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Next generation bioelectronics: advances in fabrication coupled with clever chemistries enable the effective integration of biomaterials and organic conductors

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Abstract

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Keywords

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Next generation bioelectronics: Advances in fabrication coupled with clever chemistries enable the effective integration of biomaterials and organic conductors

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Organic bioelectronics is making an enormous impact in the field of tissue engineering, providing not just biocompatible, but biofunctional conducting material platforms. For their true potential to be reached, it is critical to integrate organic conductors with other biopolymers in a targeted manner, allowing the development of devices and scaffold architectures capable of delivering a number of physical, chemical, and electrical stimuli. Herein, we provide an overview of the methods currently being employed to tailor organic conductors for bioapplications, with a focus on the development of fabrication techniques vital to the development of the next generation of intelligent bionic devices. [http://dx.doi.org/10.1063/1.4905372]

Implantable biomaterials have enabled the development of a range of prosthetic devices that have delivered clinical solutions to a wide variety of conditions. Metallic implants based on Ti provide artificial knee joints and artificial hips. Metallic materials are also used to create stents in all shapes and sizes to support reopened arteries. Biodegradable polymeric stents have more recently appeared (and disappeared!),[1,2] and polymer conduits have been implanted to facilitate nerve (re)connections.[3,4] The biomaterials used in these applications are chosen for biocompatibility and having appropriate mechanical properties to provide structural support.

In more recent studies, the biofunctional properties of polymer scaffolds have been developed and utilised in the field of tissue engineering. The inherent complexity of the material-biological interface has encouraged the development of advanced polymeric biomaterials whose physicochemical and mechanical properties can be tailored for different bioapplications. For example, 3D printed chitosan (CT) scaffolds have been shown to support the *in-vitro* development of cartilage from infrapatellar fat-derived adipose stem cells, presenting a potentially viable cell-scaffold construct that can be used to produce chondral grafts for *in vivo* implantation.[5] Poly(lactic-co-glycolic acid) (PLGA) based polymeric scaffolds loaded with the bone morphogenetic protein 2 (BMP-2) have been used to promote osteogenesis, significantly increasing new bone volume when implanted into bone defects in *in-vivo* mouse models;[6,7] and photo-curable and biodegradable polylactic acid (PLA) based polymers have been fabricated into intricately microstructured 3D scaffolds that have demonstrated good biocompatibility with a range of neuronal cells.[8]

The next level of sophistication for medical implants involves electrical communication with the human body using appropriate electrical conductors as electrodes. The cardiac pacemaker, bionic ear, and the vagus nerve stimulator (to control epilepsy or Parkinson's) are examples of such devices. To date, the electrode materials of choice have been metals such as platinum or titanium nitride.[9–11] These are materials that are relatively inert and that provide the capacity for high density charge injection.[10,12,13] In more recent times, the use of organic conductors such as

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inherently conducting polymers (ICPs), carbon nanotubes (CNTs), and most recently graphene has been investigated for use as electrodes for bionic devices (for review, see Ref. 14). Of these, ICPs are particularly exciting as polymers are the one class of material capable of providing structural, bioactive, and electronic communication. As our understanding of materials science progresses and our ability to fabricate expands into new dimensions, we are poised to see the seamless integration of polymer structures that will enable biocommunications at new levels. This research update will focus on the rise of ICPs in the area of biomedicine and biofabrication. It will highlight our growing ability to integrate molecular level functionality into ICP biomaterials, to modulate biomolecular and cellular interactions at the ICP interface, and how these materials, in concert with an array of material processing and fabrication techniques, are allowing researchers to design scaffolds that address a host of challenges in the realm of tissue engineering and scaffold design.

Broadly, implantable polymers can be broken into several categories based on their functionality. They may be designed to play a purely structural role, present both biofunctional and structural properties, or provide the capacity to transfer charge and open opportunities for electrical communication with biological systems.

Polydimethylsiloxane (PDMS) and polyurethane are the two most commonly implanted materials for use in providing simple structural integrity. These materials have proven attractive due to their biocompatibility, thermal and chemical stability, excellent mechanical properties, and ease of manipulation.[15,16] PDMS has been widely employed as a casing and structural support material for implanted devices such as pacemakers and cochlear implants, and the excellent elastomeric properties of both PDMS and polyurethanes have seen them used to insulate electronic cabling and other implanted electronics.[17–19] Their high permeability to gases and small biomolecules may provide them an additional role as a drug delivery system, where therapeutic drugs loaded into the bulk material may be passively released via a simple diffusion mechanism post implantation.[20,21] Fabrication options for PDMS are generally limited to either precast moulding or injection molding around preformed components, while polyurethanes are also amenable to electro-spinning and wet-spinning techniques,[22,23] leading to their ongoing investigation for various bioapplications.

Biopolymers are versatile materials that provide the next level of sophistication, providing both structural support and biofunctionality to scaffolds for tissue engineering. Choice of biopolymer/s, and the crosslinking method and conditions can be tailored to present appropriate physicochemical and mechanical properties to the *in-vitro* and *in-vivo* environment. For example, extracellular matrix (ECM) components such as hyaluronic acid (HA) and Collagen (CG) have been used to generate microstructured hydrogel scaffolds to promote biointerfacing with cells and tissues.[24,25] Chitosan and alginate (ALG), compounds derived from the exoskeletons of arthropods and brown algae, respectively, are highly processable biopolymers that can be used to produce hydrogels of low modulus and good structural integrity and biocompatibility.[26–30] They have been investigated as scaffold materials for cartilage,[5] muscle,[31] nerve,[32] and bone regeneration.[33,34] Biocompatibility and biofunctionality within such structures can be further enhanced by functionalising the polymer surface with extracellular matrix components and their derivatives (e.g., CG, laminin, and arginyl-glycylaspartic acid (RGB) peptide sequences).[35–37] These polymeric matrices have also been used as a reservoir for growth factors or therapeutic biocompounds whose release may be tailored by tuning the polymer porosity and/or degradation or erosion rates.[38–40] Their high processability means biopolymers are amenable to a range of fabrication techniques including reactive inkjet printing, extrusion printing, moulding, wet spinning, and electro-spinning,[41–43] providing the capacity to design and fabricate intricate scaffold architectures suitable for diverse therapeutic requirements.

Finally, the capacity to deliver electrical stimuli to excitable cells and tissues via conducting materials has provided an exciting opportunity for interfacing directly with biological systems. Nanostructured carbons have attracted extensive interest for they can combine excellent electrochemical properties with high strength, flexibility, and processability.[44–47] They also provide an extra dimension in that chemistries are available to readily tune the bioactivity, electronic and mechanical properties, as well as to manipulate processability.[48–51] CNTs have proven to be interesting platforms for electrical stimulation.[52–54] Justified or not, interest in the former has waned

dramatically since studies highlighting the cytotoxicity of free CNTs under some biological conditions.[55] Other studies have shown that CNT electrode structures are indeed accommodated in an acceptable manner by biological systems.[56]

The use of ICPs for electronic connection provides new dimensions to the development and design of advanced tissue engineering scaffolds.[14] ICPs can be designed to exhibit high biocompatibility and to perform a range of biologically relevant functions including the controlled release of therapeutic drugs and growth factors[57] and the delivery of mechanical and electrical stimuli to cells and tissues.[58,59] ICPs are also highly amenable to a range of material fabrication techniques that can be used to fashion two-[60] and three-dimensional structures,[61] thus providing a dynamic and powerful biomaterial platform that may be applied to a suite of diverse bioapplications. These organic conductors will form the focus of this research update.

