ACS Biomaterials SCIENCE & ENGINEERING

pubs.acs.org/journal/abseba

Review

Recent Advances in Designing Fibrous Biomaterials for the Domain of Biomedical, Clinical, and Environmental Applications

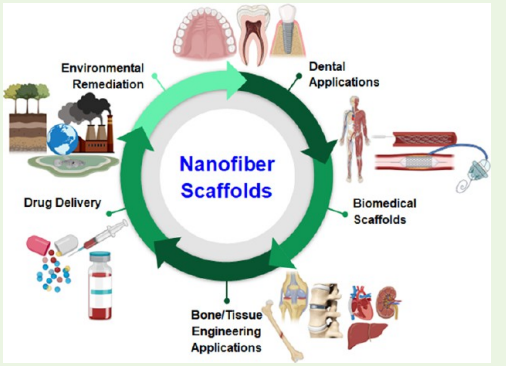
Narsimha Mamidi,* Rubén Gutiérrez García, José Daniel Hernández Martínez, Camila Martínez Briones, Andrea Michelle Martínez Ramos, María Fernanda Leal Tamez, Braulio González Del Valle, and Francisco Javier Macias Segura

Cite This: *ACS Biomater. Sci. Eng.* 2022, 8, 3690−3716

Read Online

ACCESS | Metrics & More | Article Recommendations

ABSTRACT: Unique properties and potential applications of nanofibers have emerged as innovative approaches and opportunities in the biomedical, healthcare, environmental, and biosensor fields. Electrospinning and centrifugal spinning strategies have gained considerable attention among all kinds of strategies to produce nanofibers. These techniques produce nanofibers with high porosity and surface area, adequate pore architecture, and diverse chemical compositions. The extraordinary characteristics of nanofibers have unveiled new gates in nanomedicine to establish innovative fiber-based formulations for biomedical use, healthcare, and a wide range of other applications. The present review aims to provide a comprehensive overview of nanofibers and their broad range of applications, including drug delivery, biomedical scaffolds, tissue/bone-tissue engineering, dental applications, and environmental remediation in a single place. The review begins with a brief introduction followed by potential applications of nanofibers. Finally, the future perspectives and current challenges of nanofibers are demonstrated. This review will help researchers to engineer more efficient multifunctional nanofibers with improved characteristics for their effective use in broad areas. We strongly believe this review is a reader's delight and will help in dealing with the fundamental principles and applications of nanofiber-based scaffolds. This review will assist students and a broad range of scientific communities to understand the significance of nanofibers in several domains of nanotechnology, nanomedicine, biotechnology, and environmental remediation, which will set a benchmark for further research.



KEYWORDS: *nanofiber scaffolds, spinning techniques, biomedical scaffolds, environmental remediation, drug delivery, tissue engineering*

1. INTRODUCTION

Nanofibers are emerging one-dimensional nanomaterials for a broad range of research fields and commercial applications thanks to their exceptional physicochemical characteristics and architecture. Nanofibers are small-scale strands of materials that usually have a diameter from tens to hundreds of nanometers. Nanofibers have an exceedingly high surface area and a high surface-to-volume ratio.[1] They can form networks of highly porous fiber mesh with incredible interconnectivity among their pores, making them an enticing choice for a host of superior applications. Yet, the size and length of the nanofiber depend on the application or function that it performs. Due to their high similarity with the extracellular matrix (ECM), nanofibers are applied in various fields, such as nanomedicine, biosensing, tissue engineering, drug delivery, and others.[2] Nanofibers have unique properties, making them ideal for a wide range of advanced applications.[3] Currently, synthetic fibers have gained higher demand than natural fibers because of the easy manipulation of their structure.[4] Nanofibers are capable of producing ideal advantages, including high encapsulation efficiency, controllable morphology, and high chemical and thermal stability. The properties of nanofibers could be significantly influenced by the polymeric raw material.[5] Thus, numerous polymers have been utilized to produce nanofibers. For instance, cellulose nanofibers (CNF) are promising reinforcement fillers for polymer, owing to their unique properties of low thermal expansion, high aspect ratio, low density, high stiffness, low cost, and biodegradability.[6] The different types of nanofibers can be classified according to the technology implemented for their synthesis, materials or types of polymers used, as well as their various applications. Natural polymers offer multiple advantages, such as being similar or

Received: July 11, 2022
Accepted: August 22, 2022
Published: August 29, 2022

https://doi.org/10.1021/acsbiomaterials.2c00786
ACS Biomater. Sci. Eng. 2022, 8, 3690−3716

identical to macromolecular substances present in the human body. With this, the biological environment can recognize and interact with natural polymers more efficiently. Collagen nanofibers show compatibility with some types of cells in the organism. Chitosan (CS) nanofibers show a significant potential for scaffolds in tissue engineering. In addition, synthetic polymers show the largest class of bioactive materials. Poly(ethylene-*co*-vinyl acetate) nanofibers are used to control drug delivery. Carbon and alumina nanofibers are used in dental and orthopedic implants.[7] Nanofibers can be produced by different techniques such as electrospinning, blow spinning, centrifugal spinning, and microfluidic spinning techniques. Among them, electrospinning technology is the most common approach. This technique has the advantage of being cost-effective, straightforward, and can be operated at room temperature.[8] However, this technique has some limits such as it requires specialized equipment and high voltage, as well as presenting a low deposition rate.[9] Another method is the solution blow spinning technique. This method uses a simple apparatus and a concentrated polymer solution in a volatile solvent. However, it has limits in producing the desired fiber diameter.[9] A third approach is centrifugal spinning, which utilizes centrifugal forces to produce nanofibers. Both the diameter and morphology of the nanofibers can be adjusted by controlling the viscoelasticity and rotation speed of the fluid.[10−12] One last current technique is microfluidic spinning, where two different fluids are injected into microscale channels to form a three-dimensional (3D) coaxial flow at the intersection.[10] The ability to use different approaches to fabricate nanofibers has helped researchers find different applications of these fibers in the biomedical field, tissue and bone-tissue engineering, drug delivery, and the ongoing COVID-19 pandemic.

Furthermore, nanofibers can be classified according to their structure and geometries in many ways, and they can be nonporous, mesoporous, hollow, core−shell, nonwoven, and yarn-like, among many other variations. This structural diversity depends largely on the type of precursor material utilized, along with the synthesis methodology being followed. Moreover, the final form of the nanofibers that are used largely depends on the application being sought.[13] Nanofibers can be dispersed in solution or can be used directly as free-standing meshes. In the field of biomedicine and tissue engineering, for example, nanofibrous scaffolds are ubiquitous in applications concerning tissue regeneration, as they can provide adequate conditions to promote cell adhesion and proliferation. In this review, several types of nanofiber geometries are mentioned, where nanofiber meshes in the form of scaffolds are the most commonly used.[14]

Nanofibers have different applications depending on their properties. For instance, there is a wide variety of applications in environmental remediation. Nanofibers have been used for the removal of carcinogenic chemicals released by the textile industry in water streams and soil, such as formaldehyde or heavy metal ions.[15,16] Nanofibers can act as filters for either oil spill management or waste handling. Furthermore, methylene blue is a toxic colorant that can be degraded due to the photocatalytic properties of nanofibers.[17] Outstanding characteristics of electrospun nanofibers, including high surface area, cost-effectiveness, porosity, and flexibility, make them a good choice for sensor applications. Thus, the combination of electrospun nanofibers and the incorporation of functional nanomaterials can provide an efficient platform for developing technologies such as a potential glucose sensor.[18] Nanofibers have recently been known for their great potential in the medical field. The use of nanofibers for drug delivery has increased rapidly due to their favorable properties, such as high porosity, small pore size, superior mechanical properties, and ease of surface modification. For drug delivery systems, the application consists of drug-loaded nanofiber membranes that can be prepared via electrospinning using a model drug and polymer solution. The release of the drug from the nanofiber membrane in a safe and controlled way is challenging because of the initial burst release. Employing a core−sheath design provides a promising solution for controlling the initial burst release.[19] Dentistry is another medical application of nanofibers. Nanofibers are being used for dental tissue engineering.

Tissue engineering aims to fabricate functional biomaterials for the mend and regeneration of defective tissue, in addition to the structural simulation for accelerating the repair process and achieving a high-quality regeneration.[20] This is achieved by mimicking the ECM with nanofiber scaffolds.[21] The nanofibers should be fabricated with materials that allow them to function as normal tissue, inhibiting bacterial growth, and promoting angiogenesis and cell proliferation.[22] Among the various nanomaterials, self-assembled peptide nanofibers have gained considerable attention thanks to their widespread application in biology, tissue engineering, drug delivery, biosensors, and regenerative nanomedicine.[23−29] Self-assembled peptide-based nanomaterial scaffolds were mainly made from three major categories of peptides including α-helical, β-sheet, and collagen-mimetic peptides.[23,24] A great number of advances have been reported in the area of self-assembled peptide nanofibers for regenerative nanomedicine.

Such advances explored the rational design, synthesis, and characterization of different peptide nanofibers for a wide range of applications. Among all nanomaterials considered for self-assembly functions, peptide nanofibers have attracted great attention as structure units for bottom-up manufacture, thanks to their versatility, ease of fabrication, tunable structures, low costs, and versatile attributes. Besides, self-assembled peptides form well-ordered supramolecular structures and possess many advantages including good mechanical and thermal stability, piezoelectricity, semiconductivity, and optical properties compared with individual peptides. Due to the dynamic nature of electrostatic interaction, self-assembled peptides can readily respond to multifarious external stimuli. So that self-assembled peptides recreate aspects of the dynamics present in living organisms. Self-assembly can be controlled by stimuli conditions such as chemical cues (i.e., ionic strength, pH, redox agent, competitive guest−host interfaces), physical cues (i.e., light, temperature, voltage, and magnetic field), and biological cues (i.e., proteins, and enzymes).[30−32] Such stimuli sensitivity can leverage to develop supramolecular peptide-based nanomaterials that allow the variation of characteristics in real-time in response to external stimuli, so ultimately producing smarter therapeutics. Thus, the formation of nanostructures by this self-assembly process is affected by stimuli conditions. For instance, the desired peptide nanostructures can be obtained by adjusting appropriate conditions.

