THE EVOLUTION OF BIOELECTRONIC MEDICINE

Reprogramming the Body to Fight Disease with Electricity

SetPoint MEDICAL

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The convergence of technology is all around us. The ubiquitous iPhone, which expanded the realm of mobile phones to include web browsing, texting, cameras, video, GPS and applications for almost any task that can be imagined, led to a generation of smartphones that have disrupted numerous technology markets and have forever altered the way we manage our lives. Today's popular ridesharing services, Uber and Lyft, leveraged GPS technology, cell phone apps, the popularity of on-demand shopping, cashless payments by phone, entrepreneurship, flexible work environments and national brand recognition. The result was transformative. People, who once anxiously worked to find a reputable cab service in a strange city or paid a premium for a limo service, now could access a trusted brand in any city, immediately track multiple drivers available to pick them up in minutes and pay without touching their wallets.

Some of the most important technological advances happen through convergence rather than a single discovery. Pioneers sometimes see developments around them from a different perspective. Whether by design or lucky accident, when motivated people are in the right place at the right time, they can draw from and build on developments and trends in multiple fields, apply their own expertise, make new discoveries and integrate what they learn to create new products, services and technologies that change the world.

In healthcare, the new therapeutic field of bioelectronic medicine also draws on a wave of convergence, leveraging:

- Increasing understanding of immunology and neuroscience
- Experience learned in the last few decades implanting active medical devices
- Awareness of the side effects of pharmaceuticals
- The new challenges in healthcare economics

It's a field that shows so much promise that it has garnered more than $1 billion in investment in the last three years, led by early investment from GSK and followed by other industry leaders such as Google, General Electric and others, along with the National Institutes of Health and DARPA in the public sector.

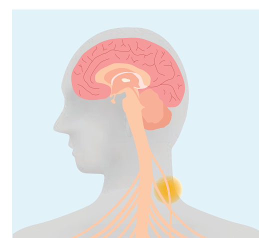
What is Bioelectronic Medicine?

Bioelectronic medicine is a new field that focuses on developing methods to treat diseases using electrical pulses instead of drugs. Bioelectronic medicine treatments can now be accomplished using a small implanted device that generates and delivers periodic digital doses to nerve bundles, creating a disease-fighting effect that can last hours or days based on mechanisms similar to drug therapies.

While this might sound like science fiction, electronic brain- and nerve-stimulating implants are already widely used for several conditions, including epilepsy, Parkinson's and bladder control. Progress with those conditions has opened potential avenues to stimulate memory, enhance eyesight, strengthen a weak gait or even improve someone's golf swing.[1]

Those self-improvement hopes are not close to prime time, but bioelectronic medicine is gaining momentum as a new way to treat challenging diseases.

While bioelectronic medicine, neuromodulation and "electroceuticals" are all terms that have been used somewhat interchangeably, there are key differences (see the Appendix for definitions). What sets bioelectronic medicine apart is the biological impact it has in the body, going beyond the mediation of symptoms to address the underlying disease by harnessing the body's own mechanisms.



With encouraging early results in several trials and additional trials underway, it's likely that bioelectronic treatments will be approved for clinical use within the next few years. Forward-thinking scientists, engineers, physicians and innovators with unique skills combined old and new discoveries in ways no one had before to make this progress possible.

Scientific Foundations of Bioelectronic Medicine

A number of key scientific discoveries, medical advances and technological developments played a crucial foundational role in the evolution of bioelectronic medicine.

Engaging the Vagus Nerve

As far back as the 1880s, researchers observed that manual massage and compression of the carotid artery in the cervical region of the neck could suppress seizures.[2] That effect stems from stimulation of the vagus nerve, which starts at the brain stem, splits into two branches and travels through the neck, chest and abdomen. It is the longest nerve in the body, and it regulates heart rate and dozens of other vital functions.

Electricity and Electric Implants

People have always been intrigued by electricity and its potential for treating ailments. It's reported that some ancient Egyptians would stand on an electric fish to control pain. The ancient Greeks used electric rays, a type of fish, to treat gout and numb the pain of surgery and childbirth.

