

REVIEW

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Electrospun aligned nanofibers for tissue engineering

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Tissue engineering aims to repair and regenerate damaged tissues using scaffolds that mimic the natural extracellular matrix (ECM). Aligned electrospun nanofibers are especially attractive because fiber orientation can regulate cell adhesion, migration, cytoskeletal organization, and lineage-specific differentiation while reproducing the anisotropic architecture of native tissues. This review examines aligned nanofibers from a design-to-function perspective. We discuss electrospinning principles, material selection, and major strategies for controlling fiber alignment, and then analyze how alignment influences regeneration of bone, neuronal, cardiac, and muscle tissues. We also discuss how bioactive cues, including peptides, growth factors, and conductive or drug-releasing components, can be integrated with aligned scaffolds to enhance performance. Representative preclinical studies are summarized, and the limited clinical translation of electrospun nanofiber platforms is critically assessed, with emphasis on the gap between random and aligned scaffolds. Finally, we outline the main barriers to broader adoption, including scale-up, reproducibility, pore architecture, and long-term *in vivo* validation, and discuss emerging directions for 3D aligned scaffolds.

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1. Introduction

Tissue engineering seeks to repair or replace damaged tissues using a combination of cells, scaffolds, and bioactive molecules, which collectively support tissue regeneration.^{1–6} A critical aspect of successful tissue engineering is the development of scaffolds that closely mimic the natural extracellular matrix (ECM) to guide cell behavior and promote tissue growth.^{7–10} Among various scaffolds, aligned nanofibers have emerged as promising candidates due to their unique structural and functional properties.⁷ Their nanoscale dimensions closely resemble the native ECM,¹¹ effectively guiding cell growth and differentiation.^{12,13} Moreover, the alignment of these nanofibers mirrors the native organization of anisotropic tissues such as skeletal muscle and peripheral nerve, aiding in the proper orientation and function of cells.¹⁴ In addition, their high surface-to-volume ratio further supports efficient nutrient

exchange and cell signaling, enhancing their utility in tissue engineering.¹⁵

Several methods exist for producing aligned nanofibers, including electrospinning,¹⁶ self-assembly,¹⁷ and template-assisted techniques.¹⁸ Among these, electrospinning stands out for its versatility and simplicity, allowing precise control over the alignment, diameter, and mechanical properties of the nanofibers.¹⁹ Aligned nanofibers have shown considerable potential across a range of applications. In musculoskeletal tissue engineering, they have been used to regenerate skeletal muscle, bone, cartilage, and tendons.²⁰ In neural tissue engineering, these nanofibers provide directional guidance for axonal growth and support neural cell differentiation.²¹ In cardiovascular applications, they promote organized blood vessel formation and growth.^{22,23} The ability of aligned nanofibers to enhance cellular adhesion, migration, and orientation closely mimics the behaviors observed in natural tissues, further supporting their use in regenerative medicine. The incorporation of bioactive molecules, such as growth factors, peptides, and drugs, into aligned nanofibrous scaffolds enhances their therapeutic potential.^{24,25} The nanofibers can provide controlled release of these agents, thereby directing cell proliferation and differentiation in a targeted manner.²⁶

Aligned nanofibers have garnered significant attention because fiber alignment is not simply a structural descriptor; it is a design variable that links scaffold fabrication to cell guidance and, ultimately, to tissue-level function. Yet literature remains fragmented. Most studies are organized by material

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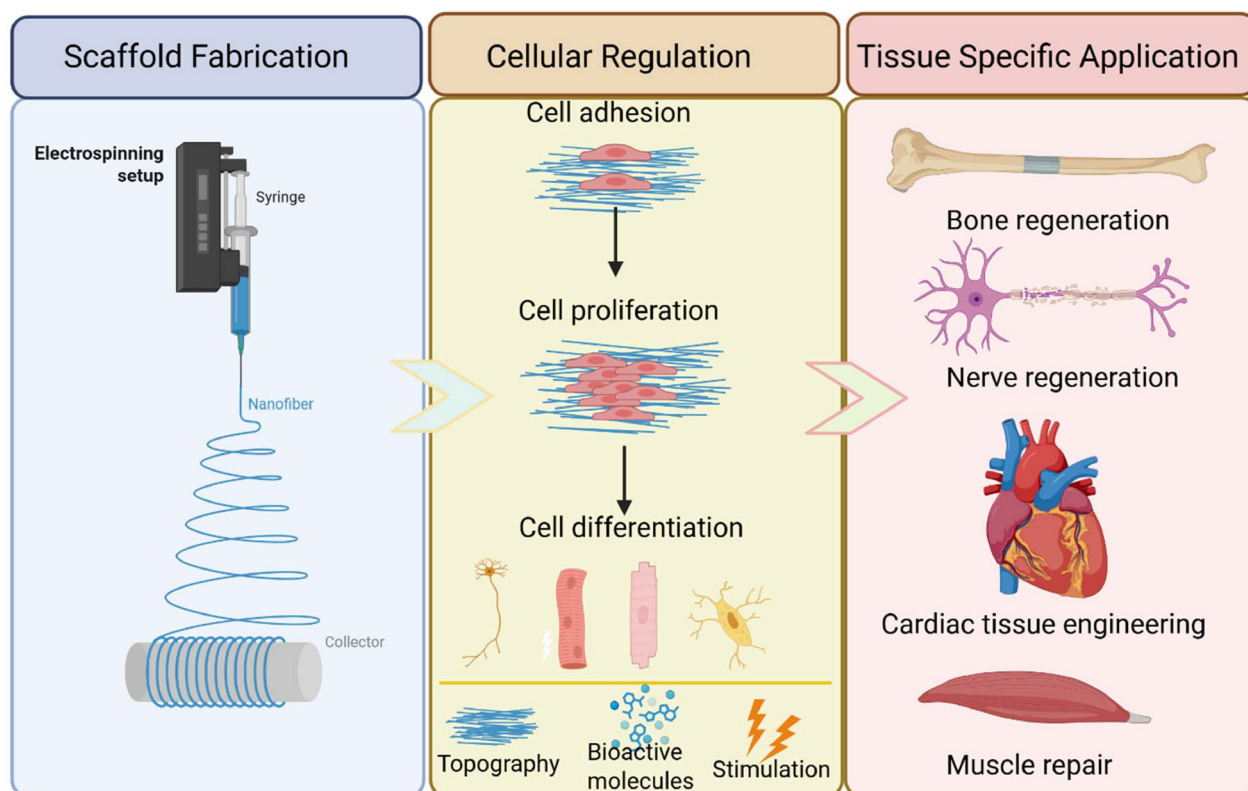


Fig. 1 Aligned nanofibers for tissue engineering. Created with BioRender.com.

class or target tissue, which makes it difficult to identify the general principles by which alignment regulates cell adhesion, migration, cytoskeletal organization, matrix deposition, and lineage specification. Although several reviews discuss electrospinning broadly,^{27–30} and a smaller number summarize alignment methods.^{31–33} A synthesis that connects fabrication strategy, alignment-dependent cell behavior, tissue-specific performance, and translational constraints is still needed. In this review, we use that design-to-function perspective to examine aligned electrospun nanofibers. We first discuss electrospinning principles, materials, and methods for generating aligned fibers. We then analyze how alignment regulates cell behavior across bone, neuronal, cardiac, and muscle systems, with emphasis on shared mechanisms and tissue-specific requirements, as illustrated in Fig. 1. Finally, we discuss emerging 3D aligned scaffolds and the main barriers to clinical translation.

2. Engineering nanofiber-based scaffolds

Nanofiber-based scaffolds are of significant interest in tissue engineering due to their high permeability, large surface area, and robust mechanical properties.³⁴ Several methods are available for fabricating nanofibers, including electrospinning, self-assembly, template synthesis, drawing, and phase separation.^{34,35} Each method has specific limitations. For

example, the drawing technique typically produces only finite-length fibers, whereas electrospinning allows for continuous nanofiber production.³⁶ Template synthesis is limited by a narrow range of fiber diameters and the challenges associated with template removal, making electrospinning a more flexible option.³⁷ Although electrospinning can utilize various biopolymers, phase separation is constrained to specific polymers.^{38,39} Furthermore, self-assembly is less efficient than electrospinning in terms of production speed.³⁶

2.1. Electrospinning

Electrospinning is the most widely used method for producing continuous nanofibers with a broad range of diameters. This technique relies on electrostatic forces to generate polymer nanofibers. Although electrospinning has been reported since 1899, it only gained significant attention in the 1990s when the term “electrospinning” was popularized for generating nanometer-scale fibers.⁴⁰ This process involves a high-voltage power source, a spinneret, a syringe pump, and a conductive collector.⁴¹ It operates based on electrohydrodynamics, where a polymer solution is pushed through the spinneret to form liquid droplets. Exposure to an electric field induces a charge in the droplets, stretching them into polymer nanofibers as the solvent evaporates.⁴² The properties of the resulting nanofibers are influenced by the polymer’s characteristics, such as viscosity, conductivity, and molecular weight.

2.2. Types of electrospinning

Electrospinning techniques offer control over fiber morphology, enhance production rates, and contribute to the versatility of the fibers.⁴³ Several types of electrospinning methods exist, including melt, near-field, magnetic-assisted, coaxial, and multi-nozzle electrospinning, each suited to specific materials or design goals. Melt electrospinning is useful for polymers that are difficult to dissolve in solvents. This method produces nonwoven mats that can serve as protective barriers in biomedical applications.^{44,45} Near-field electrospinning allows for the collection of well-patterned nanoscale fibers, essential for guiding cell growth and tissue regeneration.⁴⁶ Precise fiber placement and structure can also influence the release kinetics of therapeutic agents from the scaffolds.⁴⁷ Magnetic-assisted electrospinning uses an external magnetic field to control fiber formation and alignment. This approach produces aligned fibers that replicate the natural alignment found in native tissues.⁴⁸ Coaxial electrospinning involves two concentrically aligned hollow needles to create core-sheath nanofibers.⁴⁹ This technique is frequently used to encapsulate living cells within nanofibers and allows for controlled and sustained drug release.⁵⁰ Multi-nozzle electrospinning is utilized to increase the productivity of nanofiber generation.⁵¹

2.3. Polymers for electrospinning

The selection of suitable polymers and solvents is essential in the fabrication of electrospun nanofibers. Electrospinning pri-

marily utilizes two types of polymers: natural (*e.g.*, cellulose, collagen, chitosan, gelatin) and synthetic (*e.g.*, polycaprolactone (PCL), poly(lactic-co-glycolic acid) (PLGA), and poly(L-lactic acid) (PLLA)).^{52–54} Natural polymers are favored for their biocompatibility, low immunogenicity, and inherent antibacterial properties. However, they often suffer from limited mechanical strength. In contrast, synthetic polymers are more cost-effective, suitable for mass production, and offer tunable mechanical properties, though they may lack effective cell recognition sites. To overcome these limitations, many electrospun nanofibers are fabricated using blends of both natural and synthetic polymers, combining their respective advantages.^{55,56} For successful electrospinning, the polymer must possess an appropriate molecular weight and be soluble in a suitable solvent. Common solvents used in electrospinning include *N,N*-dimethylformamide (DMF), chloroform, hexafluoroisopropanol (HFIP), and trifluoroethanol.