Surfaces of some inorganic, organic, and biological materials are usually used as substrates to guide the self-assembly of peptide molecules to form well-ordered nanostructures such as nanofibers, nanowires, nanotubes, films, and networks.[33] This review demonstrates the current status and future evolution of nanofibers, with an emphasis on their production and

https://doi.org/10.1021/acsbiomaterials.2c00786
ACS Biomater. Sci. Eng. 2022, 8, 3690−3716

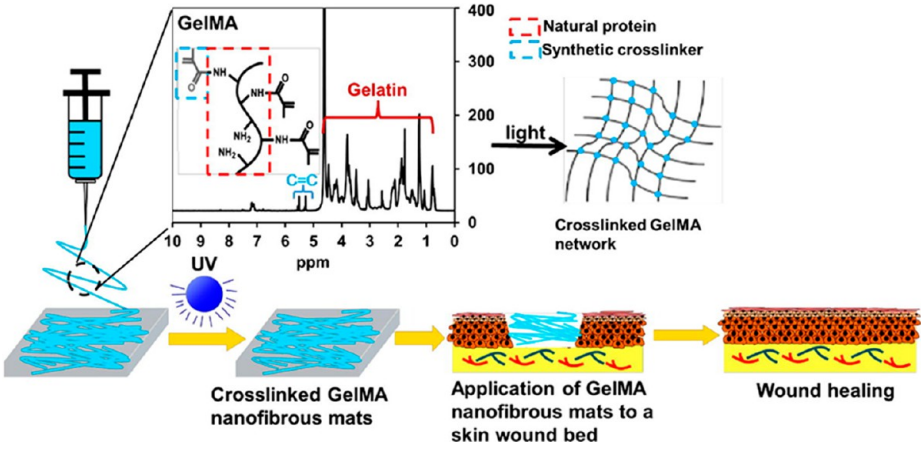


Figure 1. Schematics for the fabrication of GelMA nanofibrous mat and its subsequent application into a wound bed. The photo cross-linkable GelMA prepolymer was electrospun onto an aluminum plate and subsequently UV light-cross-linked to obtain nanofibrous mats which were applied to wound beds to promote skin regeneration. The integrated box displays the nuclear magnetic spectrum of synthesized GelMA. The gelatin component (red dashed box) was modified to contain methacryloyl groups (blue dashed box) which formed cross-linked GelMA networks upon light exposure. Reproduced with permission from ref 39. Copyright 2017 Elsevier.

applications. First, more relevant and recent developments related to the applications of nanofibers have been exhibited. Then, perspectives on the new directions, opportunities, and challenges for the future development of nanofibers are discussed. Specifically, six important areas of drug delivery, tissue and bone-tissue engineering, biomedical scaffolds, dental application, and environmental remediation were demonstrated. Despite all the developments, there are still some challenging tasks to be resolved and overcome for nanofibers to move toward evolution. In the end, we explain methods to scale up the production of nanofibers and briefly explain several types of nanofibers-based commercial products that have found widespread use in daily life.

2. NANOFIBER SCAFFOLDS FOR BIOMEDICAL APPLICATIONS

Some of the main biomedical applications of nanofibers include biosensors, contact lenses, drug delivery, and treatment implants. To achieve successful applications, it is important to consider some characteristics such as high tensile strength, elastic modulus, low density, toxicity, biocompatibility, and tunability. The most common materials for creating polymer nanofibers are hydrogel, cellulose, methacrylated gelatin (GelMA), peptides, etc.[34,35] Nanofiber scaffolds allow interactions with bodily tissues, which can offer regenerative treatments. This is especially useful. The skin is the largest organ of the human body, which acts as a barrier with immunologic, protective, and sensorial functions. Its exposure to the external environment results in several different types of injury and damage, along with the loss of variable volumes of ECM. Nanofiber scaffolds offer a viable, permanent, and effective alternative to tackle the drawbacks of skin regeneration and repair by combining cells, growth factors, and biomaterials. Nanofibers imitate ECM and use cells to help regeneration, and they can also mimic the environment under the skin. In some cases, stem cells are targeted by these scaffolds to enhance the healing process. They improve the efficiency of cells to form a natural matrix around the wound.[36] Jiang and co-workers developed 3D nanofiber scaffolds with controlled porosity and thickness using subcritical CO_2 fluid. The nanofiber scaffolds preserved the antibacterial activity of loaded antimicrobial peptide LL-37 and the fluorescent intensity of embedded coumarin 6. The 3D scaffolds have significantly improved infiltration and neotissue construction after intravenous grafting. In addition, improved blood vessel formation and the ratio of M2/M1 macrophages have been observed after intravenous implantation over 2 and 4 weeks.[37] Tetracycline hydrochloride (TCH) incorporated zein/gum tragacanth/PLA (zein/GT/PLA) nanofibers were fabricated for wound healing and anti-inflammatory applications. The TCH-embedded zein/GT/PLA/TCH nanofibers showed improved mechanical, morphological, and antibacterial properties, as well as improved cell viability. They also demonstrated antibacterial properties and degradability for tissue repair. Additionally, they encouraged cell growth, proliferation, and adhesion. Due to their biocompatibility, low degradability, and strength, these could be used for many biomedical applications.[38] In another study, natural, protein-based 3D fibrous scaffolds with favorable physicochemical properties were used for wound healing. For instance, photo cross-linkable methacrylated gelatin (GelMA) 3D fibrous scaffolds were fabricated, and their biophysical properties were investigated. The GelMA scaffolds exhibited improved stiffness, water retention, strength, degradation, cell adhesion, migration, and proliferation. Overall, the GelMA scaffolds can be used for the reconstruction of wound defects or in vitro skin reconstruction (Figure 1).[39]

Moreover, the biomedical applications of nanofibers can extend beyond the skin into other tissues. For example, Chen and co-workers developed electrospun gelatin/PLA nanofiber-based porous 3D scaffolds (3DS-1) for cartilage tissue regeneration. Furthermore, hyaluronic acid (HA) cross-linked modified scaffolds (3DS-2) were also primed to further improve cartilage regeneration. The fibrous scaffolds exhibited elastic and superabsorbent properties in the wet state. Both 3DS-1 and 3DS-2 fibrous scaffolds showed enhanced cytocompatibility against chondrocytes. Furthermore, the scaffolds were implanted in rabbits under an articular cartilage injury model to investigate cartilage regeneration.

The in vivo results demonstrated that the 3DS-2 would be a promising material for cartilage tissue repair.[40] Thermoplastic polyurethane (PU) nanofibers were fabricated by using a

https://doi.org/10.1021/acsbiomaterials.2c00786
ACS Biomater. Sci. Eng. 2022, 8, 3690−3716

trichloromethane (TCM)/2,2,2-trifluoroethanol (TFE) solvent system. This new solvent system showed improved properties, including high viscosity and better conductivity. The fiber elongation was improved while still having flexibility. There was high cytocompatibility, which makes PU nanofibers nontoxic for biomedical applications.[41] Biomedical applications of nanofibers including drug delivery, tissue engineering, bone-tissue engineering, dental application, and clinical trials of fibers-based scaffolds are discussed in the following sections.

2.1. Nanofibers for Drug Delivery. Among the various potential biomedical applications, drug delivery is one of the promising applications. The high encapsulation efficiency, high loading capacity, sustained and controlled delivery, ease of operation, instantaneous delivery of diverse remedies, and cost-effectiveness are enticing features in drug delivery. An ideal drug delivery system should carry adequate drug molecules and preserve the payload until it reaches the targeted site. Besides, a drug delivery system should have biocompatibility and biosafety. A variety of controlled delivery systems are utilized to improve the therapeutic efficiency and protection of drugs by delivering them in a controlled fashion to site action. Among the various drug delivery systems, nanofibers are the most potent vehicles for drug delivery applications. Electrospinning is the most used strategy to produce nanofibers, which yields highly porous nanofiber meshes with a large surface-to-volume ratio. Perhaps, the greatest challenge for nanofibrous meshes for drug delivery is the specificity needed in the design of each system, which leads to great obstacles when attempting to produce them at an industrial scale. Therefore, there is a great need for the study of different spinnable polymers and their interactions with individual drug molecules to achieve the desired properties of the drug delivery system.[42] Therefore, the ability of nanofibers as drug delivery systems is explored in this subsection.

Nanofibers are widely used in the pharmaceutical field and are being paid attention to due to their advantages for drug delivery depending on critical process parameters and critical material attributes for electrospinning and polymer materials, respectively.[6−8]

Sofi and co-workers reported a series of nanofibers from synthetic and natural polymers and discussed how they can be applied in different fields like drug delivery and others.[11] Ibuprofen (IBU) incorporated cellulose micro/nanofibers (CMF) were produced by electrospinning under an ionic liquid (1-butyl-3- methylimidazolium chloride). The CMF fibers exhibited improved physicochemical properties and cell viability. The drug release measurements revealed a controlled and prolonged IBU was released from the nanofibers in acetate buffer (pH 5.5).[1] Similarly, fluconazole-loaded poly(vinyl alcohol) (PVA) based electrospun fibers were manufactured to suppress side effects of the fungus *Candida albicans*, which arise from the treatment of chronic candidiasis. Moreover, these electrospun fibers showed potential to be used in the medical textile industry.[2] Nanobioactive glass (BG)/PVA/CS nanocomposite fibers were fabricated by electrospinning. Risedronate sodium was incorporated as a model drug into the BG/PVA/CS fibers and drug release was measured. The drug release results revealed sustained drug release over 96 h and followed a diffusion mechanism.[3] Akpan and co-workers developed poly(D, L-lactic-*co*-glycolic acid) (PLGA)/pluronic F127/GL/prodigiosin (PG) nanofibers for controlled drug delivery. The obtained nanofibers displayed prolonged drug delivery. In addition, the fibers exhibited improved cell viability against breast cancer cell lines. Therefore, this encourages the localizing and delivery of triple-negative breast cancer drugs in three stages. The drug release can be controlled by doses and release rates. Due to the surfactant (pluronic F127), the drug loading ability of nanofibers was increased, and the initial burst drug release was controlled.[43] In another study, different drug molecules loaded within gelatin nanofibers showed controlled drug delivery, improved cell viability, and antibacterial properties against *Staphylococcus aureus* and *Klebsiella pneumoniae*.[15,16] Kamble and co-workers reported the evolution of drug delivery through the skin. Biocompatible cellulose acetate (CA)-based nanofibers have been also used for biomedical applications. However, CA could not be degraded in the human body due to the lack of cellulase enzymes, so the biodegradation of CA nanofibers has become an issue.[19] Bhandari and co-workers developed CNF aerogels as innovative delivery vehicles for oral drug delivery. Bendamustine hydrochloride was selected as a model drug and controlled drug release was observed under physiological conditions.[22]

