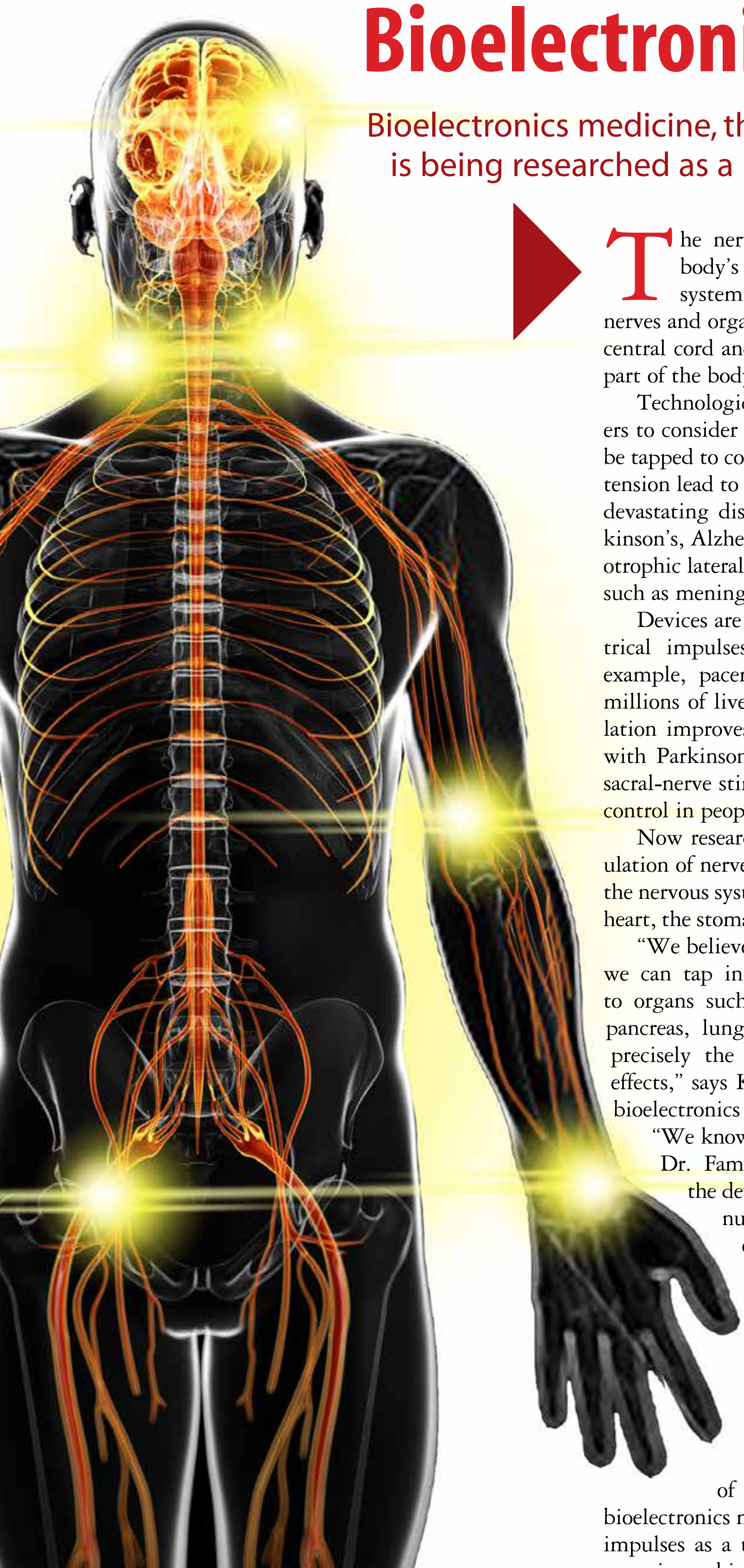
By Denise Myshko

A NEW FRONTIER: Bioelectronics Medicines

Bioelectronics medicine, the use of electrical impulses as a treatment approach is being researched as a possible therapeutic option for some disease areas.



The nervous system is essentially the body's electrical and communication system that wires together all the nerves and organs — starting at the brain and central cord and branching out to every other part of the body.