2.4. Alignment control by electrospinning

Standard electrospinning typically results in randomly oriented nanofibers. However, producing highly aligned nanofibers is achievable by precisely controlling the electric field, collector design, and spinning parameters.^{57,58} Various advanced techniques, such as gap electrospinning, rotating mandrels, magnetic field-assisted electrospinning, and near-field electrospinning, have been developed to achieve uniform

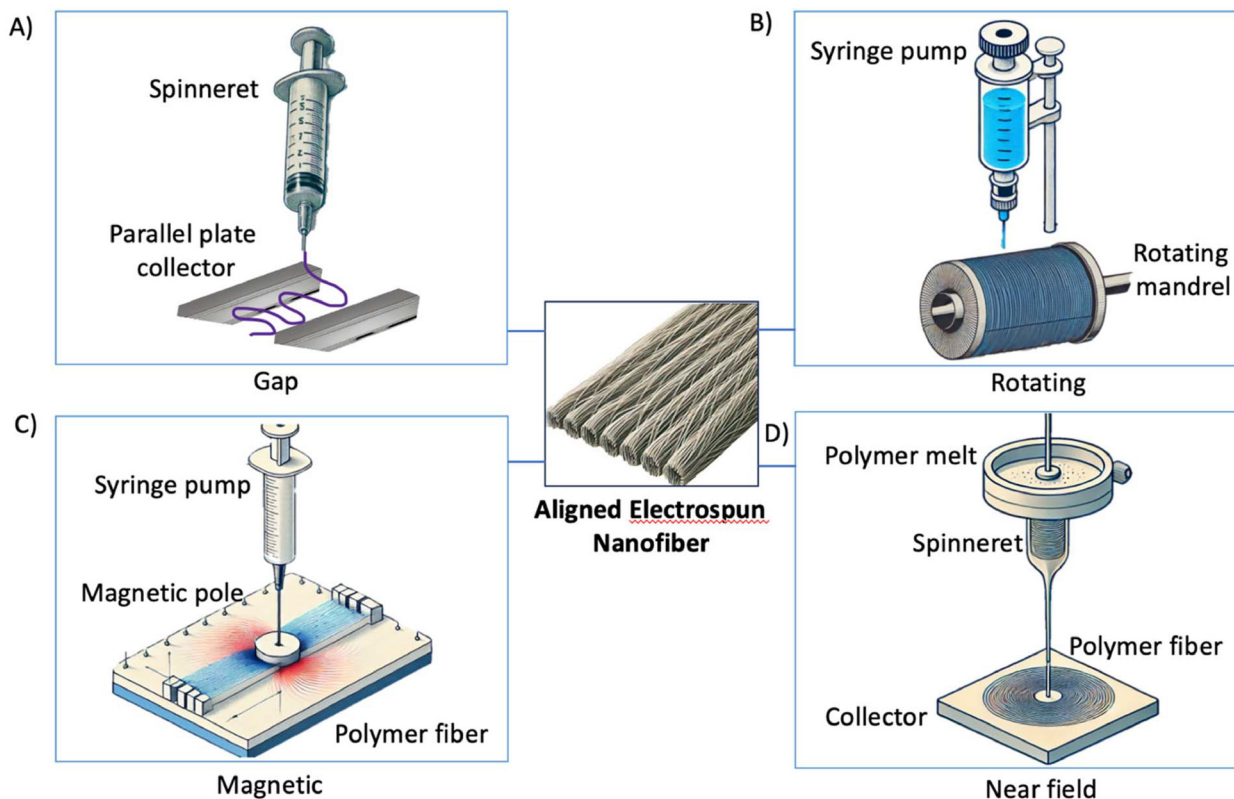


Fig. 2 Different methods for engineering aligned nanofibers include (A) gap, (B) rotating mandrel, (C) magnetic field-assisted, and (D) near-field electrospinning.

Table 1 Comparison of alignment techniques used for tissue engineering

Technique	Principle	Advantages	Limitations	Tissue engineering applications	Ref.
Gap electrospinning	-Fibers are deposited onto two separate conductive collectors, where the strong electric field between the electrodes causes the fibers to align uniaxially	-High degree of fiber alignment -Simple modification of the conventional setup	-Poor scalability -Alignment limited to short distances	-Bone regeneration, aligned nerve guidance conduits	73–77
Rotating mandrel electrospinning	-A high-speed rotating collector mechanically stretches and aligns fibers in a circular manner during the deposition process	-Suitable for producing tubular scaffolds -Scalable and easy to reproduce -Can produce scaffolds with strong anisotropic mechanical properties	-Alignment dependent on rotation speed -Limited control of 3D architecture	-Nerve conduits, tendon scaffolds, and vascular grafts	78–82
Magnetic field-assisted electrospinning	-An external magnetic field alters fiber deposition and alignment; magnetic nanoparticles may be used in some systems to enhance responsiveness, but are not universally required	-Produces localized aligned patterns over relatively large areas -Aligned mats can be transferred to secondary substrates	-Setup complexity -Performance depends on the polymer system and field geometry	-Skeletal muscle engineering and other anisotropic tissues	33, 48, 83 and 84
Near-field electrospinning	-A shorter distance from tip to collector reduces jet instability, enabling direct-write deposition of fibers in specific patterns with precise architecture	-High resolution, precision, low cost, and reproducibility -Precise fiber placement -Controlled pore size	-Nanoparticle-containing systems require biocompatibility assessment -Typically larger fiber diameters compared to conventional electrospinning -The process requires specialized equipment, including a precise programmable stage	-Three-dimensional scaffolds with adjustable structures and pore sizes, cell extension, and oriented alignment	33, 46, 85 and 86

and directional alignment of nanofibers³³ (Fig. 2). However, each method has distinct advantages and limitations when used in tissue regeneration as summarized in Table 1.

2.4.1. Gap electrospinning. The parallel-plate method is a widely used approach for aligning nanofibers with an electric field. In this method, two grounded parallel plates act as collectors and generate a concentrated electric field across the gap between them (Fig. 2A).⁷ Fiber alignment is governed mainly by electrostatic forces, so the electrical properties of the polymer solution are critical. Li *et al.* first used this configuration to produce uniaxially aligned poly(vinyl pyrrolidone) (PVP) and polyacrylonitrile (PAN) nanofibers.⁵⁹ The original setup produced fibers that were relatively short, about 10 cm in length, and very thin (Fig. 3A).⁵⁹ Subsequent modifications, including U-shaped collectors, enabled the production of much longer aligned fibers, up to 60 cm in length.⁶⁰

2.4.2. Rotating mandrel electrospinning. The rotating mandrel technique is a popular approach for collecting aligned electrospun nanofibers, utilizing a high-speed, grounded rotating mandrel (Fig. 2B).⁶¹ The mandrel's rotation speed, ranging from zero to several thousand revolutions per minute, significantly influences the arrangement of nanofibers.⁶² As the electrospun fibers wrap around the mandrel, residual repulsive charges on the fibers can affect their alignment, potentially reducing fiber thickness and altering alignment precision.⁶³ This technique is particularly effective in

producing well-aligned nanofibers. In a study by Ding *et al.*, aligned silk fibroin nanofibers were prepared using a rotating mandrel (Fig. 3B).⁶⁴ The fiber alignment was improved by repeated immersion in and withdrawal from ethanol. Furthermore, they observed high porosity, larger pore size, and improved fiber uniformity. Overall, the rotational electrospinning technique has been widely utilized in various tissue engineering applications.^{65–67}

2.4.3. Magnetic field-assisted electrospinning (MFAES). MFAES combines electrospinning with an external magnetic field to influence jet stability, deposition, and fiber orientation. In a common configuration, magnets are placed adjacent to or beneath the collector so that the local magnetic field modifies fiber deposition (Fig. 2C).^{68,69} Fiber alignment depends on field geometry and strength, applied voltage, solution properties, and spinneret-to-collector distance. Yang *et al.* first demonstrated in 2007 that magnetic fields could be used to generate well-organized nanofiber patterns.⁶⁸ In some systems, magnetic nanoparticles such as Fe₃O₄ can further enhance magnetic responsiveness and improve alignment.⁷⁰ However, aligned deposition can also be achieved without nanoparticle additives, depending on the collector configuration and polymer system (Fig. 3C).⁴⁸ Thus, MFAES is attractive because it can produce localized and transferable aligned patterns, although the benefit of magnetic additives is system dependent.

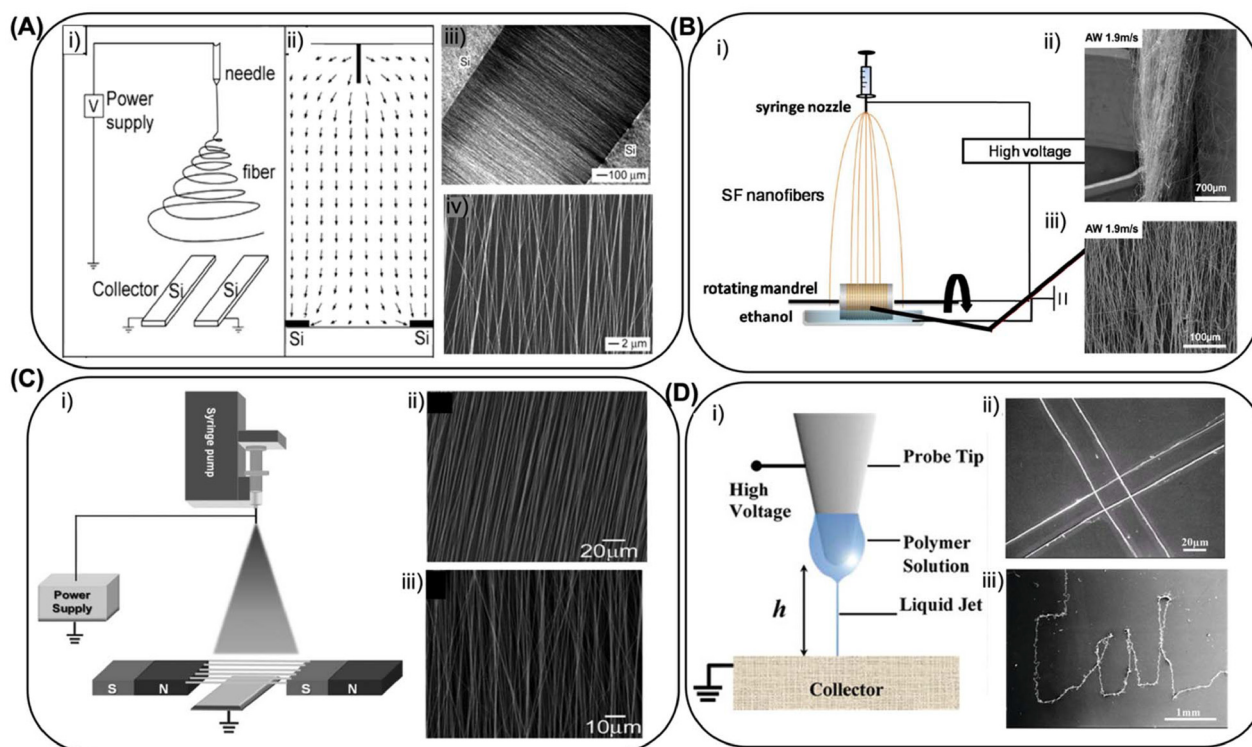


Fig. 3 Examples of fiber alignment methods in electrospinning. (A) Schematic illustration of the gap electrospinning setup; (i) the collector consists of two pieces of conductive silicon strips separated by a gap; (ii) calculated electric field strength vectors in the region between the needle and the collector, with arrows indicating the direction of the electrostatic field lines; (iii) dark-field optical micrograph of PVP nanofibers collected on top of a gap formed between two silicon strips; (iv) SEM image from the same sample, showing nanofibers deposited across the gap.⁵⁹ Copyright 2003, American Chemical Society. (B) Schematic of the rotational electrospinning setup: (i) electrospinning apparatus and setup used to fabricate highly aligned and uniform silk fibroin nanofibers; (ii) side view of aligned nanofiber collected by wet process at 1.9 m s^{-1} (scale bar: $700 \mu\text{m}$); (iii) magnified view of aligned nanofibers (Scale bar: $100 \mu\text{m}$)⁶⁴ Copyright 2017, Elsevier. (C) Schematic illustration of the (i) MFAES setup; SEM images of (ii) PLGA and (iii) PVP fiber arrays made using the MFAES method.⁴⁸ Copyright 2010, John Wiley and Sons. (D) Schematic representation of NFES setup: (i) the polymer solution is applied to the tip of the tungsten electrode similarly to a dip pen; (ii) two groups of parallel lines constructed perpendicular to each other by NFES. Scale bar: 1 mm . (iii) the three-character pattern “Cal” was manually drawn in 3 s (Scale bar: 1 mm).⁷² Copyright 2006, American Chemical Society. SEM, scanning electron microscopy; magnetic field-assisted electrospinning (MFAES); near-field electrospinning (NFES).