The seamless integration of polymeric structures to provide mechanical structural support, bioactivity, and electronic components distributed in 3D to have a maximum impact on cell behaviour is the emerging challenge facing researchers in the fields of regenerative medicine and bioelectronics. A suite of different techniques have been investigated and applied to engineer and manipulate the chemical, structural, and mechanical properties of the above biomaterials to suit specific applications. Biomaterial development is concurrently addressing material properties at a number of different dimensions, from the tuning of bulk material properties, directing microscale biological interactions by engaging material fabrication techniques, such as printing and electro- and wet-spinning to present micro- and nano-scale structures, to the addressing of molecular scale interactions through modulating polymer chemistry and nanotopography. Above all, the integration of organic conductors has added another dimension into biomaterial development, tailoring them into more intelligent and advanced materials. Hereafter, we will outline the approaches taken to integrate organic conductors with biomaterials (structural and bioactive) from the macroscopic to the micro-/nano-scopic to the molecular domains.

The integration of organic conductors into 3D macroscopic structures has been driven largely by the development of electroactive ICP-hydrogel composites. ICPs have been integrated with hydrogels to combine the inherent biocompatible and biofunctional properties of both constituent materials.[62] In particular, the coupling of ICPs and hydrogels assists greatly in resolving the disparity in the mechanical properties of ICP materials with cells and tissues, which can cause problems with biological interfacing and *in-vivo* inflammatory responses. Poly(3,4-ethylenedioxythiophene) (PEDOT) - polystyrene sulfonate (PSS) electrodes coated with alginate using a dip coating method illustrated enhanced neural recording functionality compared to non-coated PEDOT electrodes.[63] Polypyrrole (PPy) has been more intimately complexed with alginate by electrochemically polymerizing the polymer vertically through an alginate gel on a microelectrode array, providing both a soft and conductive interface.[64] The PPy-alginate gel electrode exhibited a high surface area, reducing the impedance of the electrode by an order of magnitude compared to a standard PPy film.

Semi-interpenetrating networks of polyaniline (PANI) and polyacrylamide have also been generated through electrochemical polymerization of PANI in the hydrogel pores.[65] Therein, the electromechanical properties of PANI were used to drive the release of the dye safranin using electrical stimulation, thus presenting the potential use of the composite hydrogel as a drug delivery system. In another study, PANI nanoparticles formed with the steric stabilizers poly(vinyl alcohol) (PVA) or CT were used to make nanostructured PANI-PVA hydrogels by crosslinking the PVA in the dispersion via E-beam irradiation.[66] The hydrogels were demonstrated to be non-cytotoxic with excellent cell viability of human dermal fibroblasts after 72 h.

An enormous advantage that organic conductors possess over conventional electrode materials is their high processability, allowing a suite of fabrication techniques to be employed to develop appropriate scaffold architectures that can effectively interface with biological systems at the nano- and micro-dimensions. Some widely studied fabrication techniques include inkjet printing, extrusion printing, electrospinning, and wetspinning. Inkjet printing has been used to construct patterned electroactive platforms with fine control over the spatial dimension of the printed structures.[60] Tracks of 100 μm diameter of PPy were deposited on a substrate, with CG printed directly on the PPy structures using the high precision of the inkjet printing technique.[60] The printed

tracks were shown to be electroactive and cytocompatible, with cell experiments using PC12 cells demonstrating the printed microstructures, in concert with electrical stimulation, promoted neurite outgrowth, and cell orientation. Inkjet and extrusion printing have been used to print parallel tracks of PEDOT-PSS on both glass and a biopolymer substrate.[61] Extrusion printing was successfully employed to embed PEDOT-PSS tracks into a biopolymer matrix of chitosan and hyaluronic acid, with the embedded PEDOT structures demonstrating good conductivity. This technique was proposed as promising method to introduce patterned organic conductors into biopolymer gels for use in a range of bionic applications and devices.

Electrospinning has been widely employed to generate nanostructured fibrous mats of conducting polymer for biomedical applications. This technique may involve electrospinning a biocompatible and biodegradable material, which is then coated with ICP either through electrochemical,[67] chemical[68,69] or vapour phase[70] polymerization processes, or alternatively the ICP can be directly incorporated into the spinning solution and used to make up the bulk of the fibre.[71–73] Electrospun fibrous mats incorporating ICPs have been employed as conduits for controlled drug release and for tissue engineering. The biodegradable polymers, poly($_L$-lactide) (PLLA) or PLGA, were loaded with the anti-inflammatory drug dexamethasone and electrospun onto a gold neural probe, with the fibres subsequently coated with electrochemically polymerized PEDOT.[67] The PEDOT casing around the fibres dramatically decreased the release of dexamethasome, with controlled release demonstrated by using electrostimulation to actuate the nanofibres, generating internal hydrodynamic pressure within the tubes and forcing the dexamethasone, and presumably, the degradation products of the PLLA out through the ends of the tubes or through cracks in the PEDOT casing.

Electrospun PANI-gelatin nanofibre mats have been shown to support the adhesion and proliferation of H9c2 rat cardiacmyoblast cells.[72] In another study, conductive meshes fabricated by the growth of PPy on randomly aligned electrospun PLGA fibres were shown to support the growth and differentiation of PC12 neural cells[68] (Figure 1). Electrically stimulating the scaffolds with a constant potential of 10 mV resulted in 40%-50% longer neurites and 40%-90% more neurite formation compared to unstimulated cells. Electrical stimulation of cells on aligned fibres resulted

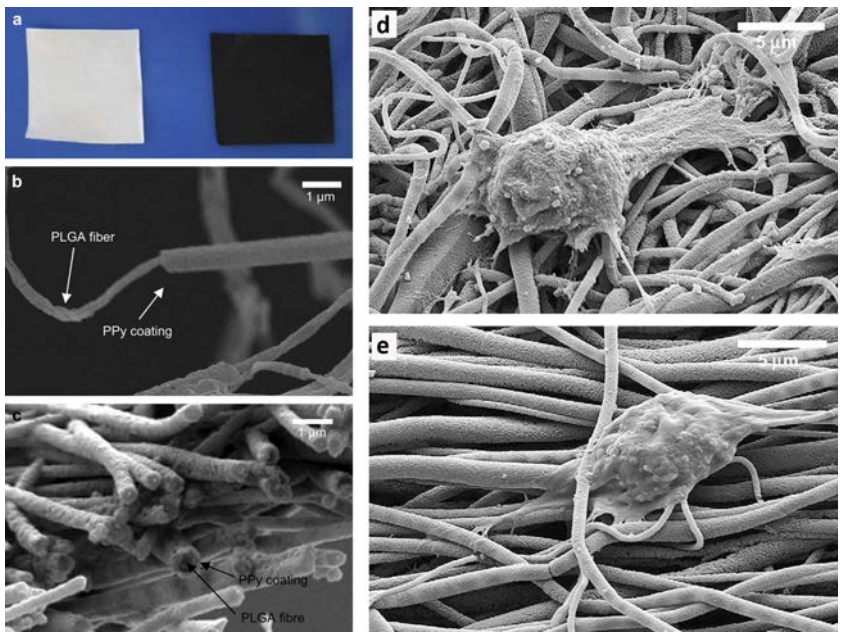

FIG. 1. PPy-coated PLGA meshes. (a) Photographs of uncoated PLGA meshes (white, left) and PPy–PLGA meshes (black, right). (b) SEM micrograph of single strands of PPy–PLGA fibers. (c) SEM image of section of the PPy–PLGA meshes. [(d) and (e)] SEM images of PC12 on (d) PPy-random fibres and (e) PPy-aligned fibres for 2 days. Reproduced by permission from Lee *et al.*, Biomaterials **30**, 4325 (2009). Copyright 2009 by Elsevier.

