COMMENT

PESKIMO/SYNERGY ART

A jump-start for electroceuticals

Kristoffer Famm and colleagues unveil a multidisciplinary initiative to develop medicines that use electrical impulses to modulate the body's neural circuits.

Imagine a day when electrical impulses are a mainstay of medical treatment. Your clinician will administer 'electroceuticals' that target individual nerve fibres or specific brain circuits to treat an array of conditions. These treatments will modulate the neural impulses controlling the body, repair lost function and restore health. They could, for example, coax insulin from cells to treat diabetes, regulate food intake to treat obesity and correct balances in smooth-muscle tone to treat hypertension and pulmonary diseases.

All this is within reach if researchers from disparate disciplines in academia and industry work together. Here, we outline what needs to be done to bring about electroceuticals and unveil a public–private research initiative and an award that we hope will catalyse the field.

Electrical impulses — action potentials — are the language of the body's nervous system. Virtually all organs and functions are regulated through circuits of neurons communicating through such impulses[1]. Two features make these circuits excellent targets for therapeutic intervention. First, they comprise discrete components — interconnected cells, fibre tracts and nerve bundles — allowing for pinpoint ▶

intervention. Second, they are controlled by patterns of action potentials, which can be altered for treatment.

Already, devices that harness electrical impulses are used to treat disease. Pacemakers and defibrillators save millions of lives each year; deep-brain stimulation dramatically improves the quality of life for people with Parkinson's disease and depression; sacral-nerve stimulation restores some bladder control in people with paraplegia, and vagus-nerve stimulation shows clinical benefits in diseases ranging from epilepsy to rheumatoid arthritis[2]. But these devices do not target specific cells within circuits.

Neural tissue is compact: unrelated circuits often run close together through brain regions and in peripheral nerves. At present, electrical devices activate or inhibit cells in an area of tissue indiscriminately, muddying clinical effects. For example, electrodes that stimulate the vagus nerve enclose approximately 100,000 fibres, which innervate many different internal organs. Similarly, deep-brain stimulation for Parkinson's disease affects many cells other than those that control movement, leading to emotional and cognitive side effects. In natural urinary control, opposite signals in adjacent nerve fibres simultaneously contract the bladder and relax the urethral sphincter — an elegant process that is poorly mimicked by today's devices.

Neither do neurostimulation devices yet generate naturalistic patterns of action potentials. Typically, devices block or stimulate with simple waveforms, rather than modulate dynamically on the millisecond scale. Precise modulation is important: in mice, stimulation of cells in the neural circuit for hunger with a simple 20-Hertz waveform causes voracious eating within minutes, and ablation of these cells causes anorexia; but food intake can be more finely modulated by the number and frequency of action potentials in specific cells[3]. Similarly, single action potentials in small sets of cortical neurons have been shown to encode sensory input or perception in mice[4]. In other words, neural circuits act through sets of precise electrical impulses generated in specific sets of cells.

PATH TO PRECISION

We believe that it is now possible to create medicines that control action potentials in individual neurons and in functional groups of them.

Many of the stepping stones are already in place, thanks to recent advances in a variety of disciplines. For example, disease-specific neural circuits, such as the reflex that controls levels of inflammatory mediators[5], are starting to be anatomically and functionally traced. Tools, such as optogenetics, that enable cellular-level control have improved researchers' ability to analyse the signals in circuits, and they provide a mechanism by which future electroceuticals could elicit action potentials[6]. Efforts to control prosthetic limbs and generate brain–machine interfaces are giving rise to architectures for electrodes that can interact with individual neurons. Researchers are designing microchips that mimic brain processing to facilitate local and low-power computation[7]. The development of cochlear and retinal implants has led to advances in neural signal processing. Nanotechnology has delivered approaches for harvesting energy to power microdevices[8]. And neurosurgery can now be done through small holes in the skull and body with the use of needles and scopes, as in precision procedures to remove herniated disc material from the spine or open new fluid channels from blocked brain ventricles.

"Researchers will need to embrace the tools of other fields, and even dream differently."

The first logical step towards electroceuticals is to better map the neural circuits associated with disease and treatment. This needs to happen on two levels. On the anatomical level, researchers need to map disease-associated nerves and brain areas and identify the best points for intervention. On the signalling level, the neural language at these intervention points must be decoded, so that researchers can develop a 'dictionary' of patterns associated with health and disease states — a project synergistic with international drives to map the human brain[9]. In circuits altered by disease, it will be important to establish how introduced electrical impulses affect the disease and which patterns yield the most effective therapeutic responses. Developing the technology to record from and stimulate a larger set of central and peripheral neurons will be crucial to this pursuit.

