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Meeting Report

Bioelectronic medicines: past, present and future. Highlights from The Society for Medicines Research Symposium

London, UK – October 1, 2019

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Summary

On October 1, 2019, the Society for Medicines Research (SMR) held its first symposium on "Bioelectronic medicines, past, present and future" at the Royal Academy of Engineering in London. The meeting was attended by 145 participants and was supported by Galvani Bioelectronics, IEEE-CAS Society, IEEE-Brain Initiative, BIOS, Heraeus, CorTec and the IT'IS Foundation.

Key words: Bioelectronic medicines – Polymer bioelectronics – In silico modeling – Closed-loop systems – Neuromodulation

Introduction

The bioelectronic/neuromodulation market is well established and continues to increase in size with a predicted value of more than USD 11 billion by 2024. Current therapies cover a broad range of indications that are based on modifying either the central or peripheral nervous system to treat a range of disorders from Parkinson's to urinary incontinence. Currently, therapy is delivered through electrodes placed directly in the brain, peripheral nerves or spinal cord and powered by pulse generators implanted subcutaneously. Emerging technologies will allow for more specific and patient-focused approaches to personalize medicines through "closed-loop" systems and implantation of devices using minimally invasive surgical techniques. With these advances in technology, robotic surgery and scientific understanding it remains a possibility that future bioelectronic medicines will start to emerge that go beyond treating patients that are refractory to standard pharmacotherapies.

The speakers for the Society for Medicines Research (SMR)'s first symposium on "Bioelectronic medicines, past, present and future" were drawn from both industry and academia and provided expert insights into successful strategies and emerging technologies that are driving the new wave of emerging bioelectronic medicines. A poster networking session was held at the close of the meeting with 21 posters presented. The prize for the best poster was awarded to Enrico Ravagli from University College London for his poster entitled, "Fast electrical impedance tomography of peripheral nerves: cross validation with microCT and neural tracers."

Themes for the day's talks included device engineering and technology, translational sciences for healthcare and innovation and clinical and industrial engineering.

Bioelectronic Medicines—Therapeutic Promise, Translational Perils and Treatment

Dr. Kris Famm, Galvani Bioelectronics, UK

The first speaker of the day was Dr. Famm from Galvani Bioelectronics who provided an overview of the therapeutic promise, translational perils and treatment features of future bioelectronic medicines. Currently, implantable

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neuromodulation devices are bringing patient benefits through, for example, cochlear implants for patients with moderate to profound sensorineural hearing loss and deep brain stimulation for patients with Parkinson's disease. However, the potential for unleashing a wider range of treatments through new devices providing precision neural control is becoming a reality. Taking as a baseline the perspective that he and others published in 2014 (1), Dr. Famm highlighted four current focus areas that have proven critical to translate from concepts to therapies:

1) **Translating chronic neural interfaces from mouse to man:** Upon proof of principle in rodent disease models, a major undertaking in the development of bioelectronic medicines targeting peripheral nerves is the design, production and iterative chronic in vivo testing of interfaces that can effectively and reliably neuromodulate. Here it is important to study it in large animal models anatomically and neuro-physiologically similar to humans and to establish that foreign body responses do not affect neural function and are stable over time.
2) **Anchoring dose response in mechanism of action:** The challenge here is the complexity of the number of variables for the potential bioelectronic "dose" (e.g., frequency, amplitude, inter-pulse intervals, pulse widths, patterns and duty cycles) as compared to dose variables for small molecule and antibody therapeutics. An understanding of the mode of action with regards to the neurotransmission, cellular and organ physiology will likely be key to exploiting the intrinsic opportunities in this complexity.
3) **Designing procedures for surgical proof of confidence using minimally invasive implantation:** Neural interfaces and pulse generators need to be specifically designed for laparoscopic implantation, and procedures need to be developed and carefully tested in cadavers and in large animal surgery. Excellence here is needed to evolve bioelectronics from a treatment of last resort to a front-line option.
4) **Enabling rich feedback in the clinic for personalized therapy optimization:** The opportunity to learn in the clinic using devices which, for example, allow detection of biomarkers or neural recording at the same time as stimulating will finally be key to access the full treatment potential of bioelectronic medicines for patients.

