic diseases are lucrative proof-of-concept markets, SetPoint has a platform technology that might, in the future, also serve diabetes, osteoporosis and many other diseases with inflammatory components.

The magnitude of the opportunity explains why SetPoint's roster of investors includes major strategics from both the pharmaceutical and medical device industries. The company has raised more than $60 million in three rounds, the most recent being its $15 million Series C-1 round in September 2015, from a group of investors that includes **Boston Scientific Corp.**, **Medtronic Plc** (through an investment by Covidien Ventures), **Abbott Laboratories,** and **GlaxoSmithKline** (through its bioelectronics-dedicated fund Action Potential Venture Capital (*see "Action Potential: A Drug Giant Bets on Neuromodulation,"* The MedTech Strategist, *October 29, 2014*). Venture investors include Morgenthaler Ventures, Flare Capital, and Topspin Partners.

A Neurosurgeon Follows Brain Signals

SetPoint Medical was founded in 2007 by Kevin Tracey, MD, a neurosurgeon and researcher who is now president of the Feinstein Institute for Medical Research, and president (as well as a professor) of the Elmezzi Graduate School of Molecular Medicine; and Shaw Warren, MD, an attending physician at Massachusetts General Hospital, who is an inflammation researcher and infectious disease clinician. The start-up is developing a vagus nerve stimulation (VNS) platform to treat inflammation-mediated disorders of the immune system.

Tracey has dedicated his career to studying the role of inflammation in acute and chronic diseases, a mission he undertook after a one-year-old burn patient under his care unexpectedly died of shock in his arms. "I couldn't explain to the family or myself the mechanism of shock. Since Janice died I have spent 31 years studying

the molecules made by the immune system that can cause disease."

During the course of animal research on molecules designed to block inflammatory cytokines, Tracey's group happened to infuse an experimental drug into the brains of the subjects to observe the effect of blocking cytokines in the brain. They discovered something unexpected: the brain treatment caused a peripheral effect; levels of cytokines throughout the body were reduced. "We had manipulated the brain, and the brain had manipulated the cytokines in the body." At the time, it was not known that the innate immune system was controlled directly by the brain; rather, it was thought to be an automatic system controlled by circulating cells.

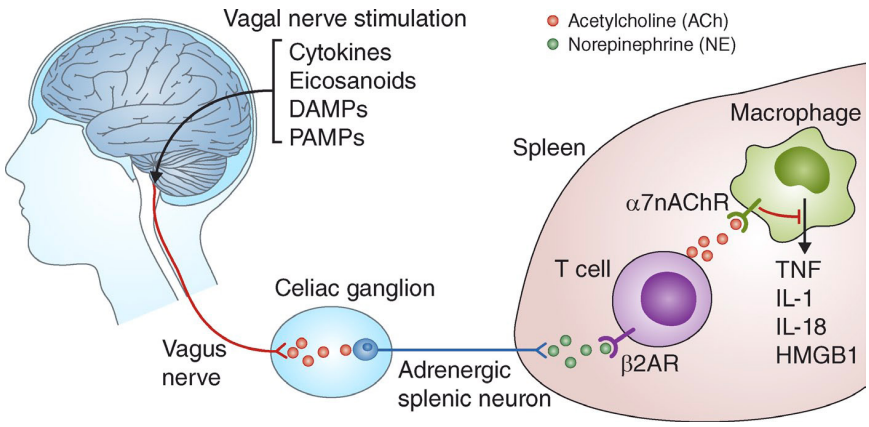
Tracey hypothesized that there is a two-way system of communication, from the body to the brain and from the brain out to the body, which he termed the "inflammatory reflex," and that the vagus nerve is a principal pathway by which communication occurs.

Starting with a Target, Rather than a Technology

Animal studies subsequently proved that the vagus nerve, which runs from the brainstem to the abdomen, innervating the heart, the esophagus, and the lungs along the way, was indeed such a signaling pathway. In May 2000, Tracey published his findings in the publication *Nature*. He described what he termed "the inflammatory reflex, whereby the body senses infection, tissue injury, and inflammation and relays this information up to the central nervous system via the vagus nerve, which then sends out a peripheral signal through the vagus nerves. The signal causes T cells in the spleen to direct monocytes and macrophages to reduce their production of the molecules that initiate and perpetuate inflammation (*see Figure 1*). "We get asked, 'wait a minute, you aren't stimulating any nerve that goes to the periphery. How do you get an affect there?'" says Arnold. "It is a systemic effect. It is changing the phenotype in the blood to make it less susceptible to inflammation and to reduce that attack on healthy tissue."

