Remodelling the Electrical Microenvironment for Facilitating Bone Regeneration: a Decade of Progress

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The increasing global incidence of bone injuries and degenerative diseases, often compounded by conditions like diabetes and osteoporosis, presents a significant health care challenge. Critical-sized bone defects frequently fail to heal due to compromised bioelectric microenvironments. This review summarises the conceptual framework of electric microenvironment remodelling in bone tissue, covering its physiological basis, disruption in disease and therapeutic modulation using electroactive scaffolds. The authors outline how the electric microenvironment of bone tissue is generated and continuously remodelled physiologically, analyse how its deficiency compromises regeneration and highlight strategies for dynamic regulation under pathological conditions. Restoring the bioelectric environment via electroactive scaffolds promotes bone healing by enhancing osteogenesis, angiogenesis and immunomodulation, while suppressing bone resorption. Diverse electroactive materials, including piezoelectric polymers and self-powered nanogenerators, are critically examined. Future bone tissue engineering will likely involve smart composite electroactive scaffolds that respond to external stimuli, enabling non-invasive, dynamic and precise modulation of electrical signalling cues for effective treatment of complex bone defects.

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The global incidence of bone injuries and degenerative diseases has risen sharply in tandem with an aging population, increased life expectancy and sedentary lifestyles.[1,2] Conditions such as osteoporosis and osteoarthritis reduce mobility and heighten fracture risks, while in clinical dentistry, bone repair is essential for implant success and maxillofacial reconstruction.[3-5] Bone has a limited self-regenerative capacity, with critical-sized defects unable to heal spontaneously, and this

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is further impaired by co-morbidities such as diabetes and osteoporosis.[6,7] Although autografts remain the gold standard, synthetic bone scaffolds have emerged as customisable alternatives that provide structural support and can be engineered to incorporate antibacterial properties, controlled growth factor release and enhanced vascularisation and innervation.[8-12]

A key focus in advanced scaffold design is replicating the bioelectric microenvironment of healthy bone, which is generated primarily through the piezoelectric effect of type I collagen fibres under mechanical stress.[6] This endogenous electrical potential coordinates critical cellular processes including osteoblast differentiation, MSC migration and extracellular matrix remodelling; its disruption at disease or injury sites severely impairs bone healing.[6,13] Electroactive materials, including piezoelectric polymers, electroconductive biomaterials, electret membranes and self-powered nanogenerators, have therefore emerged as a biomimetic strategy to restore and dynamically regulate this electrical microenvironment.[14-16] These materials can activate voltage-gated calcium channels, trigger downstream pro-osteogenic signalling cascades, promote immunomodulatory macrophage polarisation and enhance angiogenesis and neurogenesis, collectively accelerating bone regeneration.[17-22]

Despite this progress, several key issues and contradictions remain unresolved. First, while piezoelectric and electroconductive scaffolds have demonstrated efficacy in vitro and in small animal models, the translation of consistent, physiologically relevant electrical outputs to load-bearing large defects in vivo remains a significant challenge, as the mechanical environment in clinical settings is far more complex and variable.[6,14] Second, the optimal parameters for electrical stimulation, including magnitude, frequency and duration, have not been standardised, leading to contradictory findings across studies and hindering direct comparisons.[15,16] Third, balancing the competing demands of electrical performance, mechanical integrity, biodegradability and biocompatibility within a single scaffold platform remains an unresolved challenge in materials science.[17,18] Fourth, the specific cellular and molecular mechanisms by which different electroactive material platforms modulate the bone immune microenvironment, particularly under pathological conditions such as type 2 diabetes and osteoporosis, are not yet fully elucidated.[19-22] Fifth, the long-term in vivo safety and metabolic fate of electroactive materials, particularly carbon-based nanomaterials and conductive polymers, require more rigorous evaluation in large-animal models and prospective clinical studies. Addressing these gaps is critical for advancing the clinical translation of electroactive scaffolds.

A decade has passed since the concept of remodelling the electrical microenvironment to facilitate bone regeneration was first articulated,[14] and accumulating experimental and translational data now warrant a comprehensive review of the progress in this emerging field. Here, the present authors propose electric microenvironment remodelling as a unifying concept that encompasses how restoration of the deficient bioelectric environment at bone defects via implantation of electroactive scaffolds promotes healing (Fig 1),[14-16] (how electroactive scaffolds facilitate bone regeneration through immunomodulation and by enhancing osteogenesis, angiogenesis and neurogenesis (Fig 2),[17-19] and how active and dynamic modulation with electroactive scaffolds can overcome compromised bone healing under pathological conditions such as type 2 diabetes and periodontitis (Fig 3).[20-22] By restoring the natural electrical cues of injured/diseased bone tissues, electroactive scaffolds promote healing and regeneration through various mechanisms, including triggering the migration of endogenous mesenchymal stem cells (MSCs) and accelerating their differentiation into osteoblasts.[6,14-16]

Architecture of the bioelectric environment in bone tissues

The bioelectric environment in bone arises from complex interactions among various organic and inorganic components influenced by biomechanical stimuli.[23] Bone is electroactive, electrosensitive and electroresponsive, with endogenous electrical signals arising from various mechanisms,[24] as illustrated in Fig 4. A key mechanism is piezoelectricity, arising primarily from type I collagen fibres, which have a non-centrosymmetric crystalline structure.[24] Mechanical stress during physical activities causes collagen fibres to slide, reorientating molecular dipoles and generating a physiological electrical potential, known as the piezoelectric effect.[24] Charge polarity varies with deformation, with compression creating negative charges, while tension produces positive ones.[25] Although it was traditionally claimed that the electroactivity of bone stems primarily from collagen, recent studies have revealed that the inorganic crystals of hydroxyapatite (HA) also exhibit a significant piezoelectric response, arising from the non-centrosymmetric displacement of ions within the HA crystal lattice under mechanical stress.[26] Thus, both the organic collagen phase and the inorganic HA phase synergistically contribute to the overall piezoelectricity