By the 1930s and 1940s, scientists were starting in earnest to investigate the healing potential of electricity. Their efforts quickly turned to neuromodulation – using electricity to stimulate the vagus nerve, targeting the brain. Studies in animals focused on the effect of disrupting the signals that cause seizures and other conditions. Now, these devices are the standard of care for certain conditions. In 1997, the U.S. Food and Drug Administration (FDA) approved an implanted vagus nerve stimulation (VNS) device for the treatment of refractory epilepsy. In 2005, the same device was approved for chronic treatment-resistant depression.[3]

The International Neuromodulation Society describes the benefits and limitations of neuromodulation: "While they are not a cure for an underlying condition, neuromodulation therapies provide an additional means of managing symptoms of chronic conditions."

Additional medical applications of electricity include spinal cord stimulation for chronic neuropathic pain; implanted cardiac pacemakers and defibrillators for ischemic disease such as angina and peripheral vascular disease; sacral nerve stimulation for pelvic disorders and incontinence; and gastric and colonic stimulation for gastrointestinal disorders such as dysmotility or obesity.[4] Cochlear implants, which were invented and improved with research in the 1970s and 1980s and came into wide use in the 1990s, use a combination of an external electronic device with a current source and an electrode array that is implanted into the cochlea to generate electrical current, stimulating surviving auditory nerve fibers to provide hearing for people with profound or severe hearing loss.[5]

Today, more than 120,000 people around the world use cochlear implants to hear. Deep brain stimulation was approved in 2002 and is now often used to improve motor function in patients with Parkinson's disease. By 2013, it was estimated that about 40,000 patients had received deep brain implants.[6] More than 4.5 million people worldwide have implanted cardiac pacemakers.[7]

Discovery of the Inflammatory Reflex

In 2002, discovery of a new biological pathway called the Inflammatory Reflex opened the door to treating disease systemically using electricity.

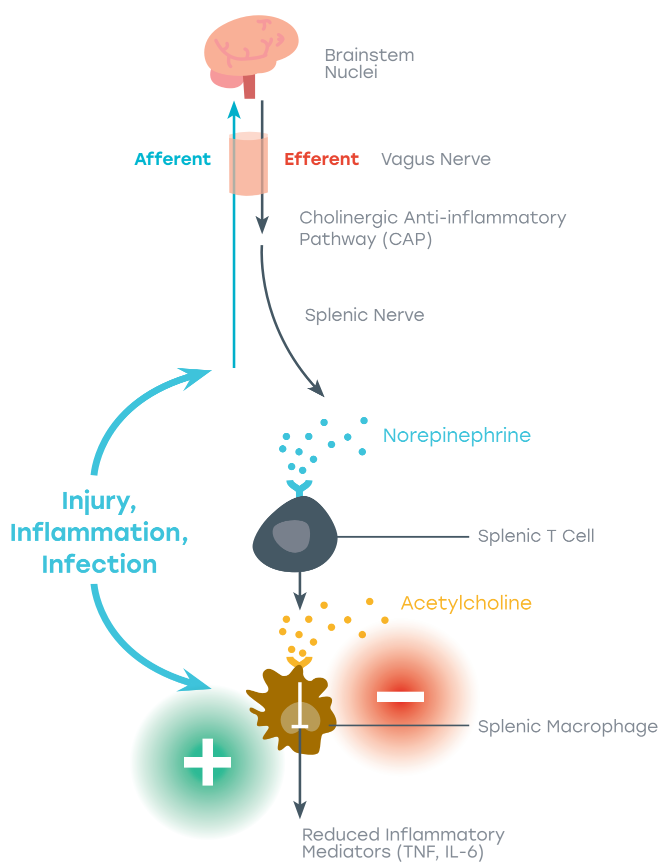
This reflex hinges on neurons both sensing and reducing acute inflammation. Just as the nervous system controls heart rate, body temperature and other vital functions, it also is very efficient at regulating the inflammatory response. That inflammatory response is implicated in a long list of immune diseases, and the list is growing.

