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Biomimetic conducting polymer-based tissue scaffolds

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Highlights

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Electrical stimulation is used in a number of FDA approved devices.

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There are no FDA approved CP-based tissue scaffolds.

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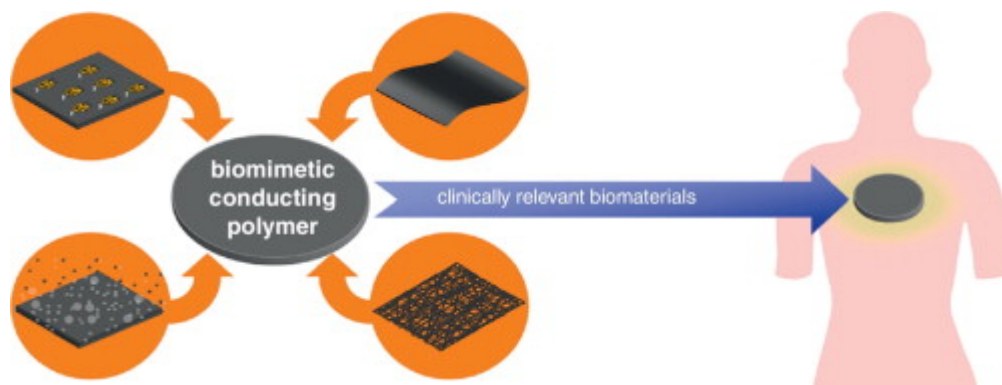
CP-based tissue scaffolds with biomimetic properties perform better *in vitro*.

-

CP-based biomaterials exhibit relatively low levels of immunogenicity *in vivo*.

Conducting polymer-based materials are promising for application as tissue scaffolds for the replacement or restoration of damaged or malfunctioning tissues, because a variety of tissues respond to electrical stimulation. This review focuses on conducting polymer-based materials with biomimetic chemical, mechanical and topological properties, and recent progress toward the fabrication of clinically relevant tissue scaffolds is highlighted.

Graphical abstract



[Figure options](#)

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Introduction

Electromagnetic fields affect a variety of tissues (e.g. cardiac, muscle, nerve and skin) and play important roles in a multitude of biological processes (e.g. angiogenesis, cell division, cell signaling, nerve sprouting, prenatal development, and wound healing), mediated by a variety of subcellular level changes, including protein distribution, gene expression, metal ion content, and action potential [1^{**}]. This basic science has inspired further research into the development of electrically conducting devices for biomedical applications including bioactuators, biosensors, drug delivery devices, cardiac/neural electrodes, and tissue scaffolds [2^{*}, 3^{*}, 4^{*} and 5^{*}]. It is particularly noteworthy that there are already a number of FDA approved devices capable of electrical stimulation of the body, including: pacemakers (bladder, cardiac, diaphragmatic and gastric), electrodes for deep-brain stimulation (for the treatment of dystonia, essential tremor and Parkinson's disease), spinal cord stimulators for pain management, vagal nerve stimulators for seizure/hiccup management, devices to improve surgical outcomes for cervical fusion surgery for patients at a high risk of non-fusion, and non-invasive devices to stimulate bone growth.

Polymer-based materials are ubiquitous in everyday life, and conducting polymers (CPs) are currently being investigated for a wide variety of biomedical applications [2^{*}, 3^{*}, 4^{*} and 5^{*}] and the most commonly employed CPs are shown in [Figure 1](#). CPs are attractive for the preparation of biomaterials due to their simple synthesis and modification, which facilitates the tuning of their bulk and surface chemistry that governs their physicochemical properties [3^{*} and 4^{*}]. However, the preparation of clinically relevant CP-based tissue scaffolds with

biomimetic chemical, mechanical and topological properties (as illustrated in [Figure 2](#)) is still challenging, and we will discuss recent progress in this direction in the following sections.