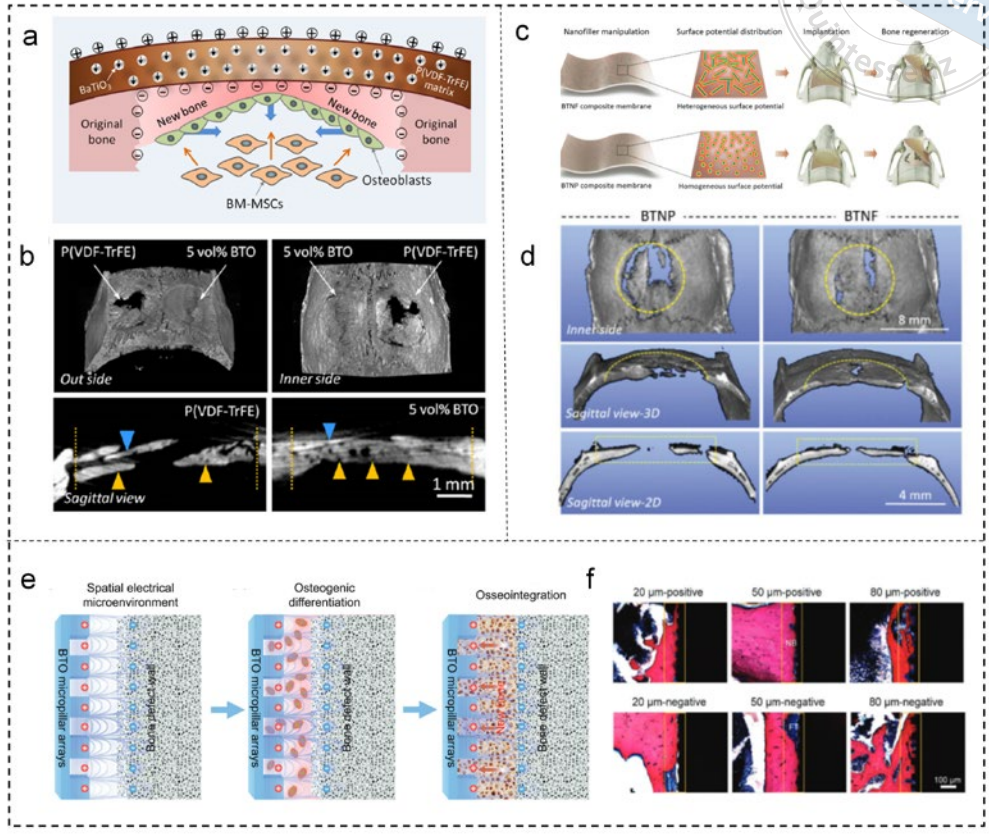

Fig 1a to f Restoration of the deficient bioelectric environment at bone defects via implantation of electroactive scaffolds promotes healing. Illustration of biomimetic electric microenvironment created by BTO NP/P (VDF-TrFE) composite membranes encouraging bone defect repair **(a)**.[14] Representative microcomputed tomography (microCT) images and sagittal view images of critical-sized rat calvarial full-thickness defects at 12 weeks post-implantation **(b)**.[14] Illustration of manipulating surface electric potential heterogeneity on BTO/P (VDF-TrFE) ferroelectric nanocomposites to promote bone regeneration **(c)**.[15] Representative microCT images and sagittal view images of critical-sized rat calvarial full-thickness defects at 12 weeks post-implantation **(d)**.[15] Illustration of a biomimetic 3D spatial electrical microenvironment created by patterning of micropillar arrays on a piezoelectric $BaTiO_3$ (BTO) ceramic substrate to enhance bone defect repair **(e)**.[16] Histological analysis of osseointegration in vivo at 12 weeks post-implantation demonstrated better osseointegration **(f)**.[16]

of bone tissue.[26] HA also serves as a stiffener, affecting mechanical load transmission to collagen fibres.[26]

Another major contributor to the bioelectric environment is the streaming potential in bone tissues arising from ion movement in interstitial fluids during physical activity, which leads to mechanical loading.[27] This flow of interstitial fluids, rich in K^+, Na^+ and Ca^{2+} ions, travels through the porous bone structure, generating an electric field as the ions move against the negatively charged bone matrix.[27] This phenomenon, called electro-osmosis, is influenced by endogenous electrical potentials like the piezoelectric effect.[28] Additionally, transmembrane potentials are generated at the cellular level among osteoblasts, osteocytes and osteoclasts due to ionic concentration differences outside and inside cells. These potentials are sustained by ion pumps and are responsive to external mechanical or electrical stimuli through ion channels.[29]

Bone tissues exhibit dielectric properties due to polarization when exposed to electric fields, stemming from hydrogen bond separation between HA and collagen.[30] Collagen fibres contribute ferroelectric properties by changing orientation spontaneously, maintaining permanent dipoles.[31] Temperature changes can distort collagen's triple helical structure, affecting charged amino acid residues and creating pyroelectric properties;[32] however, this is less significant in the stable temperature conditions of the living human body.

Collectively, these mechanisms illustrate how bone tissue under normal physiological conditions constantly senses, generates and remodels its local electric microenvironment to coordinate cell behaviour, matrix turnover and microdamage repair.[23]

The deficient bioelectric environment at defect/injury sites compromises bone healing and regeneration

At bone defect sites, the bioelectric environment crucial for homeostasis and healing is compromised.[6,23] This affects the migration, proliferation and differentiation of endogenous stem cells and extracellular matrix remodelling. When bone integrity is lost due to injury or disease, the electrical potential at the site decreases.[6,23] Healthy bone generates electrical signals via collagen's