in longer neurites and more neurite bearing cells, indicating a synergistic effect between the topographic and electrical cues. PPy-PLA scaffolds modified using admicellar polymerization have also been demonstrated to support the adhesion and migration of neural progenitor cells, with electrical stimulation on aligned fibres demonstrated to increase the expression of c-Fos (a neural activity marker) and longer neurite outgrowth compared to nonstimulated cells.[74]

Electrospun scaffolds have also been demonstrated to promote the alignment and differentiation of muscle cells.[73] An ester functionalized polythiophene-based material (poly-octanoic acid 2-thiophen-3-yl-ethyl ester) was used to generate both films and aligned electrospun fibres with the capacity for further modification of the material via hydrolysis of the ester group, making them more hydrophilic. Both films and electrospun mats supported the adhesion, proliferation, and differentiation of mouse primary skeletal myoblasts, with linear electrospun scaffolds guiding the differentiation of aligned primary myotubes, providing the potential use of these materials in *in vivo* tissue engineering applications.

Wetspinning is another approach to produce fibrous structures. Wetspinning is a process that allows the fabrication of fibres in the μm range by introducing a polymer solution dissolved in a given solvent into a chemical coagulation bath via a spinneret and has been employed to fabricate biocompatible PPy-Alginate fibres.[75] A hybrid polymeric biomaterial platform consisting of aligned wetspun fibres of PLA-PLGA (30 μm diameter) on a base of PPy-para toluene sulphonic acid (pTS) has been used to demonstrate the synergistic effects of employing multiple polymeric biomaterials in a single conduit architecture[53] (Figure 2). The scaffold was demonstrated to promote directional axonal growth and Schwann cell migration via topographic cues along the fibres and illustrate accelerated nerve growth and increased Schwann cell migration by applying electrical stimulation via the PPy polymer. Subsequent work illustrated this composite platform to promote the directional growth and differentiation of primary mouse myoblast cells.[76]

While the aforementioned fabrication techniques have been employed to address the macro- and micro-scale interactions, modulating the physicochemical properties of ICPs at the nanodomain are critical to imparting control over molecular level interactions that are essential to guiding higher order biological interactions with the ICP materials. While traditional ICP compositions have been demonstrated to provide a level of inherent biocompatibility, the integration of biomolecules and bioactive compounds into ICPs is seen as critical to enhancing both the biocompatibility and biofunctionality of ICP biomaterials. Several strategies are available to introduce biomolecules into ICP materials.[77] Biomolecules can be intimately complexed with the conjugated ICP backbone through the process of *doping*.[14] The general requirement for the dopant to be negatively charged restricts the variety of biological compounds suitable for this mode of incorporation; however, a greater suite of chemistries may be bound within the polymer matrix by simple entrapment via the polymerization of the polymer in a mixed monomer/dopant/biomolecule solution.

Incorporating ECM components into ICP biomaterials has been viewed as one approach to enhance the biomaterial interfacing with the *in-vitro* and *in-vivo* biological environment, providing a level of molecular recognition between the ICP surface with other ECM and relevant cell membrane components. ECM proteins critical to several cell behaviors, including adhesion, migration, and differentiation, have been directly incorporated into ICPs as the dopant anion. Fibronectin (FN) fragments incorporated into PPy have produced fuzzy and rough polymer surface morphologies that provided a high density of bioactive sites for neural cell binding[78] (Figure 3). Therein, glial cells were shown to attach better to the biofunctionalized PPy than to control surfaces. PPy doped with laminin fragments has also demonstrated enhanced neuronal cell attachment and neurite outgrowth,[79] as well as neuronal binding *in-vivo*.[80] For example, PPy doped with the laminin fragments CDPGYIGSR (PPy/p31) and DRNIAEIIKDI (PPy/p20) was tested for their ability to influence the attachment and differentiation of human embryonic stem cells (hESC) and rat neuronal stem cells (rNSC). PPy/p20 demonstrated enhanced neural differentiation and neural outgrowth for rNSCs, while PPy/p20 promoted hESC adhesion and spreading, as well as neural differentiation. PPy doped with p31 has also been shown to exhibit biofunctionality *in-vivo*, promoting neuron attachment when implanted in guinea pigs.[80]