2.4.4. Near-field electrospinning (NFES). NFES reduces the distance between the spinneret and the collector, enabling precise control over nanofiber deposition at the microscale to nanoscale. This contrasts with conventional electrospinning, in which the polymer jet typically travels several centimeters before deposition (Fig. 2D). Jun *et al.* first showed in 2003 that shortening the spinneret-to-collector distance to less than 10 mm could produce highly aligned fibers.⁷¹ Sun *et al.* later introduced the term “near-field electrospinning” in 2006.⁷² Using poly(ethylene oxide) (PEO) as a model system on silicon-based collectors, they showed that alignment can be tuned by the applied voltage, solution concentration, and electrode-to-collector distance (Fig. 3D).⁷² Fiber morphology can also be adjusted by controlling collector motion.

3. Tissue engineering applications of scaffolds containing aligned nanofibers

The orientation of nanofiber scaffolds is crucial because alignment provides an anisotropic topographical cue that cells convert into biological responses. Across tissues, four recurrent effects are

observed: contact guidance of cell elongation and migration; reorganization of focal adhesions and the cytoskeleton; directional deposition of newly synthesized extracellular matrix; and, when conductive or bioactive components are included, spatial control of electrical or biochemical signaling.^{57,62,63,87–90} The relative importance of these effects differs by tissue. In bone, alignment mainly influences matrix organization and vascular guidance. In neuronal and muscle tissues, it strongly regulates cellular orientation and extension. In cardiac tissues, alignment helps coordinate sarcomere organization and electromechanical coupling.

Nanofiber surface functionalization can further modulate these responses by adding biochemical ligands, conductivity, or drug-release capability.^{91–93} For that reason, the studies discussed below are organized not only by target tissue but also by the specific role that alignment plays in each setting. Representative studies are summarized in Table 2.

3.1. Bone tissue engineering

Bone tissue engineering aims to develop strategies to repair, regenerate, or replace damaged or missing bone tissue. The

Table 2 Representative studies of aligned nanofiber scaffolds in tissue engineering

Material	Cell type	Target tissue	Key alignment-linked outcome	Ref
PLGA/oHA-collagen/HAP	PIECs, MC3T3-E1 and Schwann cells	Bone	-Guided cell migration, increased vascularization, and enhanced collagen deposition <i>in vivo</i>	94
PDA-coated PLLA	hMSCs	Bone	-Promoted directional migration and organized matrix deposition during bone repair	95 and 96
PCL/lignin	PC12 and hADSCs	Neuron	-Enhanced neurite extension, differentiation, and nerve regeneration	97
PLGA/MAP-I	Neural and Schwann cells	Neuron	-Improved adhesion and accelerated peripheral nerve regeneration	98
PLGA	hiPSC-derived cardiomyocytes	Cardiac	Improved cardiomyocyte organization, survival, and cardiac function	23
PCL/SF/CNT	Cardiomyocytes	Cardiac	-Promoted alignment, maturation, and cardiac marker expression	99
PCL/collagen	Myoblasts, BMSCs, ADSCs, and Schwann cells	Muscle	Enhanced myogenic gene expression and myotube formation in coculture	100 and 101
P(EDS)UU-POSS	C2C12 myoblasts	Muscle	-Improved alignment, fusion, and myofiber maturation	102

PLGA: poly(lactic-co-glycolide); SF: silk fibroin; PCL: polycaprolactone; hMSCs, human mesenchymal stem cells; hADSCs, human adipose-derived stem cells; PIECs, porcine iliac artery endothelial cells; hiPSC, human induced pluripotent stem cell; MAP-I, fusion protein of mussel adhesive protein and IKVAV peptide.

primary goal is to create functional and biocompatible scaffolds that promote bone regeneration following trauma, disease, congenital defects, or other bone loss conditions. Scaffold design is critical, focusing on mimicking the natural bone environment to support the formation of new tissue. In bone tissue engineering, scaffolds containing aligned nanofibers are of interest because they can reproduce aspects of the native ECM of bone tissue.^{94,95,103} These nanofibers, often engineered from a combination of synthetic and natural polymers, can be tuned to approach the mechanical properties of bone tissue. The benefits of aligned nanofibers include: (1) providing physical cues to guide cells and promote tissue growth akin to native bone, (2) enhancing mechanical properties similar to natural bone, (3) guiding blood vessel formation in directions consistent with the bone matrix, and (4) enabling localized and sustained release of therapeutics to enhance bone regeneration.^{64,94,104}

In one study, Liu *et al.* employed aligned poly(lactic-co-glycolide) (PLGA) nanofibers infused with hyaluronic acid oligosaccharide-collagen mineralized microparticles (oHA-Col/HAP) to create a scaffold for bone regeneration.⁹⁴ The scaffold was designed to guide cell proliferation, and its aligned structure markedly enhanced strength in the parallel direction, compared to a randomly oriented scaffold. *In vitro* analyses showed its ECM-like structural organization, which promoted orderly cell growth and migration. Furthermore, the oHA-Col/HAP/PLGA scaffold facilitated vascularization, as evidenced by increased expression of platelet endothelial cell adhesion molecule (PECAM) and vascular endothelial growth factor (VEGF). *In vivo* analyses confirmed the scaffold's biocompatibility and demonstrated substantial collagen deposition.⁹⁴

Focusing on nanofiber-cell interactions, Stachewicz *et al.* examined the interactions between PLGA nanofibers and osteoblasts, revealing that the organized structure of the nanofibers promoted filopodia formation, thereby enhancing cellu-

lar growth. This organized growth was in stark contrast to the dispersed cell growth observed on randomly oriented PLGA scaffolds.¹⁰⁵

Lee *et al.* engineered polydopamine (PDA)-coated poly(l-lactic acid) (PLLA) nanofibers for culturing human mesenchymal stem cells (hMSCs). Bone morphogenetic protein-2 (BMP-2) was immobilized on the PDA-coated PLLA fibers. *In vitro*, hMSCs aligned along the fiber direction, and cell migration increased by more than one order of magnitude in the parallel direction relative to the perpendicular direction. In a mouse calvarial defect model, the coated aligned scaffold supported bone repair and demonstrated the value of combining alignment with surface biofunctionalization.⁹⁵ In a related study, Perikamana *et al.* compared random and aligned PLLA nanofibers and found that, although aligned fibers strongly directed cell orientation, alkaline phosphatase activity and calcium mineralization were not significantly different over 14 days (Fig. 4i). *In vivo*, the random group showed a slightly higher fraction of new bone area, whereas the aligned group produced a more anisotropic collagen organization that more closely resembled native bone (Fig. 4Aii). Together, these studies suggest that alignment may influence matrix organization more consistently than it increases total bone volume, and that the outcome depends strongly on the accompanying surface chemistry and biological cues (Fig. 4Aiii).⁹⁶

In another study, Fu *et al.* engineered PLLA nanofibers containing calcium silicate nanowires *via* a hydrothermal process. Both random and aligned versions showed improved biocompatibility relative to unmodified PLLA, indicating that inorganic reinforcement can strengthen the biological performance of PLLA scaffolds.¹⁰⁶ At the same time, related musculoskeletal studies have shown that aligned PLLA architectures can bias tissue formation toward more tendon-like organization, whereas random architectures may favor chondrogenic or ossified outcomes.¹⁰⁷ These observations suggest that alignment

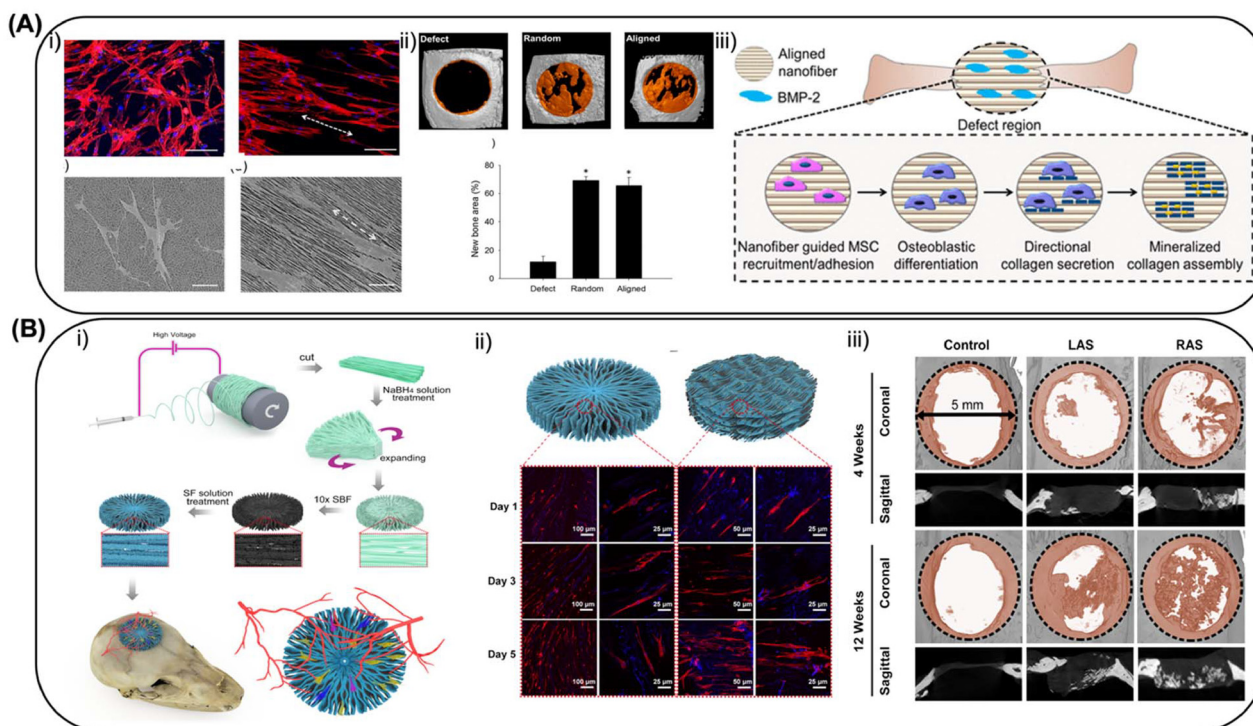


Fig. 4 Examples of aligned electrospun nanofibers used for bone regeneration. (A) Engineering bone tissue using PLLA-aligned nanofibers; (i) fluorescence and SEM images of hMSCs adhered to random and aligned nanofibers stained with F-actin (red) and nuclei (blue) after 24 h of culture (scale bars: 100 μm and 20 μm); (ii) micro-CT images and quantitative values of regenerated new bone area in skull bones implanted with random and aligned nanofibers two months after surgery; (iii) schematic of the mechanism of *in vivo* collagen assembly guided by the implanted aligned nanofibers.⁹⁶ Copyright 2015, American Chemical Society. (B) Engineering bone tissue using PCL-aligned nanofibers; (i) schematic showing the process used to fabricate the 3D radially aligned nanofiber scaffolds and their application for bone regeneration *in vivo* in a rat cranial defect model; (ii) BMSC proliferation and morphology on radially and laterally aligned scaffolds after 1, 3, and 5 days of culture; (iii) *in vivo* evaluation of radially and laterally aligned scaffolds in a critical-sized defect at 4 and 12 weeks.¹¹³ Copyright 2021, Elsevier. PLLA, poly(L-lactic acid); hMSC, human mesenchymal stem cells; SEM, scanning electron microscopy; PCL, polycaprolactone; BMSCs, bone marrow derived stem cells.

does not universally drive osteogenesis; its effect depends on the broader biochemical and mechanical context. Consistent with that view, the incorporation of nano-hydroxyapatite into PLLA generated electromechanical cues and improved cell adhesion, proliferation, and osteogenic differentiation.¹⁰⁸