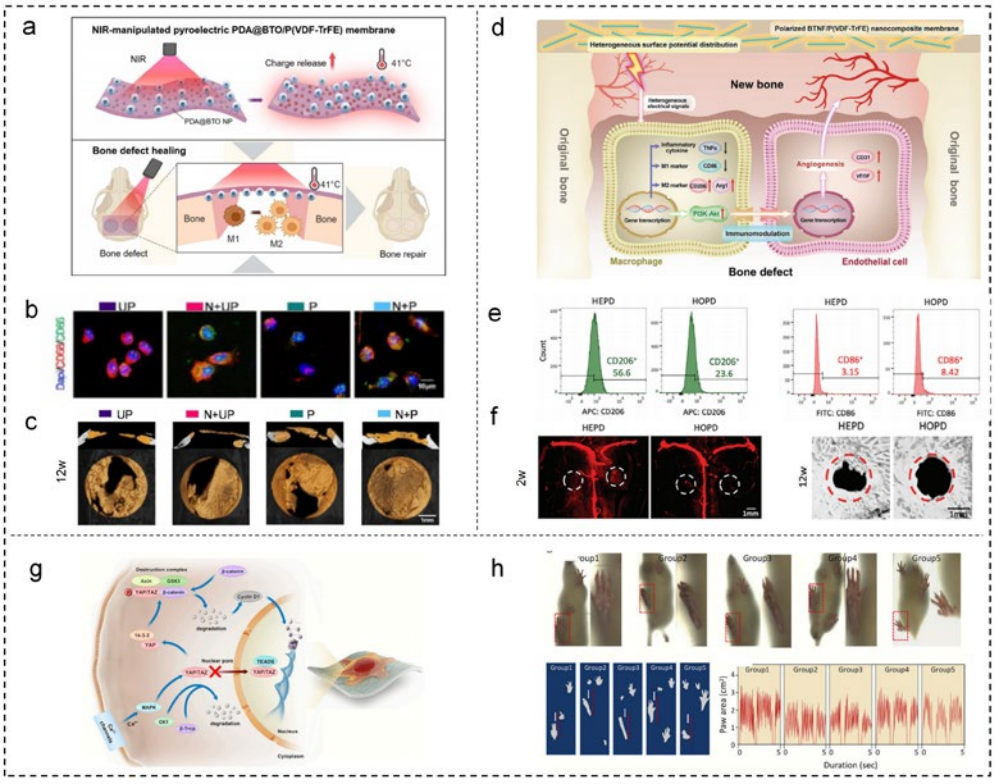

Fig 2a to h Electroactive scaffolds facilitate bone regeneration through immunomodulation and by enhancing osteogenesis, angiogenesis, and neurogenesis. Schematic illustration of how the NIR-inducible pyroelectric PDA@BTO/P(VDF-TrFE) membrane promotes bone regeneration by modulating macrophage M1/M2 polarisation within the bone defect area **(a)**.[17] Representative images of CD206 (green), CD68 (purple) and cell nuclei (DAPI, blue) on the surface of the membrane **(b)**.[17] Representative microCT images of critical-sized rat calvarial full-thickness defects treated with or without inhibitors at week 12 post-surgery **(c)**.[17] Schematic illustration of HEPD enhancing osteogenesis by promoting M2 and pro-angiogenic polarisation of macrophages that facilitate angiogenesis **(d)**.[18] HEPD enhances the M2 polarisation of macrophages in vitro **(e)**.[18] HEPD promotes angiogenesis and bone regeneration **(f)**.[18] Schematic illustration of the putative mechanisms by which a charged membrane enhances dental stem cell-based neuroregeneration upon suppression of the FAK-YAP mechanotransduction signalling axis **(g)**.[19] Combined implantation of a charged membrane with SHED and FAK-YAP inhibitor promotes recovery of neurological functions in a rat sciatic nerve injury model at 4 weeks post-implantation **(h)**.[19]

piezoelectric effect under mechanical stress,[24] which is disrupted in diseased/injured bone structures.[6,23] The deficient electrical environment hinders bone healing by disrupting cellular behaviour, signalling pathways, structural remodelling and immune responses. A fracture creates a physical gap that interrupts electrical charge transfer, obstructing natural current loops essential for bone repair, leading to a significant reduction in endogenous electrical potential at the injury site.[6,23]

Another mechanism by which a deficient bioelectric environment at the defect site impairs bone healing involves the inactivation of signalling pathways.[33] Electrical stimulation normally opens voltage-gated calcium channels (VGCCs), leading to an influx of Ca^{2+} ions that act as secondary messengers.[33] A deficient bioelectric environment fails to trigger this influx, thereby deactivating critical signalling cascades like the calmodulin/calcineurin/nuclear factor of activated T-cells (CaM/CaN/NFAT), mitogen-activated protein kinase/extracellular signal-regulated kinase (MAPK/ERK) and phosphatidylinositol 3-kinase/protein kinase B (PI3K/AKT) signalling pathways, which in turn leads to downregulation of key pro-osteogenic genes such as bone morphogenetic protein-2 (BMP-2), transforming growth factor-beta (TGF-β), runt-related transcription factor 2 (RUNX2) and osteocalcin (OCN), severely compromising bone matrix production and mineralisation.[6,23,33]

Loss of mechanosensing occurs due to a deficient electrical microenvironment in bone tissue. Endogenous electric fields (EnEFs) are essential for detecting mechanical stimuli; without them, injured or diseased bone suffers additional damage as cells cannot sense biomechanical loads required for repair.[34] In larger defects, healing capacity is lost as periosteum-like tissue fails to bridge gaps,[35] impeding bioelectric restoration. Without stable bioelectric signals, the mobilisation and function of bone-forming cells are hindered, preventing MSCs and osteoblasts from reaching injury sites and stalling repair processes.[6,23]

A deficient bioelectric environment also impairs vascularisation and innervation essential for bone regen-

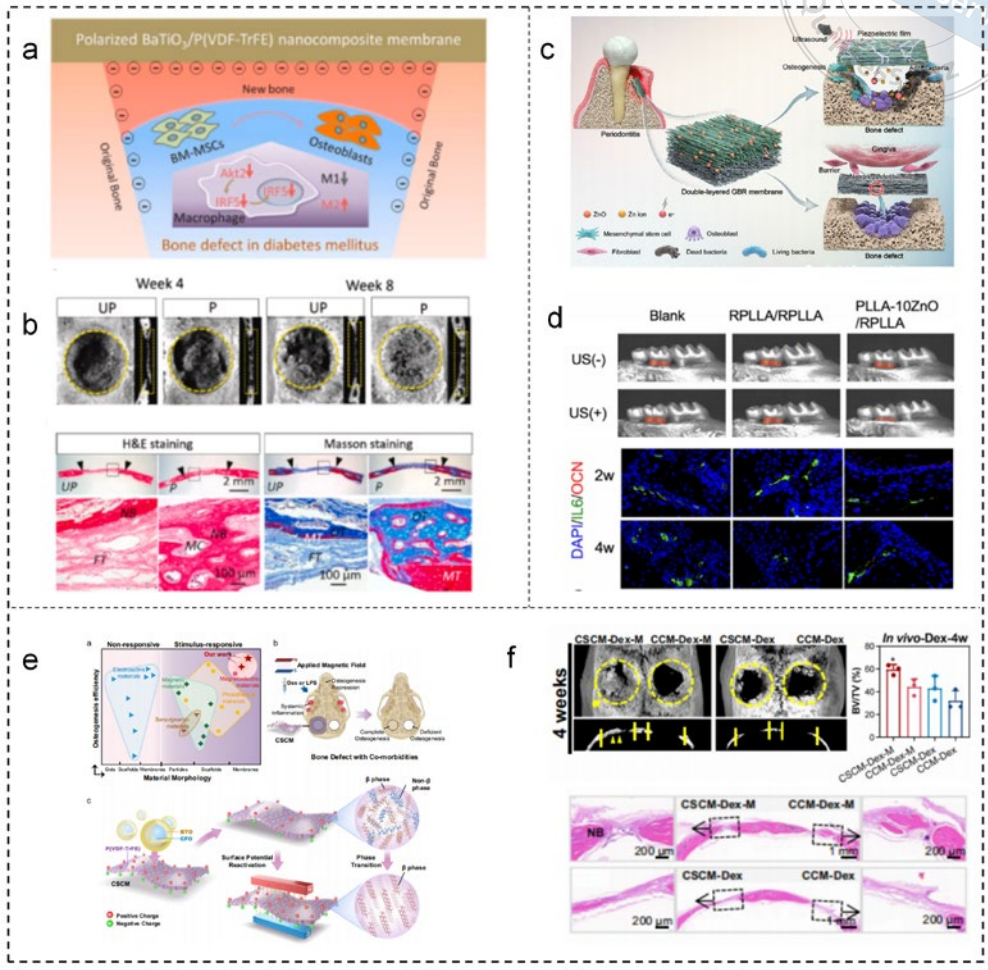

Fig 3a to f Active and dynamic modulation with electroactive scaffolds can overcome compromised bone healing under pathological conditions such as type 2 diabetes and periodontitis. The restored electrical microenvironment downregulates AKT2-IRF5 signalling that induces macrophages to the M2 phenotype under the pro-inflammatory conditions of type 2 diabetes **(a)**.[20] Representative microCT, histological haemotoxylin and eosin (HE) and Masson trichrome staining images of critical-sized calvarial full-thickness defects in diabetic rats after implantation with electroactive scaffolds **(b)**.[20] Schematic diagram of the structure and applications of the composite guided bone regeneration membrane **(c)**.[21] In vivo efficacy of composite membranes for treatment of *P. gingivalis*-mediated periodontitis **(d)**.[21] Design and working mechanisms of the CoFe2O4@BaTiO3/P (VDF-TrFE) membrane, which can enhance osteoinductivity on command upon activation by a magnetic field **(e)**.[22] Bone regeneration properties of CFO@BTO/P (VDF-TrFE) membranes in vivo under simulated pro-inflammatory comorbidity conditions induced by dexamethasone or lipopolysaccharide **(f)**.[22]