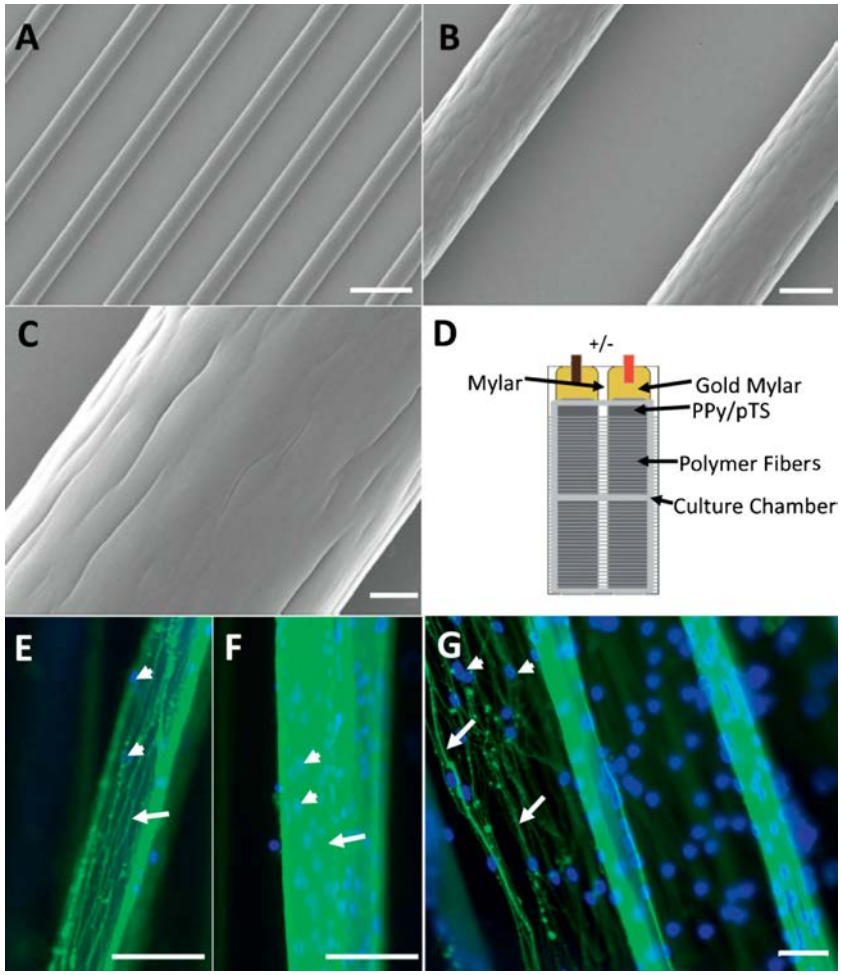

FIG. 2. SEM images [(a)–(c)] reveal a relatively smooth PPy surface, in which PLA:PLGA fibers are embedded. Tissue culture chambers were attached to the scaffold surface to facilitate dorsal root ganglion growth and stimulation (d). Axon growth (arrows) and Schwann cell (arrow heads) migration is observed on both the biodegradable fibers [(e) and (f)] and the PPy/pTS surface (g). Fluorescent microscopy images [(e)–(g)] demonstrate that axonal growth and Schwann cell migration follow the path of the embedded polymer fibers on both stimulated and unstimulated scaffolds. Scale bars 1/4 100 mm (a), 20 mm (b), 5 mm (c), and 50 mm [(e)–(g)]. Reproduced by permission from Quigley *et al.*, Adv. Mater. **21**, 4393 (2009). Copyright 2009 by John Wiley and Sons.

ECM components other than cell adhesion proteins have also illustrated to impart enhanced biocompatibility to ICPs.[81–83] PEDOT doped with heparin and HA was shown to possess electrochemical properties required for neural electrodes, with the latter comparing well with PEDOT-PSS.[84] PPy doped with HA illustrated good biocompatibility *in-vitro* using PC12 cells, with *in-vivo* experiments in rats finding PPy/HA to demonstrate enhanced angiogenesis compared to PPy/PSS films, with more blood vessels associated with the PPy/HA films after 2 week implantation.[81] The ECM components, HA and chondroitin sulphate (CS), were compared to the synthetic dopants, dodecyl benzene sulphonic acid (DBS), pTS, and 2-methoxy-5 aniline sulphonic acid (PMAS), for PPy films, with their ability to promote the adhesion and proliferation of C2C12 and primary myoblasts evaluated.[83] Dextran sulphate (DS), a known anticoagulant drug, was also investigated due to its attractive high level of sulphonation and polyanionic polyssacharide structure. In the absence of specific cell adhesion molecules (i.e., laminin), PPy doped with DS, CS, and DBS illustrated enhanced cell proliferation and differentiation compared to the other films.

The nature of protein—polymer interactions are critical to understanding the ultimate biointerfacing between the ICP biomaterial and cells and tissues, and a number of studies have investigated

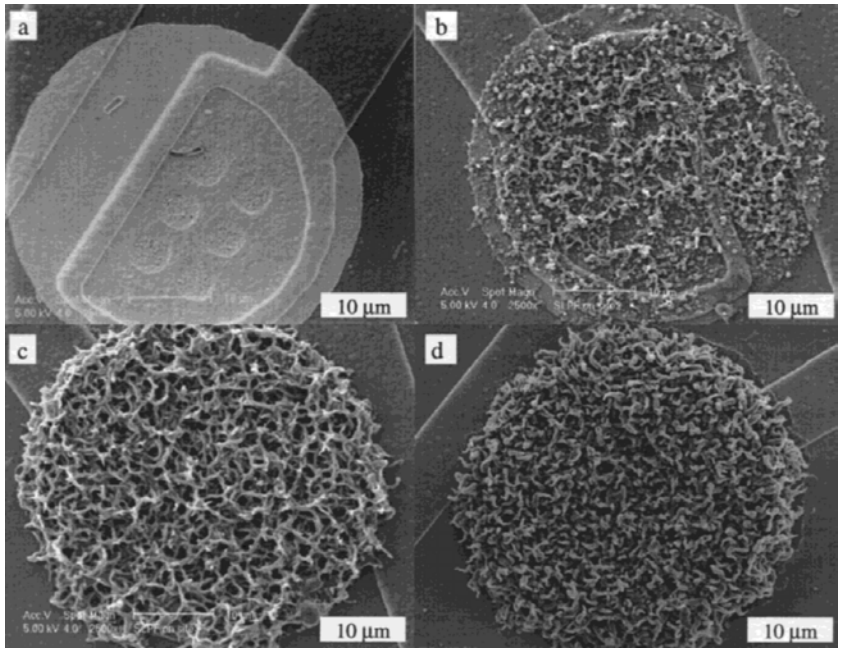

FIG. 3. SEM images of PPy doped with silk like polymer with fibronectin fragments (SLPF) coated electrode sites. From (a) to (d), the deposition time increased corresponding to a total charge passed of (a) 0 μC, (b) 1 μC, (c) 4 μC, and (d) 10 μC. The area of the uncoated electrode site is 1250 μm^2. Reproduced by permission from Cui *et al.*, J. Biomed. Mater. Res. **56**(2), 261 (2001). Copyright 2001 by Elsevier.

the influence of the composition of the ICP film and redox state on ICP interaction with proteins and cells. The binding of the extracellular matrix protein FN was studied on a PEDOT-tosylate film as a function of electrical stimulation, with FN binding shown to be greatest on the reduced, as opposed to the oxidized polymer film, with cell migration of bovine aortic endothelial cells also shown to be greatest on the oxidized polymer film.[85,86] The concentration of the dopant species, as well as polymer surface nanoroughness and redox state, has been demonstrated to influence both the mass and conformation of bovine serum albumin (BSA) and FN adsorption to PPy doped with DS.[87] Altering the loading of the biodopant DS in the PPy films modulated a range of polymer physicochemical properties, including polymer nanoroughness and wettability, altering both the mass and conformation of the adsorbed proteins. Oxidation of the polymer resulted in an increase in the total mass, and viscoelasticity, of the adsorbed FN layer. An increase in viscoelasticity was proposed to signify an increase in the bioactivity of the surface bound protein layer. In a recent study, the physical and electrochemical properties of PEDOT doped with the biological dopants DS, CS, and ALG were investigated, as well as protein and cell interactions with the polymer films.[88] While FN binding was greatest on PEDOT-DS, CG binding was greatest on PEDOT-DS and PEDOT-ALG. PC12 adhesion and cell morphology varied both as a function of the dopant and the presence/absence of a protein conditioning layer, with cells adhered to PEDOT-DS either with no preadsorbed protein layer or with a CG layer, demonstrating significantly greater cell spreading compared to all other treatments (Figure 4). The ability of cells to effectively adhere to the PEDOT-DS film was determined to result from the direct interaction between proteins resident on the cell membrane (i.e., glycocalyx) and the polymer surface.