In addition, various polymers and their combinations have been used in drug delivery. For instance, hydrophilic or hydrophobic polymers were loaded with several hydrophobic and hydrophilic drug molecules and their release performances were investigated. For this, coaxial electrospinning has been developed, and throughout the years, major advances have occurred which have led to various configurations of multiaxial fibers for drug delivery (Figure 2).[4] In wound care,

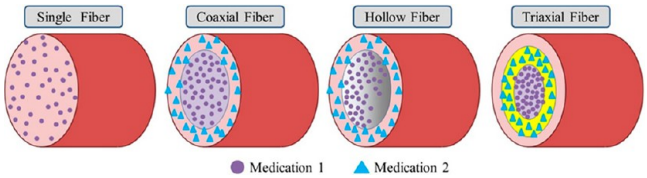


Figure 2. Schematics of the cross-sectional view of electrospun fibers in various configurations of multiaxial fibers with the loading of required agents. Reproduced with permission from ref 4. Copyright 2017 Elsevier.

antibacterial drugs such as chloramphenicol (CAM) loaded in fibrous dressing have gained major interest as an innovative topical drug delivery system. Thus, CAM-loaded polycaprolactone (PCL) and poly(ethylene oxide) (PEO)/PCL nanofibers were developed, and the composite fiber exhibited sustained drug release along with improved physicochemical properties and cell viability. Moreover, possible interactions between CAM and polymers were investigated by computational modeling and phytochemical analysis.[5]

Likewise, a poorly water-soluble drug (quercetin or tamoxifen citrate) loaded into core−shell nanofibers was used as a novel drug delivery system, and controlled drug delivery was observed.[9] Thanks to the tunability of nanofiber scaffolds for drug delivery, it is possible to solve specific challenges in different fields. For example, a short residence time of a drug inside the body is a major issue in the treatment of eye diseases because of the poor administration capability of the eye to accommodate excess liquids. The challenge was addressed by developing gellan gum/pullulan nanofibers as a prolonged ocular drug delivery system. The fibers are shaped into curved geometries to fit the eye. This ocular product with adapted geometry is an optimistic alternative for drug delivery (Figure 3).[10]

https://doi.org/10.1021/acsbiomaterials.2c00786
ACS Biomater. Sci. Eng. 2022, 8, 3690−3716

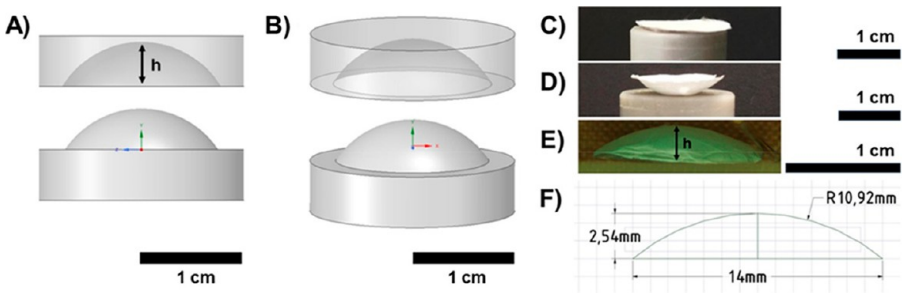


Figure 3. (A) 3D image of the lens forming matrix (side view); (B) 3D view of the forming matrix; (C) 1.5 cm diameter flat lens image of mesh immediately after preparation; (D) side view of 1.4 cm diameter lens image after curvature formation; (E) microscopic picture of the lens (side view); (F) lens construction, scaled with the measured dimensions. Reproduced with permission from ref 10. Copyright 2020 Elsevier.

In another scenario, due to the inability to control anticancer drug delivery to the affected area, low efficiency of drug effects on the solid tumor, and various other reasons, there's a high mortality rate in cancer patients. Such demerits can be addressed by using nanofiber drug delivery without side effects. Specifically, 5-fluorouracil incorporated PCL/CS nanofibers were manufactured for controlled drug delivery. The nanofibers showed sustained delivery over colorectal cancer therapy.[12] Anticancer drug Temozolomide/CS nanoparticles incorporated PCL/PU/gold-coated nanofibers were primed for advanced drug delivery. The composite fibers not only exhibit a prolonged drug delivery but also inhibit the growth of U-87 MG human glioblastoma cells. Thus, the composited fibers were considered potential candidates to treat glioblastoma cancer.[20] In another study, a local drug delivery system made of electrospun polymers was described that contained hydrophilic tea polyphenols in the core and hydrophobic 10-hydroxycamptothecin in the shell of the nanofibers. The potential suitability of the nanofibers in the localized therapy of primary and advanced orthotopic hepatomas was addressed.[21] In addition, the focus of drug delivery through the skin has been a recent topic of focus due to higher precision and accuracy compared to traditional methods. This method is not only exclusive to drug application but also improves skin quality. The advances of nanofibers products in pharmaceuticals and cosmetics sectors were explored by Kamble and coworkers.[17]

In addition to electrospinning, forcespinning (FS) is another emerging fiber manufacturing technique, which can produce fibers from both polymer solutions and pallets.[44] FS boasts high fiber fabrication rates and the ability to process a large range of materials such as polymers, carbon, ceramics, etc. FS compiled a lot of attention in recent years, in drug delivery and energy.[45−49] For instance, polycaprolactone/mercaptophenyl methacrylate functionalized carbon nano-onions (PCL/f-CNOs) nanofibers were primed by using FS for controlled anticancer drug release. Doxorubicin (DOX) is well-known anticancer drug with the ability to kill cancer cells via the inhibition of RNA and DNA biosynthesis. However, its hydrophobic nature impedes its wide range of applications. Therefore, the FS technique was used to produce PCL/f-CNOs nanofibers for the prolonged and controlled DOX release. The PCL/f-CNOs composite nanofibers exhibited pH-responsive DOX release over 15 days. Moreover, the composite nanofibers showed improved mechanical properties and cell viability against human fibroblast cells. Thus, it can be insisted that these composite nanofibers could potentially serve as a drug delivery system for achieving pH-responsive delivery of DOX.[45]

In another study, DOX-loaded bovine serum albumin (BSA)/poly 4-hydroxyphenyl methacrylate-carbon nano-onions (PHPMA-CNOs-CNOs) composite fibers were manufactured for stimuli-responsive release. The BSA composites fibers exhibited pH and temperature-responsive drug delivery. Specifically, BSA composite fibers under pH 5.0 exhibited more than 98% of DOX released at 45 °C in 15 days. In addition, improved cell viability against human fibroblast cells and other physicochemical properties were also augmented.[46] Similarly, ultrahigh molecular weight polyethylene/poly 4-hydroxyphenyl methacrylate single-walled carbon nanotube (PE/f-CNT) nanocomposite fiber membranes were developed by using FS for simultaneous drug delivery and heavy metal ions removal. Curcumin (Cur)-loaded PE/f-CNTs nanocomposite fibers displayed pH-responsive drug release in a controlled fashion. The composites fiber presented enriched cell viability against osteoblasts. Moreover, the composite fibers exhibited record mechanical properties and stood as the strongest composite material among all polymer-based composites.[47] Recently, phytochemical-based isorhamnetin glycoside (IRG) reinforced gelatin nanofibers were fabricated using FS and characterized. The gelatin nanofibers showed a controlled and sustained IRGs release (63%) under physiological pH over 3 days. The gelatin fibers displayed excellent biocompatibility with human fibroblast cells.[48]

In addition, self-assembled peptide nanofibers have also been used for the controlled delivery of proteins, drugs, and other biological payloads. For instance, an anti-inflammatory drug can be incorporated as a prosthetic group onto self-assembled peptide nanofibers through hydrolytic linkage, which enables prolonged and localized drug delivery upon hydrogelation by calcium salt.[50] Tat Cell-penetrating peptide (CPP) nanofibers hybridized with aliphatic moiety have encapsulated the hydrophobic drug paclitaxel (PTX) within their hydrophobic core. The experimental results demonstrated that Tat-CPP nanofibers could transport the encapsulated PTX into the cells through the endocytosis pathway, thus Tat nanofibers served as efficient drug vehicles.[51] Similarly, hydrophobic peptide nanofibers exhibited controlled and sustained drug release to the tumor site and considerably inhibited tumor growth in a mouse model.[52] It is also reported that enzymes produced by cancer cells can also stimulate the self-assembled peptide nanofibers. For example, cancer enzymes promoted a conformational change in self-assembled peptides that caused a controlled release of encapsulated

https://doi.org/10.1021/acsbiomaterials.2c00786
ACS Biomater. Sci. Eng. 2022, 8, 3690−3716