Poly(lactic acid) (PLA) has also attracted significant research attention. Lopresti *et al.* incorporated both micrometric (μ) and nanometric (n) hydroxyapatite (HA) particles into aligned PLA electrospun scaffolds. *In vitro* studies showed the growth of pre-osteoblast cells on nHA-aligned PLA scaffolds.¹⁰⁹ To improve the cell affinity of PLA, Hwang *et al.* coated PLA fibers with tantalum, which demonstrated enhanced osteoconductivity in a rabbit calvarial defect model.¹¹⁰ Recognizing the potency of electrical cues in guiding cell extension, Shao *et al.* developed a conductive PLA/multiwalled carbon nanotube (MWCNT) scaffold, highlighting the synergistic impact of topographic and electrical signals on osteoblast growth.¹¹¹ For enhanced bone regeneration, Shakeri *et al.* developed a multi-layer guided bone regeneration (GBR) approach with PLA-infused simvastatin (SIM) complemented by a gelatin (GT) layer enriched with thymol (THY). Their novel GT/PLA nano-

fiber showed potential in preventing bacterial infection and releasing osteoinductive signals.¹¹²

Electrospinning for bone tissue engineering scaffolds is a promising avenue, but the 2D nature of the resulting scaffolds often produces dense nanofiber mats that hinder cell proliferation in 3D. A notable advancement was made by Xiao *et al.*, who fabricated 3D PCL scaffolds using gas foaming combined with biomineralization for bone regeneration in a cranial defect model (Fig. 4Bi). They applied a silk fibroin coating on the radially and laterally aligned scaffold, enhancing cell arrangement and proliferation (Fig. 4Bii). Additionally, *in vivo* results showed more newly formed bone tissue in the radially aligned scaffold (Fig. 4Biii).¹¹³

For enhanced bone regeneration after injury, vascularization is essential. Researchers have explored co-culturing mesenchymal stromal cells (MSCs) and endothelial cells (ECs) on scaffolds. For example, in one study, human umbilical vein ECs (HUVECs) and MSCs were cultured on PCL electrospun fibers to emphasize the role of HUVECs in osteogenesis.¹¹⁴ Reinwald *et al.* also examined how intermittent hydrostatic pressure affects bone marrow-derived MSCs (BMSCs), revealing

the impact of scaffold orientation on osteogenic markers.¹¹⁵ Likewise, BMSC significantly enhanced bone regeneration by directing stem cell behavior and activating the ITGB1/PI3K/AKT signaling pathway on the scaffold of ECM/PCL.¹¹⁶ Incorporating HA into PCL nanofibers enhances the osteoconductive properties of the scaffold. He *et al.* fabricated a composite PCL/HA nanofiber scaffold that promoted osteogenesis markers (OCN, Runx2, Osterix, Col1 and OPN) in osteoblast-like cells (MG63 cells).¹⁰⁴ Similarly, PCL/HA scaffolds have shown promise for osteodentin regeneration. In a study by Lim *et al.*, dental pulp-derived mesenchymal stem cells (DPSCs) cultured on aligned PCL/HA scaffold exhibited calcium deposition and upregulation of the osteogenic marker osteopontin (OPN).¹¹⁷ Another study found dentin regeneration on a PCL scaffold incorporated with BMP4 growth factor. The sustained release of BMP4 induced dentinogenic markers (DSPP, Runx2, BSP) and mineralization.¹¹⁸

Other biomaterials, such as cellulose and silk fibroin, are emerging as promising osteogenic scaffolds. For example, Zhang *et al.* demonstrated the potential of cellulose/cellulose nanocrystal nanocomposite nanofibers in bone regeneration, particularly when combined with BMP-2.¹¹⁹ Similarly, aligned nanofibers made from silk fibroin scaffolds enabled the orderly infiltration of MC3T3-E1 pre-osteoblasts while increasing alkaline phosphatase (ALP) activity to promote osteogenic differentiation.⁶⁴

3.2 Neuronal tissue engineering

Neuronal tissue engineering is a multidisciplinary field that aims to develop artificial neural tissue *in vitro* for research and therapeutic purposes. Conventional treatments for nerve damage, such as grafting, have significant limitations due to low donor availability and limited repair efficiency. The primary objective of neuronal tissue engineering is to replicate the complex structure and function of the nervous system, enabling the study of neural development, the modeling of neurological diseases, and potentially the restoration or repair of damaged neural tissue. One promising approach in advancing neuronal tissue engineering is the application of aligned nanofibers.^{97,120,121} Electrospun aligned nanofibers can have tunable mechanical properties, physical characteristics, and composition regulated through post-fabrication modifications. Neuronal alignment and electrical conductivity are crucial for optimizing neuronal tissue substrates. Aligned nanofibers promote neurite growth and guide their spatial orientation in an organized manner.^{98,122,123} Overall, aligned nanofibers are well suited for neural tissues with limited intrinsic repair capacity.

Biomimetic scaffolds created through electrospinning are being studied for their effectiveness in nerve tissue engineering. An aligned nanofiber scaffold developed using porcine decellularized spinal cord matrix (DSC) and gelatin induced MSC differentiation into neuronal cells.¹²⁴ In another study, PCL-based electrospun aligned fibers with varying concentrations of lignin nanoparticles supported the viability and adherence of both rat pheochromocytoma (PC12) and human

adipose-derived stem cells (hADSCs). The nanofiber scaffolds also displayed a smooth surface, and the water contact angle decreased with higher lignin concentration. Moreover, increased lignin content significantly stimulated axon growth of the neurons, while markers indicating cell differentiation were significantly upregulated. *In vivo* results in a rat model with sciatic nerve injury demonstrated that scaffolds with 15% lignin content significantly enhanced neuron regeneration.⁹⁷

PCL can be coated with a wide range of biopolymers to improve scaffold effectiveness. One strategy to promote neural repair is by providing stimuli for nerve regrowth. Zhang *et al.* developed a novel laser microdissection-based axotomy model to study the effect of miR-coated PCL-aligned fiber scaffolds on axonal regeneration. The presence of miR, specifically miR132, miR222, and miR431, played a significant role in protein synthesis. Delivery of miR to injured neurons significantly enhanced axonal regrowth. The axotomized dorsal root ganglia (DRG) showed significant axonal regrowth when cultured on the miR-coated fiber scaffold. Furthermore, the scaffold demonstrated longer neurite outgrowth post-recovery from sciatic nerve transection injury than untreated cells.¹²⁰

Nanofibers composed only of PCL face limitations, including slow degradation and limited intrinsic bioactivity. In a study by Chang *et al.*, in comparison to PCL, the poly(γ -benzyl-L-glutamate) (PBG) scaffold improved retinal ganglion cell survival, neurite extension, and optic nerve regeneration. It also encouraged neurite growth in RGCs *via* glutamate receptor signaling when combined with electrical stimulation.¹²⁵ Therefore, researchers have studied PCL combined with other polymers. Quan *et al.* developed a multi-step electrospinning process to fabricate nerve guide conduits using chitosan-incorporated PCL aligned nanofibers. Schwann cells, PC12 cells, and DRG were cultured on the fibers, and Schwann cell markers (S100) and neurofilament marker (NF200) were monitored for each cell type. Mechanical testing of the polymer showed that the aligned nanofiber had better compressive performance than randomly oriented fibers. *In vivo* experiments with a right sciatic nerve defect model in mice, treated with aligned nerve conduit, showed longer axonal extension from PC12 cells and DRGs. An upregulation of activating transcription factor 3 (ATF3), cleaved caspase 3, and enhanced recovery of distal nerves were observed.¹²¹ Another nerve conduit made from silk fibroin and hyaluronic acid demonstrated greater elasticity and mechanical strength than native nerve tissue. Human Schwann cells adhered and proliferated more effectively on the nanofibers while DRG neurons exhibited longer neurite extensions on them.¹²⁶

Stimulating the immune system through macrophages can help trigger the recovery of neural tissue. Jia *et al.* created aligned and random PLLA/PCL nanofibers to observe macrophage activity. The aligned scaffold encouraged macrophages to elongate along the fiber direction and produce a pro-healing macrophage phenotype (M2 type). *In vitro* results demonstrated that macrophages improved Schwann cell migration and proliferation. *In vivo* results using a rat sciatic nerve defect model showed a higher presence of pro-healing

macrophages in the group treated with aligned nanofibers. Additionally, the aligned group exhibited a 2-fold increase in Schwann cell infiltration and a 2.84-fold increase in axon numbers.¹²⁷

Maintaining the intrinsic functionality of neural networks is crucial for proper nerve cell interactions. Carbon nanotubes (CNTs) have gained attention for their surface nanotopography, which can mimic aspects of the ECM. Electrical stimulation can also significantly impact the potential of restoring nerve cell interactions. Incorporating CNTs into methacrylated gelatin (GelMA) hydrogel fibers enhanced the proliferation and adhesion of PC12 cells, further increased by electrical stimulation. This combination promoted neuronal differentiation and neurite sprouting in neural stem cells (NSCs) and improved remyelination and axonal regeneration in a T9 spinal cord injury rat model.¹²⁸ In studies conducted by Wang *et al.* and Hu *et al.*, CNTs were incorporated into nanofibers to achieve this goal. Wang *et al.* developed a core-shell scaffold

for peripheral nerve tissue engineering by using a dry-wet electrospinning method to collect aligned conductive nanofiber yarns (NFYs) encapsulated within hydrogel. NFYs contained inside hydrogel were photocrosslinked to create a stable 3D microenvironment mimicking the native tissue structure (Fig. 5Ai). The NFYs consisted of PCL, silk fibroin, and CNTs, which induced proper neuron alignment of PC12 and DRG cells. NFY with all three diameters (25, 50, and 100 μm) showed excellent cell viability (Fig. 5Aii). The aligned scaffold supported cell growth and elongation, closely resembling the original epineurium layer.¹²² In related research, laminin-functionalized NFY made from a blend of NIPAM, PCL, and MW-CNTs demonstrated improved neurite alignment and elongation in PC12 cells and DRG neurons while reducing excessive neurite branching.¹²⁹

Hu *et al.* used amine-functionalized MWCNTs to enhance the electrical conductivity of PCL/GT nanofibers without affecting their biocompatibility. These MWCNTs were incor-