A particularly exciting field of research is the application of ICPs to communicate with biological systems at the cellular level. The ability for ICPs to transport ionic molecules and electronic charge, coupled with their high biocompatibility and biofunctionality, is allowing them the opportunity to interface and communicate with excitable cells. The simplest method of detecting biological signals from cells is to exploit the redox properties of ICPs as simple electrochemical sensors. PEDOT-PSS microelectrode sensors capable of electrochemically detecting individual transmitter release from single cells have been developed, with the release of catecholamine during exocytosis

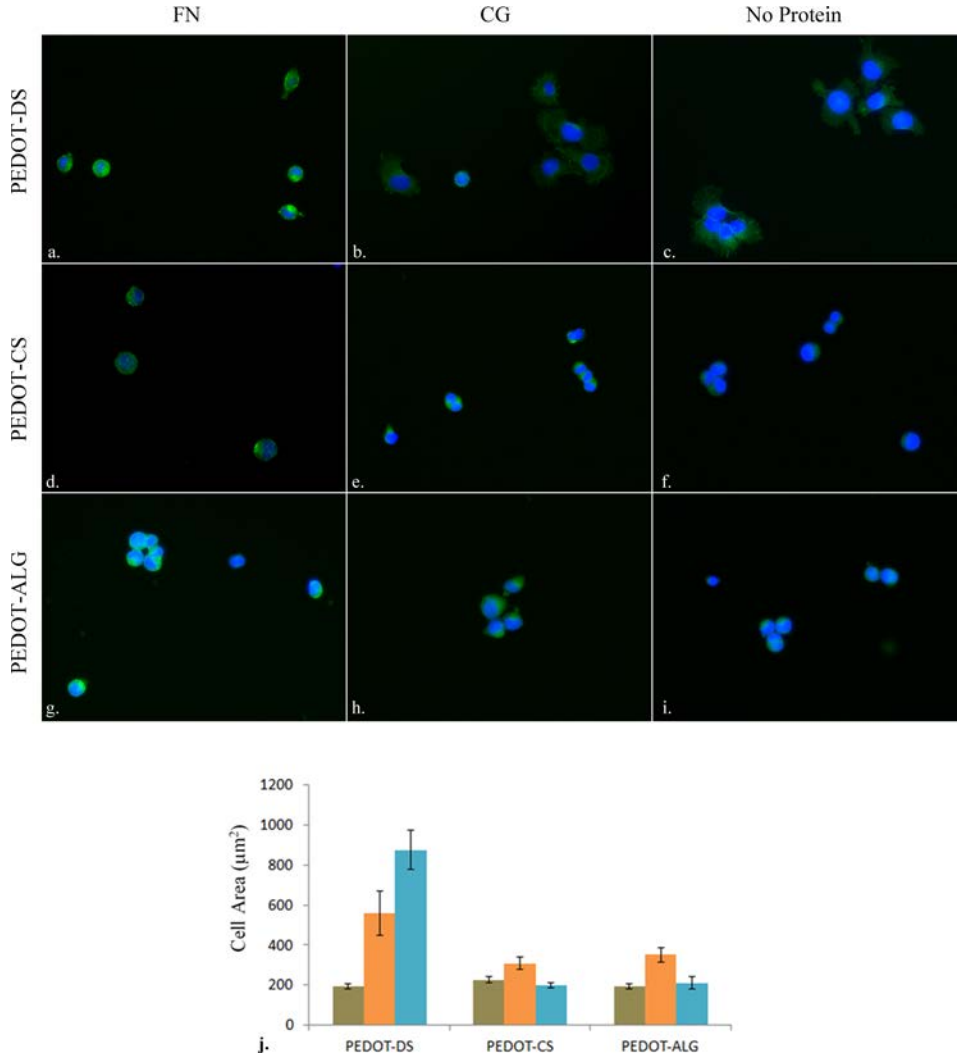

FIG. 4. (a)–(i) Representative fluorescence microscopy images of PC12 cells adhered to PEDOT-DS, CS, and ALG with or without a preadsorbed protein conditioning film. Image dimensions 220 × 180 μm. (j) Quantification of cell surface area for cells adhered to the biodoped PEDOT polymers with either FN (green), CG (orange), or no protein (blue) surface conditioning layer. Reproduced with permission from Molino *et al.*, Adv. Mater. Interfaces **1**(3), 12 (2014). Copyright 2009 by John Wiley and Sons.

recorded with a high signal-to-noise ratio.[89] Organic Electrochemical Transistors (OECTs) have, in recent years, been developed as biosensors capable of high efficacy recording of physiological events at higher sensitivities than traditional sensors. The ability of OECTs to amplify recordable signals allows them to record at a higher sensitivity and lower detection limit than conventional potentiomeric or conductomeric sensors.[90] OECTs have been used to measure the physical interaction with cells and the ICP surface, with PEDOT-PSS based OECTs used to measure changes in the surface charge and morphology of adherent cells,[91] however their most powerful and promising application lies in their ability to amplify and record electrical activity from cells and tissues. In concert with the ability to develop flexible electronic devices using ICPs, this has seen their development as highly conformable OECTs for *in-vivo* recordings.[92,93] Recently, a PEDOT-PSS based OECT embedded on a thin and flexile organic film was designed to allow the recording of electrophysiological signals on the surface of the brain[93] (Figure 5). The device was used to successfully record epileptiform discharges and was capable of measuring low amplitude brain with a high comparatively high signal to noise ratio.

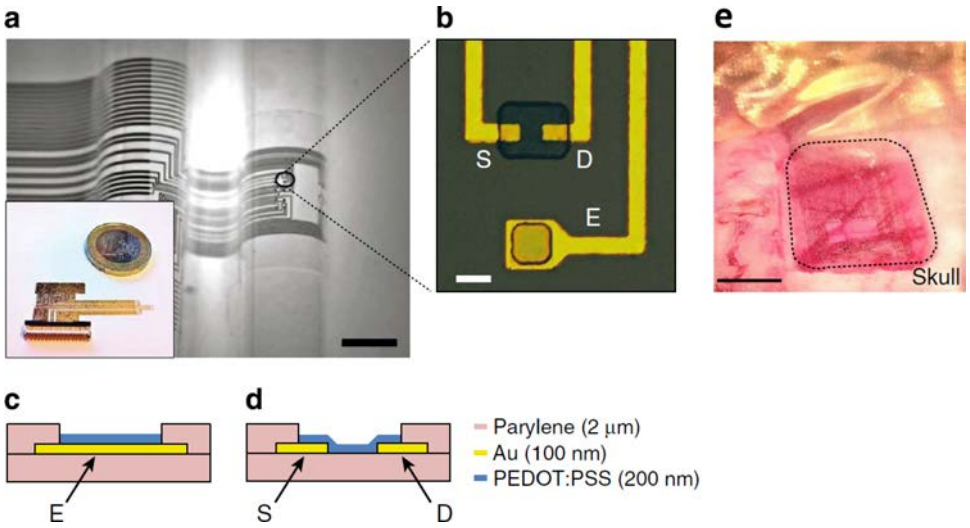

FIG. 5. Structure of the electrocorticography (ECoG) probe. (a) Optical micrograph of the probe conforming onto a curvilinear surface. Scale bar, 1 mm. The inset shows an image of the whole probe, in which the transistor/electrode arrays are on the right-hand side, whereas the external connections, onto which a zero insertion force (ZIF) connector is attached, are on the left-hand side. (b) Optical micrograph of the channel of a transistor and a surface electrode, in which the Au films that act as source (S), drain (D), and electrode pad (E) are identified. Scale bar, 10 mm. [(c) and (d)] Layouts of the surface electrode and of the transistor channel, respectively (not to scale). (e) Optical micrograph of the ECoG probe placed over the somatosensory cortex, with the craniotomy surrounded by dashed lines. Scale bar, 1 mm. Reproduced by permission from Khodagholy *et al.*, Nat. Commun. **4**, 1575 (2013). Copyright 2009 by Elsevier.