Dr. Famm concluded with two examples from recent publications which highlight the progress that is being made. Firstly, the use of vagal nerve stimulation to suppress cytokines in humans, first reported in 2016 (2), has now been achieved in a more targeted manner near the end organ in mice by using localized splenic nerve stimulation (3). Such splenic nerve stimulation is effective in mitigating clinical symptoms in a collagen-induced mouse model of rheumatoid arthritis. Secondly, recent studies show that targeted nerve stimulation at the pancreas can stop β-cell destruction in mice and thus inhibit recent-onset diabetic disease as measured by levels of glycemia (4).

Device Engineering and Technologies

Polymer bioelectronics: moving beyond the past to a more functional future

Dr. Rylie Green, Imperial College London, UK

Dr. Rylie Green spoke about her group's work on polymer-based electrodes for bioelectronic applications. She started by introducing electrodes (or neural interfaces more generally) as a means for communication between medical devices and electroactive tissues through recording and stimulation. Traditionally these have been based on inert metals such as platinum, platinum/iridium alloys and gold. Such materials have been used successfully today in a number of clinically available implantable medical devices such as cardiac pacemakers, cochlear implants and deep brain stimulators. These applications require charge injection (stimulation) capability and these electrodes (mostly platinum) have been shown to be safe to use over patient lifetimes. However, these medical devices have not advanced much since they were introduced. For example, the most advanced current cochlear implants have 22 electrodes—the same as when they were first introduced in 1982. New applications such as retinal prostheses are now requiring more, and smaller electrodes to achieve useful vision. The fundamental limitation is however the relatively low safe charge injection limit of traditional electrode materials (i.e., platinum) (5). Furthermore, there is also a mechanical mismatch between the tissue and the stiffness of the electrode itself.

Next-generation polymer bionics could be a solution here. By making the entire electrode assembly (conductor, electrode contact and insulation) using polymers these limitations can be addressed. Compared to conventional electrodes they are softer and more flexible, have high charge transfer properties (for recording and stimulation), can be manufactured using different processes, are compatible with diagnostic imaging, and there are extensive possibilities for biofunctionality. Two approaches that Dr. Green has been working on here are polymer elastomers and conductive hydrogels.

Conductive elastomers are formed by combining a conductive polymer (e.g., PEDOT) with an elastic polymer (e.g., PU) and casting this into sheet form. The sheet thickness can be varied (anything from tens to hundreds of microns) and this can then be processed thermally, chemically or laser micromachined. The properties (i.e., conductivity) of conductive elastomers varies with the PEDOT loading with the threshold being at 5wt% increasing to a maximum at 20wt%. The conductive polymer can

then be combined with a PDMS substrate to form different electrode structures. Most relevant to bioelectronic medicine are cuff electrodes that can be made using a process Dr. Green has developed based on laser patterning and spin coating (6). Experimental test of these electrodes using an ex vivo (rat sciatic nerve) setup demonstrated effective recruitment of both A and C fibers. Additionally, cyclic voltammetry revealed a significantly increased charge transfer capacity (1-2 orders of magnitude) compared to conventional electrodes. Finally, application to other electrode structures, for example planar array configurations, has been demonstrated with the possibility of high resolution.

The second approach (conductive hydrogels) involves combining the conductive polymer (e.g., PEDOT) with a hydrogel (e.g., PVA) (7). This provides a soft coating material for ameliorating properties of electrodes, imparting a high charge transfer while reducing the impedance variability. Here, both in vitro and in vivo testing has demonstrated improved electrochemical properties, chronic stability (with continual stimulation), and high charge injection limits for improving safety margin.

Dr. Green concluded that there do remain challenges and as such it may be considered to be "high risk, high reward." Most importantly such technologies need to be validated in large animal studies, and it is essential to engage with regulatory processes for human implants.

