A spark at the periphery

Electroceutical devices that stimulate the peripheral nervous system come to the fore. Emily Waltz reports.

In August, GlaxoSmithKline and Verily Life Sciences (formerly Google Life Sciences) announced a new venture, a company called Galvani Bioelectronics, which, with up to more than $700 million in funding from the two partners, will develop miniaturized electronic devices for peripheral nerve stimulation. This is the latest in a recent string of successes that the fledgling electroceuticals field has racked up, which include a breakthrough first-in-human clinical success in rheumatoid arthritis by SetPoint Medical of Valencia, California, and an approval by the UK’s National Health Service of a handheld vagus nerve stimulator for migraine and cluster headache, developed by ElectroCore of Basking Ridge, New Jersey.

Unlike electrical therapies of the past, these new commercial efforts aim to harness knowledge of neurophysiology and molecular mechanisms to guide the design of neuromodulation devices. Together with an ongoing influx of funding from several large organizations (Box 1), biomedical engineers are generating the tools and maps they need to build better, more targeted neurostimulation devices.

Striking a nerve

Devices that harness electrical impulses have been used for decades to improve health and save lives—the most common being pacemakers and defibrillators. Deep-brain stimulation is fairly widely used to treat people with Parkinson’s disease, sacral nerve stimulation is used to restore bladder control and spinal cord stimulation has been applied to treat pain. Most work in peripheral nerve stimulation (PNS) has focused largely on the voluntary or somatic nervous system in an effort to restore movement in people who have paralysis due to spinal cord injury or stroke. But that field has seen little commercial activity due to its relatively small market size.

What’s got entrepreneurs excited about PNS for the autonomic nervous system is that it has the potential to treat a wide range of diseases that are currently underserved by oral or injected drugs. But instead of circulating throughout the body and causing side effects as drugs do, PNS can send a message straight to—and only to—the target. That’s led some in the field to dub such therapies ‘electroceuticals.’ In fact, some PNS researchers are targeting the same mechanisms as those targeted by blockbuster commercial drugs.

The peripheral nervous system’s involuntary, or autonomic, nerves play a large role in organ function and immune responses and in the body’s inflammatory, respiratory, cardiovascular and urinary systems. Just how central a role it plays in these areas continues to become more apparent. “It’s starting to be very well established that the immune system can be controlled through the nervous system. Ten years ago, people may have said that was crazy,” says Kris Famm, vice president of bioelectronics R&D at GlaxoSmithKline in London.

The peripheral nervous system carries electrical impulses to and from the brain and spinal cord via action potentials. The signals travel along neural networks in different temporal patterns, like a drum beat or Morse code. These patterns dictate chemical and biological changes throughout the body. When those communication signals are disrupted or don’t fire properly, a myriad of things can go wrong.

Electrical stimulation enables researchers to hack into the nervous system, and potentially restore or correct communication. In many such devices, a pulse generator sends electrical impulses through a lead to electrodes that are placed on or near a nerve. The pulse generator ramps up intensity of the stimulation to a threshold that causes neurons to fire. Those artificially induced action potentials are indistinguishable from those produced by the body.

Compared with the pharmaceutical drug screening process, developing a stimulation therapy can be done much faster. Theoretically, once the mechanisms are identified and signal patterns of the healthy target nerves are recorded, “the therapeutic intervention is
The NIH, DARPA and GlaxoSmithKline (GSK) are all funding projects that seek to identify the functions of neural circuits, decode the signals traveling through nerve fibers and develop new tools to interface with the nervous system. “When you invest...in the science and the mechanistic underpinnings, it opens a lot of doors,” says Juan Pablo Mas, a partner at GSK’s bioelectronics venture capital (VC) arm. “It opens doors to financing. It helps bring in money when you can answer questions like, Why should this work? How does it work? And it opens the door to easier conversations with the FDA and payers because you can provide them a scientific rationale [in addition to] clinical data.”

On top of investments from the NIH, DARPA and GSK, two large centers devoted to bioelectronics are being built—one at the Karolinska Institute in Stockholm, Sweden, and the other at the Feinstein Institute in Manhasset, New York. The state of New York in March committed $50 million to its center, and the investment was matched by $600 million in private funding.