Figure 1

The Inflammatory Reflex



Source: J. Exp. Med., 2012, Vol. 209, No. 6, 1057-1068

Tracey then set out to find a way to use that knowledge to create targeted therapies for patients suffering from autoimmune diseases characterized by chronic inflammation. "In some patients with inflammatory disease, the circuit is disrupted. The immune system is out of control because the regulatory signal that should keep it in check is missing." The vagus nerve is like the brakes on the immune system, he says. As long as a person is healthy, the vagus nerve fires and keeps the immune system from overreacting. But if those brakes fail, the immune system runs amok. In the case of rheumatoid arthritis, high levels of circulating TNF alpha, IL-6, and other cytokines attack healthy joint tissue, causing erosion of the joint capsule, and ultimately pain, cardiac side effects, and other effects of inflammation.

Tracey's therapeutic target: to use the vagus nerve to restore the missing regulatory signal in patients with autoimmune diseases mediated by inflammation. It took 18 years, during which, as noted, SetPoint Medical was founded. "We started in 1998 and SetPoint's first human clinical trial was completed in 2014."

As a result of those long and exhaustive research studies, the company has amassed important IP in different areas, Arnold notes: core IP filed by Tracey around treating chronic inflammatory conditions with electrical stimulation coupled with IP from the company including method and utility patents, covering the shape, function, form, and stimulation parameters of the device itself, and how it interfaces with the nerves.

And now, at long last, the labor of love has borne its first fruit. In the July 19, 2016 issue of PNAS (Proceedings of the National Academy of Sciences) results of SetPoint Medical's 18-patient clinical study of its rheumatoid arthritis therapy were published. The study was significant, says Tracey,

because "For the first time we have shown that you can use a bioelectronic device to target the inflammatory reflex and block cytokines in humans."

VNS Therapy with a Difference

SetPoint's new platform consists of an implantable miniature neuromodulation device, a wireless charger, and an iPad prescription pad application (*see Figure 2*). The device stimulates the cervical vagus nerve, just above the collarbone. The recently published 18-patient clinical trial demonstrated that VNS therapy can reduce the production of TNF-alpha and other inflammatory cytokines, that reducing those inflammatory markers correlated with a reduction in the severity of disease symptoms, and that the therapeutic benefit was related to the therapy and when the therapy was turned off, cytokine levels increased and disease activity worsened (*see Figure 3*).

SetPoint is able to bank on the safety profile of previous VNS therapies, where Cyberonics (now LivaNova) leads the market with treatments approved for epilepsy and treatment-resistant depression. The Cyberonics VNS treatment for epilepsy has been safely used in more than 100,000 patients. SetPoint should be safer still, says Arnold, because it is operating at lower levels of energy for shorter periods of time. "An epilepsy stimulator may stimulate for 20-40% of the day or more. We stimulate for seconds per day. We activate the reflex of the body and that requires only a small amount of stimulation." Arnold compares it to a pill. "The second you take it, you don't get relief; it takes a little while for the inflammatory reflex to reduce circulating inflammatory cytokines, but when you do that for a few days, you see the signs and symptoms of the disease being to trail away."

A Device Treatment for Difficult and Costly Diseases

Approximately 1.5 million people in the US have rheumatoid arthritis, and worldwide estimates (in 2007) were 23 million. It can begin at any age and is associated with fatigue, pain, swelling, and deformation of the joints, and prolonged stiffness after rest. RA patients have been reported to experience more loss in function than people without arthritis in every domain of human activity, including work, leisure, and social relations, according to the US Center for Disease Control and Prevention's 2012 online publication, "Rheumatoid Arthritis, Impact on Health-Related Quality of Life (HRQOL)." RA is also associated with common co-morbidities, including cardiovascular disease, infection, anxiety, and depression. According to one study, RA carries a risk of mortality that is approximately 38% greater than for the general population.

Figure 2

SetPoint Medical VNS Therapy

Source: SetPoint Medical Corp.

Because neurostimulation devices require surgeries to implant them, throughout their history, they have operated as the therapy of last resort after drugs have failed. But rheumatoid arthritis—and Crohn's disease—are two conditions that, because of their consequences and the costs of treating them with drugs today, perhaps warrant a device therapy. In RA, for example, current guidelines recommend aggressive treatment, since permanent tissue destruction results from untreated disease. Crohn's disease can also result in morbid surgical resections of the GI tract.

Both chronic diseases are costly in terms of their impact on patients' lives, and sufferers rack up expensive pharmaceutical bills. As noted, the cost of biological drug therapies is about $48,000 a year per patient. Notes Arnold, "suppose you have a device that is $30,000 [although he notes that SetPoint has not determined pricing yet] and the surgery is about $20,000. In less than two years you have paid back the therapy, while potentially experiencing fewer side effects, a better risk profile, and no more infusing or injecting." In the future, patients, physicians, and payors will have a new, compelling option, he says.