This insight into the inflammatory response arose from studies of an experimental drug that was known to block cytokine production (including tumor necrosis factor, TNF-alpha) in certain organs. The drug usually was administered through the bloodstream, but Dr. Kevin Tracey, a neurosurgeon at the Feinstein Institute for Medical Research in Manhasset, N.Y., decided to see what would happen if it was injected directly into the brains of rats. He was surprised to find that the drug was significantly more effective in blocking TNF in the organs when administered this way. When the vagus nerve was severed, however, the TNF-blocking effects in the organs were lost.[8]

Intrigued, Dr. Tracey found an earlier paper from researchers at the University of Colorado and University of Virginia. When they injected IL-1, a fever-inducing cytokine, into the body of rats, but cut the vagus nerve, the rats did not get a fever, demonstrating the importance of the vagus in sensing inflammation.[9] This experiment defied the scientific consensus at that time holding that various reflexes were carried on the vagus nerve to modulate heart rate and digestion, but not the immune system.

"Putting this finding together with our results, I theorized that the vagus nerve was a conduit for information that regulates the immune system and inflammation," Dr. Tracey said.

The Inflammatory Reflex



That eureka moment led to the characterization of the Inflammatory Reflex theory and the creation of SetPoint Medical, which Dr. Tracey co-founded.

Twenty years of molecular and neuroscientific research established that the Inflammatory Reflex is essentially an autonomic reflex that detects cytokine production and inflammation and then reflexively responds to it. Electrical stimulation, it turns out, can harness this natural reflex.

The Inflammation Theory of Disease

There is a growing realization in the medical community that chronic inflammation plays a crucial role in causing and advancing many diseases. This insight opens new possibilities for treatment and therapy by blocking the inflammatory process.

Author Philip Hunter described the impact of inflammation this way: "Inflammation has long been a well-known symptom of many infectious diseases, but molecular and epidemiological research increasingly suggests that it is also intimately linked with a broad range of non-infectious diseases, perhaps even all of them."[10]

Characterizing the Inflammatory Reflex in Animals

The Inflammatory Reflex discovery pointed the way for researchers to prove the theory that vagus nerve stimulation could treat chronic inflammatory disease.

Dr. Paul-Peter Tak, a pioneer in Inflammatory Reflex work and an experienced immunologist and rheumatologist based then at the University of Amsterdam's teaching hospital, Academic Medical Centre, conducted animal studies to help characterize the Inflammatory Reflex. He investigated the Inflammatory Reflex in chronic inflammation, explored the beneficial effects of stimulating the reflex and showed the crucial role of the alpha 7 nicotinic acetylcholine receptor in rheumatoid arthritis (RA).[11] (Dr. Tak is now global head of R&D ImmunoInflammation, Infectious Diseases and Oncology at GSK, as well as a board member of Galvani Bioelectronics.)

Working together, Dr. Tak and SetPoint scientists then demonstrated that activating the Inflammatory Reflex with vagus nerve stimulation treated the rodent model of RA, preventing inflammation and damage to the joints.

These tests and others showed not only regression of RA disease, but also a reversal in bone erosion. Further tests in rodents have demonstrated lesion reductions in laboratory models of Crohn's disease.

Biomarkers

A biomarker is a measurable substance in an organism that can be indicative of some phenomenon such as disease, infection or environmental exposure. Doctors and researchers use biomarkers to measure a normal biological process in the body, a pathological process or the response of the body to a therapy.

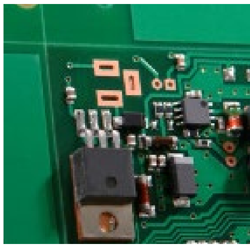
Biomarkers can accelerate research by serving as a proxy for clinical symptoms, providing information about the mechanism of action of a therapy, as well as its efficacy, safety and metabolic profile.

The idea of using biomarkers to detect disease and improve treatment goes back to the beginning of medical care. As early as 1500 BCE, Indian physicians used the practice of uroscopy – examining a patient's urine for signs of disease – to identify the symptoms of diabetes and classified the disease as "honey urine" because the urine of patients would attract ants.[12] In the 14th century, practitioners would regularly inspect the color and sediment of their patients' urine and make a diagnosis based on what they observed.[13] Today, physicians rely on white blood cell counts to detect infections, autoimmune diseases, immune deficiencies, blood disorders and other conditions.

More recently, researchers have identified a number of biomarkers for diseases ranging from cancer to inflammatory disease. Because biomarkers can predict drug efficacy more quickly than conventional clinical endpoints, they hold the potential to accelerate product development in certain disease areas. But they are not usually used in the development of device-based therapies.