Technological advances have led researchers to consider how the nervous system might be tapped to control organ function and by extension lead to advanced treatments for several devastating diseases, including epilepsy, Parkinson's, Alzheimer's, multiple sclerosis, amyotrophic lateral sclerosis, stroke, and infections such as meningitis, encephalitis, and polio.

Devices are available that can harness electrical impulses to treat some diseases, for example, pacemakers and defibrillators save millions of lives each year; deep-brain stimulation improves the quality of life for people with Parkinson's disease and depression; and sacral-nerve stimulation restores some bladder control in people with paraplegia.

Now researchers are looking at how modulation of nerve signals can control the part of the nervous system that includes the lungs, the heart, the stomach, the intestines, and bladder.

"We believe the time is approaching when we can tap into the peripheral nerves close to organs such as the spleen, liver, kidney, pancreas, lungs, and GI track to modulate precisely the signals therein for treatment effects," says Kris Famm, Ph.D., head of the bioelectronics unit at GlaxoSmithKline.

"We know that neuromodulation works," Dr. Famm says. "Neuromodulation in the device world has been around for a number of decades, largely focused on pain and the spinal cord."

Now, he says, researchers are trying to use the mechanisms of the nervous system for other disease areas. GlaxoSmithKline is working with researchers in academia as well as other companies to determine whether a new class of therapeutics can be created: bioelectronics medicine, or the use of electrical impulses as a treatment approach. The company is working with 35 universities around the world seeking proof of principle in disease areas as well as with different technologies.

Dr. Famm says early clinical trials in rheumatoid arthritis show that the nervous system exerts control over the immune system and the production of cytokines. He says the company hopes to improve on what can be done with monoclonal antibodies against TNFs and proinflammatory cytokines by instead turning down the volume in the nervous system. "Our nerve signals go from the brain through the vagus nerve and to the spleen, which is central for cells in the blood that produce cytokines," he says. "These cytokines trigger inflammation, which ultimately cause the problems in our joints that result in rheumatoid arthritis. If we could change the signals to the spleen, that changes the behavior of the cells that come through the spleen and cytokine production is reduced."

Dr. Famm says the same thing could be true for regulating the metabolism in other organs, such as the pancreas, liver, and GI track.

"If we can control how the organs respond to different steps in metabolism from the sensation of food uptake to the production of various molecules, this may lead to setting the right glucose levels in the body, for example," Dr. Famm says. "The nervous system is one important way that our body is controlled. In the future, the promise is that we will be able to tap into those natural control circuits and use them for treatment effect."

GSK's Interest

GlaxoSmithKline has made a big commitment to this area. In August 2013, GSK launched Action Potential Venture Capital (APVC), a $50 million strategic venture capital fund that will invest in companies that pioneer bioelectronic medicines and technologies.

In September 2014, GSK announced a $5 million Innovation Challenge Fund (ICF) to further encourage and advance collaborative research as part of its effort to develop bioelectronic medicines. The fund will support academic groups and small companies that want to develop solutions for GSK's Bioelectronics Innovation Challenge. This is in addition to a $1 million prize for the first team to create a miniaturized, implantable, wireless device that can record, stimulate, and block specific neural signals to and from visceral organs.

"We have a really strong bench of scientists and expertise in the biology of disease and the physiology of organs," Dr. Famm says. "We would traditionally pair this expertise with medicinal chemistry for small molecule drugs or with antibody engineering to make a monoclonal antibody or with vaccine technology. In this case, we want to see if modulating nerve signals can be used to achieve a treatment effect. It's a great opportunity."

Early Research Efforts

The vision for bioelectronic medicines is one of miniature, implantable devices that can be attached to individual peripheral nerves. Such devices will be able to decipher and modulate neural signaling patterns, achieving therapeutic effects that are targeted at single functions of specific organs.

GSK executives believe in the next one to two decades, bioelectronics medicines could become central treatments in a host of major chronic diseases such as diabetes, asthma, hypertension, arthritis, pain, and even cancer.