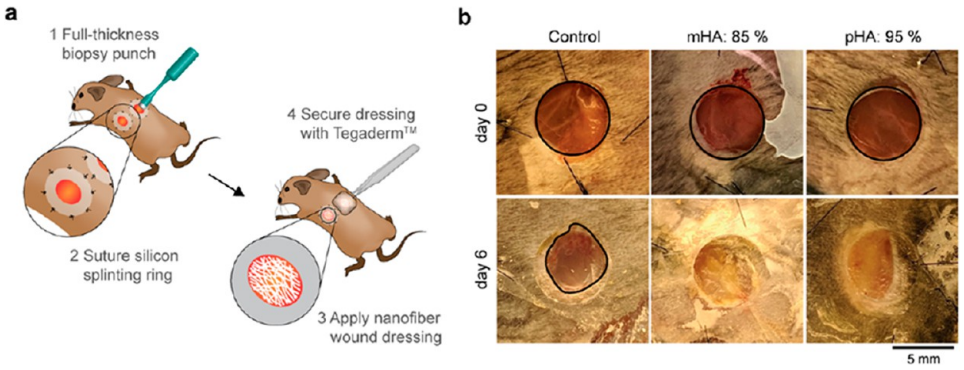


Figure 4. Porous HA scaffolds support robust wound closure and tissue regrowth. (a) Schematic of the full-thickness excisional splinting wound model procedure steps: (1) 6 mm full-thickness excisional wounds are inflicted on C57BL/6 male mice (8−10 weeks old), (2) silicon rings are sutured to the surrounding uninjured skin, (3) HA wound dressings are applied to the wound, and (4) silicon occlusive dressings (Tegaderm) are used to cover the wounds. (b) Representative macroscopic images of wounds at day 0 and day 6 postinjury for the control (only covered with a Tegaderm film dressing), mHA, and pHA dressings. HA-treated wounds reveal the formation of a scab across the entire wounded area, while controls appear still completely open. Reproduced with permission from ref 57. Copyright 2019 American Chemical Society.

chemotherapeutics.[53] Thus, several drug delivery systems were discussed in this subsection.

2.2. Nanofiber Scaffolds for Tissue Engineering. Tissue engineering is a new and intensifying branch of the medical discipline. Developed tissues and organs have been constructed by combining cells, growth factors, and biomaterials to substitute the injured tissues in the human body. To regenerate damaged tissues is also the essential goal for the less agonizing and speedy restoration of cartilage/bone to treat skin wounds. The tissue regenerated by tissue engineering and widely utilized by the patients is still very inadequate such as cartilage, skin, bone, capillary, and periodontal tissues. The major reasons for such scanty advances in clinical or preclinical applications of tissue engineering are discussed. Fundamental tissue engineering involves the scaffolds for cell expansion and differentiation, cell courses, and vehicles for growth factors.[23] Human and animal trials are the most important parts of tissue engineering. For this, some key issues to be determined for the enhancements of tissue engineering are focused on emphasizing the collaborations between medical doctors and biomaterials researchers.

The main challenge of this application is the resemblance of the extracellular matrix (ECM) and the proliferation of endothelial and epithelial cells.[54] Thus, this subsection explores an overview of nanofibers-based biomaterials encompassing fundamentals and applications in tissue engineering. Tissue engineering along with regenerative medicine has been focusing lately on the development of 2D and 3D nanofibrous scaffolds. Due to their promising properties, they are likely to contribute to the formation of new tissue in a wound. These nanofibers produced by electrospinning have a highly porous ECM which allows for the mimicking of small pore membranes. It has also been proven that the nanofibers with a sustainable release of silver nanoparticles increase the antimicrobial activity against *Staphylococcus aureus* and *Pseudomonas aeruginosa*. Compared to the 2D nanofibers, 3D nanofibers allow better interaction between cells and nutrient diffusion.[55] In another study, zein/poly(ethylene oxide) (PEO)/thyme essential oil-based nanofibers were fabricated by a portable hand-held electrospinning device and applied onto partial-thickness wounds on mice models. The results unveiled appropriate surface hydrophilicity, gas permeability, high conformability to the wound site, and antimicrobial activity against S. aureus and *E. coli*. In addition, animal-based in vivo results displayed that those nanofibers greatly improve the wound healing process along with reducing infection and cross-contamination rates.[56] Focusing on wound healing (diabetic skin issues or normal skin wounds), nanofiber scaffolds were made using ECM substances such as collagen, HA, and gelatin. For instance, HA-based nanofiber scaffolds were manufactured by using the immersion rotary jet-spinning machine technique. This technique produced a variety of scaffolds with excellent porosity, mechanical properties, and swelling behavior. The scaffolds were tested in mice and showed a high coverage of epithelial tissue and faster closing of the wound due to the porosity properties of the scaffolds (Figure 4).[57]

Similarly, diclofenac-loaded gelatin/poly(epichlorohydrin-*co*-ethylene oxide) [GL:PECO] nanofibers were fabricated by using forcespinning (FS) for tissue engineering and drug delivery. Since gelatin can easily attach to cells because of its degradability, PECO makes polymers last longer and make them more flexible and stronger. The fiber scaffolds exhibited controlled drug delivery with improved cell viability and proliferation, which aids in drug delivery and wound healing.[58] Most of the nanofibrous scaffolds including aligned and randomly oriented fibers have been used in skin repair and wound healing. However, for the first time, inspired by the basketweave-like pattern of collagen fibrils, crossed nanofibrous scaffolds were primed using electrospinning for the repair of chronic wounds. The crossed nanofibrous scaffolds were implanted in diabetic rats, and the results demonstrated excellent wound healing compared to that of aligned and random fiber scaffolds, which was proved by the accelerated migration of fibroblasts, resolution of inflammation, presence of keratinocytes, and elevation of angiogenesis.[59]

Circular gradients of active proteins accelerate cell migration and neurite extension. For instance, aligned nanofiber scaffolds were produced using circular gradients of active proteins, BSA, and copper wires. A cone-shaped container with BSA was filled with an active protein and a circular gradient was formed with BSA. The results showed that there was a faster epidermal growth because there was a high rate of migration of fibroblast and keratinocytes from the perimeter of the container to the center of the scaffold. A nerve growth factor was evaluated, and it was shown to have a radial extension of neurites. Electrospun

https://doi.org/10.1021/acsbiomaterials.2c00786
ACS Biomater. Sci. Eng. 2022, 8, 3690−3716

fibers were combined with an electrohydrodynamic jet printing technique to produce them with the active proteins, yet there is still no official method to produce them. They can be used for wound healing, optical nerve repair, cell migration, and biochemical graded scaffolds.[60] In another study, ginsenoside Rg3 (G-Rg3)-loaded electrospun poly(L-lactide) (PLLA) nanofibers were developed to diminish scar formation in a rabbit ear model. The G-Rg3−PLLA electrospun scaffolds unveiled a controlled release of G-Rg3 and prevented the proliferation of human hypertrophic scar fibroblasts (HSFs). Moreover, in vivo results exhibited inhibition of hypertrophic scar growth by reducing the thickness of the neodermis and the proliferative cells and collagen fibers.[61] It is reported that scaffold-free cell sheet lacks cell viability and mechanical properties, whereas cell-free scaffolds preserve limited biocompatibility. Therefore, the assimilation of cells with biomaterials scaffolds for high performance is very crucial in tissue engineering. These issues were addressed by Zhu and co-workers. They prepared a novel sandwich architecture of cell sheet-plasmid-membrane-cell sheet (CpMC) scaffold to reinforce cell sheets and improve cell activity for quickening wound healing. The CpMc containing two adipose-derived stem cell (ADSC) sheets on outer surfaces, and a gelatin/chitosan nanofibrous membrane (NFM) was constructed to propose a different and new way to treat wound healing. They optimized the best ratio of gelatin/chitosan (7:3) to produce the nanofibers with suitable porosity, mechanical properties, swelling, biodegradation, and bioactivity. This proved to be the most ideal structure for adhesion and proliferation.[62]

In another study, silica particles incorporated in PVA/SF-based medical-grade nanofiber scaffolds were primed for the wound healing process. The results demonstrated that the scaffolds displayed great reepithelization and hair growth ability, as well as inhibited bacterial growth such as *E. coli* and *S. aureus*.[63] Current wound dressing methods suffer from drug-resistant bacteria, high cost, and the hassle of handling. Therefore, a melamine-modified silk fibroin (SF-Mel) was synthesized to produce a series of PCL/SF-Mel nanofiber films (PSNFs) by the electrospinning technique. The PSNFs demonstrated good biocompatibility, wettability, air permeability, and antibacterial properties against *S. aureus* and *E. coli*. The in vivo experimentations showed that PSNFs are adequate to accelerate wound healing through collagen deposition and vascularized reconstruction. The PSNFs showing the best results leading to further investigations and possible applications were the PSNF-20 with a higher wound healing ability, epithelization, and angiogenesis promotion.[64] Self-assembled cell sheets composed of adipocyte-derived stem cells (ADSCs) and surface-engineered nanofibrils (NF) were successfully prepared and the NF were layered with gelatin. To test the effectiveness of the Gel/PCL NF, a dorsal wound was treated. The results showed that the highest concentration of gelatin exhibited higher wound healing rates. Also, cell sheets made of ADSCs and Gel/PCL NF showed increased levels of collagen and pan-keratin expression. In general, the Gel/PCL NF cell sheet showed effective wound healing and higher adhesion to the matrix due to the immobilized gelatin of the NF.[65]

On the other hand, peptide nanofibers also play a crucial role in tissue engineering applications, ranging from neural injury treatment to cartilage tissue repair. Peptide nanofibers with protein binding ability and cellular adhesion epitopes were experimented with a rat model to target spinal cord injuries (SCIs). The peptide nanofibers displayed heparan sulfate mimetic and laminin mimetic epitopes. The in vitro test results showed that the nanofiber supported the adhesion and viability of dorsal root ganglion neurons. The in vivo experiments demonstrated that the peptide nanofibers enhanced tissue integrity after 6 weeks of injury. The overall result suggested that the neuroactive peptide nanofibers mimicked the ECM with dual bioactivity. This means that nanofiber could be a promising therapeutic method for SCI.[66] RADA16 (RADARADARADARADA) is an amphiphilic polypeptide made of 16 amino acids, which consists of alternating arginine (R), alanine (A), and charged aspartic acid (D) that duplicate periodically throughout the composition. This arrangement of amino acids allows RADA16 to produce a highly stable and ordered β-sheet structure. Moreover, it forms an immunogenic and biocompatible 3D nanofiber hydrogel in neutral pH that facilitates the differentiation and proliferation of cells, making it extensively applied in cell culture scaffolds. Recently, RADA16 self-assembling hydrogels were also prepared by modifying the C-terminus or N-terminus of RADA16. Thus, RADA16 and RADA16-based fusion peptides are widely used in tissue repair, 3D cell culture, delivery systems, and rapid hemostasis. RADA16 is also a very attractive model to investigate damaged cartilage regeneration, as it can be a scaffold for cartilage repair.[67] It is also reported that short peptide building blocks were used as self-assembly entities. For instance, a new hydrogel made from nanofiber structures and five-residue peptides was designed for tissue engineering. The mechanical properties of the nanofiber pentapeptide hydrogel were tested using rheology and spectroscopy. Viewed by transmission electron microscopy, the fibrils exhibited a unique twisted ribbon shape. The tunable mechanical and structural properties of the hydrogel fiber allow cell expansion and remodeling. This could have different applications in tissue engineering and cell delivery.[68]