Moore's Law, Tiny Batteries, Wireless Charging and Ever-Shrinking Electronics

In 1965, Gordon Moore, who would later become one of the founders of chipmaking behemoth Intel, wrote a paper noting that the number of electronic components that could be added to an integrated circuit was doubling every year. This exponential increase came to be known as Moore's law. The rate of doubling was later reduced to once every two years in the 1970s, and, with this modification, Moore's Law has stood since then. To provide context, Intel's early 4004 chip had 2,300 transistors. Intel's Xeon Haswell E-5 chip, launched in 2014, has more than 5 billion transistors.[14]



When lithium-ion batteries became popular in the early 1990s, they offered twice as much energy for the weight as the next best alternative. Over the last 10 years, researchers have explored hundreds of new battery technologies to discover the next advance that will hold more energy, last longer, be safer and recharge easily at a lower cost.[15]

Wireless charging uses an electromagnetic field to transfer energy between two objects. The concept of wireless energy transfer has been around for more than a century, and early work is widely credited to Nikola Tesla. Current applications of the technology charge within close proximity to an inductive charging pad or mat, but far-field wireless charging is in development in various forms without the inductive pad.[16]

These advances, in turn, have fueled technological progress, shrinking the size of electronics and batteries across all industries.

Bioelectronic Medicine Convergence: Taking it to the Next Level

A number of organizations are researching the potential for bioelectronic therapies, targeting diseases ranging from diabetes, hypertension and headaches to multiple sclerosis and Alzheimer's.

Target: Inflammatory Disease

California-based SetPoint Medical is a leader in the field, with published proof-of-concept data from the first clinical trial of bioelectronic medicine in humans, two clinical trials underway and a new proprietary implant designed specifically for bioelectronic medicine.

SetPoint is working to treat and reverse conditions that are driven by inflammation running unchecked, stimulating the immune cells in the spleen, gut and elsewhere to drive a coordinated response against inflammation. The company initially is targeting rheumatoid arthritis (RA) and Crohn's disease. These common diseases can be challenging to treat with available drug therapies, which do not work for all patients, are often costly and can have severe and devastating side effects.

SetPoint is uniquely qualified to pursue this new approach, bringing together experts from both the medical device/neuromodulation and pharmaceutical fields. This enables the company to address challenges in both areas:

- For pharmaceutical companies, using neural stimulation to control the immune system may sound intriguing, but they lack the advanced engineering experience to develop sophisticated implantable hardware and tend to be skeptical that people would choose surgery over taking an infusion or a pill.

- Traditional neuromodulation companies have little experience with inflammatory physiology and do not typically use biomarkers to guide clinical development. The concept of bioelectronic medicine, using brief electrical doses once or a few times per day to create a lasting effect, is fundamentally different from traditional neuromodulation applications designed to mask symptoms. In contrast, bioelectronic medicine stimulates the body's natural mechanisms to treat the disease.

Though the concept of using electrical pulses to treat patients has been around for decades, recent advances have propelled SetPoint's progress in the new field of bioelectronic medicine, targeting the first identified and best understood neuro-immune pathway: the Inflammatory Reflex. These findings set the stage to determine how to best deliver this type of treatment most effectively in humans.

Determining Dosage and Discovery of Lasting Response

Early bioelectronic medicine research used relatively primitive technology with constant voltage and large amounts of stimulation (for example, continuous or semi-continuous stimulation for more than 30% of the day), mirroring other applications of neural stimulation. However, with the discovery of the Inflammatory Reflex, SetPoint researchers set out to characterize the pathway and harness it for clinical use, defining which fibers in the vagus nerve to target, determining what happens in the spleen when activated and pinpointing the most effective bioelectronic dose.

Leading this effort, Yaakov Levine, PhD, Director of Applied Research at SetPoint Medical and an expert in the cholinergic anti-inflammatory pathway (CAP), discovered that the nerve fibers that reduce inflammation have a relatively low activation threshold – as little as 250-millionths of an amp, which is a fraction of the charge used to suppress epileptic seizures, for example.

