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Editorial

Conductive and Electroactive Biomaterials and Bioelectronics

The human body consists of various electroactive organs and tissues, such as the heart, brain, peripheral nervous system, and skeletal muscle. Electrical signal propagation across these tissues, and among or within the cells at micro- and nanoscale levels, is central to their normal physiological function and the overall health of the body. Endogenous electrical fields and piezoelectric properties also permeate some tissues not typically considered electroactive, opening avenues of regeneration of wounds, bone and cartilage. Recent progress in the design and development of electroconductive biomaterials has generated enormous momentum in successful engineering of electroactive tissue substitutes with native-like properties. These engineered tissues have shown great promise in regenerative medicine and have enabled the mechanistic understanding of how abnormalities in electrical signal propagation among the cells lead to pathophysiological conditions and disease manifestation in the body. Over the past few years, a variety of electroconductive biomaterials, composed of either natural or synthetic components, have been carefully designed to mimic the extracellular matrix of the target tissues and impart multi-dimensional physiochemical cues to modulate cell-cell/cell-microenvironment interactions. In addition to tissue engineering, recent innovations in the development of electroconductive materials have also opened exciting avenues in the bioelectronics field through the convergence of biology and electronics. Bioelectronics devices have widely been utilized as flexible, stretchable, and adaptable sensing or stimulation platforms for screening, management, or regulation of biological and physiological functions of the body. This special issue of *Acta Biomaterialia* highlights the recent advancements in the areas of Electroconductive Biomaterials and Bioelectronics. This issue brings together a total of 19 high-quality original research and review articles, from experts in their relevant fields, within these exciting and growing fields.

This issue begins with a review article by Li and colleagues on the recent advances in the design and the development of a conductive polymer-based hydrogel for broad applications in tissue engineering. In this article, the authors highlight preparation and functionalization methodologies of conductive polymers discussing hydrophilic conducting polymer complexes, side-chain modified conducting polymers, as well as conducting graft polymers. They also discuss physical and chemical cross-linking strategies for the fabrication of conductive polymers. Finally, this article highlights applications of conductive polymers for myocardial, neural, and skeletal muscle regeneration [1].

This themed issue further brings a collection of six articles, including three reviews and three original research manuscripts, focused on neural tissue engineering and regeneration. Schmidt and colleagues review the characteristics of carbon-based electroconductive materials, covering polypyrrole (PPY), polythiophene (PT), poly(3,4-ethylene dioxythiophene) (PEDOT) derivates, polyaniline (PANI), graphene, and fullerenes (i.e., carbon nanotube, buckyball structures). They further provide an overview of the applications of these carbon-based conductive materials for peripheral nerve, spinal cord, brain, eye, and ear tissue regeneration [2]. In another review article by Detamore's group, the authors primarily discuss the current therapeutic strategies, including regenerative medicine, rehabilitation, and neuromodulation, for the treatment of spinal cord injury (SCI). They further discuss the promise of carbon-based materials, metallic particles, and conductive polymers to complement the conventional treatment modalities of SCI towards synergistic regenerative rehabilitation [3]. Another review article by Malliaras and Oldroyd presents the recent progress in the engineering of thin-film flexible electrodes for neurostimulation and treatment of neurological disorders. In this article, the authors discuss the interactions of engineered electrodes with the surrounding host tissue environment and comprehensively outline the technical challenges which may lead to electrode failure. They conclude their manuscript by highlighting the alternative design strategies to enhance the stability of the electrodes within a biologically active (i.e., tissue) environment [4]. In a research article, Li and colleagues report the development of a photoactive, antioxidant, and electrically conductive micro-fibrous membrane using poly(3- hexylthiophene), polycaprolactone, and PPY. They utilized an *in vitro* culture system to test the utility of the proposed electrospun polymeric patch for neuronal differentiation [5]. Duan and co-workers report synthesis and characterization of a new class of electrically conductive composite nanofiber yarns, by using poly(p-dioxanone) biopolymer incorporated with carbon nanotubes, for peripheral nerve regeneration. The authors demonstrated successful culture of rabbit Schwann cells and human adipose-derived mesenchymal stem cells (hADMSCs) within the proposed polymeric system, where the addition of electrical stimulation further led to maturation and differentiation of hADMSCs to Schwann-like cells [6]. The last research article by Tang and colleagues demonstrates that laminin-coated Ti3C2TxMXene conductive films support differentiation and network formation of neural stem cells (NSCs). Integration of electrical stimulation with the conductive films significantly promoted NSC proliferation [7].