Perhaps one of the most important applications in biomedicine for nanofiber scaffolds is tissue repair of all kinds, thanks to the biocompatibility of these materials. Lidocaine hydrochloride (LID) and mupirocin-loaded chitosan/polycaprolactone (CSLD-PCLM) fiber scaffolds were produced by the dual spinneret electrospinning technique. The obtained scaffolds exhibited interfacial interaction with blood cells and excellent blood coagulation capacity. The CSLD-PCLM scaffolds displayed rapid release of LID and sustained release of mupirocin. Nonetheless, the CSLD-PCLM scaffold also proved efficient as an antibacterial and collagen deposit, enhancing the healing process in the epithelial tissue. Furthermore, it showed less inflammation, homeostasis during the healing process, granular tissue growth, and epidermis and dermis generation.[69] To mimic blood vessels, support cell proliferation, and help tissue reconstruction, pectin hydrogel nanofiber scaffolds were prepared by a multistep methodology such as electrospinning, periodate oxidation, and adipic acid dihydrazide cross-linking. It was proven that the hydrogel nanofiber scaffolds promoted mesenchymal stem cell (MSC) separation into vascular cells (by gene expression). Physicochemical characteristics, including hydrophobicity and stiffness, can be controlled by changing cross-linking levels of the hydrogel.

Live/dead staining measurements unveiled the superior viability of the MSCs cultivated on the fiber hydrogel scaffolds over 14 days. Real-time polymerase chain reaction findings indicated that the softer fiber scaffold promoted MSCs

https://doi.org/10.1021/acsbiomaterials.2c00786
ACS Biomater. Sci. Eng. 2022, 8, 3690−3716

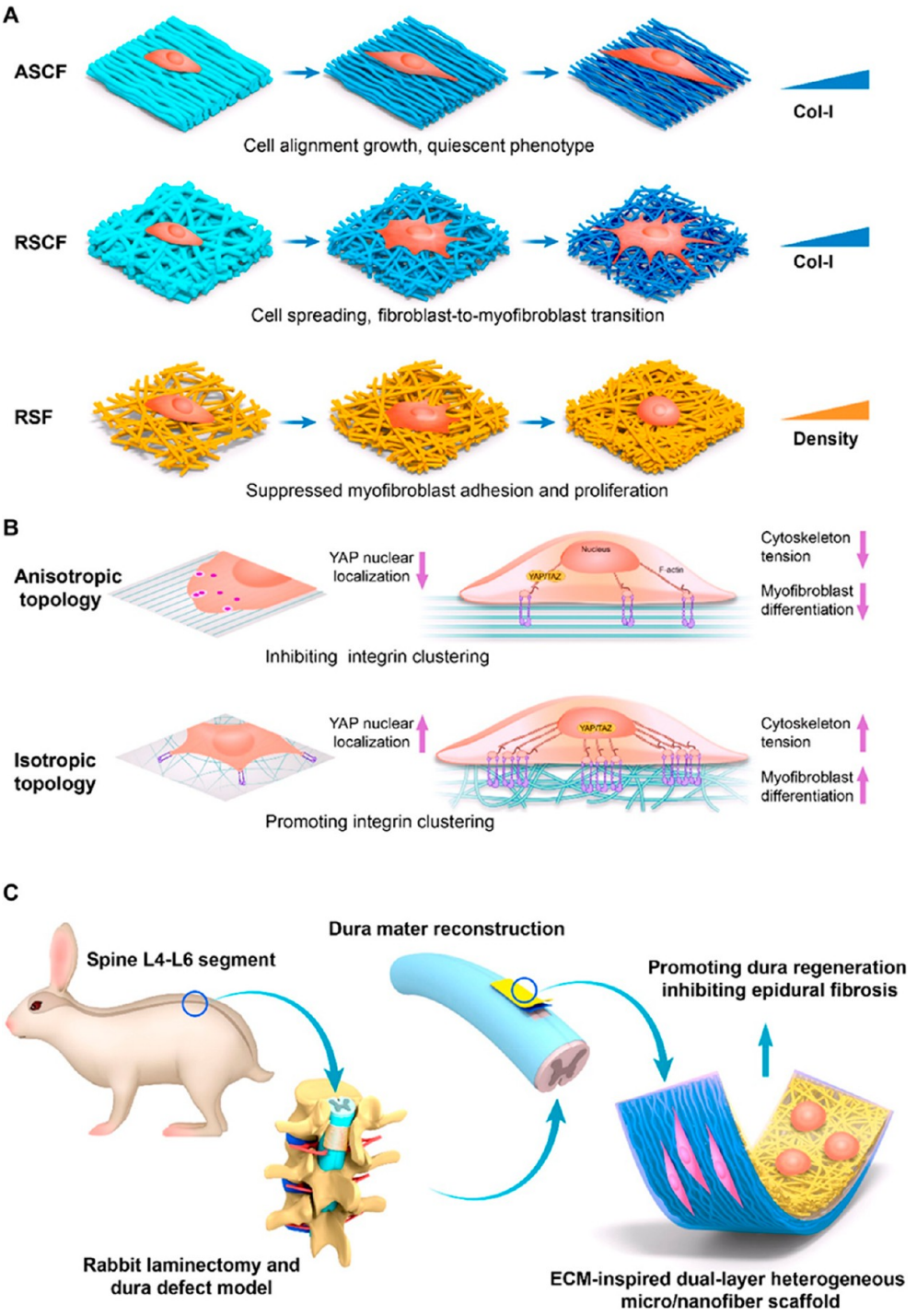


Figure 5. Schematic illustration of surgical procedure for creating dura defect in rabbits and implantation of biomimetic designed scaffolds for promoting the regeneration of dura mater and preventing epidural fibrosis. Reproduced with permission from ref 75. Copyright 2020 Science.

differentiation into endothelial cells, while the stiffer fiber hydrogel scaffold enabled the differentiation of MSCs into vascular smooth muscle cells.[70] Aligned fibers are proven to be more useful in the field of tissue engineering since they encourage cell reproduction and structural advantages. For instance, gelatin/zein-aligned nanofibers were manufactured by FS. The aligned nanofibers displayed hydrophilicity, biocompatibility, and noncytotoxic properties. Moreover, adding the benefits of 3D models, the scaffolds presented benefits such as cell reproduction, cell growth, and adhesion.[71] Similarly, Cur-loaded forcespun gelatin/PLA nanofibers were developed for tissue engineering applications.[72] In another study, polydopamine (pDA)-coated water-insoluble PVA 3D scaffolds were developed for tissue regeneration, drug delivery, and environmental remediation.[73] It is known that tendon injury in athletes may result in disability or late recovery. To surmount this, PCL, PCL-PCL, and PCL-SF/poly(L-lactic aciepsilon-caprolactone) (PLCL) microfiber scaffolds were developed to test the biocompatibility and tendon tissue regeneration. Among them, the PCL-SF/PLCL scaffold proved to be the most biocompatible, yielding the highest proliferation and better regeneration. This is the result of the nanofibers' ability

https://doi.org/10.1021/acsbiomaterials.2c00786
ACS Biomater. Sci. Eng. 2022, 8, 3690−3716

to bind to cell membrane receptors and mimic the ECM tendon regeneration. On the other hand, the microfibers provided mechanical support.[74] A nonwoven cholesteryl ester liquid crystal (CLC) with electrospun nanofibers scaffold was fabricated along with PCL. The PCL polymer functioned as the structure while the CLC established a viscoelastic fluidlike interface.

The scaffold showed a favorable result because it played an important role in cellular homeostasis and signal processes. Additionally, its wettability aided by the nanofibers enhanced the attachment among cells and allowed for their proliferation. Compared to the usual elastic nanofibers, this technique was able to provide a more fluidlike interface.[76] Heterogenous dual-layer nanofiber scaffolds using silk fibroin and collagen I were constructed to experiment with its function in repairing dura mater tissue. The nanofiber scaffold presented an effective fibroblast adhesion and growth. It was also discovered that while the density of the SF fiber increased, the adhesion and growth were inhibited. When the nanofibers were aligned in the inner layer of the scaffold regeneration and repair of tissue were promoted. However, with random SF fibers, the formation of scar fibrosis in the tissue was prevented. The nanofiber scaffold fabricated showed good biocompatibility and great mechanical properties (Figure 5).[75,77] It is also reported that nanofiber-based hydrogel composites have demonstrated the ability to induce angiogenesis. For instance, PCL/HA hydrogels were primed that mimicked the mechanical and structural characteristics of ECM. The fiber network of hydrogel exhibited the filtration of macrophase and led them to the regenerative phototype. The hydrogel promoted the expression of cytokines and pro-angiogenic growth factors after subcutaneous injection in rabbit and rat models.[78] An amphiphilic PU tubular nanofiber scaffold was constructed to regulate the expression of both epithelial cells (EC) and smooth muscle cells (SMC). The fabricated scaffolds were implanted into a Beagle's defective urethra. The amphiphilic nanofiber enhanced hydrophilicity, cell compatibility, and mechanical properties that resembled those of the natural urethra. The fiber also induced the formation of new blood vessels without causing foreign body responses.[79] A recombinant human angiotensin-converting enzyme 2 (rhACE2)-electrospun fibrous scaffold was designed to treat myocardial infarction. The patch was able to release rhACE2 encapsulated from a hyaluronic acid poly(L-lactic acid) (PLLA) core−shell structure.