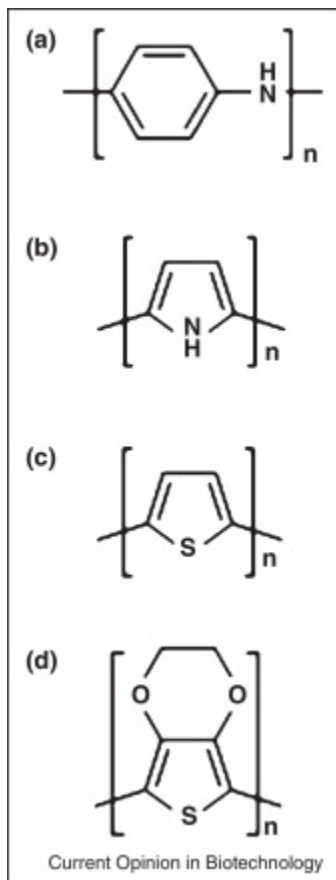


Figure 1.

The structures of common conducting polymers. **(a)** Polyaniline. **(b)** Polypyrrole. **(c)** Polythiophene. **(d)** Poly(3,4-ethylenedioxythiophene).

[Figure options](#)

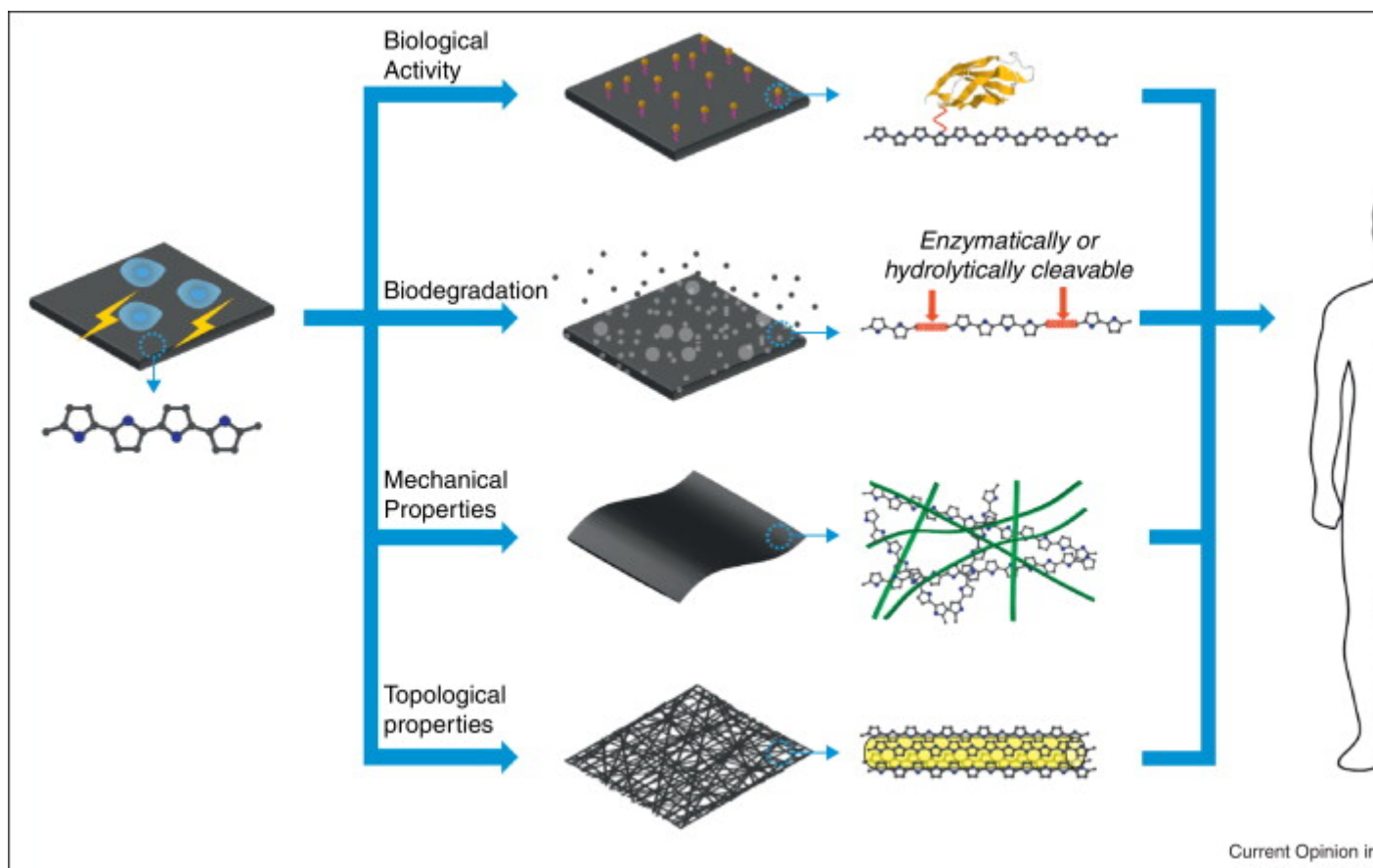


Figure 2.

Schematic illustrating the most important aspects considered when designing biomimetic conducting polymer-based materials.

[Figure options](#)

Synthesis of conducting polymers

CPs are most commonly synthesized either via electrochemical polymerization of the constituent monomers at the surface of an electrode [6] or in the solution/solid state in the presence of a catalyst (e.g. an oxidant such as FeCl_3) [7]. To conduct electricity, conjugated polymers need to be oxidized or reduced; the processes of oxidation or reduction result in the backbone of the polymer being ionized, which necessitates the presence of counter ions that are commonly known as dopant ions (in analogy to the 'doping' of inorganic semiconductors). The dopant ions can be introduced during or after the synthesis of the CPs, either via simple mixing or chemical immobilization of the dopant on the backbone of the polymer. In cases where the polymer and dopant interact purely through non-covalent interactions it is possible for low molecular weight dopants to leach out of the CP matrix into the biological milieu [8], concomitant with a reduction in the conductivity of the material. This phenomenon is used for CP-based drug delivery devices which function by proactively expelling the biologically active dopant from the material upon electrical stimulation [9]. By contrast, in cases where the dopant is covalently attached to the polymer, the polymer is referred to as 'self-doped' [6].