Using biomarkers to measure response, SetPoint researchers confirmed that only a brief stimulation at this low level activated the anti-inflammatory response, and it lasted in excess of 24 hours, analogous to taking a pill once a day. Additional studies suggested that a single, brief delivery of an accurate electric dose could control inflammation for a substantial period.[17]

“What we found was that there is a subset of T-cells that is reprogrammable by stimulation, which ultimately results in macrophage changes that lead to TNF alpha, IL-1 and IL-6 suppression,” Dr. Levine said. “When we stimulate the vagus nerve with a short, precisely measured bioelectronic dose once a day, patients have responded with a prolonged reduction of proinflammatory cytokine production.”

Where and How to Stimulate

The next challenge was to determine the exact location in the body to deliver the bioelectronic dose, and then determine the type of delivery system that would provide the highest efficacy in that location.

One approach was stimulation directly on the nerve, which could be accomplished several different ways. Another option was near-field stimulation, from outside the body or through a vein or blood vessel wall – the vagus nerve is adhered to several veins that could provide access through their thin walls. Looking beyond the vagus nerve presented the option to stimulate the spleen directly, through the splenic nerve.

SetPoint researchers began by exploring up and down the vagus nerve for the optimal location to stimulate the reflex, testing different stimulation approaches. They used a bioassay that provided biomarkers to evaluate the effectiveness of neural stimulation using transvascular, proximity and direct cuffing of the vagus and splenic nerves. They also drew on technologies with reported promise in other applications, trying transcutaneous electrical, transcranial magnetic and vibratory stimulations, but they eliminated these due to poor or unpredictable efficacy and off-target effects in favor of a surgical implant.

"Using biomarkers to measure anti-inflammatory response gave the research team a fast and objective way to determine which approach and location would be most effective," said Mike Faltys, Chief Technical Officer at SetPoint. "We determined that activating myelinated fibers within the vagus nerve between the brain and celiac plexus was the best location, and that directly cuffing the vagus nerve was by far the most reliable approach."

By using the assays described above, engineers and scientists were able to quickly evaluate, test and titrate different nerve interfaces and dosing parameters to determine which was best at suppressing the production of key biomarkers such as TNF-alpha. SetPoint research confirmed that placing an implantable stimulator directly on the vagus nerve provided the most effective and predictable delivery of the digital doses.

Proving the Concept in Patients

Once SetPoint researchers finalized the best location and delivery method, they adapted and reprogrammed an existing neuromodulation device – one originally designed for traditional continuous delivery – and initiated the first-in-human proof-of-concept clinical trial in patients with rheumatoid arthritis.

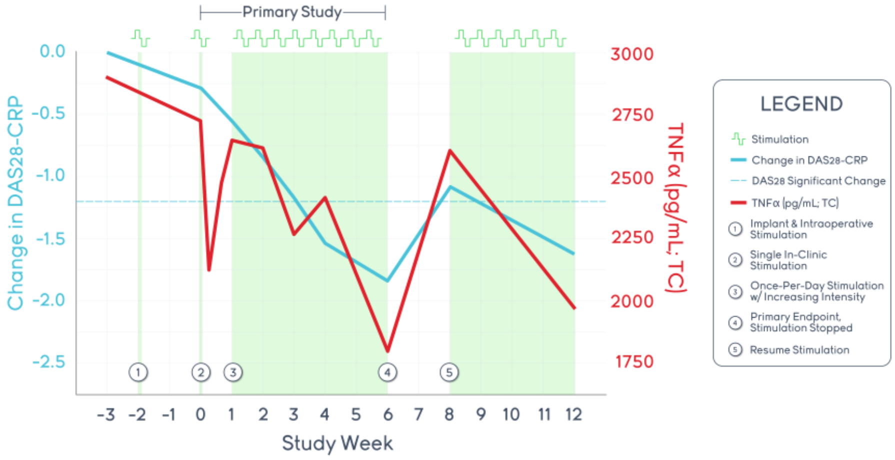
Based on Dr. Tak's international renown for high-quality clinical studies and his preclinical animal research around the Inflammatory Reflex and RA, SetPoint approached Dr. Tak to lead the first-in-human clinical trial as international principal investigator.

"We had concerns that RA patients would be hesitant to participate in a clinical trial for a treatment that included surgery, when all other available treatments were drugs," Dr. Tak said. "However, our fears were proven to be unfounded. We conducted an interview about the trial with a Dutch news program, and the day after the story appeared, we received more than 1,000 calls from rheumatoid arthritis patients begging to participate."

