MEETING REPORT

Bioelectronic medicine*

The field of bioelectronic medicine represents the convergence of concepts from multiple disciplines, including biomaterials science, biomedical engineering, neuroscience and medicine, in a fast-developing manner to treat chronic diseases. Significant progress in this area has resulted in the development of implantable devices, such as neuromodulation devices for chronic pain management, wirelessly powered devices to support organ functionalities and stimulation devices for enhanced bone healing.

Our ability to precisely control cell functionalities has been identified as a critical underpinning factor in these impressive developments. However, many research outcomes from academia have still not been translated to bioelectronic devices. In particular, the intermittent delivery of properly tuned dynamic electrical stimulation demonstrated the potential in modulating neurogenic/osteogenic/myogenic/chondrogenic differentiation of stem cells. However, many such research outcomes are still not translated to clinical studies. In addition, recent developments in bioresorbable electronics, soft/flexible electronics, and non-invasive bioelectronics has created a spark in the field of biomedical science.

In order to accelerate innovation to translate biomaterials-based biophysical stimulation towards the development of bioartificial organs, an international workshop was held online recently.

The key objectives of this workshop were: (1) To develop an in-depth understanding about the biomaterials-based bioengineering approaches by bringing the community together with insightful discussions and presentations by global experts as well as young researchers. (2) To understand the critical role of electroactive biomaterials to deliver bioelectrical cues for regulating cell-fate processes. (3) To expand the fundamental concepts about the physical phenomenon, observed at the tissue–electrode interface. (4) To obtain an overall idea about the recent advancements in nanoelectronic devices, together with the emergence of state-of-the-art flexible and transient electronics as next-generation bioelectronic devices with a more stable and compatible biointerface.

The one-day virtual workshop consisted of four sessions with a total of 18 technical talks of 30–45 min duration, which were delivered by renowned speakers and young researchers from across the globe. More than 250 participants covering over 50 institutions/universities from various countries, including the United Kingdom, Germany, Saudi Arabia, Ireland, USA, etc. enthusiastically participated in the workshop. The workshop began with an introductory speech outlining the theme of the workshop by Dr Ashutosh Kumar Dubey (Indian Institute of Technology (BHU), Varanasi). Details of each technical session are mentioned as below.

The first session, covering four technical talks, was chaired by D. S. Nagesh (Sri Chitra Tirunal Institute for Medical Sciences and Technology (SCTIMST), Thiruvananthapuram) and Bikramjit Basu (Indian Institute of Science (IISc), Bengaluru). It began with a scientific overview of the workshop as well as a brief discussion concerning the Indian landscape in bioelectronic medicine by Basu. He elaborated about the Indian research scenario and market potential in the field of healthcare, which can be summarized as follows: (a) research groups involved in the area of bioelectronic medicine, (b) the compound annual growth rate of the Indian healthcare market in contrast to the Global medical device market, (c) an overview of key translational research in biomaterials and implants, (d) the status of published research papers from India and research funding for biomaterials and implants by the Indian Government, (e) recommendations to develop an ecosystem with various companies and medical institutions and (f) importance of industry–academia–clinician collaborations in transforming the Indian healthcare scenario.

The second lecture was delivered by John A. Rogers (Northwestern University, USA) on bioresorbable electronic materials/devices. He presented cutting-edge developments on soft, flexible and water-soluble bioelectronic systems, which are composed of a stretchable form of silicon supported on elastomeric substrates. Bioresorbable electronics can eliminate unnecessary device load on the body in a way that it negates the need for secondary surgical extraction. Moreover, their detailed applications in devices for neural stimulation, cardiac pacing and programmable drug release were also described. Specifically, the application of such a soft bioelectronic system in developing bioresorbable intracranial pressure sensors to treat traumatic brain injury was discussed. Rogers suggested such a strategy as a potential alternative to overcome the limitations of the currently available non-transient intracranial monitor, such as second injury, restricted movement and infection. He also detailed the design and working principle of wirelessly controlled bioresorbable drug delivery devices for programmed drug delivery applications. The mechanistic aspects of dissolution kinetics of drug delivery devices were also presented. Rogers also spoke on the design, dissolution study and implantation procedure of a bioresorbable, wireless nerve stimulator to treat nerve injury. He provided the key aspects to develop a bioresorbable wireless cardiac pacemaker, which can potentially eliminate the need for second surgery as well as heart failure associated with a temporary cardiac pacemaker. Detailed device structure and surgical procedure (*in vivo* demonstration) were thoroughly discussed. Overall, the insightful presentation by Rogers may allow young researchers to develop the notion of translational approaches in bioelectronics medicine using multidisciplinary methods across the field.