The perspective of in silico modeling in bioelectronic medicine

Prof. Niels Kuster, IT'IS Foundation and ETH Zurich, Switzerland

Prof. Niels Kuster spoke about the work that is performed in his organization to develop methods and a comprehensive software platform for the in silico modeling needed for bioelectronic medicine. He started his presentation by using two examples (i.e., neural control of the heart and breathing) to illustrate the complexity of biological systems. The key needs to be able to apply neuromodulation to such systems were then identified:

- filling the gaps in knowledge (e.g., organ electrophysiology and functional connections with other organs and the brain);
- identifying organ access points for treatment (e.g., specific nerve branches);
- decoding neuroelectrical brain-organ communication in healthy and pathological conditions;
- design of efficient, safe and potentially miniaturized neural interfaces;
- effective translation of ex vivo and in vivo data to human electrophysiology minimizing the number of prototyping implanted devices (translation to human);
- effective treatment planning.

Computational methods (electromagnetic and neuromodeling) could greatly assist in addressing the abovementioned needs or challenges if a) they permit the integration of models from end to end (organ to nerve to implant); b) they span from qualitative to quantitative; c) they are predictive; and d) they can integrate within the regulatory framework. To achieve this, a collaborative neuroscience approach is essential to ensure models are verifiable, reproducible, shareable, sustainable and open to all.

Prof. Kuster then described the competencies of the IT'IS Foundation that has a core expertise in electromagnetic dosimetry, virtual functionalized computational phantoms, in vitro exposure systems, in vivo human studies and magnetic resonance imaging testing. The Sim4Life platform (8) has been specifically developed as a framework for life science simulations and in silico device design and treatment planning. It allows for advanced visualization and structural modeling based on the Virtual Population (ViP), a library of 17 human anatomies, and the virtual fauna (ViZoo), including rodent, pig, dog and monkey models. Sim4Life provides the possibility to adjust body posture/limb position and morph these to different body sizes/shapes. Multiphysics simulations can then be set up using several different optimized solvers including radiofrequency and low frequency, flow, acoustic, and thermal structured and unstructured solvers. In addition, IT'IS provides a comprehensive tissue parameter database including specific detail on the central and peripheral nervous system and vasculature), electromagnetic/physical properties and electrophysiology.

Prof. Kuster then gave three examples where the Sim4Life platform has been successfully used in recent research. Firstly, for the modeling, visualization and optimization of selective stimulation of a patient with spinal cord injury in a study by Grégoire Courtine (EPFL) and his group (9). Secondly, for providing the computational modeling required for developing the temporal interference noninvasive neuromodulation method, used by Nir Grossman and Ed Boyden (Imperial College London and MIT) (10). Finally, to implement a cloud-based platform (called o^2S^2PARC) for the NIH SPARC initiative (11). o^2S^2PARC is an open-access simulation environment developed for the neuroscience community to integrate and execute models but also enable sharing, collaboration, cross validation, scalability, sustainability and reproducibility. It also allows end users to receive credit for their contributions.

Prof. Kuster concluded that the aims that have been set for bioelectronic medicine in general are high, and to be successful, effective and efficient collaboration is essential. Together with his team, the vision is to contribute to this endeavor by providing an image-based quantitative and predictive in silico modeling platform that is validated and meets the regulatory-grade requirements.

Graphene-based bioelectronic devices for recording and stimulation in brain pathologies

Prof. Kostas Kostarelos, University of Manchester, UK

Prof. Kostarelos described the efforts of his lab (Nanomedicine Lab) in collaboration with colleagues at the Catalan Institute of Nanotechnology (ICN2) and the Institute of Microelectronics (CIBER/CSIC), both in Barcelona, in applying graphene to neural interfaces as part of the EU Graphene Flagship project. He started the talk by introducing graphene and outlining the many desirable properties it has as a material both from electrical and mechanical perspectives. His vision is that graphene-based neural interfaces can leverage the unique combination of these properties to provide both recording and stimulation capabilities (12).