In addition to recording biochemical and electrical events from cells and tissues, ICPs have been used to controllably deliver specific transmitter molecules to cells in order to regulate or activate targeted cellular processes and responses. The electrochemical characteristics of ICPs have been exploited for the development of ion pumps, allowing precise electronic control over the delivery of transmitter molecules to excitable cells. A potassium ion pump device using PEDOT-PSS was successfully applied to regulate intracellular Ca^{2+} signalling in neuronal cells, with the miniaturization of the device allowing for the stimulation of single cells to be achieved.[94] In another study, the *in-vivo* delivery of neurotransmitters from a PEDOT-PSS based ion pump was demonstrated to directly modulate mammalian sensory function.[95] The neurotransmitter glutamate was delivered into the cochlear of a guinea pig using an implanted PEDOT-PSS ion pump device. The efficacy of the device to trigger a sensory response was confirmed by monitoring the auditory brainstem response, which confirmed the delivery and activity of the neurotransmitter at active levels.

In conclusion, the rise of organic bioelectronics in the fields of tissue engineering and biological interfacing is providing unprecedented opportunities for the development of new technologies for therapeutic medicine. Coupling organic conductors with an array of ever expanding material fabrication techniques is allowing bioelectronics to be applied in new ways that can be tailored for specific applications. Further improvement in material chemistry is critical to tailoring their performance for individual bioapplications. ICP chemistries continue to evolve, with an emphasis on the incorporation of various biopolymers in order to improve biofunctionality. This must continue, in concert, with efforts to understand fundamental molecular and cellular level interactions with ICPs as a function of polymer chemistry, nanostructure, and redox state that are vital to addressing the biointerfacing of the materials in *in-vivo* settings.

The integration of organic conductors and hydrogels is critical to providing a new suite of materials with mechanical and structural properties suited to various *in-vivo* bioapplications. This work has already begun including the development of ICP based biodegradable hydrogels.[96] The next generation of materials under development promises more intimately complexed ICP—hydrogel chemistries that will offer materials with improved conductivity while retaining favorable material mechanical properties.

Recently, graphene has emerged as an alternative to CNTs for bioapplications,[97,98] providing the ability to tune mechanical and electrical properties in biopolymer composites. The addition of graphene into hydrogels has proved a highly successful approach through which to improve the mechanical properties of the bulk gel material and making them more suitable for biological applications.[99,100] Graphene alone or as an integrated component of a biocomposite has been used to communicate with living cells.[101] The application of graphene, in particular the ability to functionalize graphene for improved processing and device fabrication, is delivering new opportunities for its use in a diverse range of biomedical applications.[100]

The integration of organic conductors with more traditional biopolymers has greatly enhanced the materials inventory available to the modern bioengineer. The ability to transcend size domains from the macroscopic to the nanoscopic enables us to conceive of architectures that will enable more efficient communication with biosystems across these domains.

Our ability to create these architectures is inextricably linked to the development of protocols and machineries, which allows us to create them. 3D printing is impacting greatly on this pursuit.[102] It is enabling us to step out of the equivalent of the "world is flat" era, into a brave new world, much more relevant to living systems. It is likely that not one, but several fabrication techniques will likely be required to construct devices and tissue engineering scaffolds that will allow the precise placement of various organic conductors and other biopolymers in an organized manner, providing a 3D environment where physical, chemical, and electrical stimuli are presented and delivered in an appropriate manner.

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[1] R. S. Stacks, R. M. Califf, H. R. Phillips, D. B. Pryor, P. J. Quigley, R. P. Bauman, J. E. Tcheng, and J. C. Greenfield, Am. J. Cardiol. **61**(10), 3F (1988).
[2] H. Tamai, K. Ihaki, E. Kyo, K. Kosuga, A. Kawashima, S. Matsui, H. Komori, T. Tsuji, S. Motohara, and H. Uehata, Circulation **102**, 399 (2000).
[3] G. R. D. Evans, K. Brandt, A. D. Niederbichler, P. Chauvin, S. Hermann, M. Bogle, L. Otta, B. Wang, and C. W. Patrick, J. Biomater. Sci. **11**(8), 869 (2000).
[4] H. S. Koh, T. Yong, W. E. Teo, C. K. Chan, M. E. Puhaindran, T. C. Tan, A. Lim, B. H. Lim, and S. Ramakrishna, J. Neural Eng. **7**, 14 (2010).
[5] K. Ye, R. Felimban, K. Traianedes, S. E. Moulton, G. G. Wallace, J. Chung, A. Quigley, P. F. M. Choong, and D. E. Myers, PLoS One **9**(6), e99410 (2014).
[6] Y.-C. Fu, H. Nie, M.-L. Ho, C.-K. Wang, and C.-H. Wang, Biotechnol. Bioeng. **99**(4), 996 (2008).
[7] C. V. Rahman, D. Ben-Daid, A. Dhillon, G. Kuhn, T. W. A. Gould, R. Muller, F. R. A. J. Rose, K. M. Shakesheff, and E. Livne, J. Tissue Eng. Regener. Med. **8**(1), 59 (2014).
[8] V. Melissinaki, A. A. Gill, I. Ortega, M. Vamvakaki, A. Ranella, J. W. Haycock, C. Fotakis, M. Farsari, and F. Claeyssens, Biofabrication **3**, 12 (2011).
[9] G. M. Clark and R. J. Hallworth, J. Laryngol. Otol. **90**(7), 623 (1976).
[10] T. L. Rose and L. S. Robblee, IEEE Trans. Biomed. Eng. **37**, 1118 (1990).
[11] A. Norlin, J. Pan, and C. Leygraf, J. Electrochem. Soc. **152**(2), J7 (2005).
[12] X. Beebe and T. L. Rose, IEEE Trans. Biomed. Eng. **35**, 494 (1988).
[13] J. D. Weiland, D. J. Anderson, and M. S. Humayun, IEEE Trans. Biomed. Eng. **49**(12), 1574 (2002).
[14] G. G. Wallace, S. E. Moulton, R. M. I. Kapsa, and M. J. Higgins, *Organic Bionics* (Wiley-VCH, Wienheim, 2012), p. 238.
[15] R. J. Zdrahala and I. J. Zdrahala, J. Biomater. Appl. **14**(1), 67 (1999).
[16] A. Mata, A. J. Fleischman, and S. Roy, Biomed. Microdevices **7**(4), 281 (2005).
[17] G. S. Pande, Pacing Clin. Electrophysiol. **5**(1), 858 (1983).
[18] V. Barbaro, C. Bosi, S. Caiazza, P. Chistolino, D. Ialongo, and P. Rosa, Biomaterials **6**, 28 (1985).
[19] T. Stover and T. Lenarz, GMS Curr. Top Otorhinolaryngol. Head Neck Surg. **8**, 22 (2009).
[20] A. Simmons, A. D. Padsalgikar, L. M. Ferris, and L. A. Poole-Warren, Biomaterials **29**, 2987 (2008).
[21] F. F. Ghavi, H. Mirzadeh, M. Imani, C. Jolly, and M. Farhadi, J. Biomed. Mater. Res. Part B **94B**(2), 388 (2010).
[22] S. A. Guelcher, Tissue Eng Part B **14**(1), 3 (2008).
[23] J. Kucinska-Lipka, I. Gubanska, H. Janik, and M. Sienkiewicz, Mater. Sci. Eng. C **46**, 166 (2015).
[24] C. R. Correia, L. S. Moreira-Teixeira, L. Moroni, R. L. Reis, C. A. van Blitterswijk, M. Karperien, and J. F. Mano, Tissue Eng., Part C **17**(7), 717 (2011).
[25] S. Mollers, I. Heschel, L. H. H. Olde Damink, F. Schugner, R. Deumens, B. Muller, A. Bozkurt, J. G. Nava, J. Noth, and G. A. Brook, Tissue Eng., Part A **15**(3), 461 (2009).
[26] H. J. Kong, M. K. Smith, and D. J. Mooney, Biomaterials **24**, 4023 (2003).
[27] J. L. Drury, R. G. Dennis, and D. J. Mooney, Biomaterials **25**, 3187 (2004).
[28] Z. Li and M. Zhang, J. Biomed. Mater. Res. A **75A**(2), 485 (2005).
[29] R. Jin, L. S. Moreira Teixeira, P. J. Dijkstra, M. Karperien, C. A. van Blitterswijk, Z. Y. Zhong, and J. Feijen, Biomaterials **30**, 2544 (2009).
[30] M. P. Ribeiro, A. Espiga, D. Silva, P. Baptista, J. Henriques, C. Ferreira, J. C. Silva, J. P. Borges, E. Pires, P. Chaves, and I. J. Correia, Wound Repair Regener. **17**(6), 817 (2009).