Surya K. Mallapragada (Iowa State University, USA), the third speaker of session I, presented a talk entitled 'Biomaterials and electrical stimulation for control of stem cell fates'. She elaborated on the development of a micropatterned polymer

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scaffold to facilitate peripheral nerve regeneration, using Schwann-like cells, produced from transdifferentiation of bone marrow-derived mesenchymal stem cells (MSCs) as a biological cue to enhance the secretion of nerve growth factors. She discussed the role of bioelectrical cues and growth factor secretion to facilitate nerve regeneration. Mallapragada presented the graphene circuits supported on polyimide substrate to electrically stimulate the MSCs to transdifferentiate into Schwann-like cells. An elaborate discussion of the electrical stimulation-mediated lineage commitment of stem cells was presented using various case studies. The fundamental concepts and experimental design to guide cellular migration using electrical stimulation were also presented.

The last technical talk of session I was delivered by Nagesh, on the 'Development of Chitra left ventricular assist device (LVAD)'. The information related to a range of LVAD, available in the global market, together with their classifications was discussed. The key objectives and motivation behind the development of LVAD were elaborated, emphasizing the importance of indigenous biomedical devices in the current Indian healthcare system. The presentation provided an overview of the development of LVAD by a team of engineers/scientists/clinicians at SCTIMST under the Technical Research Centre (TRC) programme of the Department of Science and Technology, Government of India. The working functionalities of the third-generation LVAD, which is a type of continuous-flow device with magnetic bearing were presented. The advantages of a continuous flow pump as well as its challenges in terms of biocompatibility were also discussed. The talk was summarized with a blueprint to develop biomedical devices at an affordable cost to the Indian population.

The second session covered four technical talks and was chaired by Dubey and Shilpee Jain (IISc, Bengaluru). The session began with a lecture on 'Electric field guided stem cell differentiation on electroactive biomaterials' by Greeshma Thrivikraman (Indian Institute of Technology-Madras, Chennai). She focused on the key aspects of controlling the decision-making processes of stem cells via electric field stimulation on electro-conductive biomaterials. Specifically, she covered some examples showing how we can divert the lineage commitment of MSCs towards neural-like cells by varying the material conductivity as well as electric field strength. Other examples of the development of novel nanoscale conducting materials combined with dual electric field stimulation parameters to direct the differentiation of stem cells towards neural or cardio myogenic-like cells were also presented in the talk. Greeshma suggested that such biophysical stimulation plays a crucial role towards the development of implantable culture platforms, as it can foster advanced regenerative therapies for neural and cardiovascular disorders.

In the second lecture of session II by Kimihiro Yamashita (Tokyo Medical and Dental University, Japan), the principle and fabrication method of hydroxyapatite electrets along with their physical and chemical properties were detailed. The stimulating effects of hydroxyapatite-based electrets on living cells, both *in vitro* and *in vivo*, were also discussed. Based on various results, Yamashita suggested that hydroxyapatite electrets are a promising bio-stimulant for cell and tissue regeneration.

Miho Nakamura (Faculty of Medicine, University of Turku, Finland), the third speaker of session II, talked about 'Designed biomaterials to mimic the mechanical properties of bone'. She discussed the development of carbonate hydroxyapatite along with electrically charged surfaces. Further, the influence of electrical polarization on surface free energy, surface wettability, protein adsorption, osteoblast adhesion, osteoclast differentiation and resorption of hydroxyapatite and carbonated apatite was elaborately discussed. Nakamura suggested that the surface characteristics significantly affect cellular behaviour, such as adhesion and differentiation.