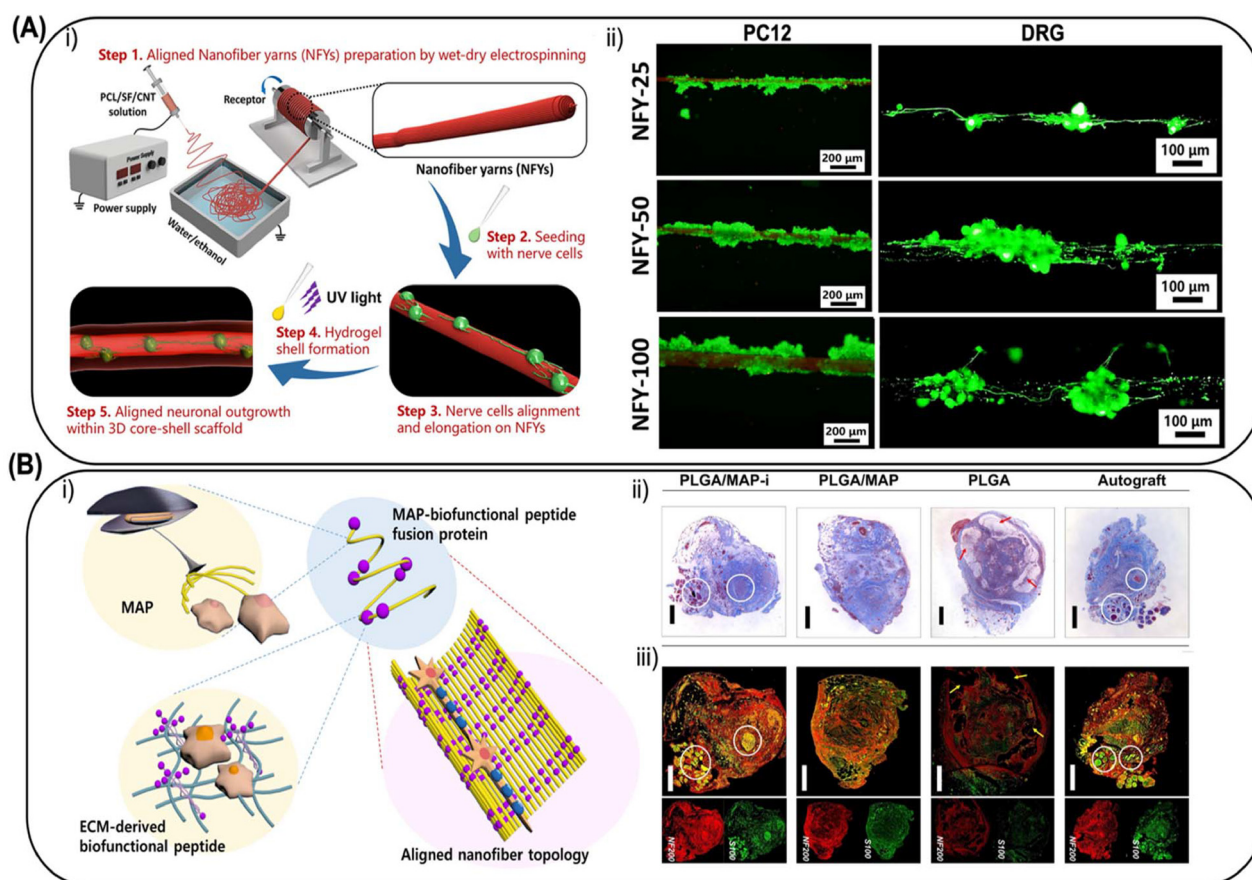


Fig. 5 Examples of aligned electrospun nanofibers used for neuronal regeneration. (A) Engineering neuronal tissue using PCL/silk fibroin aligned nanofiber; (i) scheme for preparing conductive nanofiber yarns and promoting neuronal outgrowth within 3D core-shell scaffolds; (ii) live/dead staining of PC12 and DRG cells cultured on aligned NFY-25, NFY-50, NFY-100 after 1 day of culture.¹²² Copyright 2019, Elsevier. (B) Engineering neuronal tissue designed by PLGA aligned nanofibers; (i) schematic representation of functional nerve regeneration on aligned nanofiber; histological analysis *in vivo* nerve regeneration (ii) using MT staining; and (iii) immunohistochemistry of the middle section of regenerated nerve tissues. The red stain indicates nerve cells, and the green stain indicates Schwann cells. Circles and arrows indicate endoneurium structures and voids, respectively. Scale bars: 250 μm .⁹⁸ Copyright 2019, Elsevier. NFY, nanofiber yarns; PCL, polycaprolactone; DRG, rat dorsal root ganglia. PLGA, poly (lactic-co-glycolic acid); MAP-I, a fusion protein of mussel adhesive proteins and IKVAV peptide.

porated into the nanofibers to create random and aligned conducting scaffolds. The aligned conducting nanofibers significantly improved the differentiation of BMSCs to Schwann cells, enhancing peripheral axonal regeneration in both *in vitro* and *in vivo* experiments.¹³⁰ In another study, Wang *et al.* used electrospun PLGA and MWCNTs to create a scaffold, which was then coated with poly-L-lysine. This composite scaffold had favorable electrical properties, thanks to the hydrophilic surface of the scaffold that enabled good cell attachment for PC12 cells. Additionally, DRG neurons were properly oriented along the fiber direction to promote neurite growth. When exposed to a 40 mV electrical stimulus, PC12 cells and DRG neurons showed longer neurites, higher proliferation, increased differentiation, and enhanced myelination.¹³¹ Among promising materials, PDA nanoparticles promote neuron stimulation and direct axonal growth. Antonova *et al.* found that PDA-coated nylon nanofibers enhanced neurite length and sped up neuron differentiation when exposed to NIR light.¹³²

A noteworthy characteristic of PLGA is its potential for drug delivery. Tang *et al.* utilized this feature to create a specialized biofunctional scaffold made of LysoGM1-functionalized PLGA, which has the added benefit of promoting neuron growth and brain tissue regeneration. The aligned scaffold acted as a guide for neurite outgrowth and facilitated the organization of the neural network. *In vitro* testing showed that the scaffold stimulated synapse formation while maintaining neuronal viability. Moreover, *in vivo* studies conducted on rats with traumatic brain injuries revealed significant recovery when implanted with the aligned PLGA-LysoGM1 scaffold, compared to the blank control. The addition of LysoGM1 to the scaffold resulted in positive outcomes, indicating that other PLGA derivatives may also have favorable results.¹²³

In another study, Cheong *et al.* incorporated mussel adhesive proteins-I (MAP-I), a bio-engineered fusion protein of MAP and IKVAV (a peptide derived from laminin $\alpha 1$ chain) into PLGA to induce nerve regeneration (Fig. 5Bi). They fabricated a scaffold using electrospun PLGA fused with MAP in an aligned orientation, which improved solubility and mechanical strength. *In vitro* studies using Schwann cells revealed better adhesion due to the integrin activity of ECM molecules, whereas treatment with PLGA/MAP-I in a rat sciatic nerve defect model showed rapid recovery and the formation of endoneurium structures and nerve fascicles (Fig. 5Bii). The PLGA/MAP-I treated condition showed more neural and Schwann cells in the regenerated nerve tissues, suggesting it can be an effective and versatile bio-inspired solution for nerve regeneration (Fig. 5Biii). The authors proposed that faster proliferation, quicker differentiation, and axonal growth could stimulate regeneration.⁹⁸

PLLA is a synthetic polymer particularly well suited for neuronal tissue engineering because of their strength, biocompatibility, and biodegradability. A study by Barroca *et al.* found that electrical polarization could be used to create a platform for neural tissue regeneration. *In vitro* studies using neuroblastoma cell cultures indicated that retinoic acid triggered neuro-

nal differentiation. Moreover, embryonic cortical neuron differentiation on poled-aligned nanofibers improved neurite outgrowth by 30% compared to seeding onto non-poled-aligned nanofibers.¹³³ Furthermore, Ziemba *et al.* improved the functionality of PLLA fibers by modifying their surface by coating PLLA fibers with silk fibroin (SF) through an immersion process in a coating solution. This method allowed the SF self-assemble within the solution, inducing beta sheet formation. *In vitro* tests showed that DRG cells were better able to attach to the SF-coated scaffold and exhibited longer neurite growth.¹³⁴

Aliphatic polyesters, such as PLLA, poly (3-hydroxybutyrate-co-3-hydroxyvalerate) (PHBV), and polyhydroxyalkanoate (PHA), are known for their biodegradability. In a study by Hu *et al.*, PHBV was electrospun in random and aligned orientations and used to culture adipose-derived mesenchymal stem cells (ADSCs) treated with fibroblast growth factor 2 (FGF2) and miR-218. The FGF-miR-218 treated stem cells, when implanted into 10 mm transected rat sciatic nerves, resulted in proper motor function restoration along the fiber-alignment direction, showing nerve damage recovery.¹³⁵ A study by Lizarraga-Valderrama *et al.* used a blend of poly(3-hydroxybutyrate) (P3HB) and poly(3-hydroxy octanoate) (P3HO) in a ratio of 25 : 75 to create polyhydroxyalkanoates (PHA). They fabricated electrospun nanofibers used as guiding lumen structures for nerve conduits. NG108-15 neuronal and RN22 Schwann cells showed that PHA blends nanofibers improved growth and assisted with neuron-aligned distribution. Additionally, a direct relationship was observed between fiber diameter and neuron growth. Co-culture of the two cell lines drastically increased neuronal growth.¹³⁶

Aromatic polymers can provide useful mechanical and electrical properties and high chemical stability. Among the polymers that have potential applications in neuronal regeneration, polyethersulfone (PES), polyurethane (PU), and polypyrrole (PPy) are noteworthy. Ghollasi *et al.* created a nerve regeneration scaffold using aligned laminin-immobilized PES and cultured human-induced pluripotent stem cells (hiPSC). They produced two types of fibers – random and aligned – using electrospinning, followed by O₂ plasma treatment for laminin binding. The functionalized scaffolds showed improved neuronal gene expression compared to the control group. Furthermore, in the aligned functionalized fibers, hiPSCs revealed neurite growth along the direction of the fibers. The aligned pure fiber exhibited increased expression of neuron-specific enolase, Tuj-1 (axonal marker), and microtubule-associated protein 2 (dendritic marker). Overall, the hydrophilicity and biocompatibility of functionalized aligned PES fibers demonstrated good adhesion, proliferation, and differentiation of hiPSCs into neurons.⁹² Shrestha and colleagues developed a hybrid material of PU, silk fibroin, and functionalized multi-walled carbon nanotubes (fMWCNTs) *via* electrospinning. The material was found to be hydrophilic and biocompatible, with significantly improved electrical conductivity due to the addition of fMWCNTs. *In vitro* experiments using Schwann cells and PC12 showed high proliferation and neurite out-

growth, respectively. The cells along the aligned fibers grew in an axis-aligned manner, which was not observed in the randomly oriented scaffold.⁹³ Elashnikov *et al.* also investigated another conducting polymer, PPy. In their study, they found that electrical stimulation from PPy induced nerve regeneration. The research group created nanofibers of PPy-coated cellulose acetate butyrate (PPy/CAB) with both uniaxial and random orientations. The scaffold's topography improved the wettability of the nanofibers. *In vitro* studies through culturing neuroblastoma cells onto the PPy/CAB nanofibers, which were stimulated by 100 mV mm⁻¹ at 1 Hz pulses, revealed that the uniaxially aligned and stimulated nanofibers had enhanced cell adhesion and neurite outgrowth.¹³⁷ In a similar study, aligned PCL nanofibers integrated with Fe₃O₄ and coated with PPy, were stimulated with a static external magnetic field. This stimulation increased calcium ion influx into Schwann cells, activating the CREB/BDNF signaling pathway. As a result, Schwann cells secreted more BDNF, which promoted nerve regeneration.¹³⁸

Natural polymers like chitosan and silk fibroin are excellent biomaterials that promote neuronal cell adhesion and proliferation. Multiple stimuli can be employed to initiate neural tissue engineering, which can be incorporated into a single scaffold for long-term release. Li *et al.* utilized silk fibroin fibers functionalized with laminin. *In vitro* evaluations based on culturing PC12 cells showed that this scaffold stimulated directional axonal extension and provided other signals for neurite outgrowth. The observed neurites were similar in length to native neurons, indicating a good use of silk fiber as a nerve graft.¹³⁹ In another study, silk fibroin was mixed with melanin to produce randomly oriented and aligned conducting composite scaffolds. *In vitro* culture of SH-SY5Y cells showed that they adhered properly and had good viability. The composite was highly antioxidant, removing free radicals. Additionally, the aligned polymer prompted the differentiation of neuroblastoma cells into neurons, guiding their proper orientation.¹⁴⁰ Furthermore, Rao *et al.*¹⁴¹ developed a hydrogel made of aligned chitosan fiber, created through liquid electrospinning and then manipulated using mechanical stretching processes. The hydrogel was then grafted with RGI (Ac-RGIDKRHWNSQGG) and KLT (Ac-KLTWQELYQLKYKGIGG) peptides. RGI is a brain-derived neurotrophic factor-mimetic peptide, whereas KLT mimics vascular endothelial growth factor (VEGF) activity. These bioactive peptides are essential in aiding nerve regeneration and angiogenesis, respectively. *In vitro* tests using Schwann cells showed cell reorientation and proliferation on the scaffold, resulting in increased production of neurotrophic factors. The hydrogel generated nerve regeneration and induced vascular penetration when injected into rat sciatic nerve defects. After 12 weeks, the rat model showed functional recovery at the injury site.¹⁴¹

3.3 Cardiac tissue engineering

Cardiac tissue engineering is a specialized field of regenerative medicine focused on developing functional and contractile cardiac tissue to repair or replace damaged or diseased heart

tissue caused by myocardial infarction (MI) or congenital heart defects. Adult cardiomyocytes (CMs), the specialized contractile cells of the heart, have limited proliferative capacity after injury. Therefore, the application of biomimetic substrates, such as aligned nanofiber scaffolds, holds great potential to help restore functional cells in cardiac tissue. The aligned fibrillar structure provides topographic signals for cell orientation in cardiac tissue, which has inherent anisotropic textures and functions.^{142,143} These scaffolds provide mechanical stability, biocompatibility, and a microenvironment for cellular communication.^{144,145} The constant movement of cardiac tissue and complex cellular networks is crucial for proper function.