[31] Z. G. Chen, P. W. Wang, B. Wei, X. M. Mo, and F. Z. Cui, Acta Biomater. **6**, 372 (2010).
[32] Y. Suzuki, M. Tanihara, K. Ohnishi, K. Suzuki, K. Endo, and Y. Nishimura, Neurosci. Lett. **259**, 75 (1999).
[33] Z. Li, H. R. Ramay, K. D. Hauch, D. Xiao, and M. Zhang, Biomaterials **26**, 3919 (2005).
[34] Y. Zhang, J. R. Venugopal, A. El-Turki, S. Ramakrishna, B. Su, and C. T. Lim, Biomaterials **29**, 4314 (2008).
[35] N. O. Dhoot, C. A. Tobias, I. Fischer, and M. A. Wheatley, J. Biomed. Mat. Res. **71A**(2), 191 (2004).
[36] S.-H. Hsu, S. W. Whu, S.-C. Hsieh, C.-L. Tsai, D. C. Chen, and T.-S. Tan, Artif. Organs **28**(8), 693 (2004).
[37] Y.-C. Huang, C.-C. Huang, Y.-Y. Huang, and K.-S. Chen, J. Biomed. Mater. Res., Part A **82A**(4), 842 (2007).
[38] T. Alexakis, D. K. Boadi, D. Quong, A. Groboillot, I. O'Neill, D. Poncelet, and R. J. Neufield, Appl. Biochem. Biotechnol. **50**, 93 (1995).
[39] D.-H. Kim and D. C. Martin, Biomaterials **27**, 3031 (2006).
[40] A. M. Puga, A. Rey-Rico, B. Magarinos, C. Alvarez-Lorenzo, and A. Concheiro, Acta Biomater. **8**, 1507 (2012).
[41] E. Sachlos and J. T. Czernuszka, Eur. Cells Mater. **5**, 29 (2003).
[42] B. Dhandayuthapani, Y. Yoshida, T. Maekawa, and D. S. Kumar, Int. J. Polym. Sci. **19** (2011).
[43] W. Zhu, C. O'Brien, J. O'Brien, and L. G. Zhang, Nanomedicine **9**(6), 859 (2014).
[44] M. R. Falvo, G. J. Clary, R. M. Taylor, V. Chi, F. P. Brooks, S. Washburn, and R. Superfine, Nature **389**, 582 (1997).
[45] A. Krishnan, E. Dujardin, T. W. Ebbesen, P. N. Yianilos, and M. M. J. B. Treacy, phys rev **58**, 14013 (1998).
[46] J. H. Kim, K.-W. Nam, S. B. Ma, and K. B. Kim, Carbon **44**, 1963 (2006).
[47] L. Tang, Y. Wang, Y. Li, H. Feng, J. Lu, and J. Li, Adv. Funct. Mater. **19**, 2782 (2009).
[48] R. Ramasubramaniam, J. Chen, and H. Liu, Appl. Phys. Lett. **84**, 2928 (2003).
[49] C.-S. Lee, S. E. Baker, M. S. Marcus, W. Yang, M. A. Eriksson, and R. J. Hamers, Nano Lett. **4**(9), 1713 (2004).
[50] H. Hu, Y. Ni, V. Montana, R. C. Haddon, and V. Parpura, Nano Lett. **4**(3), 507 (2004).
[51] C. X. Guo, S. R. Ng, S. Y. Khoo, X. Zheng, P. Chen, and C. M. Li, ACS Nano **6**(8), 6944 (2012).
[52] P. Galvan-Garcia, E. W. Keefer, F. Yang, M. Zhang, S. Fang, and A. A. Zakhidov, J. Biomater. Sci., Polym. Ed. **18**(10), 1245 (2007).
[53] A. F. Quigley, J. M. Razal, B. C. Thompson, S. E. Moulton, M. Kita, E. L. Kennedy, G. M. Clark, G. G. Wallace, and R. M. I. Kapsa, Adv. Mater. **21**, 4393 (2009).
[54] J. A. Kim, E. Y. Jang, T. J. Kang, S. Yoon, R. Ovalle-Robles, W. J. Rhee, T. Kim, R. H. Baughman, Y. H. Kim, and T. H. Park, Integr. Biol. **4**, 587 (2012).
[55] C.-W. Lam, J. T. James, R. McCluskey, and R. L. Hunter, Toxicol. Sci. **77**, 126 (2004).
[56] D. A. X. Nayagam, R. A. Williams, J. Chen, K. A. Magee, J. Irwin, J. Tan, P. Inis, R. T. Leung, S. Finch, C. E. Williams, G. M. Clark, and G. G. Wallace, Small **7**(8), 1035 (2011).
[57] R. T. Richardson, B. Thompson, S. Moulton, C. Newbold, M. G. Lum, and A. Cameron, Biomaterials **28**(3), 513 (2007).
[58] C. E. Schmidt, V. R. Shastri, J. P. Vacanti, and R. Langer, Proc. Natl. Acad. Sci. U. S. A. **94**(17), 8948 (1997).
[59] A. Gelmi, M. J. Higgins, and G.G. Wallace, Biomaterials **31**, 1974 (2010).
[60] B. Weng, R. Shepherd, and G. G. Wallace, Synth. Met. **162**, 1375 (2012).
[61] C. A. Mire, A. Agrawal, G. G. Wallace, P. Calvert, and M. in het Panhuis, J. Mater. Chem. **21**, 2671 (2011).
[62] A. Giuseppe-Elie, Biomaterials **31**, 2701 (2010).
[63] D.-H. Kim, J. A. Wiler, D. J. Anderson, D. R. Kipke, and D. C. Martin, Acta Biomater. **6**, 57 (2010).
[64] D.-H. Kim, M. Abidian, and D. C. Martin, J. Biomed. Mater. Res., Part A **71**(4), 577 (2004).
[65] L. M. Lira, S. I. Cordoba, and C. Torresi, Electrochem. Commun. **7**, 717 (2005).
[66] C. Dispenza, M.-A. Sabatino, A. Niconov, D. Chmielewska, and G. Spadaro, Radiat. Phys. Chem. **81**, 1456 (2012).
[67] M. R. Abidian, D.-H. Kim, and D. C. Martin, Adv. Mater. **18**, 405 (2006).
[68] J. Y. Lee, C. A. Bashur, A. S. Goldstein, and C. E. Schmidt, Biomaterials **30**, 4325 (2009).
[69] T. Sudwilai, J. J. Ng, C. Boonkrai, N. Israsena, S. Chuangchote, and P. Supaphol, J. Biomater. Sci. **25**(2), 1240 (2014).
[70] X. Liu, J. Chen, K. J. Gilmore, M. J. Higgins, Y. Liu, and G. G. Wallace, J. Biomed. Mat. Res., Part A **94A**(4), 1004 (2010).
[71] I. S. Chronakis, S. Grapenson, and A. Jakob, Polymer **47**, 1597 (2006).
[72] M. Li, Y. Guo, Y. Wei, A. G. MacDiarmid, and P. I. Lelkes, Biomaterials **27**, 2705 (2006).
[73] R. D. Breukers, K. J. Gilmore, M. Kita, K. K. Wagner, M. J. Higgins, S. E. Moulton, G. M. Clark, D. L. Officer, R. M. I. Kapsa, and G. G. Wallace, J. Biomed. Mat. Res., Part A **95A**(1), 256 (2010).
[74] T. Sudwilai, J. J. Ng, C. Boonkrai, N. Israsena, S. Chuangchote, and P. Supaphol, J. Biomater. Sci. **25**(12), 1240 (2014).
[75] J. Foroughi, G. M. Spinks, and G. G. Wallace, J. Mater. Chem. **21**, 6421 (2011).
[76] J. M. Razal, M. Kita, A. F. Quigley, E. Kennedy, S. E. Moulton, R. M. I. Kapsa, G. M. Clark, and G. G. Wallace, Adv. Funct. Mater. **19**, 3381 (2009).
[77] N. K. Guimard, N. Gomez, and C. E. Schmidt, Prog. Polym. Sci. **32**, 876 (2007).
[78] X. Cui, V. A. Lee, Y. Raphael, J. A. Wiler, J. F. Hetke, D. J. Anderson, and D. C. Martin, J. Biomed. Mater. Res. **56**(2), 261 (2001).
[79] W. R. Stauffer and X. T. Cui, Biomaterials **27**, 2405 (2006).
[80] X. Cui, J. Wiler, M. Dzaman, R. A. Altschuler, and D. C. Martin, Biomaterials **24**, 777 (2003).
[81] J. H. Collier, J. P. Camp, T. W. Hudson, and C. E. Schmidt, J. Biomed. Mater. Res. **50**(4), 574 (2000).
[82] J. S. Moreno, S. Panero, M. Artico, and P. Filippini, Bioelectrochemistry **72**, 3 (2008).
[83] K. G. Gilmore, M. Kita, Y. Han, A. Gelmi, M. J. Higgins, S. E. Moulton, G. M. Clark, R. M. I. Kapsa, and G. G. Wallace, Biomaterials **30**, 5292 (2009).
[84] M. Asplund, H. von Holst, and O. Inganas, Biointerphases **3**(3), 83 (2008).
[85] A. M. D. Wan, D. J. Brooks, A. Gumus, C. Fischbach, and G. G. Malliaras, Chem. Commun. 5278 (2009).
[86] A. Gumus, J. P. Califano, A. M. D. Wan, J. Huynh, C. A. Reinhart-King, and G. G. Malliaras, Soft Matter **6**, 5138 (2010).
[87] P. J. Molino, M. J. Higgins, P. C. Innis, R. M. I. Kapsa, and G. G. Wallace, Langmuir **28**, 8433 (2012).
[88] P. J. Molino, Z. Yue, B. Zhang, A. Tibbens, X. Liu, R. M. I. Kapsa, M. J. Higgins, and G. G. Wallace, Adv. Mater. Interfaces **1**(3), 12 (2014).