CP-based tissue scaffolds with biomimetic chemical properties

The natural extracellular matrix (ECM) is a mixture of proteins and polysaccharides that display biochemical cues that influence cell behavior, and determine how efficiently cells adhere to them via interactions with glycoproteins displayed on the cell surface. Integrins are an important class of cell adhesive glycoproteins that recognize specific peptide sequences in ECM proteins such as collagen, fibronectin, laminin and vitronectin, and biomimetic biomaterials intended for use as tissue scaffolds commonly display cell adhesive proteins and peptides [10 and 11].

CP-based materials with ECM-mimetic chemical properties can be produced in a variety of ways. It is possible to non-covalently incorporate both high and low molecular weight components/derivatives of the ECM as dopants during electropolymerization reactions, for example, the adhesion of PC12 cells to poly(3,4-ethylenedioxythiophene) (PEDOT) films was improved by doping with collagen [12], or low molecular weight peptides derived from laminin [13]. Electropolymerization also offers the potential to covalently incorporate ECM-derived dopants by polymerizing monomer functionalized ECM derivatives (e.g. collagen [14] or hyaluronic acid [15]). Although electropolymerization is typically used to produce thin 2D films of CPs, it is also applicable to 3D substrates such as interpenetrating networks of PEDOT and ECM protein-based foams (derived from decellularized tissues) [16], and excitingly, the preparation of PEDOT hydrogels *in vivo* [17*].