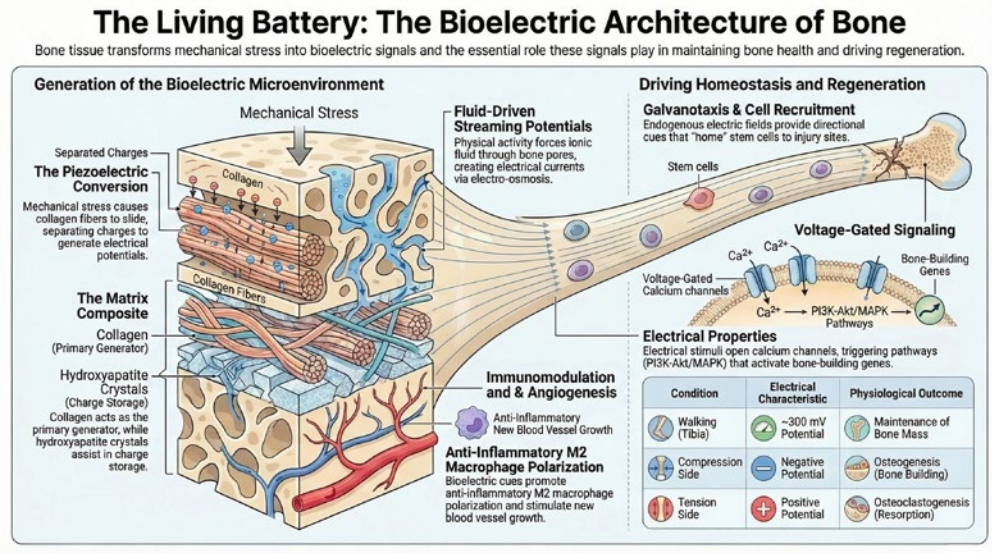

Fig 4 Schematic illustration of how endogeneous electrical potential is generated within bone tissue and the role that it plays in driving bone homeostasis and regeneration.

eration.[36] Insufficient bioelectric signals fail to stimulate vascular endothelial growth factor (VEGF) release, resulting in inadequate nutrient and oxygen supply.[37] Moreover, electrical activity is crucial for calcitonin gene-related peptide (CGRP) release, which delays regeneration of neural signalling networks necessary for angiogenesis and osteogenesis.[38]

The immune system's sensitivity to the bone microenvironment's bioelectric state is critical for bone regeneration. A deficient bioelectric environment stagnates macrophages transitioning from pro-inflammatory M1 to anti-inflammatory M2 phenotypes, failing to suppress cytokines like TNF-α and IL-6.[20,39] This issue is particularly exacerbated in diabetes, as hyperglycaemia fosters M1 polarisation, disrupting bioelectric signalling required for M2 polarisation and bone repair.[20]

Electroactive scaffolds promote regeneration by restoring the natural bioelectric environment of healthy bone tissues

Electroactive scaffolds enhance bone regeneration by mimicking the bioelectric properties of healthy bone, addressing deficiencies in critical-sized defects (Fig 1). This was demonstrated by a previous study by the present authors on guided bone regeneration with a BTO/P (VDF-TrFE) nanocomposite membrane.[14] In subsequent studies, it was demonstrated that bone regeneration can be further enhanced by more closely mimicking the natural electrical microenvironment of bone tissues via heterogeneous presentation of electrical signalling cues[15] and by utilising 3D micropillar topography.[16]

Electroactive scaffolds facilitate bone regeneration via five primary mechanisms (Fig 5): promoting osteogenesis (Fig 2c and f and Fig 3b and f), enhancing vascularisation (Fig 2d and f) and innervation (Fig 2g and h), osteo-immodulation (Fig 2a, b and d and Fig 3a), inhibiting osteoclastogenesis and resorption, and exerting antibacterial effects (Fig 3d). Each of these will be discussed in turn. Within the conceptual framework of electric microenvironment remodelling, these scaffolds act as therapeutic tools that re-establish and actively reshape local electrical signalling cues temporospatially, partially recapitulating the physiological remodelling dynamics that are lost at defect sites.[6,14]

Electroactive scaffolds boost osteogenesis by activating molecular signalling pathways in bone-forming cells like MSCs and osteoblasts.[6] Electrical stimuli open voltage-gated calcium channels (VGCCs), allowing Ca^{2+} influx, which in turn activates the CaM/CaN/NFAT pathway to upregulate pro-osteogenic genes such as BMP-2, TGF-β and Runx2.[6] These stimuli also facilitate mechanotransduction via focal adhesion changes, enhancing integrin clustering and activating focal adhesion kinase (FAK), promoting Yes-associated protein/Transcriptional co-activator with PDZ-binding motif (YAP/TAZ) nuclear translocation crucial for the osteogenic differentiation of MSCs.[15] The present authors' previous study demonstrated that heterogeneous presentation of electrical signalling cues can enhance mechanotransduction-driven osteogenesis of MSCs (Fig 1c and d).[15] Moreover, electroactive scaffolds also restore the bioelectric environment, inducing a "galvanotactic" effect that attracts MSCs and osteoblasts to the defect site.[6,23] Quantitatively, endogenous electric fields in bone tissue typically range from approximately 10 to 100 mV/mm, with values up to 100 mV/mm reported to be required for effective MSC osteogenic differentiation.[40] These physiological field magnitudes correspond to membrane potential changes that can depolarise the resting cell membrane (normally between −40 and −90 mV), thereby reaching the activation threshold of L-type voltage-gated calcium channels. This controlled Ca^{2+} ion influx then triggers the downstream CaM/CaN/NFAT and MAPK/ERK signalling cascades that drive osteogenesis.[40]

Electroactive scaffolds also enhance bone regeneration by promoting angiogenesis and vascularisation, improving nutrient and oxygen supply to defect sites.[6] They increase the production of pro-angiogenic growth factors like VEGF and fibroblast growth factors (FGFs) from vascular endothelial and osteogenic cells, initiating new capillary development.[6] Other factors such as interleukin-8 (IL-8), placental growth factor (PLGF) and nephronectin are also upregulated by electrical stimuli.[6,40] These scaffolds can activate various molecular signalling pathways in endothelial cells, including VEGF/VEGF receptor (VEGFR), PI3K/Akt, endothelial nitric oxide synthase/nitric oxide (eNOS/NO) and MAPK/ERK, driving vascular formation.[6,41] The electrical environment modulates endothelial activity vital for blood vessel construction by inducing cell proliferation and electrotaxis towards the defect site.[6,41] The present authors' previous study demonstrated that heterogeneous surface potential distribution can promote pro-angiogenic macrophage polarisation via activation of the PI3K-Akt signalling pathway (Fig 2d to f).[15] Additionally, electroactive scaffolds support sensory nerve growth during bone regeneration, promoting CGRP release, which further stimulates VEGF expression and synergises the nervous and vascular systems for accelerated bone repair.[38] It is important to recognise, however, that successful bone remodelling requires a carefully balanced interplay of multiple concurrent processes, namely osteogenesis,