The patients selected for the trial underwent a surgical procedure to have the customized pulse generator implanted in their chest similar to where a pacemaker is placed, just under the skin and above the muscle, with a wire attached to their vagus nerve. The device delivered its pre-programmed stimulation in electric doses via the wire in periodic short bursts.

In 2016, SetPoint Medical, with Dr. Tak (et al.), published positive results from the study in *Proceedings of the National Academy of Sciences of the United States of America (PNAS)*, confirming the company's preclinical findings that a bioelectronic approach could treat chronic inflammatory disease: Twelve of 17 patients saw a clinically meaningful drop in their DAS28 (Disease Activity Score), reductions in tender and swollen joints, significant quality of life improvements as measured by the HAQ-DI score. Seven of the ten patients that had failed to respond to multiple biologic agents of differing mechanisms demonstrated robust DAS28 responses. The findings indicate that active electrical stimulation of the vagus nerve inhibits tumor necrosis factor (TNF) production in RA patients and significantly attenuates RA disease severity.[18] As of this writing, this important paper ranks in the top one percentile of 250,000 publications accessed in this prestigious journal.

Correlation: Bioelectronic Medicine Dose Delivery, Rheumatoid Arthritis Disease Activity Score (DAS) Improvement & TNF Suppression



Mean change in the Disease Activity Score (DAS28-CRP) and mean LPS-induced TNF release over time by study visit day. Changes in the DAS28-CRP and TNF release follow a similar temporal pattern in response to initial stimulation, stimulation withdrawal and stimulation reinitiation

Envisioning a New Device to Treat Inflammatory Diseases

In parallel with the proof-of-concept study, SetPoint began developing a much smaller proprietary implantable device designed for the delivery of bioelectronic doses for inflammatory conditions.

Like the commercial device SetPoint adapted for its proof-of-concept study, almost all commercially available devices used for neuromodulation consist of two implanted elements: an implantable pulse generator and a connected wire, requiring two areas for surgical implantation with inherent susceptibility to lead breakage. SetPoint wanted to simplify this system and minimize the invasiveness of the procedure. The goal was to make SetPoint's bioelectronic medicine device as small and easy to implant as possible with the least disruption to the patient's life.

The research team knew that with the targeted amount of current and delivery time required, the implanted device could be rechargeable and very small. As circuitry continued to shrink, ultra-low power microprocessors and a highly reliable compact implantable battery made it possible to design and build a self-contained device without a lead wire that could be charged wirelessly through the skin.

SetPoint's patented small MicroRegulator (pulse generator) contains a rechargeable battery, integrated circuit and telemetry hardware enclosed within a ceramic and titanium case and wrapped in a silicone wrapper called the Positioning and Orientation Device (POD), which holds the MicroRegulator in the correct position adjacent to the nerve. Electric doses delivered via the device are prescribed and managed by physicians with a powerful, yet user-friendly, iPad app. In addition, the MicroRegulator can be updated to incorporate new discoveries in bioelectronic medicine.

SetPoint MicroRegulator

SetPoint researchers spent seven years working with surgeons to refine the POD, the nerve channel on the MicroRegulator and the implantation procedure. This is the first self-contained bioelectronic medicine device on the vagus nerve that requires only one surgical site, making implantation shorter with less risk for patients.

Additional Targets and Clinical Studies

SetPoint is following up its proof-of-concept trial with a U.S. pilot trial in RA using its proprietary MicroRegulator device that began in late 2017.

Describing the promise of bioelectronic medicine to treat RA, Dr. David Borenstein, a rheumatologist at George Washington University Medical Center in Washington, D.C., wrote, “This isn’t pie in the sky. It’s a potentially viable alternative to what’s available now for RA.”[19]

Crohn’s disease is another hot target for bioelectronic medicine. In a small study of seven patients with Crohn’s disease, Bruno Bonaz and colleagues at the University Hospital in Grenoble, France, found that after vagus nerve stimulation, five showed signs of clinical and biological remission, including restored vagal tone.[20]