This type of research is analogous to the target-identification and validation steps at the core of modern molecular-drug discovery. The circuit maps that emerge will provide the design specifications for future treatment devices. Early prototypes might use microchip-controlled electrode arrays similar to those used today in interfaces for prosthetic limbs to modulate neural signals (see 'It's electric'). Second-generation micro- and nanoscale devices may instead leverage light, mechanical or magnetic energy to achieve such modulation in specific cells within targeted circuits.

How will all this come about? Disease biologists will need to work with neuroscientists to map circuits and with bioinformaticians to identify the action-potential signatures of diseases. To develop treatment devices, bioengineers designing biocompatible interfaces will need to collaborate with electrical engineers to develop microchips for real-time signal processing; with nanotechnologists to create energy sources; and with neurosurgeons to ensure that these designs can be implanted and connected. Researchers will need to embrace the languages and tools of other fields, and perhaps even dream differently: much of the challenge lies in translating biological understanding into engineering specifications.

MULTIDISCIPLINARY JOURNEY

We think that initial progress will come from targeting circuits that have accessible and peripheral intervention points. For example, it has been shown that hypertension can be controlled through signals in carotid-sinus and renal nerves, and the production of certain inflammatory molecules in rheumatoid arthritis can be modified through the splenic nerve. A range of conditions — cardiovascular, metabolic, respiratory, inflammatory and autoimmune — are likely to have similarly accessible intervention points, given that they involve organs and functions that are under neural control.

We envision adaptive or 'closed-loop' electroceuticals that can record incoming action potentials and physiological parameters, analyse these data in real time and modulate neural signalling accordingly. This capability, together with that of spatially targeting a specific set of neurons, will underpin the selective therapeutic effect that we expect from electroceuticals. But these closed-loop therapies can be realized only if the required disciplines come together early on.

We also hope that this effort will result in interdisciplinary advances that can be brought to bear on disorders of the brain itself. Correcting such disorders with treatment in their own electrical language and by individually addressing a larger set of neurons in brain circuits could be the approach that proves commensurate with the body's most complex of organs. In the long run, it could be the most revolutionary aspect of electroceuticals.

Critics will argue that we underestimate the complexity of the nervous system; the challenges in reliably, durably and non-disruptively manipulating groups of individual neurons and the sheer volume of neural information flowing through these circuits. We would argue that miniaturization and big-data handling have been among the most rapidly advancing areas of scientific research in the past decade. Starting off with peripheral intervention points and simpler circuits should also help.