The last talk of technical session II was delivered by Jonny Blaker (The University of Manchester and Henry Royce Institute, UK). He introduced the mission as well as core research theme of the Henry Royce Institute, The University of Manchester, UK. Blaker also introduced Royce technology platforms and their research impact on healthcare in the UK, as well as their global perspectives.

The third session had six technical talks and was chaired by Basu. Sarah Cartmell (The University of Manchester, UK) delivered the first talk of the session on 'Electrical stimulation for orthopaedic repair', wherein she discussed diverse approaches utilizing electrical stimulation for osteogenic differentiation of MSCs. The importance of the faradic by-product of H_2O_2 proximal to the cathode under direct electrical stimulus as well as its subsequent role in affecting the proliferation of primary MSCs was presented. The electrical stimulation of cells on conducting polymers and piezoelectric materials was also discussed. Cartmell suggested that these bioreactors can potentially be utilized as stimuli for *in vitro* bone-tissue engineering. She mentioned that this has enabled us to further understand the mechanism by which the activity of primary human mesenchymal stem cells (hMSCs), such as cell differentiation and proliferation, is altered.

In the second invited talk of session III, Manus Biggs (National University of Ireland, Galway) presented a talk entitled 'A self-powered piezo-bioelectric device for tendon repair'. The lecture was focused on piezoelectricity-based bioelectronic devices owing to their ability to eliminate the need of external power sources and complement existing mechanotherapy to promote the tendon repair processes. Specifically, the dynamic response of tendon cells through piezoelectric collagen-based scaffold, composed of ferroelectric poly (vinylidene fluoride-*co*-trifluoro ethylene)-aligned nanofibres was explained. Biggs discussed that motion-powered electromechanical stimulation of tendon cells with such a piezoelectric device led to ion channel modulation *in vitro* which further controls specific tissue regeneration signalling pathways, *in vivo*.

Asish Kumar Panda (IISc, Bengaluru), the third speaker of session III, talked about 'Modulation of bioelectrical cues to direct stem cell differentiation on multifunctional biomaterial platforms'. His discussion was based on the processing technique to develop multifunctional polymeric-based material for electrical stimulation-directed differentiation of stem cells. The conductivity and electroactivity of polyvinylidene fluoride (PVDF)-based nanocomposites, 'multiwalled carbon nanotubes and barium titanate', as the reinforcing phase were explained. He elucidated that the electric field stimulation on multiwalled carbon nanotubes-reinforced PVDF nanocomposites directed the differentiation of hMSCs to neuron-like cells. Moreover, the improved electroactive β-phase with the addition of barium titanate in the conducting PVDF matrix aided the lineage commitment of hMSCs to glial-like cells. Panda also presented the electrical waveform-dependent osteogenesis on barium titanate reinforced PVDF composite. He discussed strategies regarding the critical role of the biomaterial functionalities to tailor bioelectrical cues in driving cellular differentiation.

S. Lanceros-Mendez (University of Minho, Braga, Portugal) delivered the fourth talk of session III on 'The interplay of morphology and active response in electroactive microenvironments for tissue regeneration'. He spoke on the development of a polymer-based electroactive scaffold to guide electrical signals to cells under mechanical solicitation. Development of the biomimetic microenvironment was presented, showing the importance of piezoelectric scaffold-based bioelectrical stimulation for tissue repair. The cellular response of piezoelectric scaffold under electro-mechanical stimuli was also discussed. Lanceros-Mendez suggested that the smart/active platforms can tailor cell responses, and bioinspired electromechanical signals are quite beneficial all along the regeneration process.

The fifth presentation of technical session III was based on 'Technology for bioelectronic medicine' by George Malliaras (University of Cambridge, UK). He first introduced the engineering concepts in bioelectronic medicine, providing some of the examples such as deep-brain stimulator, vagus-nerve stimulator, etc. The limitations of conventional approaches in bioelectronics such as biomechanical compatibility of devices with tissues and their electronic performance was discussed. Strategies to develop bioelectronic devices to minimize the invasiveness of a device and foreign-body reaction were presented. Malliaras also spoke about the new technologies needed to establish stable and efficient interfaces between electronics and the human body. He presented some case studies regarding the design aspect of bioelectronic devices to demonstrate the efficacy of soft robotics to reduce the invasiveness of the conventional surgical procedure.