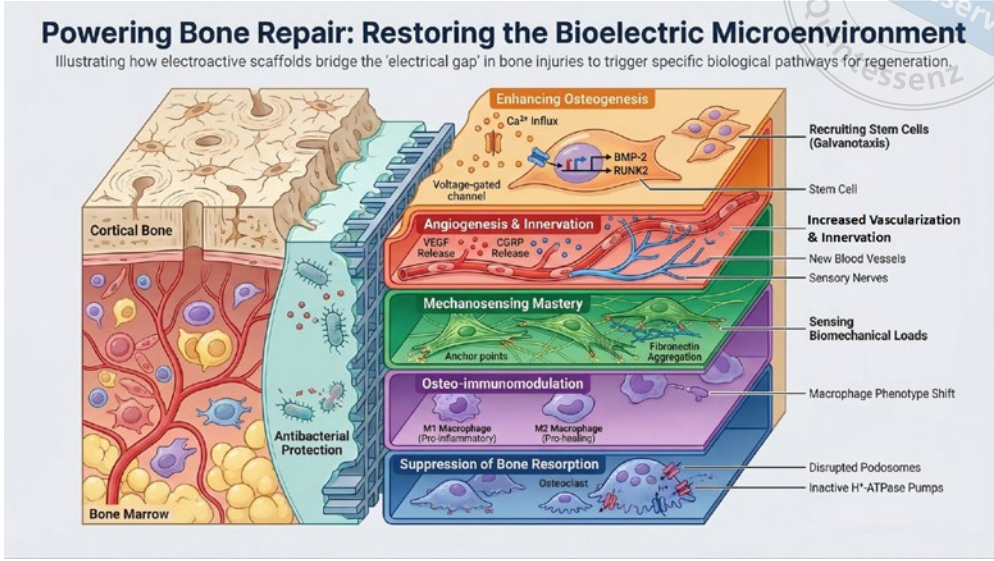

Fig 5 Schematic illustration of the mechanisms by which electoactive scaffolds promote bone repair.

angiogenesis and immunomodulation, that cannot be driven by electrical stimuli alone. Local biochemistry and the presence of specific growth factors, particularly BMP-2, TGF-β and VEGF, are equally indispensable in establishing the required microenvironment for tissue engineering. The synergistic combination of electrical stimulation with controlled delivery of these biochemical cues has been shown to more effectively guide MSC differentiation and vascular ingrowth than either modality alone.[33,42] Achieving this balance between electrical and biochemical signalling is therefore a critical design consideration for tailored bone tissue engineering scaffolds.

Yet another mechanism by which electroactive scaffolds enhance bone regeneration is through osteoimmunomodulation, inducing macrophage transition from pro-inflammatory M1 to anti-inflammatory M2 phenotypes, as demonstrated by previous studies conducted by the present authors.[17,18,20] They suppress pro-inflammatory cytokines (TNF-α, IL-6) and promote healing factors, especially in type 2 diabetes.[20] M2 macrophages, influenced by electrical signals, display increased pro-angiogenic markers and secrete growth factors, boosting endothelial cell angiogenesis.[18]

Restoration of the bioelectric environment through electroactive scaffolds also enhances regeneration by inhibiting osteoclastogenesis and bone resorption.[43-45] Electrical signalling induces Ca^{2+} ion influx into osteoclasts, disrupting podosome formation and resorption capability.[46-48] This also activates phospholipase C pathways, inhibiting plasma membrane vacuolar H^+-ATPase, further preventing bone matrix resorption.[46-48] Additionally, electrical stimuli downregulate key osteoclast-related genes like RANK, DC-STAMP and CD44, critical for osteoclast precursor recruitment, differentiation and fusion.[48]

Finally, electroactive scaffolds can also enhance bone healing by protecting against bacterial infections.[49] Their electrical charges disrupt bacterial membranes and respiratory chains, while also stimulating reactive oxygen species (ROS) production, which acts as an antibacterial agent and may modulate osteogenesis at controlled levels.[49] In a previous study, the present authors developed a biodegradable piezoelectric Janus membrane with enhanced antibacterial and osteoinductive properties for periodontitis therapy (Fig 3c and d).[21]

Hence, based on accumulated experimental data within the scientific literature, electroactive scaffolds can be viewed as engineered mediators of electric microenvironment remodelling, capable of partially substituting for the endogenous regulatory machinery of healthy bone.[6]

Scaffold topology and porosity and heterogenous versus homogenous presentation of electrical signals

Besides the electroactive nature of the developed materials, the topology and porosity of the scaffolds also play a critical role in bone tissue engineering. The permeability of a scaffold, determined by its pore size (optimally 200 to 500 μm), interconnectivity and overall porosity, directly governs the transport of nutrients, oxygen and metabolic waste products throughout the

scaffold volume.[50] Adequate permeability ensures that fluid flow-induced wall shear stress reaches embedded cells, providing a mechanical stimulus that synergises with bioelectric cues to promote osteoblast activity and matrix mineralisation.[50] Conversely, insufficient permeability leads to necrotic core formation and impaired vascular ingrowth, ultimately compromising bone regeneration outcomes. Thus, the design of electroactive bone scaffolds must carefully balance electrical performance with optimised topological and porous architecture to ensure effective nutrient transport and cellular colonisation throughout the entire scaffold.

A previous study by the present authors demonstrated that the heterogenous presentation of electrical signals in bone scaffolds is significantly more advantageous than homogeneous presentation, because it more accurately mimics the natural micro- and nanoscale electrical environment of healthy bone tissue (Fig 3).[15] Bone scaffolds utilising heterogeneous surface potential distribution (HEPD) provide several key advantages that accelerate bone healing and regeneration.