Aligned nanofibrous scaffolds have gained attention in cardiac tissue engineering.^{99,146} Researchers have found that human-induced pluripotent stem cell-derived cardiomyocytes (hiPSC-CMs) resemble immature CMs in terms of morphology and function. Li *et al.* developed high-quality cardiac tissue-like constructs (CTLs) by seeding hiPSC-CMs onto aligned PLGA scaffolds (Fig. 6Ai). The nanofiber mat was fixed in a silicone frame for handling, and the cultured cells exhibited a highly organized, complex, and pronounced elongation *in vitro*. The cells expressed increased cardiac tissue-specific markers such as β -MHC on aligned fibers compared to flat surfaces. α -Actinin-positive sarcomeres and cardiac troponin T (cTnT)-positive myofilaments were also well-defined and positioned along the aligned fiber compared to random and flat surfaces (Fig. 6Aii). In an MI rat model, CTLs on damaged heart tissue showed positive results for repairing the tissue (Fig. 6Aiii). The hiPSC-CMs expressed human TnT in the heart tissue 14 days after transplantation.²³

Quantifying the contractile force of CMs or engineered heart tissues is needed to assess function. Electrospun scaffolds can be used to create beating myocardial constructs. In a study by Eom *et al.*, hiPSC-CMs exhibited functional multi-axial contraction on an aligned-random heterogeneous PCL nanofiber mat. The mat had distinct areas with either aligned or random orientation, allowing CMs to be guided in the correct orientation through directional cues by the aligned section. The random orientation of the mat supported stability. The thin nanofiber mat exhibited a contraction velocity about 20 times faster than the thick nanofiber mat and flat surface.¹⁴⁷ Similarly, in a study by Ding *et al.*, iPSC-derived cardiac progenitor cells (CPCs) exhibited contraction when placed on the aligned PCL nanofiber. The surface of the scaffold was designed to allow for cell adhesion and triggered cell differentiation into functional CMs by inhibiting Wnt and BMP signaling. After 14 days of treatment with an inhibitor, the cells displayed spontaneous contraction. The functionality of the CMs was confirmed through additional evaluations of cTnT expression and intracellular Ca²⁺ oscillation. The aligned scaffold provided an ideal microenvironment for the proper maturation of iPSC-CPCs, resulting in efficient contraction.¹⁴⁸ In addition, it was found that treating PCL fibers with oxygen plasma and sodium dodecyl sulfate solution improved the ability of hiPSC-CM cells to adhere to the surface. The cells

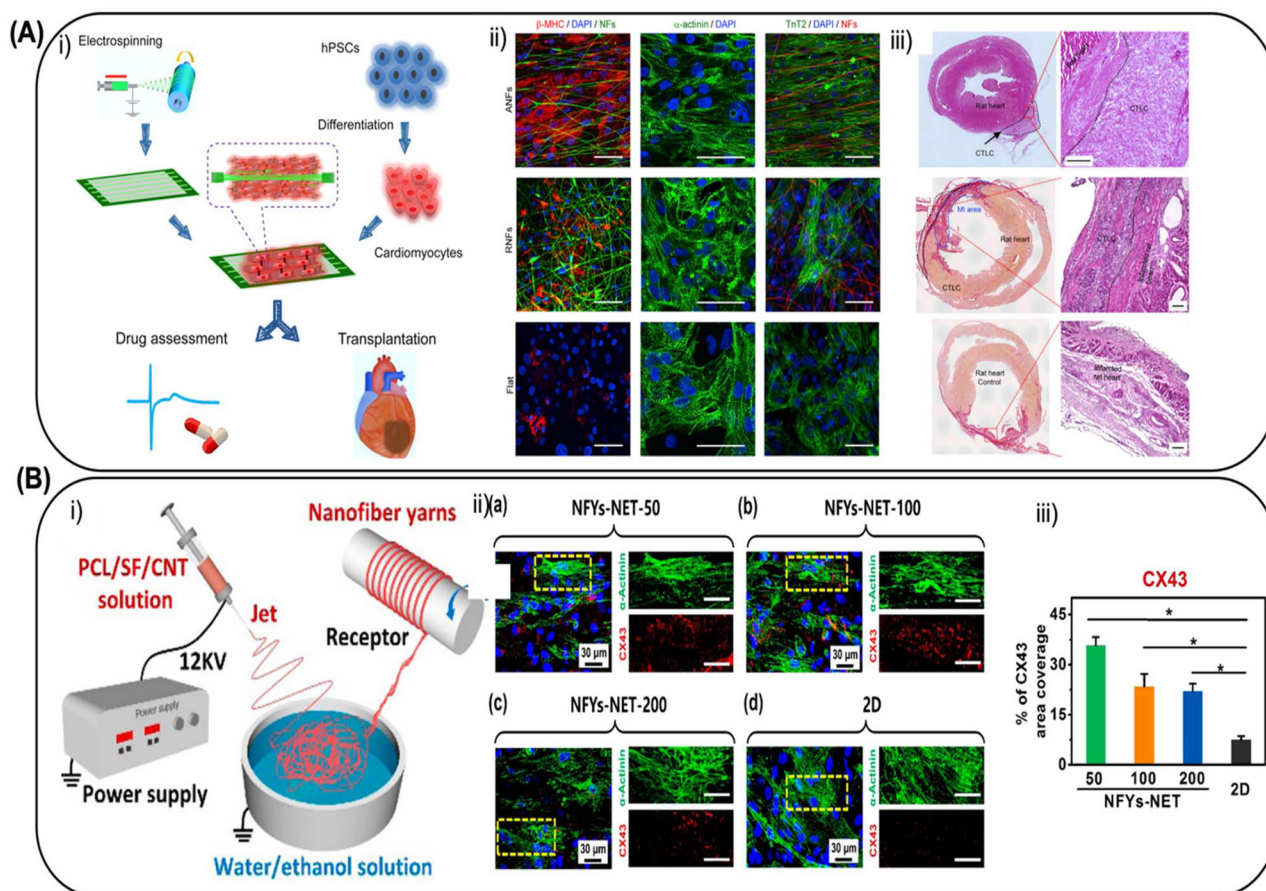


Fig. 6 Examples of aligned electrospun nanofibers used for cardiac regeneration. (A) Engineering cardiac tissue designed by PLGA-aligned nanofiber; (i) schematic illustrating the detailed experimental approach for cardiac tissue regeneration on aligned nanofibers; (ii) immunostaining images of β -MHC (red), α -actinin and cTnT (green). Cardiomyocytes were cultured on different substrates: aligned nanofibers (ANFs), random nanofibers (RNFs), and a gelatin-coated flat substrate (Flat). Nanofibers were fabricated with green or red dyes added before cell seeding. Scale bar, 50 μ m; (iii) histological sections of CTLCs after transplantation onto the rat heart without (a) or with myocardial infarction (b) and MI heart with acellular nanofiber (c).²³ Copyright 2017, Elsevier. (B) Engineering cardiac tissue designed using PCL/SF aligned nanofibers; (i) schematic diagram of the PCL/SF/CNT NFYS prepared using a developed wet–dry electrospinning technique; (ii) immunofluorescence staining of sarcomeric α -actinin (green), nuclei (blue), and CX43 (red) revealed phenotypic differences between cardiac tissues on NFYS-NET scaffolds (a–c) and the 2D control group (cultured for 8 days). The scale bar, 30 μ m; (iii) the relative percentage of area coverage by CX43 was quantified on NFYS-NET scaffolds and in the 2D group, respectively.⁹⁹ Copyright 2017, American Chemical Society. CTLC, cardiac tissue-like constructs; MI, myocardial infarction; PCL, polycaprolactone; SF, silk fibroin; CNT, carbon nanotube; NFYS-NET, conductive nanofiber yarns network.

also displayed a more elongated shape aligned with the direction of the fibers compared to cells grown on random fibers or a culture plate. Additionally, the scaffold enhanced sarcomere organization, spontaneous synchronous contraction, and the expression of mature genes in the CMs.¹⁴⁹

Achieving an anisotropic cardiac structure can be challenging. Wu *et al.* developed an aligned conductive nanofiber-yarn network (NFYS-NET) using a weaving technique. The scaffold is composed of PCL, silk fibroin, and CNTs encapsulated inside a GelMA hydrogel shell after photocrosslinking. The structure closely resembled the intricate interwoven nature of native cardiac tissue (Fig. 6Bi) and enabled CMs to elongate and align across each layer by regulating cellular orientation. Multiple cardiac markers were highly expressed, such as sarcomeric α -actinin and gap junction protein con-

nexin-43 (CX43) in 50 μ m diameter NFY (NFY-50) (Fig. 6Bii). Quantitative analysis also showed the highest percentage of CX43 area in the treated scaffold (Fig. 6Biii). This scaffold shows promise for 3D cardiac anisotropy therapeutics.⁹⁹

One strategy for repairing damaged heart tissue is to create patches that approximate the mechanical properties of the heart. These patches should be able to stretch, contract, and maintain their natural elasticity. Cesur *et al.* produced patches made of random PLA, PLA/PEG (polyethylene glycol), PLA/PEG/collagen, and aligned PLA/PEG/collagen. The aligned nanofiber patch had the highest tensile strength (5.90 ± 4.00 MPa) and degradation ratio compared to the random fiber. Furthermore, the human CMs (H9C2) grew uniformly and aligned with the aligned PLA/PEG/collagen fibers.¹⁵⁰ Cardiac patches can also be used as scaffolds to transfer stem cells or

differentiated cardiac cells to the heart tissue. A promising patch made of PLA/chitosan nanofiber was seeded with primary CMs for myocardial regeneration. An aligned scaffold made of PLA/chitosan nanofiber with an ideal ratio of 7:1 was found to have enhanced hydrophilicity and a small fiber diameter. The aligned fiber had better mechanical properties and promoted biocompatibility while stimulating the elongation of primary CMs. Additionally, it was found to stimulate the expression of sarcomeric alpha-actinin and contractile protein (troponin I).¹⁵¹

When engineering cardiac tissue, selecting appropriate biomaterials is a significant challenge. However, in recent years, polyurethane (PU)-based scaffolds have shown promise.^{143,152} A composite scaffold of PU, chitosan, and CNTs has shown potential for regenerating infarcted myocardium. The scaffold includes randomly oriented and aligned fibers replicating the ECM structure. PU provided structural stability, chitosan ensured biocompatibility, while CNTs added electrical conductivity. H9C2 cells were cultured onto the nanofibers, demonstrating excellent cell proliferation and viability on the aligned composite scaffold.¹⁴⁴ PU composites are widely used because of their tunable mechanical properties, favorable degradation rates, and general biocompatibility. Anisotropic PU and ethyl cellulose scaffolds with aligned nanofibers have demonstrated high mechanical strength, making them ideal for supporting contractile cardiac tissues. *In vitro* experimental results have shown that these scaffolds promote the proliferation and viability of cardiac myoblast H9C2 cells.¹⁵³

Chen *et al.* developed aligned and randomly oriented degradable polar/hydrophobic ionic polyurethane (D-PHI) and polycarbonate polyurethane (PCNU) composite scaffold. D-PHI, a material selected for its immunosuppressive activity, was used to deliver CMs into the tissue as a potential treatment for myocardium repair. After one week, combining hiPSC-derived CMs with the scaffold resulted in a similar level of cardiac troponin-T but a much higher level of ventricular myosin light chain-2 compared to the cells cultured on a tissue culture plate. Additionally, the cells on the aligned scaffold were beating synchronously, similar to those cultured in the control group.¹⁴⁵ Similarly, polyester urethane urea (PEUU) blended with gelatin scaffolds maintained shape during cyclic deformation, while CMs cultured on the aligned scaffold proliferated well due to its anisotropic characteristics.¹⁵⁴

3.4. Muscle tissue engineering

Muscle tissue engineering seeks to restore muscle tissue function for various purposes, such as regenerative medicine, drug testing, and disease modeling. One way to enhance muscle tissue engineering is by utilizing aligned nanofibers as scaffolds.^{155,156} Aligned nanofibers provide a biomimetic environment for muscle cells to mature, orient, and function in a manner similar to native muscle tissue. The alignment of the nanofibers mimics the complex organization of muscle fibers, promoting the formation of intricate muscle tissue constructs.¹⁵⁷ Aligned nanofiber scaffolds for muscle tissue regeneration can be made from various biocompatible materials,

including synthetic polymers (*e.g.*, polycaprolactone, poly(lactic-co-glycolic acid)) and natural polymers (*e.g.*, collagen, fibrin).^{100,158,159} Muscle cells, such as primary myoblasts or stem cells, can be induced to differentiate on these fibers.^{160–162} To induce muscle tissue formation, differentiation can be promoted by providing specific growth factors and culturing the cells under conditions that mimic the biochemical and mechanical cues of native muscle tissue.