An in vitro assay demonstrated that the rhACE2 patch can prevent cardiomyocyte apoptosis from hypoxic stimuli. This is critical to treating cardiac fibrosis. After a wound healing study, results showed that the rhACE2 patch can suppress cardiac fibroblast migration and proliferation in vitro. The in vivo experiment was made with a mice MI model to remodel the function of the patch. The rhACE2 patch provided antiremodeling effects and prevented the development of heart failure.[80] It has been observed that nanofibers can be used to enhance the healing of tissues of many types, perhaps one of the areas seeing the most development in tissue engineering through nanofibers is neural regeneration. Electrospun fibers were implanted into acute spinal cord injuries in rats to promote neural differentiation of MSCs. In addition to sustained release of nerve growth factors, the fiber scaffolds proved to be able to regulate the inflammation response and reduce scar tissue formation. In the in vivo experimentation, the promotion of angiogenesis and differentiation at the injury site enhanced the recovery of the tissue.[81] Inspired by the shape memory properties of the poly(lactide-*co*-trimethylene carbonate) (PLATMC) polymer, a self-forming multichannel nerve guidance conduit was fabricated. The inside surface of the conduit was fabricated from aligned nanofibers. This conduit helps during peripheral nerve regeneration due to the deformation of a tubular shape to a planar fibrous mat allowing uniform loading of cells. These variations in shape are produced by thermal changes. At room temperature, the tubular shape transforms into a fibrous mat, and at 37 °C, the fibrous mat recovers the tubular shape. The favorable results of the cell repair and proliferation of rat sciatic nerve defects demonstrated the substantial potential of smart fibers in peripheral nerve regeneration.[82] A reduced graphene oxide-GelMA-PCL composite nanofibrous scaffold was fabricated for nerve tissue engineering. The electrospun composite nanofibers were randomly oriented and formed a 3D interconnected porous network. The properties of the composite scaffold were tuned by modifying the rGO concentrations. The in vitro study showed that low concentrations (0.25 and 0.5 wt %) of rGO proliferated more than the other samples. Moreover, the hybrid nanofibers can activate epithelial-mesenchymal transitions and produce the expression of Schwann cells. The in vivo studies showed that the nanofiber was biocompatible and had great conductive substrates, which could have further applications.[83] In another study, highly crystallized aligned PCL nanofibers were primed by using a touch-spinning strategy for neural constructs.

It was observed that the elastic modulus and crystallinity of touch spun nanofibers were better than that of electrospun PCL nanofibers. The growth and differentiation of neural stem cells (NSCs) were significantly improved on the aligned touch-spun nanofibers. Serum albumin incorporated into the touch-spun fibers increased the expression of neuron-specific class III β-tubulin.[84] When designing nanofibrous scaffolds for tissue engineering, it is important to consider the precursors being used as well as the processes involved in improving the properties of the final product. There have been many advances in both starting materials and production methods that deserve to be mentioned. As it has been discussed that electrospun-based tissue engineering scaffolds are mostly made up of natural polymers, however, due to the low availability and weak mechanical properties, synthetic polymers are used, which are cheaper and have improved properties. Synthetic aliphatic polyesters are recommended because of their physical properties and low degradation rate in water. However, they need to be modified with harmful techniques to improve their properties. To improve synthetic polymers through safer methods, we used the nonthermal plasma technology (using argon/helium in nanofiber scaffolds) to enhance cellular interactions, where the plasma treatments are made using nontoxic substances in the gaseous phase. There is no residue or contamination after using the procedure, in vitro practices are enhanced, and there is a significant rise in functional group density. However, the plasma treatment aging affects its efficiency on cell interaction. There are still a lot of gray areas to discover in this plasma method for nanofibrous scaffolds.[85] Similarly, polyester-aligned fibrous scaffolds, especially 3D-aligned nanofibrous scaffolds, have developed as a promising solution for tissue regeneration. They possess advantages like physical changes in size, degradation, higher solubility, and molecular immobilization. These scaffolds respond to external stimuli, including light, pH, or magnetism, and can be

https://doi.org/10.1021/acsbiomaterials.2c00786
ACS Biomater. Sci. Eng. 2022, 8, 3690−3716

Table 1. Different Nanofiber Scaffolds for a Wide Range of Tissue Engineering Applications

types of nanofibers	cell lines	application	ref
2D and 3D nanofibrous scaffolds	ECM	formation of new tissue in a wound. mimicking small pore membranes	55
PCL-SF/PLCL scaffold.	cell membrane and tendon ECM	tendon tissue regeneration	74
self-forming multichannel nerve guidance conduit (inspired by PLATMC polymer)	satellite cells and Schwann cells (peripheral nervous system)	peripheral nerve regeneration	82
nonwoven cholesteryl ester liquid crystal (CLC) with electrospun nanofibers scaffold with polycaprolactone (PCL)	myoblast cell lines	cellular homeostasis and cell proliferation	76
heterogenous dual-layer nanofiber scaffolds using silk fibroin and collagen I	ECM	repairing dura mater tissue	75, 77
PCL/HA hydrogels	ECM	angiogenesis induction and promotion of the expression of cytokines and pro-angiogenic growth factors in rabbits and rats	78
cell sheet-plasmid-membrane-cell sheet (CpMC) containing two ADSC sheets and an electrospun gelatin/chitosan nanofibrous membrane (NFM)	endothelial, epidermal, and fibroblast cells	wound healing; cell adhesion and proliferation	62
silica-particle-incorporated PVA/SF-based medical-grade nanofiber scaffolds	epithelial cells	wound healing, hair growth promotion, inhibited bacterial growth such as *E. coli* and *S. Aureus*	63
reduced graphene oxide-GelMA-PCL composite nanofibrous scaffold	epithelial and mesenchymal cells	nerve tissue engineering	83
PCL/SF-Mel nanofiber films (PSNFs).	endothelial cells and epithelial cells	acceleration of wound healing, epithelization, and angiogenesis	64
surface engineered nanofibrils	adipocyte-derived stem cells	treatment of dorsal wounds	65
crystallized aligned PCL nanofibers	neural stem cells	neural constructs	84
amphiphilic PU tubular nanofiber scaffold	epithelial cells and smooth muscle cells	formation of new blood vessels	79
chitosan/polyvinyl alcohol nanofiber. (CS/PVA)	dermal papilla multicellular spheroids.	inducing hair follicle growth	92
PCLMA:GelMa nanofiber scaffolds		abdominal hernia tissue repair	93
PPy composite fiber scaffolds		nerve, vascular, and cardiac muscle tissue engineering	94
electrospun fibers	MSCs	regulate inflammation response and reduce scar tissue formation	81
rhACE2-electrospun fibrous scaffold	cardiomyocytes	prevent the development of heart failure and treat myocardial infarction	81
hydrogel fiber		tissue engineering and cell delivery	68
nanoband air	liver cells	effectively reduced inflammation and wound healing	95
polycaprolactone (PCL)	MG63 cells	prevention of adhesion and biofilm formation of bacteria	96
electrospun nanofibers containing Gymnema Sylvestre extracts and antibiotics combination.	proliferation of fibroblasts and keratinocytes	potent antibacterial activity and wound healing	97
bacterial nanocellulose with pullulan zinc oxide nanoparticles and aminoalkyl silane (A-*g*-BNC/Pul-ZnO)	proliferation of L929 fibroblast cells	faster healing and re-epithelialization in wounds	98
Cur-loaded chitosan/poly(ethylene oxide)/collagen (CS/PEO/Col) nanofibers		increase conductivity of polymer solution, control bacterial growth, and wound healing	99
silk nanofiber hydrogel loaded with desferrioxamine (DFO)	endothelial cells	treatment of diabetic foot ulcers	100
gelatin methacryloyl (GelMa) coated 3D nanofiber scaffold	dermal fibroblasts and bone marrow-derived MSCs	tissue constructs and wound healing	101
SLg, ALg, and SLe peptide nanofiber gels	primary human umbilical vein endothelial cells	proangiogenesis in skin regeneration	102
Nap-FFEG-IVGGYPWWMDV	human umbilical vein endothelial cells	cardiac function	103
nanofibrous membrane with PVDF and PMBU polymers	resembled ECM	healing acute and chronic wounds	104

produced in 3D molds to be more efficient in tissue engineering.[86]

On the other hand, it is known that electroactivity is necessary for cells to perform tasks. In this case, nanofiber polymeric scaffolds are being investigated to boost myoblasts, osteoblasts, and neural crest cells (which all have electroactivity) to repair damaged tissue or organs. However, creating nanofibrous scaffolds with conductive polymers decreases biocompatibility and degradation in the body. Yet, intrinsically conductive polymers like polyaniline (PANI) or polypyrrole (PPy) are compatible with cell tissues and contain antioxidant characteristics.[87]

Among the newer techniques being explored, the 3D electrospinning method produces 3D aligned nanofiber scaffolds to mimic isotropic tissues that grow in a specific orientation and address optical tissue regeneration. This technique is different because it can produce contact lenses and tissues for the eyes or 3D wounds, all of which need hemispherical or look-through structures. It also controls renal cell carcinoma reproduction rate. These nanofibers can be used for biomolecules conjugation, drug delivery systems, and therapy that involve other methods (like surface treatments). By having a 3D model, the scaffolds can imitate eye structures such as the cornea. These scaffolds also allow the entry of

https://doi.org/10.1021/acsbiomaterials.2c00786
ACS Biomater. Sci. Eng. 2022, 8, 3690−3716