Through its SPARC program, the NIH has committed $248 million to the field over seven years and plans to announce by October the recipients of the core of that funding. The bulk will go toward anatomical and functional mapping of organs and associated nerves. The agency will also fund projects aimed at improving tools such as electrodes that better interface with nerves, and ways of recording how end organs change when associated nerves are stimulated. A substantial portion will also go toward projects with industry to study new uses for existing neuromodulation devices.

DARPA’s nearly $60-million program called ElectRx is similarly focused on the physiology of nerve circuits and unconventional technologies that record and interact with peripheral nerve targets. The agency wants to apply these efforts toward inflammatory diseases and mental health, particularly post-traumatic stress disorder, says Weber, at DARPA. The agency in March announced another PNS program—the ‘Targeted Neuroplasticity Training’ program—to explore how stimulation of peripheral nerves can enhance learning processes in the brain. It plans to announce the winning research proposals by November.

The NIH’s Peripheral Nervous System (PNS) program funds research teams. “The unknowns and technological shortcomings have forced companies to shoot rather randomly and broadly at a nerve and hope the therapy reduces symptoms. That’s a far cry from the drug industry’s approach of finding and then targeting a known mechanism underlying a disease or disorder. “The pharma industry begins with a molecular target and moves to screening for drugs,” says Tracey. Bioelectronic medicine should begin the same way, he says. Then, instead of screening drug candidates, companies essentially screen stimulation parameters that will recruit the groups of nerve fibers associated with that mechanism. “That’s the challenge to how the device industry has to move forward,” he says. “You can’t just build a device and stick it in a bunch of people and see what happens when you turn it on.”

The push for using mechanisms as a guide to building stimulation devices has been echoed among researchers both in academia and industry. Most of these new resources are being focused on peripheral nerve stimulation, rather than brain or spinal cord, partly because the opportunity to understand the mechanisms underlying PNS are more accessible than those of the central nervous system. The degree of complexity and integration of the cells of the brain—thousands of connections for each cell and billions of cells—is mind blowing, says Moncef Slaoui, GSK’s chairman of global vaccines, who was instrumental in establishing GSK’s investments in the field of bioelectronics.

And honestly, it’s a miracle that when you do [deep brain stimulation] people have a benefit on the other side of it. Because you have no idea what you’re doing,” he says. Deciphering those connections “is going to take an incredible amount of time” and will probably have to be hammered out in academic settings, he says.

Nerves of the periphery, on the other hand, are far less complex, making the decision to tackle those first a pragmatic one for companies. “Where the nerve hits the organ, you’re talking about several hundred or thousand nerve fibers...as compared to billions in the brain,” says Slaoui. Working in the periphery also allows researchers to target organs in a way that’s more specific than can be accessed through the central nervous system, adds Famm at GSK.

### Getting down to size

It helps that a large pharma company has publicly announced its interest in the field. Over the last three years, GSK has set up a 30-person R&D unit, nearly 50 external research collaborations and a $50-million venture capital
(VC) arm, all devoted to bioelectronics, and specifically PNS. In June, the company notified three independent research groups that they were finalists for a $1-million prize GSK had first dangled in front of the field in 2013. The first group to show that it can record, stimulate and block neural signals in one of four organ systems will win.

GSK’s announcement August 1 that it is partnering with Verily to establish a new bioelectronics company is a big deal for the field of PNS, in that it brings together two pharma and tech powerhouses. Verily, an Alphabet (formerly Google) company, will contribute its technical expertise in the miniaturization of low-power electronics, device development, big data analytics and software development. “It became clear to us that we needed a strategic partner that would bring the engineering,” says Slaoi. In looking for that partner, GSK had engaged most of the big players in the tech space and found that many were intrigued but were also very concerned by the regulatory requirements of putting their devices in the human body. With Verily, “there was a complete alignment of vision for bioelectronic medicine and appetite for risk and willingness to give this a chance,” he says.

GSK’s VC arm, called Action Potential Venture Capital, is also investing in companies with enabling technologies, such as micro-electronics and wireless powering. Such advancements will be key to interfacing PNS systems with the tiny nerves that adjoin end organs, and to appeasing patients. Most stimulation devices on the market require the implantation of a pacemaker-sized pulse generator, plus a lead and an electrode cuff that goes around the entire nerve.