ECM-mimetic properties can also be imparted to materials by covalently modifying their surfaces with ECM derivatives, commonly employing carbodiimide chemistry [18, 19 and 20], although a variety of other methodologies exist, some of which are capable of generating surfaces that can spatially control cellular interactions through ECM derivative functionalization (i.e. printing patterned surfaces) [21]. It is moreover possible to modify surfaces using non-covalent interactions, typically relying on protein adsorption through non-specific interactions, however, phage display can be used to identify peptides that interact selectively with CP substrates (e.g. THRTSTLDYFVI with polypyrrole), and these peptides can be modified to display biologically active peptides such as the laminin derived IKVAV peptide [22 and 23].

The ECM is inherently biodegradable and is subject to extensive remodeling during the natural wound healing process, consequently, degradable CP-based tissue scaffolds are desirable as they facilitate their eventual replacement with natural functional tissue. Materials composed of polymers within the molecular weight threshold appropriate for renal filtration (<50 kDa) [24] that degrade via the solubilization of an initially water insoluble polymer (with or without changes in their chemical structure) are referred to as bioerodible. By contrast, polymer-based materials that degrade due to scission of the backbone of the polymers (e.g. enzymatic or hydrolytic bond cleavage) are referred to as biodegradable [25]. Ideally the degradation process should result in the formation of non-toxic components. Commonly employed CPs (see [Figure 1](#)) are neither bioerodible nor biodegradable, and are therefore not well-suited for clinical application as tissue scaffolds; however, it is possible to prepare bioerodible or biodegradable CP-based scaffolds.

The Schmidt group reported fully biodegradable conducting polyester-based scaffolds that are suitable for the attachment and proliferation of human neuroblastoma cells *in vitro*, and

moreover, non-immunogenic *in vivo* in rats (albeit in the undoped state) [26*]. It is also possible to prepare biodegradable CP-based scaffolds by grafting water soluble conducting oligomers to the surface of a biodegradable scaffold. Several groups (notably those of Albertsson and Wei) have grafted conducting oligomers of aniline (most commonly an aniline pentamer) to the surfaces of a variety of biodegradable polymers of natural and synthetic origins [27, 28, 29 and 30]. These systems tend to show low levels of cytotoxicity *in vitro*, although studies have clearly demonstrated that the aniline oligomers released upon biodegradation are toxic [30 and 31]. Interestingly, keratinocyte cells were shown to attach and proliferate on conductive scaffolds composed of oligoaniline-modified polycaprolactone [28], the electrical stimulation of PC12 cells attached to oligoaniline-modified polylactide films enhanced neurite extension *in vitro* (see Figure 3a1–a3) [31], and the electrical stimulation of preosteoblastic MC3T3-E1 cells attached to oligoaniline-modified poly(ester amide) copolymer films increased levels of intracellular free Ca^{2+} ions and alkaline phosphatase activity *in vitro*, which are early markers of osteogenic differentiation [30]. An elegant alternative was recently described by the Langer group, who reported the fabrication of scaffolds composed of naturally derived melanins (a class of electrically conducting biopolymers), and demonstrated that they were suitable for the attachment and proliferation of Schwann cells and PC12 cells *in vitro*. Interestingly, melanin films implanted in rats were slowly bioresorbable (>2 months) and the authors hypothesized that the fragility of the films led to their fracture after implantation, followed by their uptake by macrophages and giant cells [32*].