There are a few noteworthy unknowns,

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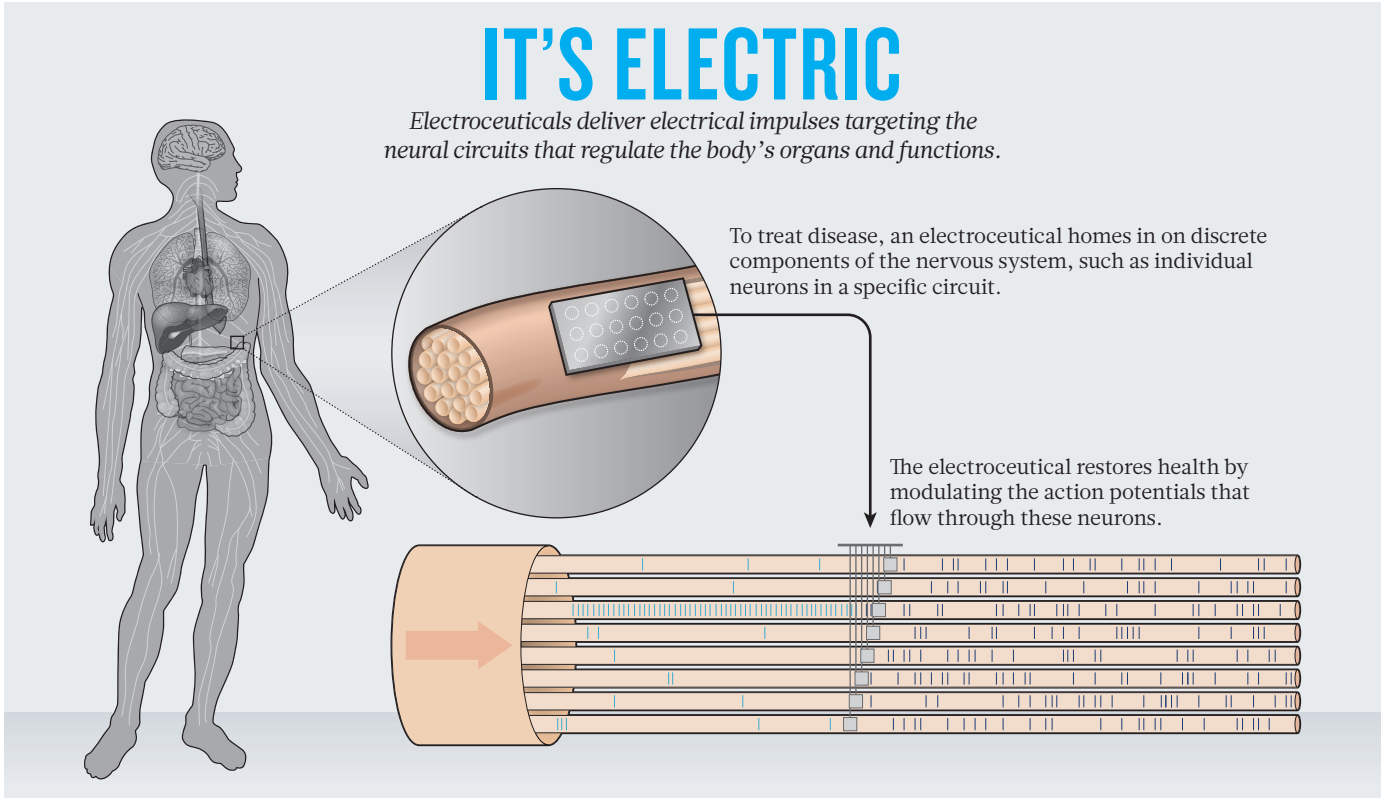

but these will be resolved only when the approach is put to test. To what extent does mapping of the neural language in animal models translate to the human setting? In which diseases will modulation of the relevant neural circuits suffice to reverse or control disease progression? Could the degree of circuit redundancy or plasticity limit the efficacy of treatment?

CATALYSING THE FIELD

At GlaxoSmithKline (GSK) and in academia, we are confident that this field will deliver real medicines, and we are mobilizing resources for this journey. This summer, the University of Pennsylvania will open its Center for Neuroengineering and Therapeutics, which will bring together researchers in medicine, engineering and business. University investigators (including B.L.) are already mapping neural circuits in humans and in cats, dogs, rodents and other models of disease. They are also building and deploying devices that modulate circuits at the neuronal level, using cloud computing to mine 'big' neural data and translating these technologies for use in tools such as antiseizure devices.

At the Feinstein Institute for Medical Research (where K.J.T. is president), scientists are trying to establish the neural codes that underlie diseases of immunity and inflammation, identify intervention points and conduct exploratory clinical work. Results so far indicate that it is feasible to identify and manipulate neural signals specific to different inflammatory mediators in standard laboratory models.

At the Massachusetts Institute of Technology, researchers (including E.S.B.) are collaborating to map and modulate neural circuits using technologies that range from optogenetics[6] to scalable, automated electrophysiology[10] — and they are distributing the genetic codes, hardware and software necessary to put these inventions into practice.

At GSK, we (K.F. and M.S.) are committed to acting as a catalyst for this emerging field, through three immediate steps. The first, a programme that will fully fund up to 40 researchers in up to 20 external labs conducting exploratory work mapping disease-associated neural circuits, launches this week (www.gsk.com/bioelectronics). Funding for the first year will be awarded after a rapid review and approval process that should take roughly one month. Early findings will be shared among researchers in this network, and intellectual-property rights will remain with the inventors. Throughout this exploratory phase, the network will be encouraged to shape longer-term efforts in research and development.

"Could the degree of circuit redundancy or plasticity limit the efficacy of treatment?"

In December, as a second step, GSK will hold a global forum for research leaders to chart an integrated path forward and to collectively identify a key hurdle in the field. After the forum, the company will launch the third step: a US$1-million prize for innovation, to be awarded to the group that overcomes this hurdle.

Clearly, open innovation and flexibility in dealing with intellectual property will be important. As the poet Cesare Pavese said: "If you wish to travel far and fast, travel light. Take off all your envies, jealousies, unforgiveness, selfishness and fears." Together we can bring about the era of electroceuticals. ■

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