Aligned PCL nanofiber scaffolds are commonly used for muscle tissue engineering as they trigger myotube formation and skeletal muscle morphogenesis.¹⁶³ However, their hydrophobic nature and low degradation rate negatively affect post-implant resorption. In a study by Simoncini *et al.*, aligned PVA fibers showed a higher fusion index than PCL fiber.¹⁶⁴ Therefore, PCL is often combined with other biopolymers in scaffold fabrication to improve biological properties.^{165–167} For example, Cai *et al.* blended PCL with collagen to enhance biocompatibility. The study demonstrated that Schwann cells promote myoblasts' myogenic differentiation when cocultured on aligned PCL-collagen I nanofibers. Myoblasts upregulated the myogenic markers such as myosin heavy chains 2 (MYH2) and MYOG (myogenin) after 28 days of culture in the presence of Schwann cells and adipose-derived mesenchymal stromal cells (ADSCs). This study highlights the interactions between Schwann cells and other cell types, potentially opening new avenues for tissue engineering and regenerative medicine applications.¹⁰⁰ A recent study found that when primary myoblasts and MSCs were co-cultured on a combination of PCL and collagen I in a serum-free environment, it resulted in the highest upregulation of myogenic markers. The nanofiber scaffolds provided a conducive environment for the growth and proliferation of both cell types under serum-free conditions. The upregulation of myogenin markers was 5.2-fold in ADSC/myoblast and 2.1-fold in BMSC/myoblast. Furthermore, the formation of multinucleated myotubes significantly enhanced myogenic differentiation. The use of serum-free conditions eliminates risks associated with animal-derived serum, making the nano scaffolds more suitable for therapeutic purposes in potential clinical translation.¹⁰¹

Witt *et al.*¹⁶⁰ found similar results when studying the co-culture of MSCs and myoblasts. The study involved using aligned electrospun PCL collagen-I nanofibers and adding hepatocyte growth factor (HGF) and insulin-like growth factor-1 (IGF-1) to differentiate myoblast cells into mature muscle cells. The combination of HGF and IGF-1 stimulation positively impacted the differentiation of both MSCs and myoblasts towards a myogenic lineage. By facilitating the expression of muscle-specific markers (desmin, myocyte enhancer factor 2, MYH2, and alpha-sarcomeric actinin), the growth factors aided in forming functional muscle fibers in the scaffold. The study concluded that providing the appropriate biochemical cues, HGF and IGF-1 enhanced the differentiation of MSCs and myoblasts into mature muscle cells, which was crucial for successfully generating functional muscle tissue *in vitro*.¹⁶⁰

The combination of PCL with decellularized muscle ECM led to improved tensile mechanical properties of the electro-

spun scaffold. Using an aligned nanofiber scaffold resulted in a significantly higher myosin heavy chain (MHC) to collagen ratio compared to untreated volumetric muscle loss (VML) injured models 28 days post-implantation. The group treated with the blend showed significantly higher upregulation of myogenic markers such as myogenic differentiation factor-1 (MyoD) and myogenin than the control group. The aligned structure of the nanofibers facilitated cell organization and supported the formation of new muscle tissue *in vivo*.¹⁵⁸ Another nanofiber blend of poly(L-lactide-co-caprolactone) (P(LLA-CL)) and collagen, prepared as nanoyarn with a topology similar to native collagenous fiber, showed promising results for stress urinary incontinence sling applications when cultured with placental stem cells (PSCs). The cells adhered well to the nanoyarns, exhibited good viability and proliferation, and the myoblast-nanoyarn resembled muscle tissue. The expression of myoblast markers such as α -SMA, desmin, and collagen types I and III was increased on the scaffold.¹⁶⁸

Likewise, a blended nanofiber yarn made of PCL, silk fibroin, and polyaniline was developed using a dry-wet electrospinning method. This yarn showed excellent biocompatibility, alignment, and elongation. Myoblasts enhanced MHC expression when cultured on nanofiber yarn/hydrogel core-shell scaffolds. Furthermore, the scaffolds maintained the mechanical properties needed for functional muscle tissue. The hydrogel shell creates a bioactive environment for nutritional exchange, facilitating myoblast differentiation into mature muscle cells.¹⁶⁹

Modifying nanofiber surfaces is an effective way to enhance cell behavior. In tissue engineering, the surface engineering of scaffold materials plays a crucial role since these properties determine cellular behaviors such as adhesion, proliferation, migration, and differentiation.^{170,171} In a study by Ku *et al.*, the surface of PCL nanofibers was modified with polydopamine (PDA), which resulted in improved behavior of skeletal myoblasts. The surface modifications with PDA exhibited a higher fusion index (27%) and maturation index (38.4%) than those without modifications, which showed 17.1% and 14.1%, respectively. The PDA-modified PCL nanofibers significantly increased MHC expression and myoblast fusion.¹⁶² The PCL fiber underwent surface modifications through PDA treatment, which was then combined with poly(3,4-ethylenedioxythiophene):poly(styrenesulfonate) (PEDOT:PSS) to create an electroconductive material. These matrices mimicked the structural and functional features of native muscle tissue, including their capacity to transmit electrical signals that were essential for muscle contraction. This supported a conducive environment for muscle cell adhesion, proliferation, and differentiation. Additionally, the matrices' electroconductive properties facilitated the transmission of electrical signals, which further promoted muscle cell alignment and maturation.¹⁷² Combining surface modifications with surface topography can significantly increase myoblast differentiation.

In a study by Zhang *et al.*, PCL nanofibers were coated with gold nanoparticles to enable electrical stimulation, enhance alignment, and promote the maturation of myotubes

(Fig. 7Ai). The spacing between microgrooves also significantly impacted the elongation and orientation of myotubes. When the microgrooves were spaced at 200 μm , defined by a gold nanolayer, H9c2 myoblast cells showed highly aligned behavior compared to the 300 μm size (Fig. 7Aii). Additionally, rolling the scaffolds allowed the nanofibers to resemble aligned microscale basal lamina by expressing MHC (Fig. 7Aiii).¹⁷³ The topographical cues provided by the scaffolds influenced cell alignment, elongation, and organization, which are important characteristics of mature muscle cells. Cha *et al.* found that micropatterned PEG hydrogels on PCL nanofibers produced distinct effects on myogenic differentiation. The mature myogenic marker MHC was expressed at a low level in the random pattern, while it was highly expressed in the aligned nanofiber.¹⁷⁴

Cell electrospinning (CE) offers several advantages, including micropatterned guidance, uniform cell distribution, and enhanced nutrient accessibility in 3D environments. CE enables cells to grow on micro/nanofibrous structures, which can significantly influence their behavior. In a study by Yeo *et al.*,¹⁷⁵ a micro/nano-hierarchical scaffold was combined with cell printing of myoblasts, leading to enhanced differentiation and alignment of the cells. They used a bioink composed of polyethylene oxide (PEO) and alginate on PCL struts containing myoblasts. When printed in an aligned pattern, this setup demonstrated rapid cell proliferation and differentiation. Compared to random and unpatterned scaffolds, the aligned scaffold exhibited a greater number and length of myotubes. After 20 days of culture, there was a significant upregulation of myogenic genes, such as MyoD, myogenin, and troponin T, in the aligned scaffold.¹⁷⁵

In a subsequent study, Yeo *et al.*¹⁷⁷ used a bioink containing C2C12 myoblast-laden alginate/PEO to electrospin an aligned nanofibrous bundle onto a PCL strut in an anisotropic manner. This setup promoted a highly organized and multinucleated morphology of myoblasts within the fibers. The cell-electrospun fibers exhibited higher levels of myogenic markers, including myosin heavy chain (MHC), and showed enhanced myotube formation and fusion compared to scaffolds lacking aligned micropatterns.¹⁷⁶ Additionally, the micropatterned PCL strut provided increased mechanical stability and induced myotube formation. The combination of alginate and PEO nanofibers facilitated the alignment of myoblasts. The scaffold's micro/nanoscale hierarchical topography promoted myogenic differentiation, with the highest MHC marker expression observed in alginate-electrospun PVA-leached PCL (patterned PCL strut) compared to non-patterned alternatives. The patterned strut also resulted in the longest myotubes ($225.3 \pm 51.4 \mu\text{m}$), attributed to synergistic topographical cues and efficient cell-to-cell interactions. Furthermore, the patterned strut significantly upregulated myogenic genes (MyoD, Myog, MHC, and TnT) after 28 days of culture. Notably, a collagen-coated strut displayed a comparable MHC maturation index and length to that of the PCL strut. This study underscores the potential of alginate/PCL scaffolds with nano/microscale topographical design to induce myoblast alignment and promote myogenic differentiation.¹⁷⁷