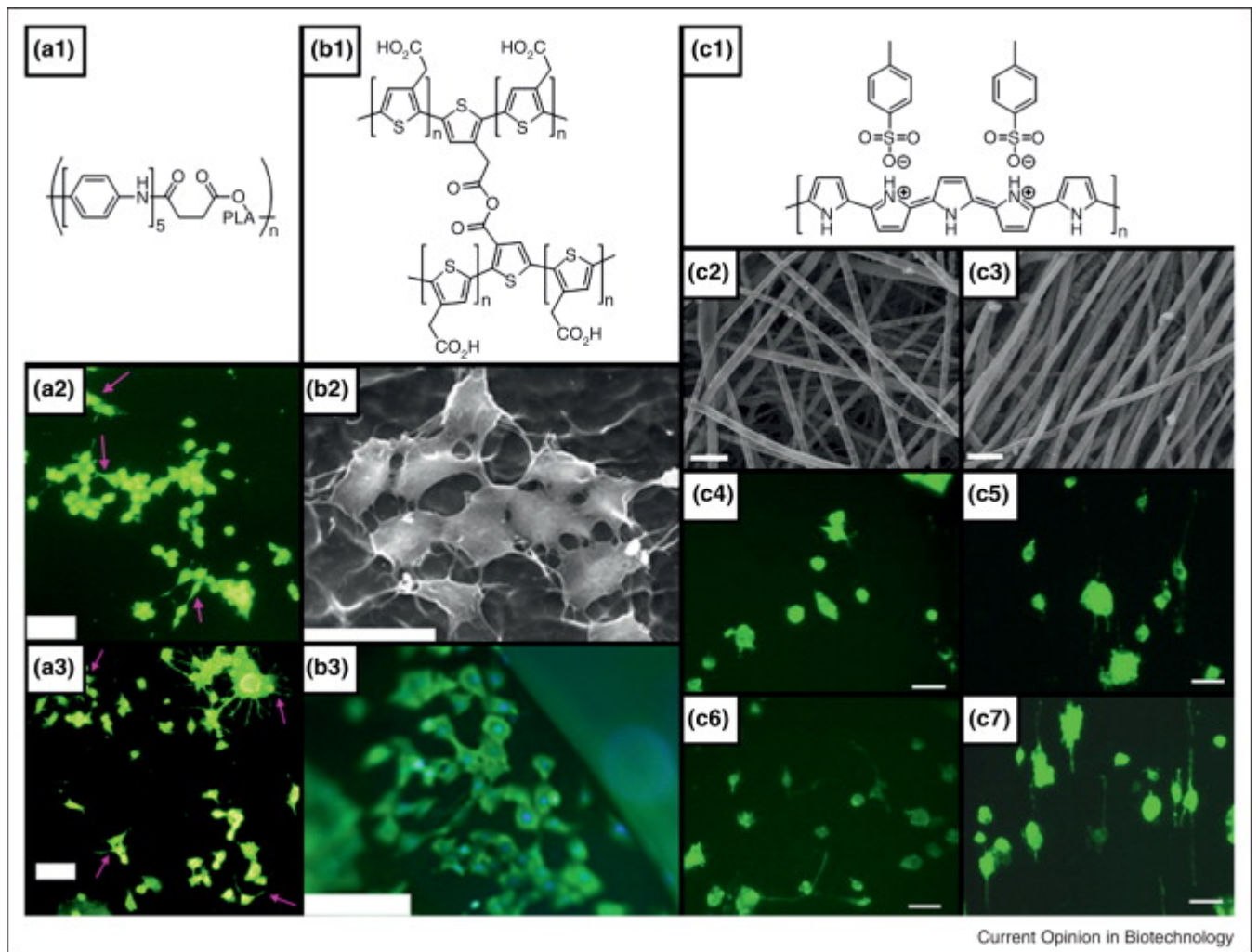


Figure 3.