Much work remains to be done before that can happen. Arnold points out that the recently-published clinical trial was a small, open-label study, the success of which paves the way for a larger study.

Neuromodulation Becomes Bioelectronic Medicine

SetPoint Medical is unusual; it's a medical device company, but its device affects molecular targets, and the efficacy of its therapy is measured with assays of blood-based biomarkers. Is it a device or a drug company? "It's a device with a drug-like effect," says Arnold, who notes that the FDA has determined that it should be regulated as a device, by its CDRH (Center for Devices and Radiological Health) branch.

As a medical device company, it's perhaps most unusual, however, in understanding the molecular mechanism of action of its therapy, and that gets at the distinction between the terms "neuromodulation" which tends to be used by device companies, and "bioelectronic medicine," which was coined on the pharma side. Neurostimulation is a decades-old technology whereby device companies have adapted their expertise in engineering, electronics, leads, and implantable devices to develop therapies that control organs that are electrical in nature (the heart or the brain, for example) with electricity, or to elicit a functional reaction from an organ by pacing a nerve or a muscle.

In contrast, SetPoint, GSK and others investing in bioelectronic medicine aim to launch a new era of medicine where electricity is used, not to actively control physiological processes but to trigger them so the body takes over and does the rest. "We are trying to elicit a natural reflex and they [conventional neurostimulation devices] are trying to control the system," says Arnold.

Now it becomes increasingly important for therapy developers to understand the mechanism of action of their devices. "We aren't taking a device approach to this problem. We start with a disease and pick a molecular target, but instead of screening for molecules that go after that mechanism, we screen, identify, or discover neural mechanisms that control that target," says Kevin Tracey. "Only then, when you know the target, the mechanisms, and the nerves, do you develop the device. Only then."

Tracey adds that in the past, in not knowing the mechanism of action of their devices, neurostimulation companies have operated at somewhat of a disadvantage. "They have succeeded in building devices that work in some number of patients. But if it doesn't work in some patients, or it doesn't work in a clinical trial, you can't fix it if you don't know the mechanism."

Arnold points out that SetPoint's novel therapy has required a team with feet in both the pharmaceutical and device industries. For example, one of the company's earliest employees, Mike Faltys, is a neuromodulation expert who formerly worked on cochlear implants at Advanced Bionics. Under the leadership of Faltys, the product development team has created a stimulator that is extremely small, autonomous, and programmable by iPad. In terms of technology, "The large companies are trying to get to the point where we already are," says Arnold. The company's chief medical officer, Ralph Zitnik, MD, was a former clinical director at Immunex and Amgen, where he helped launch *Enbrel*. "Ralph was one of SetPoint's first employees and has been integral to the success of the company. Ralph's deep knowledge of the mechanism of action, biologics, and leadership in trial design and execution has helped ensure that SetPoint conducts world-class studies similar to those conducted in the pharma industry," says Arnold.

As the company gets closer to market, there will still be a few hybrid pharmaceutical/device issues to overcome; for example, referral patterns in specialties that haven't yet had a paradigm of referring patients off to surgery, i.e. rheumatology, and the corresponding lack of strategic marketing resources in that area. But again, notes Arnold, "10% of this market is bigger than anything strategics do in neuromodulation today. They'll invest in the resources!"

Figure 3

CLINICAL TRIAL DEMONSTRATES SETPOINT THERAPY'S EFFICACY

Study Design:

- **18 patients with active disease were enrolled. (One patient was subsequently diagnosed with Whipple disease and was excluded from the efficacy analysis).**
- **7 patients (cohort 1) had active disease despite therapy with methotrexate and had either never received a biological TNF antagonist or had previously failed treatment with TNF antagonists because of drug toxicity.**
- **10 patients (cohort 2) had failed conventional therapy with methotrexate and had also failed treatment with at least two biological agents with different mechanisms of action (anti-TNF, anti-IL-6 receptor, B-cell therapy and/or T-cell costimulation inhibitor)**
- **The treatment consisted of a single daily 60-second stimulation of up to 2.0 mA. On day 28, frequency of daily stimulation was increased to four times in patients who had not achieved at least a moderate clinical response.**
- **Between days 42 and 56, the stimulator was turned off and restarted again on day 56 until the study end on day 84.**

Results:

- **There were no deaths, serious adverse events, or withdrawals from the study because of adverse events or infections.**
- **Clinical response correlated with significant reductions in TNF release.**
- **On day 42, TNF production in cultured peripheral blood went down by more than 40%**
- **On day 56 (after a period of no therapy), TNF production had risen by 47%.**
- **On day 84 (therapy was turned on again for 28 days), TNF production dropped by 24%.**
- **On day 42, the percentage of patients achieving an ACR20 score was greater than 70%.**

Source: PNAS, July 19, 2016, 113, 29: 8284-8289