Most notably, cellular mechanosensing and adhesion are enhanced by HEPD via the formation of a meshwork pattern of fibronectin (FN) aggregation, which increases the flexibility of FN fragments and provides more anchor points for cells.[15] This pattern in turn enhances integrin clustering and the formation of focal adhesions, which are essential for stable cell attachment and spreading. By increasing the traction of actin fibres, heterogeneous signals amplify intracellular mechanotransduction, promoting the nuclear translocation of YAP/Runx2, which are critical drivers of osteogenesis.[15]

Indeed, it has been demonstrated conclusively that bone scaffolds with heterogeneous electrical signal presentation are significantly more effective at promoting the differentiation and mineralisation of MSCs, as attested by significantly higher expression levels of pro-osteogenic markers, such as BMP-2 and osteopontin (OPN).[15] The increased cellular mechanosensitivity triggered by HEPD leads to enhanced matrix mineralisation, facilitating faster bone repair.[15]

Furthermore, it was also demonstrated that immune responses to implanted bone scaffolds are highly sensitive to heterogenous versus homogenous distribution of electrical signalling cues, with heterogenous electroactive substrates significantly better at inducing pro-regenerative M2 polarisation of macrophages than homogenous substrates.[15] Mechanistically, the heterogeneous presentation of bioelectric signals activate the PI3K-Akt signalling pathway in macrophages, which induces them to take on a pro-healing and pro-angiogenic phenotype, as attested by upregulated expression of pro-angiogenic gene markers.[18] These modulated macrophages enhance the angiogenic function of endothelial cells, leading to increased neovascularisation, which is crucial for delivering nutrients and oxygen to the healing bone defect.[18]

The combined effects of heterogenous bioelectric signal presentation on mechanosensing, osteogenesis and immunomodulation were demonstrated to result in markedly improved in vivo bone healing outcomes. In experimental animal models, polarised nanocomposite membranes with heterogeneous electrical charge distributions facilitated nearly complete healing of supercritical-sized defects within 12 weeks, whereas those with homogeneous electrical charge distributions failed to achieve continuous nascent bone formation.[15] Hence, heterogeneous presentation of bioelectric signalling cues in bone scaffolds effectively bridges the "gap" in bone regeneration by providing the specific micro-scale cues required for coordinated cell recruitment and tissue integration during the complex healing process.[15]

Dynamic regulation of the bioelectric environment under chronic disease conditions with smart electroactive scaffolds facilitates bone healing and regeneration

Electroactive scaffolds can dynamically regulate the electrical environment, providing a therapeutic strategy for bone regeneration under chronic disease conditions like type 2 diabetes, periodontitis and osteoporosis, which further disrupt bioelectric microenvironments and metabolic processes.[6] Under these pathological conditions, the intrinsic capacity of bone tissue to appropriately remodel its electric microenvironment over time is further compromised, necessitating dynamic and externally controllable interventions (Fig 3). Smart electroactive scaffolds therefore enable a higher level of electric microenvironment remodelling, in which electrical signalling cues are dynamically modulated in real time according to disease stage and healing needs.[51-53]

In type 2 diabetes, chronic inflammation hampers bone healing due to excessive M1 macrophages, preventing the shift to pro-healing M2 macrophages. Electroactive scaffolds facilitate this transition through immunomodulation. This was demonstrated by previous studies conducted by the present authors in which polarised ferroelectric BTO/P (VDF-TrFE) scaffolds restore the physiological electrical microenvironment, encouraging the M1 to M2 switch by inhibiting AKT2 and IRF5 in the PI3K-AKT pathway and the RhoA/ROCK pathway (Fig 2d to f and Fig 3a and b).[18,20]

Moreover, innovative ultrasound-responsive scaffolds such as KNN/PCL allow for real-time electrical signalling regulation. Low-intensity ultrasound (L-US) initially enhances BMSC recruitment via M1 modulation, while high-intensity ultrasound (H-US) later promotes M2-driven osteogenic differentiation.[54]

Osteoporosis involves excessive osteoclast-mediated bone resorption compared to osteoblast activity. Electroactive scaffolds inhibit osteoclastogenesis through electrical signalling, which downregulates key differentiation genes like RANK, DC-STAMP and CD44.[42-48] Additionally, electrical signalling also disrupts actin ring formation and podosome expression in osteoclasts, halting bone matrix resorption.[48] Advanced magneto-responsive scaffolds, combined with pulsed electromagnetic fields or self-powered systems like TENGs, have shown effectiveness in boosting bone mineral density and mitigating bone loss in osteoporotic models by simulating natural load-bearing signals.[55-57]

The dynamic regulation of the bioelectric environment by smart scaffolds has been demonstrated to activate vital signalling pathways for osteogenesis, facilitating bone healing amid co-morbidities. For example, in a previous study, the present authors developed a flexible CoFe2O4@BaTiO3/P (VDF-TrFE) nanocomposite membrane that can activate osteogenesis via increased surface potential upon remote stimulation with a magnetic field, which enhanced bone regeneration under pro-inflammatory conditions induced by dexamethasone or lipopolysaccharide (Fig 3e and f).[22] Electrical signalling cues trigger Ca^{2+} ion influx through voltage-gated calcium channels, activating the CaM/CaN/NFAT pathway for osteogenesis.[6] Surface electrical charges enhance protein conformation, triggering integrin clustering and the activation of FAK and YAP/TAZ/Runx2 signalling, thereby promoting osteogenesis.[15] Additionally, modulating the bioelectric environment upregulates VEGF and FGF for enhancing angiogenesis and CGRP for enhancing neurogenesis, ensuring nutrient and signalling modulation for long-term bone healing.[36-38]

From the perspective of our proposed framework, these examples illustrate how electric microenvironment remodelling can be dynamically modulated in pathological settings[6] using smart, stimuli-responsive scaffolds to provide stage-specific and patient-tailored electrical signalling cues.[11]

The diverse categories of electroactive materials utilised in bone scaffolds

Electroactive materials for bone scaffolds are classified by chemical composition and electrical signal delivery mechanisms. They can mimic the natural electrophysiological environment of healthy bone to enhance healing. Different material platforms enable distinct modes and variable degrees of electric microenvironment remodelling, ranging from passive restoration of baseline potentials to actively programmed, stimuli-responsive modulation of local electrical signalling cues. Major categories include piezoelectric biomaterials,[58] electroconductive biomaterials,[59] electret biomaterials,[60] self-powered nanogenerators,[61] zwitterionic hydrogels[62] and biophysical stimuli-responsive electroactive materials.[17,22] Often, combinations of these materials are used to further enhance the pro-osteogenic properties of composite bone scaffolds. While this review mainly focuses on piezoelectric materials, which play a particularly prominent role by autonomously generating electrical signals in response to physiological mechanical loading without requiring an external power source, the importance of the other categories of electroactive materials, particularly conductive materials, should not be underestimated. Conductive bone scaffolds, incorporating materials such as graphene, carbon nanotubes or conductive polymers, excel at uniformly propagating and amplifying endogenous or externally applied electrical signals across large defect areas, thereby enhancing the local bioelectric microenvironment.[63] Their distinct mechanism of action makes them valuable complements to piezoelectric platforms in composite scaffold designs.