A process flow for fabricating arrays of graphene field effect transistors (gFETS) for neural recording was described using wafer-based semiconductor processing techniques. A number of sample devices have been prototyped including 64 and 128-channel high density epicortical mapping grids, and intracortical penetrating probes. The grids have been tested in an epileptic rodent model demonstrating the ability to observe high-quality recorded neural signals. One highly desirable property reported was the ability to record DC/infraslow (low frequency) activity—this is thought to contain valuable neurological information and illustrate the capability to record across the frequency spectrum.

Exploiting graphene for neural stimulation requires a different fabrication process and material type—effectively fabricating a highly porous graphene substrate as the active part of the electrode. Here, the highly porous rGO thin film can achieve a high charge injection capability (compared to standard electrode coatings, e.g., Pt, PtIr, Au). Several different electrode structures have been demonstrated, for retinal probes, nerve cuffs and rigid MEAs. It was mentioned that some technical challenges exist in robustly manufacturing large surface area electrodes compared to small (micron scale) surface area electrode contacts that can be reproducibly fabricated.

In conclusion, initial data for graphene-based neural devices have shown very promising results both for recording and stimulation but there still remains work to do. One key challenge will be translation to human clinical applications that will require regulatory approval of this new material.

Translational Sciences for Healthcare and Innovation

Translational scaling of dose for bioelectronic medicines

Prof. Warren Grill, Duke University, USA

Starting the second of the day's sessions, Prof. Grill discussed translational scaling of dose for bioelectronics medicines and highlighted the challenge of translation of stimulation parameters. This covered four key areas: a) challenges of selecting dose, b) an example of vagus nerve block for obesity, c) an example of conduction block of vagus nerve, and d) model-based translational scaling. An implantable pulse generator can generate many stimulator parameter combinations such as amplitude, frequency, pulse width, duty cycle, ramp time, variable waveforms, etc., and the big challenge is to select an effective, or optimal dose. This involves translating and scaling parameters from anatomically small, or large animal models such as rats, or pigs to humans, and also adjust stimulation parameters for individual differences (13). The other crucial factor is to address the heterogeneity in fiber populations in target nerves in CNS and PNS which requires different intensities of electrical stimulation for nerve activation based on fiber diameter and conduction velocity (14).

Prof. Grill then highlighted an example of Vagal Nerve Blocking for Obesity Control (VBLOC) by EnteroMedics Inc. (15). As an alternative treatment for obesity, the company EnteroMedics developed an implantable neural stimulation device to deliver VBLOC therapy. A cuff electrode is placed around each abdominal vagus nerve, near the level of the esophageal-gastric junction to deliver 5 kHz of electric current via an implanted pulse generator. The therapy's objective is to cause weight loss by blocking conduction of neural signals in the vagus nerves. The therapy is thought to block hunger signals traveling to the brain, as well as blocking efferent signals from the brain that cause the release of digestive enzymes.

The company has conducted two randomized, controlled, multicenter clinical trials. Both trials hit the primary efficacy and endpoint of at least 10 percentage points more excess weight loss in the treatment group than the control group. Thus, the first trial, EMPOWER, failed to meet this objective (16, 17). Both groups received the same implant, but the treatment group received 5 kHz stimulation at 3-8 mA for 5 min on and 5 min off, while the control group received 40 Hz stimulation up to 1 mA during the 5-min on period, as well as 13 impulses of 1 kHz at 3 mA at t = 0 min and t = 3 min of each on period. Nevertheless, in January of this year, EnteroMedics received U.S. Food and Drug Administration (FDA) approval for VBLOC therapy to treat obesity. This raised questions such as if VBLOC therapy blocks conduction in the vagus nerve, is it possible to block small autonomic fibers and what were the characteristics of block? To investigate this question, they used both computational models (18) and experiments in which they measured the response of vagus nerve to kilohertz frequency signals when three cuff electrodes were placed on the rats' vagus nerves. They found that block thresholds are higher with higher frequencies (approx. 1 mA at 10 kHz and 7 mA at 70 kHz) and slower conduction speeds (approx. 4-12 mA for 0.5 −2m/s conduction velocity) (19). They also showed longer carryover effects with lower kHz frequency, higher amplitude and

faster fiber conduction speeds. In parallel, a computational model of the abdominal vagus nerve was developed which produced strikingly similar results to the experiments and thus optimized the stimulation parameters.