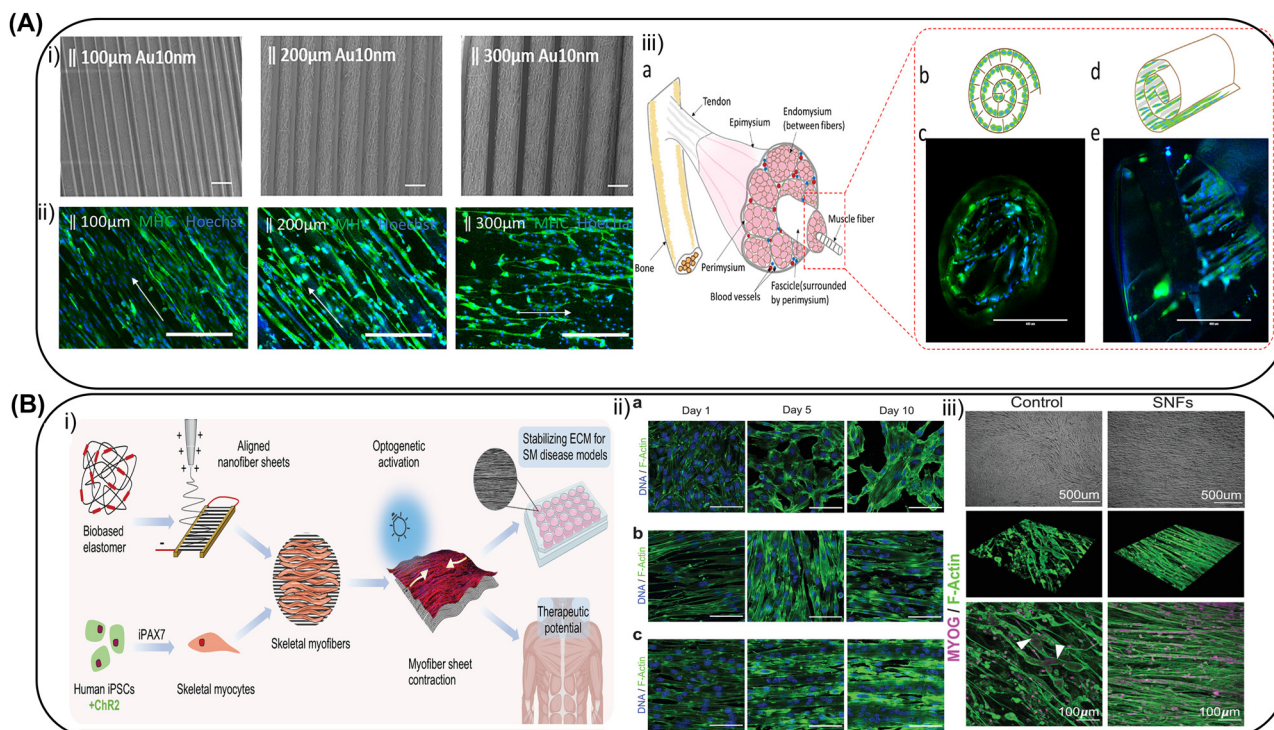


Fig. 7 Examples of aligned electrospun nanofibers used for muscle regeneration. (A) Engineering muscle tissue using PCL aligned nanofibers: (i) scanning electron microscope images of aligned nanofiber scaffolds with gold-coated microgrooves spaced at 100 μm , 200 μm , and 300 μm apart. Scale bar = 200 μm . (ii) cell alignment and myotube formation after 7 days of culture on scaffolds with spacing of 100 μm , 200 μm , and 300 μm . (iii) schematic representation and fluorescence images of skeletal muscle tissue from lateral (a) and cross-sectional (b) views after being cultured with H9c2 cells for 7 days. Myosin heavy chain (green) and Hoechst (blue) staining. Scale bars = 400 μm .¹⁷³ Copyright 2020, Elsevier. (B) Engineering muscle tissue using polyester-based PUU elastomer aligned nanofibers: (i) schematic of bio-based elastomer nanofibers guiding iPSC-derived differentiation of skeletal myofibers. Aligned nanofibers are created by applying an electrostatic field between two aluminum electrodes. Differentiation of ontogenetically controlled skeletal myocyte progenitors from iPSCs is achieved using iPax7 forward programming. (ii) morphology and differentiation of myotubes on elastomer nanofibers. C2C12 myoblasts stained for F-actin (green) and DNA (blue) grown on glass coverslips (control) (a), randomly oriented (b), and uniaxially aligned (c) P(EDS)UU-POSS electrospun nanofibers on days 1, 5, and 10. Scale bars = 100 μm .¹⁰² Copyright 2022, John Wiley and Sons. Abbreviations: iPSC, human induced pluripotent stem cell; P(EDS)UU-POSS, polyester-based PUU elastomer; EDS, ethylene-diethylene succinate; POSS, polyhedral oligomeric silsesquioxane; PUU, polyurethane-urea.

Nanofibers loaded with single cells provide benefits such as 3D accessibility to nutrients and effective cell-to-cell/matrix interactions; however, these interactions may take longer to establish. To address this limitation, Yeo *et al.*¹⁷⁸ developed spheroid-laden nanofibrous structures to achieve a high degree of alignment and differentiation of myoblasts. The spheroid-laden alginate/PEO nanofiber on the PCL strut effectively promoted myoblast alignment, leveraging the structural cues provided by the nanofibers to guide cellular organization. The aligned scaffold showed enhanced maturation and myotube formation, highlighting its potential for muscle tissue engineering.¹⁷⁸

Biomolecules incorporated into scaffolds can provide sustained delivery, optimizing their use for muscle tissue engineering applications. In a study by Moghadasi *et al.*, the myogenic differentiation of human mesenchymal stem cells (hMSCs) was investigated with a focus on surface topography and the controlled release of transforming growth factor-beta 1 (TGF- β 1). Their results indicated that hMSCs expressed smooth muscle cell markers at significantly higher levels when

cultured on polycaprolactone/poly(L-lactic acid) (PCL/PLLA) nanofibers coated with TGF- β 1-loaded chitosan nanoparticles, compared to a standard culture plate, after 15 days of culture. The sustained release of TGF- β 1 from the scaffold enhanced hMSC differentiation more effectively than a bolus delivery method. The mechanism behind TGF- β 1 release involved the degradation of chitosan and diffusion through the PCL nanopores, as explained by the authors.¹⁷⁹

Another innovative approach involved developing aligned nanofibers composed of RGD peptide-displaying M13 bacteriophage, poly(lactic-co-glycolic acid) (PLGA), and graphene oxide (GO) to promote myogenesis. The RGD peptide, recognized for its ability to promote cell adhesion, was displayed on the surface of the bacteriophage. The incorporation of GO provided electrical conductivity, which is known to enhance myogenic differentiation. The aligned nanofibers mimicked the natural alignment of muscle fibers, thereby further promoting myogenesis. The nanofiber sheets significantly upregulated the expression of myogenin and myosin heavy chain (MHC) genes, markers of muscle differentiation.¹⁵⁹

Cheesbrough *et al.* leveraged the hyperelastic properties of P(EDS)UU-POSS nanofibers to create nanofiber sheets with unique optical properties (Fig. 7Bi). These properties enabled precise control over the behavior of human-induced pluripotent stem cell (iPSC)-derived skeletal myofibers through the projection of blue light and inducible Pax7 (iPax7) (Fig. 7Bii). The nanofibers facilitated the organization of myofibers in a specific orientation, enhancing their contractile properties by over 200% and specific force by more than 280%. Additionally, they promoted an increase of approximately 32% in myotube fusion and around 50% in myofiber maturation (Fig. 7Biii).¹⁰²

Silk fibroin, a naturally elastic and hydrophilic polymer, is widely used in biomedical tissue engineering. Manchineella *et al.* developed a conductive fiber by combining silk fibroin with melanin. This fiber not only supported the growth of mouse myoblast C2C12 cells but also enhanced their differentiation into aligned, high-aspect-ratio myotubes compared to random films. Additionally, the scaffold demonstrated impressive antioxidant properties and effectively reduced intracellular reactive oxygen species (ROS) levels, further supporting a conducive environment for myogenesis.¹⁶¹

4. Three-dimensional (3D) aligned nanofibers for tissue regeneration

Traditional electrospinning methods typically produce two-dimensional (2D) nanofiber mats. However, advancements in electrospinning technology have facilitated the creation of three-dimensional (3D) electrospun nanofiber-based scaffolds, enabling the development of more complex 3D structures.^{180–186} These innovations have significantly enhanced the design and fabrication of nanofiber scaffolds for tissue regeneration.

5. Clinical applications of electrospun nanofibers

Numerous preclinical investigations have explored the use of electrospun fibers in tissue regeneration, as documented in several studies.^{94,95,97,110,113,127} However, to establish relevance for human applications, further clinical research is essential. While animal models provide valuable insights, they cannot fully capture the complexities of human physiology. Despite the availability of a few commercially developed electrospun nanofiber scaffolds, clinical evidence remains limited, highlighting the need for studies that establish safety, function, and durability.

It is important to distinguish between the clinical translation of electrospun nanofibers as a general platform and the clinical translation of aligned electrospun scaffolds specifically. Most registered clinical studies, as well as the marketed products discussed below, involve random or unspecified fiber architecture rather than deliberately aligned constructs. Available clinical evidence therefore supports the manufacturability and biocompatibility of electrospun materials more strongly than supports the clinical efficacy of alignment itself. This distinction should be explicit, because aligned scaffolds are expected to be most beneficial in tissues that require anisotropic guidance, yet they still face additional hurdles in large-area manufacturing, batch-to-batch control of alignment, sterilization without structural distortion, and long-term validation of anisotropic function *in vivo*.

The products currently on the market are best viewed as evidence of translational readiness for electrospun biomaterials rather than as direct precedents for aligned nanofiber scaffolds. Representative examples include AVflo, NovaMesh, Bioweb, HealSmart, ReBOSSIS, and SurgiCLOT.^{187–192} Likewise, the clinical studies summarized in Table 3 mainly demonstrate clinical interest in nanofiber-based materials, but they do not yet establish a mature clinical pipeline for aligned electrospun scaffolds.

Table 3 Clinical studies involving electrospun nanofiber-based materials relevant to tissue engineering

Clinical Trials. gov identifier	Study title	Intervention/treatment	Condition/disease	Sponsors	Ref.
NCT04325789	Rotator Cuff healing using a nanofiber scaffold in patients greater than 55 Years	Device: nanofiber scaffold	Rotator Cuff tears	Atreon orthopedics	193
NCT03690960	Antimicrobial effect of modified antibiotic nanofibers for regenerative endodontics procedures	Procedure: electrospun TAP nanofibers Procedure: modified TAP paste	Necrosis, pulp	Cairo University	194
NCT03242291	Evaluation of marginal integrity of hydroxyapatite nano-fiber reinforced flowable composite <i>versus</i> conventional resin-based flowable composite in initially demineralized pits and fissure: a one year, randomized clinical trial	Other: conventional resin-based flowable composite Other: hydroxyapatite nanofiber reinforced flowable composite	Marginal integrity of hydroxyapatite nanofiber reinforced flowable composite	Cairo University	195
NCT03264105	Retention Rate of hydroxyapatite nano-fiber reinforced flowable composite <i>versus</i> conventional	Other: hydroxyapatite nanofiber reinforced flowable composite Other: conventional resin-based flowable composite	Retention rate of flowable composite in demineralized pits and fissure	Cairo University	196

6. Conclusion and perspectives

This review has discussed biomedical applications of aligned nanofibers for regenerating bone, neural, cardiac, and muscle tissues. In bone regeneration, aligned nanofibers can reproduce aspects of the hierarchical architecture of natural bone. For neural tissue regeneration, they provide crucial guidance cues for nerve regeneration, including directional axon growth. In cardiac tissue engineering, aligned nanofibers mimic the myocardium's anisotropic structure, guiding cardiac cell orientation and supporting functional tissue regeneration. Incorporating conductive materials further enhances electrical conductivity, important for electrical signaling in cardiac tissues. Additionally, elements promoting angiogenesis can be integrated to improve tissue vascularization. In muscle tissue regeneration, the anisotropic structure and mechanical strength of aligned nanofibers promote muscle cell growth and the formation of aligned myotubes and muscle fibers.

Despite their potential, aligned nanofibers still face challenges that are specific to anisotropic scaffold design. The first is quantitative control: alignment is often described qualitatively, while metrics such as angular dispersion, spatial uniformity, and batch-to-batch reproducibility are not standardized. The second is the trade-off between alignment and pore architecture. Methods that improve fiber registration often also increase packing density, which limits cell infiltration, vascular ingrowth, and scaffold thickness. The third challenge is scale. Many alignment methods work well over small areas or short collection distances but become less reliable when extended to clinically relevant dimensions, curved geometries, or tubular constructs. Finally, the biological value of alignment is tissue-dependent. In some settings, alignment improves matrix organization, electrical conduction, or guided extension more consistently than it improves new tissue volume, and this distinction should be evaluated explicitly in future studies.

Future work should therefore move in four directions. First, fabrication protocols should report standardized alignment and pore metrics together with mechanical and degradation data. Second, scaffold design should aim to decouple orientation from porosity, for example by combining aligned electrospinning with sacrificial elements, patterned collectors, or multiscale assembly strategies. Third, alignment should be integrated with secondary cues that are spatially coordinated, such as electrical conductivity, ligand patterning, or controlled factor release, rather than added independently. Fourth, preclinical studies should test whether alignment produces durable functional advantages, not just early histological organization, in tissues with clear anisotropic demands such as peripheral nerve, myocardium, tendon-to-bone interfaces, and skeletal muscle. Advances along these lines, especially when combined with additive manufacturing and 3D culture models, are likely to define the next stage of aligned nanofiber-based tissue engineering.

Conflicts of interest

There are no conflicts to declare.

Data availability

No primary research data, software or code are associated with this article. This is a review article and no new datasets were generated or analyzed. All data supporting the conclusions of this work are available within the published articles cited in the reference list.

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