(a1) Biodegradable conducting multiblock copolymers composed of blocks of aniline pentamers and polylactide (PLA). **(a2)** Fluorescence photomicrograph of fluorescein isothiocyanate stained PC12 cells cultured on the surface of films of the copolymers without electrical stimulation, arrows indicate neurite extensions (scale bar = 50 μm). **(a3)** Fluorescence photomicrograph of fluorescein isothiocyanate stained PC12 cells cultured on the surface of films of the copolymers with electrical stimulation, arrows indicate neurite extensions (scale bar = 50 μm). **(b1)** Poly(3-thiophene acetic acid) crosslinked via carbonyldiimidazole to form conducting hydrogels. **(b2)** SEM image of C2C12 myoblast cells cultured on the surface of hydrogels based on poly(3-thiophene acetic acid) (scale bar = 50 μm). **(b3)** Fluorescence photomicrograph of Phalloidin-Alexa 488 stained C2C12 myoblast cells cultured on the surface of hydrogels based on poly(3-thiophene acetic acid) (scale bar = 200 μm). **(c1)** Polypyrrole-based coating for PLGA nanofibers. **(c2)** SEM image of randomly oriented PLGA nanofibers coated with polypyrrole (scale bar = 2 μm). **(c3)** SEM image of aligned PLGA nanofibers coated with polypyrrole (scale bar = 2 μm). **(c4)** Fluorescence photomicrograph of Phalloidin-Alexa 488 stained PC12 cells cultured on the surface of randomly oriented PLGA nanofibers coated with polypyrrole without electrical stimulation (scale bar = 50 μm). **(c5)** Fluorescence photomicrograph of Phalloidin-Alexa 488 stained PC12 cells cultured on the surface of aligned PLGA nanofibers coated with polypyrrole without electrical stimulation (scale bar = 50 μm). **(c6)** Fluorescence photomicrograph of Phalloidin-Alexa 488 stained PC12 cells cultured on the surface of randomly oriented PLGA nanofibers coated with polypyrrole with electrical stimulation (10 mV/cm) (scale bar = 50 μm). **(c7)** Fluorescence photomicrograph of Phalloidin-Alexa 488 stained PC12 cells cultured on the surface of aligned PLGA nanofibers coated with polypyrrole with electrical stimulation (10 mV/cm) (scale bar = 50 μm).

Images (a2) and (a3) were adapted with the permission of the authors and publishers from [31]. Images (b2) and (b3) were adapted with the permission of the authors and publishers from [34]. Images (c2)–(c7) were adapted with the permission of the authors and publishers from [50].

[Figure options](#)

The first bioerodible CP-based scaffolds were also reported by the Langer group, composed of a sparingly water soluble self-doped CP, poly(pyrrole-4-butyric acid). The scaffolds were shown to erode via slow dissolution of the polymer over a period of weeks at physiological pH values, and to be suitable for the attachment and proliferation of human mesenchymal progenitor cells *in vitro* [33]. The Wallace group subsequently reported erodible multilayer films composed of a self-doped polyanionic polythiophene and polycationic polyethyleneimine. The films were shown to erode over a period of 3 months and to be suitable for the attachment and proliferation of L929 and C2C12 cells *in vitro* [34].

CP-based tissue scaffolds with biomimetic mechanical properties

Biological tissues have characteristic mechanical properties, and cellular behavior is known to be influenced by mechanical stimuli through a variety of mechanisms broadly classed as mechanotransduction [35]. Mismatch between the mechanical properties of a tissue scaffold and the tissue in which it is implanted may lead to inflammation of the surrounding tissue, followed by the encapsulation of the implanted scaffold within an avascular network of fibrous tissue [36]. Hence, the fabrication of CP-based materials with biomimetic mechanical properties is of great interest.

Materials composed of CPs alone tend to be relatively inelastic because the polymers have limited conformational freedom in 3D, consequently, films prepared via electropolymerization rip easily. This represents a significant problem as the handling properties of biomedical products are of key importance to their successful translation from the laboratory to the clinic.

Flexible CP-based tissue scaffolds are particularly interesting for muscle (e.g. cardiac) tissue engineering. In previous studies, flexible conductive materials were created by dispersing a sufficient quantity of conductive filler (e.g. CP nanoparticles) within an elastomeric matrix, such as polycaprolactone [37] or polyurethane [38], upon which C2C12 myoblasts were shown to adhere, proliferate and differentiate into myotubes *in vitro*. Flexible CP-based tissue scaffolds can also be prepared from multiblock copolymers composed of alternating blocks of conducting and elastomeric blocks, such as polypyrrole and polycaprolactone, upon which PC12 cells have been shown to adhere and proliferate, and electrical stimulation was observed to enhance neurite extension *in vitro* [39].