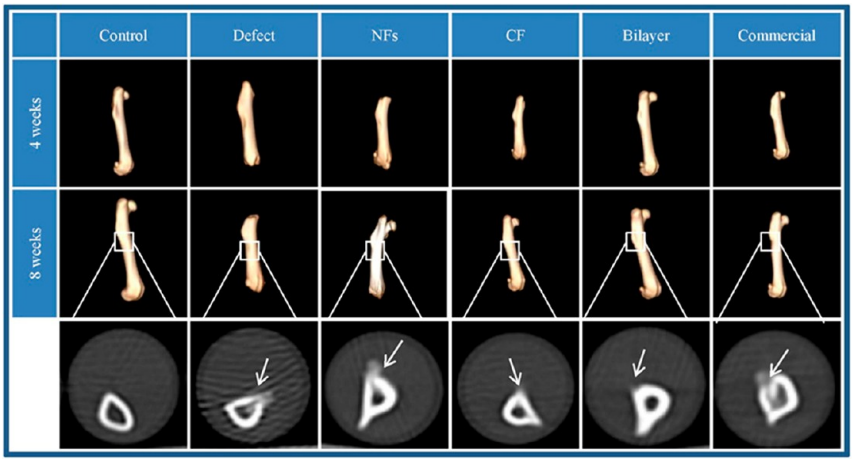


Figure 6. Images obtained by 3D CT of bone regeneration at the bone−implant interface in rats at 4 and 8 weeks. Reproduced with permission from ref 110. Copyright 2021 Frontiers.

collagen into the ECM.[88−90] On the other hand braided/woven/knitted yarn networks, aligned nanofiber yarns, and composites made of fibrous yarns and hydrogels displayed potential in stimulating the differentiation of MSCs to anisotropic soft tissues. For heart valve engineering it can be possible to produce scaffolds using woven fabric as well as a bioactive hydrogel.[91] Aside from materials and methods, new nanostructures have also been explored.

A CS/PVA nanofiber sponge was fabricated to help the construction of efficient and functional multicellular spheroids. To determine the biocompatibility, a CCK-8 assay was performed and the result showed that CS/PVA nanofibers were noncytotoxic. It was speculated that cell infiltration and nutrient transport were favorable due to the porosity of the nanofiber. The nanofiber had an open-cell cellular structure and high elasticity, enhancing multicellular spheroid formation. Through experimentation with mice, it was shown that dermal papilla multicellular spheroids helped the hair follicle-inducing ability.[92] In addition, several other nanofiber scaffolds for tissue engineering applications are presented in Table 1.

2.3. Nanofibers for Bone Tissue Engineering. Bone tissue engineering is involved with constructing implantable bone substitutes and bone regeneration for critical bone defects that cannot heal unaided. Degenerative disease, traumatic injury, surgical removal of tumors, and congenital defects can cause large defects of bone that necessitate medical intervention to achieve complete healing and functional restoration. These large bone defects can be fixed by using conventional standard treatments such as inert metallic devices, bone autografts, and allografts. However, bone-metal fixation devices often required ensuing surgical removal, while the use of bone autografts causes additional illnesses associated with the healing of the donor site. The use of bone allografts is linked with a risk of infection transmission from the donor materials. These risks linked with bone grafts are notably acute in aging people. Thus, bone-tissue engineering had witnessed substantial advancements toward biomaterials that enable the bone regeneration process at the defect site without acquiring these risks. In the typical bone regeneration paradigm, a blend of biomaterials and cells are planted into composite biomaterial scaffolds to regenerate implantable "osteogenic" implants.

Lucrative materials design for bone-tissue engineering necessitates an understanding of the structure and composition of native bone tissue, and an appropriate selection of biomimetic natural, or tunable biomaterials including metals, polymers, bioceramics, and composites. Scalable production methods that facilitate control over construct design at multiple length scales can be utilized to process these biomaterials into suitable scaffolds for bone-tissue engineering. High tensile modulus, high tensile strength, and osteoinductive properties are the essential characteristics of bone. However, mimicking bone grafts involving cells, ECM, scaffolds, and osteogenic growth factors are key challenges in bone-tissue engineering.[105] Because of the hierarchical shape of bone and its natural growth processes in the course of fracture healing and embryonic development offer insight into novel approaches for bone-tissue regeneration. A typical bone comprises distinctive cell types encircled by ECM with biologically active molecules unified within the ECM or produced by cells. The bone ECM is akin to a bone-tissue engineering scaffold, containing a framework of cross-linked protein fibrils (collagen type I), inorganic minerals (calcium phosphate, and carbonate hydroxyapatite), and multiple cell types. This structural combination of components and their hierarchical arrangement of bone transmits the mechanical characteristics of bone. Therefore, the researchers of bone-tissue engineering materials intend to enumerate the physical structures, or functions of the protein, cellular, and mineral components of bone, to enable the growth of new bone tissues and refurbish their functionalities. Several nanomaterials (electrospun nanofibers) have been used to regenerate bone ECM. For instance, Wang and co-workers engineered flexible bioactive glass (SiO_2−CaO) nanofibers followed by assembling them into 3D nanofiber scaffolds by using CS as a linker. Upon implantation, the elastic nanofiber scaffolds showed self-deployment and were well mounted into the irregularly shaped bone defects. Particularly, the $85SiO_2$−15CaO/CS nanofiber scaffolds exhibited significant support for bone regrowth and vascularization in the osteoporotic calvarial defect in a rat.[106] In another study, an artificial bone scaffold was made by using lignin/PCL nanofibers. The lignin/PCL nanofibers helped with the formation of human bone-like hydroxyapatite (HAp). The results showed a morphology similar to that of native bone.

The tensile measurements revealed that the scaffold presented an elastic modulus of 5.57 GPa, which is within the elastic modulus range of cortical bone and cancellous bone

https://doi.org/10.1021/acsbiomaterials.2c00786
ACS Biomater. Sci. Eng. 2022, 8, 3690−3716

(i.e., 1 to 20 GPa). In addition, the CCK-8 test displaced the formation of HAp by the mineralization promoted cell proliferation. The augmented cell adhesion and spreading were observed in the presence of lignin.[107] However, the authors found that PCL/HAp composites are not entirely enough for bone repair. Therefore, poly(ethylene phosphoric acid) (PEPA) was added to the composite and enhanced mechanical properties and biodegradation were observed. The presence of PEPA in the nanofiber confirmed an efficient binding to the vancomycin, which presented a great response against *Staphylococcus aureus*. This antibacterial activity was tested using the Kirby−Bauer test.[108] It is also reported that 3D nanofiber aerogels can be used as bone grafts for bone regeneration thanks to their biomimetic morphology, porous structure, and composition. This 3D nanofiber aerogel can be improved by adding miR-26a with a suitable polymeric vector targeting bone marrow-derived MSCs, providing a solution for bone regeneration. The cellular results presented high biocompatibility. Overall, healing of rat cranial bone defects by implanting the 3D hybrid nanofiber aerogel was achieved.[109] In another study, Zhang et al. developed berberine-loaded mineralized collagen/CS nanofibers for bone regeneration. These hybrid composite fibers exhibited augmented mechanical properties, cell attachment, proliferation, and controlled drug release. In addition, improved new bone regeneration in a rat femoral bone defect model was reported (Figure 6).[110]

In addition, Cheng et al. reported that BMP-2 could also improve the early accretion of osteoblast cells in injury sites. Thus, BMP-2 modified black phosphorus-incorporated nanofibers recruited osteoblast cells and accelerated the biomineralization process supported by both in vitro and in vivo measurements.[111] A 3D printed scaffold was prepared by partial cross-linking of TEMPO-oxidized cellulose nanofibril/alginate hydrogel and used as a promising solution for bone-tissue engineering.[112] Natural bone-inspired, and HAp-incorporated aligned and mineralized bacterial cellulose (AMBC) nanofibers were primed. For this, aligned bacterial cellulose was mineralized by using $CaCl_2$ and K_2HPO_4. The composite displayed an elastic modulus of 10.91 GPa and a hardness of 0.37 GPa. It also reported that AMBC presented a much higher elastic modulus (210%) and hardness (95%) compared to that of nonaligned mineralization BC fibers. Moreover, the mechanical properties of AMBC resembled those of natural bone.[113] It is worth mentioning that the subsequent release of different growth factors from the nanofiber scaffolds would hasten bone formation. Thus, BMP-2 and connective tissue growth factor (CTGF)-incorporated multilayer core−shell SF/PCL/PVA nanofibers scaffolds were fabricated by Cheng and co-workers. The prolonged release of BMP-2 enhanced bone formation while the release of CTGF had a proangiogenic effect on bone healing. The in vivo results presented around 43% of improvement in bone regeneration.[114] In another study, a nanofibrous membrane was fabricated to aid bone regeneration. This nanofibrous membrane was composed of low-immunogenicity fish collagen and bioactive nano HAp enhanced with poly(lactide-*co*-glycolide). The results obtained from the physicochemical properties and morphology study showed that the fish collagen and the nano HAp were homogeneously dispersed in the PLGA fiber membrane. It was noticed that the incorporation of fish collagen modified the degradation behavior of fibers and accelerated the degradation rate of the whole membrane. The PLGA membrane presented good cytocompatibility not only with human gingiva fibroblasts cells but also with bone MSCs. The most important observation of this new membrane was that it satisfied the requirements of the "biological evaluation of medical devices".[115]

It is well-known that titanium implants are used in bone-tissue engineering. However, titanium implants may become loose and displaced, delaying the healing of the bone. Additionally, the bacteria spreading evolve into worse cases such as bone loss or amputation. For this reason, graphdiyne (GDY)/TiO_2 nanofibers were fabricated to combat implant infections due to their prolonged antibacterial ability and enhanced photocatalysis. Due to the presence of GDY, the GDY/TiO_2 composite presented outstanding osteoinductive properties. The GDY/TiO_2 composite exhibited good cell adhesion and biocompatibility to allow cell proliferation.[116] In addition, a new strategy was developed to produce nanofibrous membranes. The strategy consisted of recycling lactic acid (LA) to synthesize calcium lactate (CaL), an osteoinductive biomolecule. This strategy was applied to produce a 3D bioactive PCL/CaL fibrous scaffold for bone-tissue engineering. The 3D PCL/CaL was successfully converted from lactic acid to CaL and presented an enhanced biomineralization capacity, proliferation rate, cell infiltration, and osteoblastic differentiation. The composition of lactic acid had a significant influence on viscosity, electrical conductivity, and density. The overall results showed that the PCL/CaL could be a potential scaffold material for both soft and hard tissue repair.[117] The effect of nanofibrous architecture on stem cells was explored with capable of confining a single stem cell on a micro island of a nanofibrous matrix. This new design was able to reduce any potential intercellular communications.