In the last segment of the talk Prof. Grill spoke about in silico computational modeling based translational scaling from rats to humans and presented the pipeline for simulation of activation and block of populations of nerve fibers with autonomic nerves (20) [NIH SPARC OT2 OD025340]. Computational platforms such as Image J and COMSOL Multiphysics can be used to create Finite Element Models to create electrode geometry, trace morphology from nerve histology and implement electrical properties of tissue and materials to generate electric potential in nerves. Nerve fiber geometries and nerve fiber ion channels in the format of different nonlinear cable models (a-type, b-type, c-type, etc.) can be further added to the model to generate thresholds for activation and block in nerve populations. In addition to using such models for translational scaling of stimulation parameters, they can also be used for optimizing waveforms and electrode geometries for efficient and selective nerve stimulation.

Embracing the complexity of neuromodulation as a clinical therapy

Dr. Kip Ludwig, University of Wisconsin-Madison, USA

Elaborating upon parallel translation, Dr. Ludwig emphasized building on five key points: a) reverse translation to establish and optimize animal model relevance, b) building and validating computational models that span murine to human with better tools, c) importance of using high-resolution technology in animals to optimize low-resolution human biomarkers, d) iterate on device design and biomarkers for humans earlier in process, and importantly, e) bringing industry relevant questions back to basic neuroscience labs. For this he highlighted the example of CVRx BAROSTIM NEO. CVRx has developed a proprietary implantable technology designed for the treatment of heart failure and high blood pressure by inhibiting the sympathetic activity and enhancing the parasympathetic activity in the autonomous nervous system (21). A 2-mm^2 electrode is attached to the carotid artery and connected to the implantable pulse generator, to electrically activate the baroreceptors. An implantable pulse generator is inserted under the skin, below the collar bone, delivering an electrical stimulation through the lead. A programmer system enables the clinician to customize therapy to the patients' needs. The unique on/off capability can promote the observation of the differences that BAROSTIM THERAPY makes in blood pressure and other hemodynamic parameters. During the product development lifecycle, the safety questions raised with the procedural outcomes in the devices clinical trial, i.e., Rheos Pivotal trial, seem to have been addressed with the smaller, easier to implant second-generation device and electrode, the BIOSTIM NEO (22). However, in another smaller clinical trial of 18 patients' side effects it may have limited efficacy. Surprisingly, similar side effects are also observed in vagus nerve stimulation (23, 24). Therefore, Dr. Ludwig proposed that identifying more anatomically relevant animal models, or using a computational platform pipeline (similar to Prof. Grill's talk) we could identify and avoid the pathways responsible for therapy-limiting side effects in human patients during preclinical development. For instance, anatomically the human vagus nerve is 10 times bigger than mouse vagus nerve but is approximately similar to that of pigs (20). Lastly, Dr. Ludwig highlighted the need for understanding the mechanisms by which electrical stimulation interacts with neuronal and non-neuronal elements—e.g., neuropil, cell bodies, glial cells, etc., because there remains a lack of consensus regarding how electrical stimulation leads to the therapeutic effects during neuromodulation therapies such as deep brain stimulation. He gave an example of a novel experimental paradigm combining subthalamic nucleus electrical stimulation with single-photon calcium imaging of the dorsal striatum via a head-mounted miniature microscope in healthy and 6-hydroxydopamine-lesioned Parkinsonian mice during minimally constrained behavior capable of measuring stimulation-evoked changes in neural activity (25).