The first investment of GSK's fund was in SetPoint Medical. SetPoint Medical has started a proof-of-concept open label trial for moderate-to-severe Crohn's disease across five centers in Europe, says Anthony Arnold, CEO of SetPoint Medical. The trial will enroll about 15 patients. Eventually, the company plans to field a large randomized pivotal style blinded trial in many centers around the world with a hundred or more patients.

"The body has a control network called the inflammatory reflex, which modulates autoimmune signs and symptoms, specifically inflammation," Mr. Arnold says. "In that network, the primary communication avenue is the vagus nerve, which is located in the neck next to the jugular and carotid arteries. This is a major nerve bundle that goes directly from the brain and innervates all the visceral organs, including the spleen and the liver.

"We have learned that patients who have autoimmune disorders, particularly those with elevated levels of inflammation and inflammatory cytokines, have reduced activity in the vagus nerve," Mr. Arnold continues. "There is not a lot of communication from the brain down. We are trying to produce this communication through a bioelectronic medicine by briefly stimulating the nerve with a specific electrical pattern to help the body regulate itself again and to turn on that regulating pattern. When it does, there is a rapid decline in patients' cytokine production, TNF alpha, IL1, and IL6, which are drug targets."

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Dr. Kris Famm
GlaxoSmithKline

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ANTHONY ARNOLD
SetPoint Medical

Mr. Arnold says the work SetPoint is doing is different from neuromodulation that would typically be seen in treating pain patients.

"If we stimulate the vagus nerve with just a brief dose, the patient responds with a reduction of pro-inflammatory cytokine production for a couple of days," he says. "There is an immediate depression of objective markers. The response is more characteristic of a drug than a device. And unlike a device where the idea is to stimulate a nerve directly and elicit a response in the brain — such as perception of sound or pain — we're are trying to modify the disease. There is a subset of T-cells that is reprogrammable by stimulation, which ultimately results in macrophage changes that lead to TNF alpha, IL1, and IL6 suppression. In that sense, the device behaves very much like a drug. We are targeting the specific population of T-cells in the spleen and gut to drive a systemic response that ultimately lowers inflammation dramatically."

Mr. Arnold says SetPoint has seen success already in a first-in-human study in rheumatoid arthritis. At the primary end point, two of the eight patients in the study achieved DAS remission, and six of the eight had a positive ACR 20 response, results similar to those typically achieved in larger studies with drugs currently used to treat RA.

"Within a few days, the patient's signs and symptoms of RA begin to melt away very rapidly," he says. "Now we want to see if we can achieve similar results in Crohn's disease."

Public Research Efforts

In addition to GSK's and SetPoint Medical's work, public programs are investigating this area of research. The National Institutes of Health has a begun a $248 million program called Stimulating Peripheral Activity to Relieve Conditions (SPARC). The Common Fund's SPARC program supports efforts to develop proof of concept for an entirely new class of neural control devices. The SPARC program tentatively plans to support interdisciplinary teams of investigators to deliver neural circuit maps of several organ systems, novel electrode designs, minimally invasive surgical procedures, and stimulation protocols, driven by an end goal to develop new neuromodulation therapies.

Begun in June 2014, the program will develop high-resolution neural circuit maps and next-generation neural modulation devices — implants that can stimulate nerves — and will demonstrate the use of these tools in the development of new therapeutic strategies.

In August 2014, the Defense Advanced Research Projects Agency launched the $79 million Electrical Prescriptions (ElectRx) program. This program is seeking innovative research proposals for neuromodulation therapies for a wide range of diseases.

In support of the White House's Brain Research through Advancing Innovative Neurotechnology (BRAIN) Initiative, ElectRx is also seeking to understand specific neural circuits and their role in health and disease. Future therapies based on targeted peripheral neural stimulation could promote self-healing, reduce dependence on traditional drugs, and provide new treatment options for illnesses.

The BRAIN Initiative is part of a Presidential focus launched in April 2013 aimed at revolutionizing the understanding of the human brain. Since its launch, the BRAIN Initiative has grown to five participating federal agencies as the Food and Drug Administration and Intelligence Advanced Research Projects Activity join the NIH, National Science Foundation (NSF), and DARPA. NIH has announced $46 million in new grant awards and all of the participating agencies are committing to engage in BRAIN Initiative-related work in fiscal year 2015. PV