Electrically conductive hydrogels [5 and 40] are particularly attractive as tissue engineering scaffolds because of their high water content, porosity, and mechanical properties analogous to soft tissues (typically ranging from sub-kPa to hundreds of kPa). Notable examples of electroconductive hydrogels come from the groups of Guiseppi-Elie, Martin, Poole-Warren, Wallace and Yaszemski. Conducting hydrogels composed of polypyrrole and photocrosslinked oligo(polyethylene glycol) fumarate were demonstrated to be suitable for PC12 cells to adhere and extend neurites into the scaffold *in vitro* [41], and biodegradable conducting hydrogels formed via crosslinking poly(3-thiophene acetic acid) with carbonyldiimidazole, were shown to be suitable for the adhesion and proliferation of C2C12 myoblast cells *in vitro* (see Figure 3b1–b3) [42].

CP-based tissue scaffolds with biomimetic topological properties

Natural tissues are 3-dimensional (3D) composite materials with characteristic topological properties that are essential for their function [43]. Anisotropic features are commonly observed in functional tissues (including cardiac, ligament, musculoskeletal, nervous and vascular tissues), often in the form of anisotropically distributed components of the extracellular matrix, which influences the alignment, morphology and behavior of the resident cells. The development of tissue scaffolds that mimic such intricately structured natural tissues has been the focus of significant interest in recent years, and a number of CP-based tissue scaffolds with biomimetic topological properties (e.g. aligned nanofibers) have been investigated.

Electrospinning is a popular method of preparing nanofibrous tissue scaffolds with a tunable degree of fiber alignment. Electrospinning CP-based composites is a simple way to prepare electrically conductive nanofibrous tissue scaffolds. For example, nanofibers composed of polyaniline and gelatin were shown to support the adhesion and proliferation of cardiomyocytes *in vitro* [44]. The incorporation of polycaprolactone into analogously spun fibers was observed to moderately improve their mechanical properties, and electrical stimulation of the scaffolds was demonstrated to improve the proliferation and neurite outgrowth from nerve stem cells cultured upon them *in vitro* [45]. Likewise, nanofibers composed of polyaniline and either poly(l-lactide-co- ϵ -caprolactone) [46] or polycaprolactone [47] were shown to be suitable for the attachment and proliferation of fibroblasts and myoblasts *in vitro*.

Chemically modifying the surface of non-conductive fibers with CPs is another simple method to generate electrically conducting nanofibrous tissue scaffolds. For example: it is possible to coat the surface of non-conductive polymer (e.g. poly(lactic acid-co-glycolic acid)) nanofibers deposited on the surface of an electrode with CPs (e.g. PEDOT) via electropolymerization [48]; or via vapor phase polymerization of CPs from fibers containing an initiator (e.g. iron(III) *p*-toluenesulfonate) when exposed to a suitable monomer (e.g. pyrrole) [49], or indeed, the bulk polymerization of CPs (e.g. polypyrrole) in solution in the presence of nanofibers [50]. Interestingly, electrical stimulation of PC12 cells cultured on such scaffolds was observed to enhance neurite outgrowth from the cells *in vitro* (see Figure 3c1–c7) [50], and moreover that immobilization of nerve growth factor on the surface of conducting nanofibers further improves neurite outgrowth [51].

It is generally accepted that printing in 2- and 3-dimensions will play an increasingly important role in the future development of CP-based tissue scaffolds with biomimetic topological properties [52]. Excitingly, it has already proven possible to print CP-based composites incorporating biopolymers (e.g. chitosan, hyaluronic acid or collagen) via extrusion or ink-jet printing [2, 52, 53 and 54], and moreover, to apply a submicrometer level pattern to them via a low-energy infrared laser [55]. Interestingly, printed composites of polypyrrole and collagen were shown to be suitable for the attachment and proliferation of PC12 cells, and electrical stimulation of the cells cultured on micrometer-scale lines was observed to enhance neurite outgrowth and their orientation (preferentially along the long axis of the printed lines) *in vitro* [56].