Translation of near-organ neuromodulation of immune function via bioelectronic medicine

Dr. Alexandra McSloy, Royal Veterinary College, UK

Dr. McSloy presented the work done jointly at Dr. Justin Perkin's lab at the Royal Veterinary College which was funded by Galvani Bioelectronics. She began with a description of the inflammatory reflex, a biological pathway where the brain senses inflammation and activates a reflex circuit to control immune responses via release of neurotransmitters (i.e., NA/ACh) in the spleen (26). The discovery of this pathway created the possibility of treating chronic autoimmune disease using bioelectronic medicine. For example, Set Point Medical has developed an implantable microregulator pulse generator to address diseases, such as Crohn's disease and rheumatoid arthritis by electrical modulation of the vagus nerve (2, 7). Stimulation of the vagus nerve in principle may cause activation of several afferent and efferent pathways making determination of stimulation parameters difficult as well as affecting nontarget circuits. Dr. McSloy therefore described the potential of precision stimulation and moving closer to the end organ, i.e., stimulation of the splenic nerve instead of vagus to control the immune function. During her presentation, Dr. McSloy demonstrated results from proof-of-principle in rodents to selection of an optimal large animal model of the human splenic nerve covering anatomical and histological aspects and translation of charge requirements for nerve activation. Finally, results from immune modulatory effects in conscious animals were also presented.

Clinical and Industrial Engineering

The translation of bioelectronic systems: platform architectures, business models and partnerships

Prof. Tim Denison, University of Oxford, UK

Following an introduction highlighting the major burden of neurological disease on the individual, carers and society overall, Prof. Tim Denison from the University of Oxford went on to discuss unexploited opportunities offered by bioelectronics and the potential for developing virtuous loops to translate these opportunities to the clinic and market.

A key development for future bioelectronic therapies, highlighted by Prof. Denison, is to exploit the potential of bioelectronics to adaptively respond to an individual patient's needs through a closed-loop system. Currently, changing device response settings generally require a clinical setting with devices adjusted to compromise settings from the patient's perspective. This can result in less than optimal responses with example shown in the incomplete control of essential tremor, Parkinson's or epilepsy. Compounding issues here are the absence of objective physiologic responses or biomarkers and the lack of knowledge of optimal stimulation parameters to achieve ideal resolution of a neurological condition. The invasive nature of fitting devices for neurologic conditions for conditions such as Parkinson's disease and the patient acceptance of such procedures remain an issue. Finally, Prof. Denison highlighted that health economics is, as with all medical interventions, a critical factor with investors needing to see an appropriate NPV, and the healthcare system looking for "total cost < value generated" (value defined through quality of life-adjusted years, and incremental cost effectiveness ratios).

A key proposition from Prof. Denison to address the economics issue is to spread the cost of developing the new technology required to advance bioelectronics by establishing a common platform approach applicable across multiple indications. This contrasts with conventional pharmaceuticals where most therapeutics have application in a single or at most a limited range of indications despite the investment required to bring each medicine to market. A parallel was drawn here to, for example, motor vehicle manufacture where Audi/VW can get economy of development and production by use of the same parts across models and the two brands.

To realize a closed-loop adaptive system multiple features are required. Not only is an implanted stimulation and control device required but so are new sensing devices, identification of relevant biomarkers to prompt a response and algorithms to calculate patient state and optimal stimulation parameters or a classifier and control policy—all with a clinical interface (27). While stimulation devices are now established there is a need with these closed-loop approaches for the development of significant new science and technology.

To facilitate this research, Prof. Denison highlighted the BRAIN initiative (Brain Research through Advancing Innovative Neurotechnologies, https://braininitiative.nih.gov/) and OpenMind Consortium (https://openmind-consortium.github.io/). These are giving early access to technology and science to help accelerate innovation in this field.

Risk management is clearly key in any therapeutic and for a closed-loop system having a clinician-defined "safe mode" is required (28). While safety is paramount a platform approach can help to generate a safer device as safety issues associated with the device, once identified and addressed, will be applicable across the whole range of indications for which the platform is suitable.