SetPoint has an ongoing study in Crohn’s disease. The study is running in five centers in Europe and includes 18 patients with severe Crohn’s who are not responsive to traditional TNF-targeting drug therapy. Severe Crohn’s is measured by a specific disease activity index. When initial results were published, six of the eight patients had seen a substantial reduction in their index scores, and three were in remission from the disease.[21]

Explosive Growth Trajectory

Using bioelectronics to address inflammatory and other diseases is a potential game changer, and the field has created sustainable momentum to fuel startups and ongoing funding. SetPoint counts among its investors medical device leaders Medtronic and Boston Scientific and global venture firm NEA. SetPoint also was the first company funded by the new GSK Action Potential Venture Capital (APVC) Limited, a strategic venture capital fund for companies pioneering bioelectronic medicines and technologies, when it was founded in 2013. SetPoint is joined by other companies that have recently entered the bioelectronic medicine field, including Galvani Bioelectronics (a $700 million joint venture by GSK and Google’s Verily).

“Many factors are coming together to make this the golden decade when we can potentially take bioelectronic medicines from a promising biological concept to implants that can help patients,” said Kris Famm, President of Galvani Bioelectronics, in a McKinsey and Company report.[22]

GSK is not alone among biopharma companies banking on the future of bioelectronic medicine. Johnson & Johnson's venture fund co-led a $29.6 million investment into CVRx, a Minneapolis startup that's developing an implantable device to treat hypertension and heart failure. Boehringer Ingelheim also struck a three-year deal with Menlo Park, CA-based Circuit Therapeutics to investigate the role of neural pathways in psychiatric disorders.[23]

The public sector also is actively pursuing bioelectronic medicine to advance the science and its application. The National Institutes of Health funded a $248 million program called Stimulating Peripheral Activity to Relieve Conditions (SPARC). SPARC's program supports efforts to develop proof of concept for an entirely new class of neural control devices.[24] DARPA, the Defense Advanced Research Projects Agency, has a $60 million program called ElectRx, which will investigate physiology of nerve circuits and devices for inflammatory diseases along with other conditions.[25]

The convergence required to create the sweet spot that made bioelectronic medicine possible has taken decades to evolve. However, those working in the field believe that the translational platform created will fundamentally change the way doctors think about how to treat disease.

"We're encouraged by the RA patients treated with our bioelectronic therapy. We have been following them for several years now, and we see that their results have not diminished," said David Chernoff, MD, Chief Medical Officer at SetPoint. "We believe our extensive research and positive clinical results show that bioelectronic medicine could provide a life-changing alternative for patients with immune diseases that are poorly served by drugs and a disruption to what we previously believed was possible in treating chronic conditions."

Appendix

Bioelectronic Medicine

Bioelectronic medicine uses a small implantable device to deliver targeted electrical pulses along existing physiologic pathways to trigger the body's biological responses, creating a targeted disease-fighting effect based on specific molecular mechanisms. It is designed to provide 'built-in' therapy at a lower cost and is intended to improve safety compared with drugs or biologic solutions.[26]

Neuromodulation

Neuromodulation alters nerve activity through targeted delivery of a stimulus, such as electrical stimulation or chemical agents, to specific neurological sites in the body. The molecular mechanism is often unknown. The most common neuromodulation treatment is spinal cord stimulation for chronic neuropathic pain. In addition to chronic pain relief, other neuromodulation treatments now used or studied include deep brain stimulation for essential tremor, Parkinson's disease, dystonia, epilepsy and disorders such as depression, obsessive compulsive disorder and Tourette syndrome; sacral nerve stimulation for pelvic disorders and incontinence; gastric and colonic stimulation for gastrointestinal disorders such as dysmotility or obesity; vagus nerve stimulation for epilepsy, obesity or depression; carotid artery stimulation for hypertension; and spinal cord stimulation for ischemic disease such as angina and peripheral vascular disease.[27]

Vagus nerve stimulation

Vagus nerve stimulation (VNS) refers to a method to stimulate the vagus nerve, including manual or electrical stimulation. Left cervical VNS is an approved therapy for refractory epilepsy and for treatment-resistant depression.[28]

Electroceuticals

Electroceuticals is another term sometimes used to describe bioelectronic medicine; a merging of "electronic" and "pharmaceuticals" to reference the use of electric doses as a way to target and treat diseases as drugs do.

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