Piezoelectric biomaterials generate electrical signals under mechanical stress via the direct piezoelectric effect, utilising natural physical movements for electrical stimulation without external power. Synthetic piezopolymers like polyvinylidene fluoride (PVDF), polyvinylidenefluoride-trifluoroethylene [P(VDF-TrFE)], poly-L-lactic acid (PLLA) and polyhydroxybutyrate (PHB) provide flexibility and a compatible elastic modulus with bone, although some are non-degradable.[64,65] Natural counterparts include collagen, cellulose, chitin and silk fibroin, which are noted for their biocompatibility and biodegradability but typically exhibit lower piezoelectric coefficients.[64,65] Inorganic piezoceramics such as barium titanate, potassium sodium niobate, and zinc oxide have high piezoelectric coefficients but often require polymer combinations due to their brittleness.[66,67] It is important to note, however, that many of the most widely studied piezoelectric ceramics, including $BaTiO_3$ and $PbTiO_3$, contain potentially harmful heavy metal ions (barium and lead, respectively) that raise long-term biosafety concerns.[67] The development of fully biocompatible, lead-free piezoelectric materials, such as potassium sodium niobate (KNN), zinc oxide (ZnO) and natural biopolymers , remains an active and

critical area of research. For clinical translation, the electrical output of such materials must be demonstrated to be sufficient to elicit the desired biological responses, while their potential toxicity risks must be rigorously evaluated through comprehensive in vitro and in vivo studies.[67]

Electroconductive biomaterials enhance cell-substrate interfaces for improved bioelectric signals and electrical stimulation. Carbon-based nanomaterials like graphene, CNTs, and CNFs offer excellent electrical conductivity and protein attachment but raise long-term toxicity and biodegradability concerns.[68] Conductive polymers, such as polypyrrole (PPy), polyaniline (PANI) and poly (3,4-ethylenedioxythiophene) (PEDOT), are flexible and adjustable for complex bone defects but face issues with rigidity, brittleness and biocompatibility.69 Metallic nanoparticles, including Au and Ag, possess strong mechanical properties and conductivity, with Ag providing antibacterial benefits, yet may be cytotoxic and non-biodegradable.[70]

Electret biomaterials are electroactive dielectrics that retain electric charges or dipole polarisation without external power, resembling permanent magnets in the electrostatic realm.[59,71] They provide a stable, long-lasting potential that simulates healthy bone conditions, unlike piezoelectric materials that only signal under mechanical stress.[59,71] The surface potential of electret membranes can be tailored by adjusting material concentration or polarisation. Examples include SiO_2/PDMS membranes,[72] hydroxyapatite electrets,[73] chitosan membranes[74] and MEW-printed ZnO/PCL scaffolds,[75] which can effectively attract Ca^{2+} ions and enhance mineralisation.

Self-powered nanogenerators, such as triboelectric nanogenerators (TENGs) and piezoelectric nanogenerators (PENGs), convert biomechanical energy into electrical signals in bone scaffolds.[76-78] TENGs rely on the triboelectric effect[76,77] whereas PENGs harness the piezoelectric effect from nanomaterials,[78] generating power from small movements like muscle stretches. Hybrid nanogenerators (HTP-NGs) combine both effects to enhance efficiency and provide biphasic electrical pulses for improved biofeedback in regeneration.[79] Although these devices reduce risks from external power sources, challenges include achieving biodegradability, miniaturisation for complex sites and stable output in variable environments. A critical limitation that must be acknowledged is that current self-powered nanogenerators do not yet provide sufficient electrical power to independently supply implanted devices. Most research in this area reports the measurement of generated voltage, which can indeed be rather high; however, the generated currents remain extremely low due to the high output impedance of TENGs and PENGs, resulting in overall low power densities that restrict their standalone use as power sources for active implantable electronics.[80] Overcoming this power gap through device engineering, impedance matching and energy storage integration remains a key challenge for the field.

Zwitterionic hydrogels are electroactive gels formed from crosslinking zwitterionic polymers with both positive and negative charges, and have shown promise in bone tissue engineering.[62] They offer structural support, high ionic conductivity and excellent biological integration, which are crucial for maintaining physiological balance during bone repair mineralisation.[62] A study successfully created a polyzwitterionic hydrogel scaffold (PDMAPS) with methacrylated gelatin, which enhanced bone regeneration.[81]

Next-generation smart biophysical stimuli-responsive electroactive materials effectively respond to specific external signals, including ultrasound, magnetic fields and near-infrared light, to facilitate bone repair via precision control of electrical signalling cues.[64] Ultrasound-responsive scaffolds, part of "sonopiezoelectric nanomedicine", involve activation of piezoelectric materials using non-invasive ultrasound waves, allowing for deep tissue penetration and stable surface charges that stimulate osteogenesis. They can achieve temporal immunomodulation, regulating macrophage phenotypic M1/M2 transitions to align with healing stages.[82] Research demonstrates synergy between autonomous cell traction and ultrasound, enhancing scaffold-generated electrical signals.[83] Photo-responsive scaffolds harness near-infrared light to create microelectric currents with minimal damage to healthy cells. Materials like bismuth sulphide generate electrical signals upon exposure.[84] Magneto-responsive scaffolds employ external magnetic fields for electrical and magnetic stimulation, using magnetoelectric nanoparticles that modulate osteogenesis in situ.[85] The various categories and subcategories of electroactive materials utilised in bone scaffolds are summarised in Table 1. Magnetic fields offer superior deep tissue penetration while minimising harm to surrounding tissues, making them ideal for treating complex bone defects, such as those due to periodontitis. Additionally, these systems can serve as remotely controlled drug delivery platforms, allowing magnetic, light or ultrasound stimuli to trigger the controlled release of growth factors like BMP-2 from the scaffold.[86]

Table 1 Summary of the various categories and subcategories of electroactive materials utilised in bone scaffolds, detailing their advantages, deficiencies and limitations.