Jain, the last speaker of session III, dealt with 'Advanced biomedical devices with decreasing dimension and external electric field stimulations'. She briefly introduced the role of electric field stimulations to control the functionality of bioelectronic devices. She explained how to overcome the Brownian motion of micro/nanoparticles to control and navigate dual-nature Janus microbots using electrical stimulations and enhance cellular uptake for effective delivery of intracellular therapeutic agents. The use of conducting carbon electrodes to promote the rate of neurite outgrowth of nerve cells was also mentioned.

Session IV covering four technical talks was chaired by Greeshma. Alok Kumar (Harvard Medical School, Boston, USA) presented the first lecture of this session on 'Substrates and conditions to modulate the osteoblasts functions'. His research was focused on the electroactive biomaterials, particularly hydroxyapatite-based composite (HA-$TiSi_2$), developed using spark plasma sintering technique. The results on electrical conductivity, fracture toughness, cytocompatibility as well as *in vitro* bioactivity of HA-$TiSi_2$ composites were presented. His study on electrical stimulation of osteoblast cells in static and dynamic conditions to modulate cell functionalities was also elaborated.

In the second lecture of session IV, Ravi Kumar (University of Pittsburgh, USA) spoke on 'Engineered biomaterial mediated electric field stimulation in order to evoke the specific response of cells in culture-theory and practice'. Presentation began with some of the fundamental examples explaining the interaction between cells and electric fields along with their applications. He further discussed two case studies – (i) hMSC response to electric field on hydroxyapatite – calcium titanate for bone tissue engineering applications, and (ii) electric field-stimulated mouse myoblast response on PVDF – carbon nanotubes polymer composites. Ravikumar provided a solid introductory background on cell-electric field interaction with a curated set of experimental studies.

Sunil Kumar Boda (University of Minnesota Medical School, USA), third speaker of session IV, delivered a talk on 'Magnetic field stimulation and magneto-responsive biomaterials for bone tissue engineering'. He presented two case studies: (i) hydroxyapatite–magnetite composites, where the synthesis, characterization and their performance in accelerating the osteogenic differentiation of hMSCs was presented, and (ii) strontium ferrite nanoparticles, where the role of strontium release in guiding the osteogenic differentiation of hMSCs was discussed. His case studies threw light on magneto-responsive biomaterials due to their ability to promote the osteogenic differentiation of hMSCs under a static magnetic field. Boda also presented a mechanistic understanding of the biomaterial-based magnetic field stimulation in bioelectronic medicine.

The last lecture of the session IV was presented by G. K. Anil Vishnu (IISc, Bengaluru) entitled 'Micro-engineered implantable devices and related technologies for neural recording and brain tissue analysis'. He discussed the multi-pronged neural recording and stimulation approach for diagnostic and therapeutic applications using multichannel silicon-based microneedle electrodes. The fabrication strategy to develop flexible electrode arrays supported on a biocompatible polyimide substrate was also presented. Vishnu elucidated how the signals at three different neurophysiological conditions, such as baseline signals, chemically induced epileptiform discharges and the recovered baseline signals after anti-epileptic drug administration, were recorded using implantable devices. Details on designing a hand-held steerable probe integrated with micro-engineered devices and piezoelectric, micromachined ultrasound transducers for brain tumour delineation were also elaborated.

Overall, the workshop provided a platform to exchange advanced knowledge and ideas regarding recent developments in bioelectronic medicine through a series of insightful presentations and discussions. Critical analysis and thoughtful adaptation of such understanding in bioelectronics can address many existing challenges in regenerative engineering and bench-to-patient translational bioelectronic medicine. The development of a holistic and interdisciplinary research theme may trigger advanced scientific approach among young researchers and participants of this workshop to address the existing clinical challenges.

The Henry Royce Institute, The University of Manchester, UK mentioned and promoted this event on their official website: https://www.royce.ac.uk/news/ (published on 20 December 2021).

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