CP-based tissue scaffolds *in vivo*

CP-based materials are attractive candidates as scaffolds for bone, muscle and nerve tissues which are responsive to electrical stimuli (Table 1). A factor of key importance for the clinical translation of CP-based tissue scaffolds is their immunogenicity, which is ideally very low. Histological analyses of tissue in the vicinity of polypyrrole-based tissue scaffolds implanted subcutaneously or intramuscularly in rats, reveal immune cell infiltration compared to FDA-approved poly(lactic acid-co-glycolic acid) [57], or FDA-approved poly(d,l-lactide-co-glycolide) [58]. Likewise, there was no significant inflammatory response to polypyrrole-based tissue scaffolds implanted around the coronary artery of rats after 5 weeks [59], or to polypyrrole-based sciatic nerve guidance channels implanted in rats after 8 weeks [39], or indeed, polypyrrole-coated electrodes in rat brains after 3 or 6 weeks [60]. Implantation of poly(3,4-ethylenedioxythiophene) coated electrodes in rats brains elicited a modest global tissue reaction of approximately the same magnitude as for silicon probes, and is therefore potentially ascribable to mechanical mismatch between the hard electrode and the

soft brain tissue [61]; whereas, poly(3,4-ethylenedioxythiophene)-based materials implanted subcutaneously elicited no observable immune response after 1 week [62]. Similarly, histological analyses of tissue in the vicinity of polyaniline-based tissue scaffolds implanted subcutaneously in rats, revealed very low levels of inflammation after 4 [63], or 50 weeks [64]. Although we acknowledge that differences in individual studies (i.e. the composition/structure of the tissue scaffolds, the animal/tissue models, and the methods used to evaluate immune responses) make it difficult to directly compare the results of each study, it appears that CP-based biomaterials exhibit relatively low levels of immunogenicity in comparison with other FDA-approved biomaterials, and are therefore promising candidates for clinical translation in the future.

Table 1.

A selection of promising systems for tissue regeneration

Clinical application area	System	Key benefits	Reference
Bone tissue scaffolds	Poly(ester amide) copolymers displaying tetraaniline oligomers	<ul style="list-style-type: none"> Fully biodegradable Increased levels of Ca²⁺ Upregulation of ALP activity 	[30]
	Composites incorporating hydroxyapatite and oligoanilines	<ul style="list-style-type: none"> Fully biodegradable Biomimetic chemical composition 	[70]
Muscle tissue scaffolds	Poly(thiophene-3-acetic acid)-based hydrogels	<ul style="list-style-type: none"> Fully bioerodible Biomimetic mechanical properties 	[42]
	Polypyrrole-based actuators	<ul style="list-style-type: none"> Mechanical stimulation of cells 	[65]
Nerve tissue scaffolds	Electrospun composites of polyaniline, polycaprolactone, and gelatin	<ul style="list-style-type: none"> Alignment of fibers acts as a topological guidance cue 	[45]
	Printed composites of polypyrrole and collagen	<ul style="list-style-type: none"> Printing well-defined μm scale topological guidance cues 	[56]

[Table options](#)

Conclusions

In this review we have chosen to focus on CP-based tissue scaffolds with biomimetic chemical, mechanical and topographical properties, highlighting recent progress toward the fabrication of clinically relevant tissue scaffolds. The results of both *in vitro* and *in vivo* studies suggest that CP-based tissue scaffolds are promising candidates for the electrical stimulation of the recovery of bone, muscle and nerve tissues in the clinic.

We believe that there is great potential for the development of more complex CP-based tissue scaffolds, and we expect to see examples of CP-based drug delivery devices [9] integrated in tissue scaffolds, and moreover, muscle tissue scaffolds incorporating CP-based actuators [65]. We also foresee the development of CP-based tissue scaffolds with electrically switchable bioactivity that make it possible to achieve temporal control over cellular behavior [66, 67, 68 and 69].

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