To exemplify some of this discussion, Prof. Denison highlighted work by the University of California, San Francisco (Dr. Phil Starr), to identify a biomarker of dyskinesia using an external "patient activation" system to identify dyskinesia events coupled with implanted sensors to detect changes in cortical power spectral density associated with those events. Detection of the biomarker signal above or below a specified threshold through the closed-loop system triggered appropriate adaptive deep brain stimulation to manage the dyskinesia (29). Examples of chronic brain sensing in a locked-in amyotrophic lateral sclerosis (ALS) patient (30) and novel neural networks (31) were given as key building blocks for the system.

Prof. Denison summarized his experience of building a virtual platform through

- examples of positive outcomes—an architecture to generate closed-loop therapy can be built that enables research across disease states
- examples of areas for improvement—placement of a device in particular for CNS indications is invasive and signals from the heart can create artifacts which must be dealt with
- areas for significant thinking (beyond engineering)—the need to support clinical groups for human research, especially the obligations for long-term care and the implications on the platform design.

Finally, to help catalyze discussion, Prof. Denison suggested that a winner-take-all situation could develop for the group that developed the most versatile platform, similar to other platform economies such as social media and search engines.

Development and supply of new electrodes for clinical research: challenges and solutions

Dr. Jörn Rickert (CEO) and Dr. Martin Schüttler (CEO+CTO), CorTec GmbH, Germany

Dr. Rickert introduced the technology CorTec is developing including closed-loop systems with extensive

computational power. The extent of the technology they offer covers the full range of implantable technology starting with single components like implantable flexible electrodes, hermetic packaging, interfaces to the nervous system and wireless communication (and power supply) through to complete system design for therapeutic use. A key point emphasized by Dr. Rickert is that the company avoids introducing new materials and instead of focusing on market approval and sales to end users (patients) it builds on the versatility of its Brain Interchange technology for development of new therapies by partners and customers. To demonstrate market readiness of the technology, the AirRay Cortical Electrode, designed for the recording and stimulation of brain activity from the cortical surface, has received market clearance from the FDA in the United States for invasive neuromonitoring in the CNS.

The AirRay technology includes both flat electrodes and cuffs that can be made in a number of diameters down to 50 µM. Flexibility of the Pt/Ir electrode is provided by cutting a meandering track which also reduces the stiffness of the metal electrode relative to the less stiff polymer insulation, assisting bonding of the two materials.

The challenge of supporting both the research community while meeting the requirements of regulatory bodies and patients was discussed. For research flexibility of design, including various connection systems, sizes and electrode configurations coupled with small batch sizes and versatility in looking at multiple indications are considered key factors. In contrast, medical devices in the regulatory environment need a fixed design for a single indication coupled with high volume manufacture under stringent control.

Application of the CorTec cuff was demonstrated in several preclinical examples:

- Modulation of rat carotid sinus nerve activity using a chronically implanted CorTec sling cuff as an approach to treat type 2 diabetes. Nine weeks of stimulation restored insulin sensitivity and glucose tolerance which was reversed on withdrawing the stimulus.
- Significant improvement of the disease activity index of experimental colitis was achieved using implanted CorTec tunnel cuff electrodes in the superior mesenteric nerve with twice daily 5-min stimulation sessions.
- In an acute human experiment CorTec cuff electrodes were placed on the radial and median nerves. Stimulation allowed selective activation of muscles to produce multiple independent hand and forearm movements in a tetraplegic patient.

Finally, some learnings on managing cable connectors of implants were discussed. Avoiding loops where cables can rub against each other while allowing for some extra cable to allow for movement are both important to maximize the lifetime of the implants.

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R.A. Porter is an independent chemistry consultant without company affiliation; the other authors are in paid employment of their respective organizations. R.A. Porter and M. Hann are Society for Medicines Research Committee members for which no remuneration is paid.

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