Recruiting fewer, more targeted fibers could reduce side effects, such as vomiting and hoarseness—common with vagus nerve stimulation—and prevent neural circuits from becoming desensitized from overstimulation. Such improvements could also reduce the power drawn from the pulse generator, which enables such devices to be smaller. In terms of neurostimulation, “there is a general sense that we are probably overdoing it,” says Morris at NeuSpera. The moment one learns which fibers are the ones that need to be stimulated to drive a particular effect, “everything else is an overdose,” he says. NeuSpera has licensed from Stanford University a powering technology that enables placement of ultra-miniaturized stimulation devices at deep tissue targets in the body through an injection, rather than a surgical incision. That technology, called midfield powering, can wirelessly power injected stimulation devices by propagating electromagnetic waves within tissue. The company plans to license the powering technology and also apply it to its own ultra-miniaturized stimulation device for an undisclosed therapeutic indication. The company’s investors include GSK’s Action Potential Venture Capital and New York-based Windham Venture Partners.

Some of the newer, smaller players in the neuromodulation field are putting more time and resources into basic science. That’s the strategy being taken by SetPoint Medical, which is developing an implantable vagus nerve stimulator to treat inflammatory diseases such as Crohn’s disease and rheumatoid
arthritus. The company was co-founded by Kevin Tracey at Feinstein and is also backed by Action Potential.

SetPoint’s technology is built on the grounds that the nervous system regulates immune responses and can inhibit inflammation. SetPoint, Tracey and other academic collaborators reported in July that they had demonstrated in humans that they could inhibit the production of tumor necrosis factor (TNF) and other inflammatory cytokines by stimulating a subset of 4,000–5,000 vagus nerve B fibers. TNF is the target of several rheumatoid arthritis drugs on the market, and cytokines are the target of a $50-billion industry.

The experiment was novel in that the underlying neurophysiology and mechanism of action of the neural circuit were characterized first, and that guided the researchers where and how to stimulate. The results are “very strong,” says Warren Grill, a biomedical engineer at Duke University in Durham, North Carolina, who did not participate in the study, and has been a consultant for SetPoint.

Tracey’s group is now headed back to the laboratory. He wants to see the number of target nerve fibers narrowed from B fibers to a smaller subgroup. He also wants to know what the patterns of action potentials in healthy nerve fibers look like so he can replicate them with electrical stimulation in the nerves of people with rheumatoid arthritis. “That’s what I have ten people working on right now,” he says.

Commercial limits on R&D

That kind of splicing is severely limited by anatomical access. And many of the tools that could less invasively identify the role of individual populations of fibers are still in their infancy, and limited to animal models. Optogenetics, in which light is used to control neurons that have been genetically modified to express light-sensitive ion channels, is one option. Chemogenetics and magnetogenetics, in which a custom small molecule or a magnetic field, respectively, are used to control engineered receptors expressed in subsets of cells are additional options.

Devoting the resources needed to get that level of detail may be beyond what many companies are able or willing to bankroll. “There really isn’t a clear way to stimulate only a subset of the neurons without doing a tremendous amount of splicing out nerves and testing each one,” says J.P. Errico, chief science and strategy officer at ElectroCore, which is developing a handheld, non-invasive vagus nerve stimulation device to treat migraines, cluster headaches and other conditions. “I don’t know how practical that will be in the commercial environment or real-world clinical practice.”

ElectroCore has focused much of its R&D dollars on understanding how stimulation of the vagus nerve plays a role in modulating neurotransmitters, how that affects inflammation and what the clinical effects of that are. Stimulation of the vagus nerve seems to enhance production of inhibitory neurotransmitters, such as serotonin, acetylcholine, norepinephrine and GABA, helping bring them back to normal levels, says Errico. That helps balance the levels of excitatory neurotransmitters, such as glutamate, which has been implicated in primary headaches and other disorders.

“You have a little glimmer of understanding here and there. But in general, we don’t have a map,” Kris Famm, GSK.

From empiricism to mechanism

Success will continue to be limited, however, without digging deeper into the mechanisms.

If a device isn’t working in a third of patients and researchers have no idea why, it’s hard to improve on that therapy. “For every successful trial you have a number of unsuccessful trials where something was tried and it did not meet its primary endpoint,” says Civillico. “In many cases, it didn’t meet its primary endpoint in a very scientifically tantalizing way, in that it worked for some of the people really well, and didn’t work for a lot of the people. So that creates the possibility that there’s a huge room for improvement if we understood why it’s working sometimes and not other times.”