In the area of cardiac tissue engineering, there are five articles, including three reviews and two research manuscripts, in this special issue. Three review articles, presented by the groups of

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Nikkhah [8], Shin and [9], and Wang [10], comprehensively summarize the recent advancements in the use of electrically conductive polymeric biomaterials and nanomaterials for cardiac tissue engineering, covering *in vitro* and *in vivo* studies. These articles primarily outline the application of electroconductive polymeric materials such as PPY, PANI, and PEDOT for the engineering of electroconductive cardiac tissues. They also highlight various types of nanomaterials such as carbon-based, metal-based (i.e., gold, silver), and silicon-derived nanomaterials, which notably promote electrical synchronicity in cardiac cells. Finally, these articles provide valuable insights and directions to address the biological knowledge gaps in this area [8–10]. Following these review articles, there are two research manuscripts. Zorlutuna and colleagues report the development of a composite hydrogel construct, with electrical conductivity and topographical features, for the culture and maturation of stem cell-derived cardiomyocytes. They utilized aerosol jet printing technology to print Ti3C2TxMXene on polyethylene glycol (PEG) hydrogel to generate cardiac patches with defined architecture. Their study demonstrated that the proposed engineered tissue constructs led to the formation of highly organized and mature cardiac tissues, as indicated by synchronous contractility of the cells and upregulation of cardiac-specific genes [11]. In another study, Zhang and co-workers report the development of electrically conductive and anisotropic cardiac patches, made by electrospinning of reduced graphene oxide/silk matrices. Notably, the authors demonstrated significant utility of the proposed electrically conductive cardiac patch in the regeneration of the left ventricular tissue in a rat model of myocardial infarction [12].

There is also one manuscript focused on investigating the role of electrically conductive materials for bone tissue engineering. Cartmell's group utilized pure titanium discs and electrical stimulation, within a custom-made bioreactor setup, to investigate the fate of mesenchymal stem cells. They demonstrated significantly higher cellular proliferation, cytoskeletal alignment, and enhanced alkaline phosphatase production (indicating osteogenesis) upon exposure of the cells to electrical stimulation [13].

Next, there are three research articles in this issue focused on piezoelectric and stimuli-responsive materials for drug delivery, antimicrobial surfaces, and protein patterning applications. Ciofani's group report synthesis of drug-loaded piezoelectric nanoparticles for treatment of glioblastoma multiforme (GBM) tumors. They specifically utilized nutlin-3a-loaded ApoE-functionalized P(VDF-TrFE) nanoparticles and demonstrated that remote ultrasound-based mechanical stimulation led to inhibition of proliferation and invasion of GBM cells [14]. In another study by Lanceros-Mendez and colleagues, the authors generated a thin piezoelectric polymeric film made of poly(vinylidene fluoride-co-trifluoroethylene) (PVDF-TrFE) and silver nanoparticles, for antimicrobial applications. They showed that in the presence of mechanical vibration and subsequent generation of an electrical potential, the proposed nano-engineered films sensitize *Escherichia coli* and *Staphylococcus epidermidis* bacteria and significantly inhibit their growth [15]. Vilarinho and colleagues also reported the development of a stimuli-responsive thin film made of poly (L-lactic acid). Induction of mechanical stress, using atomic force microscopy, led to a polarization of an electrical field, utilized for selective protein (i.e., fibronectin) adsorption and patterning [16].

This special issue finally brings together two review articles and one research manuscript in the area of bioelectronics. In a review article by Green's group, the authors introduce commonly used conductive polymers, including PANI, polyphenylenes, poly(paraphenylenevinylene), PPY, and PTs. They further highlight their polymerization mechanisms and material characteristics such as chemical stability and solubility. They also discuss additive manufacturing of these polymers for specific applications in bioelectronics [17]. In another review article, Liu and colleagues report the recent advancements and opportunities in flexible electronics for the development of smart skins. They discuss the applications of E-skins for monitoring and sensing of biophysical (i.e., strain, pressure, temperature, etc.), metabolic, and electrophysiological signals. They also highlight recent innovations in implantable flexible electronics [18]. Lastly, in a research article, Cicoira and colleagues report synthesis of a self-healing and conductive epidermal patch using polyvinyl alcohol hydrogel and a conductive polymer dispersion, namely PEDOT:PSS. They characterized adhesion strength, electrical conductivity, as well as self-healing properties of the proposed conducting polymer. They also demonstrated the excellent capability of this polymeric system for bioelectronics applications, specifically for high-resolution recording of electrophysiological signals (ECG, EMG) [19].

It has been a pleasure to organize this themed issue focused on Conductive and Electroactive Biomaterials and Bioelectronics for *Acta Biomaterialia*. This special issue provides an overview of the latest advancements and future areas of exploration through a series of insightful review articles and original research manuscripts. We hope the collection of these articles will stimulate the community to open new avenues of research and push the boundaries of innovation toward the next generation of electroactive biomaterials and bioelectronics. The guest editors would like to thank all the authors who contributed to this special issue, Editor-in-Chief William R. Wagner, Editor Sarah Heilshorn, and the fantastic editorial staff, especially Vera Kucharski and Victoria Groce.

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