Category	Subcategory	Advantages	Deficiencies and key limitations	References
Piezoelectric biomaterials	Synthetic piezopolymers (e.g., PVDF, PLLA, PHB)	High flexibility and low stiffness; easy to process into diverse structures like nanofibres or films; good mechanical strength	Non-biodegradable types (PVDF) require secondary removal surgery; degradable types (PLLA/PHB) often have lower piezoelectric coefficients and unstable electrical signals	65,66
	Natural piezopolymers (e.g., collagen, cellulose, chitin)	Excellent biocompatibility and biodegradability; negligible cytotoxicity; mimic natural bone components	Very low piezoelectric coefficients compared to synthetic materials; poor mechanical stiffness; high degradation rates	65,66
	Piezoceramic materials (e.g., barium titanate, KNN, ZnO)	High piezoelectric coefficients; mechanical hardness similar to natural bone	Inherently very brittle and fragile; difficult to process for irregular defects; some types (lead-based like PZT) are highly toxic	67
Electroconductive biomaterials	Carbon-based nanomaterials (e.g., graphene, CNTs)	Excellent conductivity and mechanical reinforcement; large surface area for drug loading	Low biodegradability; dose-dependent cytotoxicity; tendency to aggregate/disperse poorly in scaffolds	68
	Conductive polymers (e.g., PPy, PANI, PEDOT)	High electrical conductivity and processing flexibility (some are injectable); unique reversible doping for drug release	Mechanically rigid and brittle once synthesised; non-degradable; conductivity declines over time due to dopant loss	69
	Metallic nanoparticles (e.g., Au, Ag)	Robust mechanical strength and high conductivity; specific types (Ag) provide broad-spectrum antibacterial effects	High material cost (Au/Ag); low biodegradability and risk of systemic organ accumulation; dose-dependent cytotoxicity via ROS generation	70
Electret biomaterials	Specific examples: SiO_2/PDMS membranes, HA ceramics, chitosan membranes, MEW ZnO/PCL	Stable, persistent "long-acting" built-in potential without external power or continuous high movement; self-powered and non-invasive	Relatively underdeveloped field for bone repair; polarisation often requires harsh voltage/temperature; surface charges can be neutralised by adsorbed proteins in vivo	71-75
Self-powered nanogenerators	TENGs (triboelectric)	Higher voltage output and mechanosensitivity; harvest large-scale energy from walking or joint rotation	Highly sensitive to moisture and liquids, requiring complex protective encapsulation; frictional efficiency can be low	76,77
	PENGs (piezoelectric)	Good stability and endurance during long-term bending; harvest energy from small stresses like heartbeats or pulses	Low voltage output performance and power density compared to TENGs; limited mechanical deformation pathways in vivo	78
	HTP-NGs (hybrid)	Synergistic combination of piezoelectric and triboelectric effects; significantly higher energy conversion efficiency	Complex architectonics and design; challenges in ensuring full biodegradability of all integrated components	79
Zwitterionic hydrogels	Carboxybetaine-based (i.e., PCBMA)	Unique ionic conductivity and favourable biocompatibility; high hydrophilicity and effective antifouling/antibacterial properties	Single-network types have poor mechanical strength; lack of established industrial mass production; long-term metabolism of products needs evaluation	62,81
	Sulphobetaine-based (i.e., PDMAPS, PSBMA)			
	Phosphobetaine-based (i.e., PMPC)			
Stimuli-responsive materials	Ultrasound-responsive	Remote, non-invasive spatiotemporal control; wireless deep tissue penetration	Highly dependent on external energy sources; periodic application is not conducive to continuous treatment	82,83
	Photoresponsive	Synergy between photoelectric and photothermal multi-repair (e.g., killing tumours/bacteria)	Very limited tissue penetration depth for light activation; most wavelengths are absorbed by skin/fat	84
	Magnetoresponsive	Remote precision with superior deep-tissue penetration compared to light or ultrasound	Mechanism of controlling polarisation through magnetic fields is not yet fully understood; lacks broad clinical scientific support	85

Ag, silver; Au, gold; CNTs, carbon nanotubes; HTP-NGs, hybrid triboelectric-piezoelectric nanogenerators; KNN, potassium sodium niobate; MEW, melt electrowriting; PANI, polyaniline; PCBMA, poly (carboxybetaine methacrylate); PCL, polycaprolactone; PDMAPS, poly (3-dimethyl (methacryloyloxyethyl) ammonium propane sulphonate); PEDOT, poly (3,4-ethylenedioxythiophene); PENGs, piezoelectric nanogenerators; PHB, polyhydroxybutyrate; PLLA, poly (L-lactic acid); PMPC, poly (2-methacryloyloxyethyl phosphorylcholine); PPy, polypyrrole; PSBMA, poly (sulphobetaine methacrylate); PVDF, polyvinylidene fluoride; SiO2/PDMS, silicon dioxide/polydimethylsiloxane; TENGs, triboelectric nanogenerators; ZnO, zinc oxide.

Conclusion and future outlook

A decade has elapsed since the concept of remodelling the electrical microenvironment to facilitate bone regeneration was first articulated, and the collective body of evidence reviewed herein demonstrates that this field has matured considerably. The physiological bioelectric environment of healthy bone, generated through the piezoelectric effect of type I collagen fibres, streaming potentials from interstitial fluid flow and transmembrane potentials of bone cells, is now well characterised, and its disruption at defect or disease sites has been established as a key impediment to bone healing. Electroactive scaffolds, encompassing piezoelectric biomaterials, electroconductive platforms, electret membranes, self-powered nanogenerators, zwitterionic hydrogels and stimuli-responsive systems, have demonstrated compelling preclinical efficacy in restoring this compromised bioelectric environment, thereby enhancing osteogenesis, angiogenesis, innervation, osteo-immunomodulation and suppression of bone resorption at critical-sized defects.[87-89]

From a mechanistic standpoint, the activation of voltage-gated calcium channels and the downstream CaM/CaN/NFAT, MAPK/ERK and PI3K/AKT signalling cascades by electroactive scaffolds have been consistently identified as central mediators of osteogenic and immunomodulatory responses. The galvanotactic recruitment of mesenchymal stem cells, the promotion of pro-angiogenic macrophage polarisation and the inhibition of osteoclast activity through disruption of podosome assembly collectively underscore the multifaceted role of bioelectric cues in orchestrating the bone regeneration cascade. Notably, the dynamic regulation of these cues using smart, stimuli-responsive scaffolds activated by ultrasound, near-infrared light or magnetic fields has demonstrated particular promise for treating bone defects under challenging pathological conditions such as type 2 diabetes, osteoporosis and periodontitis, where the intrinsic bioelectric regulatory capacity of bone tissue is further compromised.

Looking ahead, the future trajectory of bone tissue engineering will likely converge on the development of smart composite electroactive scaffolds that integrate multiple electroactive modalities with biological functionalities. The incorporation of controlled growth factor delivery, gene therapy vectors and patient-derived stem cells into electroactive scaffold platforms represents a particularly promising avenue for personalised bone regeneration. Additionally, various biophysical stimuli can be applied together with electroactive scaffolds to facilitate angiogenesis and vascularisation during bone regeneration.[90] Advances in additive manufacturing and bioprinting technologies will enable the fabrication of patient-specific scaffolds with spatially heterogeneous electrical properties that more faithfully recapitulate the complex bioelectric architecture of native bone. Furthermore, the integration of wireless sensing capabilities and real-time feedback control into self-powered nanogenerator-based systems could enable closed-loop, adaptive modulation of electrical signalling cues in response to the evolving demands of the healing process. Ultimately, the convergence of electroactive biomaterials science with precision medicine approaches holds transformative potential for addressing the growing global burden of bone injuries and degenerative diseases, particularly in aging populations with complex co-morbidities. An ideal development strategy for electroactive scaffolds in clinical practice should encompass the simultaneous optimisation of biocompatibility, biodegradability, mechanical integrity and electroactive output, properties that are often in tension with one another. The ideal scaffold would be fabricated from lead-free, biocompatible piezoelectric or conductive materials with a topologically optimised porous architecture that ensures adequate permeability, and would be capable of autonomously generating physiologically relevant electrical signals in response to daily mechanical loading. In this design endeavour, the role of AI and machine learning should not be underestimated. AI-driven computational modelling and data-driven optimisation algorithms can efficiently navigate the vast multidimensional design space of composite electroactive scaffolds, predicting material degradation kinetics, electromechanical performance and cell-material interactions prior to fabrication, thereby dramatically accelerating the translation of ideal electroactive scaffolds from the laboratory bench to clinical reality.[91]

Conflicts of interest

The authors declare no conflicts of interest related to this study.

Author contribution

Drs Boon Chin HENG, Yang LIU, Yun Yang BAI, Xiao Na ZHENG, Jia SONG, Qun CUI and Wan Li SONG contributed to writing different sections of the manuscript; Drs Xue Hui ZHANG and Xu Liang DENG contributed to the supervision and revision.

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