[89] S. Y. Yang, B. N. Kim, A. A. Zakhidov, P. G. Taylor, J.-K. Lee, C. K. Ober, M. Lindau, and G. G. Malliaras, Adv. Healthcare Mater. **23**, 4 (2011).
[90] R. M. Owens and G. G. Malliaras, MRS Bull. **35**, 449 (2010).
[91] P. Lin, F. Yan, J. Yu, H. L. W. Chan, and M. Yang, Adv. Mater. **22**, 3655 (2010).
[92] D. Khodagholy, T. Doublet, M. Gurfinkel, P. Quilichini, E. Ismailova, P. Leluex, T. Herve, S. Sanaur, C. Bernard, and G. G. Malliaras, Adv. Healthcare Mater. **23**, 4 (2011).
[93] D. Khodagholy, T. Doublet, P. Quilichini, M. Gurfinkel, P. Leleux, A. Ghestem, E. Ismailova, T. Herve, S. Sanaur, C. Bernard, and G. G. Malliaras, Nat. Commun. **4**, 1575 (2013).
[94] J. Isaksson, P. Kjall, D. Nilsson, N. D. Robinson, M. Berggren, and A. Richter-Dahlfors, Nat. Mater. **6**, 673 (2007).
[95] D. T. Simon, S. Kurup, K. C. Larsson, R. Hori, K. Tybrandt, M. Goiny, E. W. H. Jager, M. Berggren, B. Canlon, and A. Richter-Dahlfors, Nat. Mater. **8**, 742 (2009).
[96] D. Mawad, K. Gilmore, P. J. Molino, K. Wagner, P. Wagner, D. L. Officer, and G. G. Wallace, J. Mater. Chem. **21**, 5555 (2011).
[97] Y. Zhang, T. R. Nayak, H. Hong, and W. Cai, Nanoscale **4**, 3833 (2012).
[98] D. Kuzum, H. Takano, E. Shim, J. C. Reed, H. Juul, A. G. Richardson, J. de Vries, H. Bink, M. A. Dichter, T. H. Lucus, D. A. Coulter, E. Cubukcu, and B. Litt, Nat. Commun. **5**, 5259 (2014).
[99] L. Zhang, Z. Wang, C. Xu, Y. Li, J. Gao, W. Wang, and Y. Liu, J. Mater. Chem. **21**, 10399 (2011).
[100] Y. Wan, X. Chen, G. Xiong, R. Guo, and H. Luo, Mater. Exp. **4**(5), 429 (2014).
[101] S. Sayyar, E. Murray, B. C. Thompson, S. Gambhir, and D. L. Officer, Carbon **52**, 296 (2013).
[102] G. G. Wallace, R. C. Cornock, C. D. O'Connell, S. Beirne, S. M. Dodds, and F. Gilbert, *3D Bioprinting: Printing Parts for Bodies*, ARC Centre of Excellence for Electromaterials Science, Australia, 2014.