That point was illustrated in a series of recent clinical trials that put one company out of business. The trials tested vagus nerve stimulation as a treatment for heart failure. Animal studies conducted by different research groups looked promising. Although the mechanisms were unclear, vagal nerve stimulation seemed to have positive effects on the heart, such as reduced ventricular arrhythmias, anti-inflammatory effects, a normalizing of nitric oxide synthase levels and general improvement of heart failure symptoms.

Encouraged by the preclinical results, BioControl Medical, based in Yehud, Israel, developed a vagus nerve stimulator called

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CardioFit. The device aimed to stimulate B fibers in the vagus nerve that travel to the heart. In a couple of pilot studies involving small numbers of patients, the CardioFit device was found to be safe and improved patients’ quality of life, exercise capacity and their hearts’ blood pumping efficiency. The clinical endpoints and heart failure barometers were all going in the right direction,” says Ehud Cohen, former CEO of BioControl Medical.

BioControl ramped up its next trial to over 700 patients. Called INOVATE-HF, the trial compared the efficacy of the CardioFit device to standard care in people with heart failure. But four months after investigators completed enrollment, in December 2015, the company had to stop the trial. There were no reductions in hospitalizations or deaths—the primary endpoints—compared with the control group. BioControl Medical shut down operations in July.

Boston Scientific’s vagal nerve stimulator trial for heart failure, called NECTAR-HF, did not translate well from preclinical experiments either. In the 96-patient study, effects on cardiac function were not significant compared to the control group, although some patients reported better quality of life and exercise capacity.

What went wrong in the INOVATE and NECTAR studies is unclear. Each study used different stimulation parameters. And in none of the clinical studies did investigators know exactly which fibers they were stimulating. “I think it’s a matter of not using the right levels of stimulation,” says Benjamin Scherlag, a cardiac physiologist at University of Oklahoma College of Medicine in Oklahoma City.

Cohen at BioControl Medical says INOVATE-HF’s failure was a result of the design of the study. Partway through, the company realized that about half of the patients—those who hadn’t responded to a first-line electrical therapy for heart failure called Cardiac Resynchronization Therapy (CRT)—were also not responding to vagus nerve stimulation. That’s supported by research by Minneapolis-based CVRx, which is developing a vagal nerve stimulator device for hypertension and heart failure. The company in 2015 reported that results were particularly positive in heart failure patients who had not been treated with CRT.

But in BioControl’s case, the company had not built into the trial the flexibility to steer away from this subpopulation of patients mid-study. “In retrospect, we could have done a clinical design that is more adaptive,” Cohen says. Device companies need to take note of the more sophisticated clinical studies common in the pharma industry, he says.

For LivaNova, a missed endpoint in a clinical trial may have set back not just the company, but possibly the field of vagus nerve stimulation. In 2005, the company (then called Cyberonics), received FDA approval for its vagal nerve stimulator device in people with treatment-refractory depression, giving the company a large potential market outside of epilepsy. Several payers initially reimbursed for the device, and it was implanted in several thousand people. But almost two years later, the US Centers for Medicare and Medicaid Services (CMS) announced it would deny coverage of the device.

The decision was based on a primary endpoint that the company had missed in a clinical trial. After CMS’s decision, private payers stopped covering the device for depression, leaving LivaNova without that market. “I think you would have seen a more rapid growth in PNS if the company were able to convince CMS to render a favorable coverage decision,” says Morris at NeuSpera, who was previously senior vice president of R&D at Cyberonics. “The company had a couple of false starts and had to redefine itself” by turning to the epilepsy market, he says.

LivaNova says it continues to work with investigators and with CMS to find a pathway for access to its vagal nerve stimulation therapy in people with depression. The market is large and many people with depression don’t like or don’t respond to commercial drugs for the condition. PNS offers an alternative for those people, and LivaNova says it knows much more about the technology today than when its pivotal trial was designed. “The results [in depression] I’ve seen are quite compelling—particularly the long-term ones,” says Morris. Presenting better studies and more knowledge of the mechanisms may help get these payers on board.

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