The experimental results demonstrated that the nanofibrous architecture enhances BMSC differentiation through the FAK/Rho/YAP1 pathway.[118] The composite fiber scaffolds mimic the fibrous structure of the ECM with around 95% of porosity, which enhances the ability of cell migration, adhesion, differentiation, and proliferation in bone-tissue engineering. Thus, a series of electrospun fiber scaffolds with a sandwich architecture based on PCL and CS/PEO composites were developed by Yahia et al. The sandwich composite scaffolds regenerated the bone defects within 28 days via osteogenesis and angiogenesis.[119] There is a lot of research that proves the interdependent role existing between osteogenesis and angiogenesis in bone-tissue engineering. However, there is not much information available to explore how functional blood vessel networks are organized to initiate bone regeneration. Based on a previously constructed layer-by-layer BMSC electrospun nanofiber, a deeper understanding of spatiotemporal regulation of angiogenesis could be discovered. This study demonstrates that by combining tissue engineering strategies and advanced imaging technology the key role of vessel specification in the control of bone formation can be accomplished. With this, effective and uniform bone regeneration can be achieved.[120] An electrodeposition-promoted 3D calcium phosphate nanofibrous scaffolds were developed to mimic the bone matrix of mineralized collagen that facilitates cell migration and bone regeneration. The results showed that the rate of mineralization was augmented at a higher voltage and temperature, whereas calcium release was decreased under the same conditions. This was associated with high crystallinity and a

https://doi.org/10.1021/acsbiomaterials.2c00786
ACS Biomater. Sci. Eng. 2022, 8, 3690−3716

high hydroxyapatite content. Bone regeneration could be enhanced by manipulating initial conditions.[121]

To mitigate these shortcomings, cryoelectrospun PCL (CE) nanofibers surrounded by a macroporous gelatin/heparin cryogel (GH) were developed by Lee and co-workers. In this combination, the GH component was able to increase the hydrophilicity of CE, which mimicked a better cellular environment. On the other hand, the CE component improved the mechanical properties of the scaffold and induced osteogenic differentiation. This new CEGH nanofibrous scaffold maintained a sustainable release of BMP-2 over 40 days. This factor also contributed to the enhancement of osteogenic differentiation.[122] Similarly, PLLA membranes can mimic the ECM, but their hydrophobic nature and poor osteoinductive properties restrict their use in bone regeneration. Thus, a GelMA/nHA/PLLA nanofiber membrane was primed.

This new membrane had a saturated adsorption rate of 8 wt %, nearly 7 times higher than that of the pure PLLA membrane. The GelMA/nHA/PLLA membrane had excellent cytocompatibility, promoting the spreading and proliferation of hBMSC. Additionally, the membrane exhibited greater bone formation compared to the other groups tested. It was able to regenerate the cranial bone of a rat almost entirely.[123] Similarly, preosteoblastic cells exhibited improved cell adhesion and proliferation on chitosan-based composite fibers.[124] The periosteum is a dense layer of vascular connective tissues, stem cells, and osteoprogenitor cells. It plays a key role in bone regeneration. However, current artificial periosteum materials suffer from poor mechanical characteristics, osteogenic differentiation, bionic structure construction, and vascularization capabilities. To address this issue, Zhang and co-workers developed a PCL/whitlockite (WH) artificial periosteum by electrospinning. According to the cellular studies, WH doping did not show cytotoxicity to BMSCs and the PCL/WH nanofibers promoted migration of HUVECs as the concentration of WH increased. The composite nanofibers were proven to regulate cell adhesion, proliferation, and osteogenesis differentiation. Figure 7 shows histological images of different nanocomposite fiber membranes with H&E staining for 7 and 14 days.[125]

In another case, silk fibroin (SF)/PLGA coaxial nanofibers for bone regeneration, were developed, which were cranially implanted in a rat. The result demonstrated a new bone formation over 8 weeks.[126] Similarly, silk fiber-based hydrogels were developed for bone regeneration.[127] A 3D printed biodegradable PGSLP/gelatin fiber scaffolds were developed for angiogenesis and osteogenesis. The scaffold was implanted in a rat skull and augmented bone regeneration was observed128. It is also reported that DFO-loaded fiber membranes could promote osteogenic differentiation of hMSCs and MC3T3-E1. Also, these membranes presented a rapid wound healing rate when compared to that of the control (DFO 0).[129] It is also known that ceramics are widely used in bone regeneration. Biodegradable porous ceramics, such as calcium phosphates (CaP), are usually employed to treat bone regeneration due to their similarities with bone characteristics. However, the CaP ceramics are brittle, which impedes their wide range of applications. Therefore, a biphasic calcium phosphate (BCP) sponge was developed and integrated with interwoven nanofibers. This allows the sponge to have an open cell geometry and high porosity. This sponge can be modified into different shapes. For instance, the sponge can be

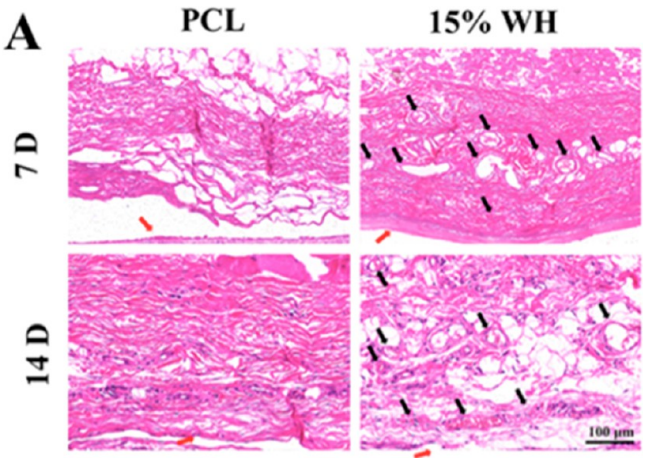


Figure 7. Histological images of different nanocomposite fiber membranes with H&E staining for 7 and 14 days (red arrows, boundaries of materials and skin; black arrows, blood vessel). Reproduced with permission from ref 125. Copyright 2021 American Chemical Society.

introduced through a syringe into a bone defect in a compacted state, and after being wet, it expands to its original shape. The in vitro testing demonstrated that the sponge degrades gradually and mineralizes rapidly when immersed in simulated bodily fluid. Additionally, it absorbs a significant quantity of proteins and supports attachment, proliferation, and osteogenic differentiation of humans (MSCs).[130]

Calcium silicate is also a bioceramic material, and it is used for bone treatment because it provides bioactive ions (Ca^{2+} and Si^{4+}) that invigorate bone regeneration. Therefore, calcium silicate-based electrospun fibers were fabricated followed by calcination at a high temperature. The obtained nanofibers were characterized and implanted into rat calvarial defects. The in vivo results demonstrated that the nanofibers calcined at 1000 °C showed augmented bone generation. Thus, osteogenesis was improved using calcium silicate nanofibrous scaffolds.[131] Treating osteoporotic bone defects with irregular shapes has been a major challenge because the bioactive glass that has been used so far is limited due to its inherent brittleness. Therefore, a bioactive glass was assembled into 3D fibrous chitosan ($85SiO_2-15CaO$ NF/CS). The new scaffold presented improved mechanical properties, including excellent flexibility, allowing a maximal bending of 180°. The new scaffold exhibited a full recovery of 80% compression over 1000 cycles of compression underwater. When implanted, the fiber scaffold was able to deform and fit into the shape of bone defects even if they were irregular, achieving a perfect match with the cavities. The osteoporotic calvarial defect in a rat model demonstrated that the composite scaffold promoted bone regrowth and vascularization.[106] Inspired by natural self-assembling peptides found in indigenous proteins, deliberately designed and engineered peptides show outstanding biodegradability, biocompatibility, and ECM-mimicking microenvironments. Specifically, peptide nanofibrous scaffolds showed promising abilities for bone regeneration and regenerative medicine. By having a controlled release of signal molecules and operative modifications, the peptide nanofibers can increase their biological activity, yet they lack mechanical strength. Other materials, including polymers, demineralized bone matrix, hydroxyapatite, and metal materials, have been

https://doi.org/10.1021/acsbiomaterials.2c00786
ACS Biomater. Sci. Eng. 2022, 8, 3690−3716

reinforced within peptide scaffolds based on the requirement of different bone defects to solve this issue (Figure 8).[132]

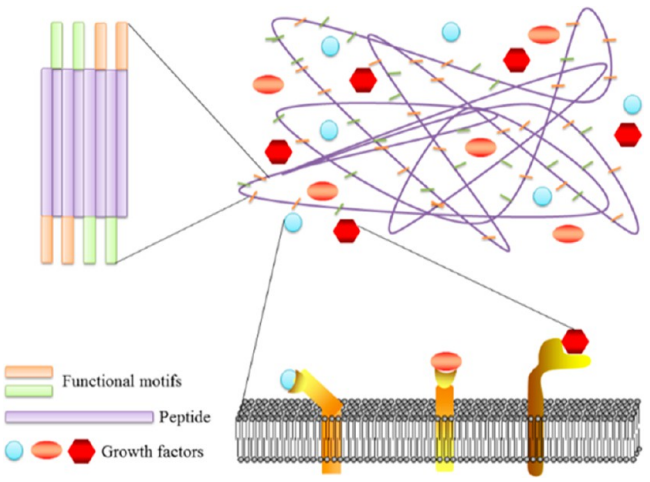


Figure 8. Ways to produce self-assembling peptides using motifs and growth factors. Reproduced with permission from ref 132. Copyright 2018 Elsevier.

Similarly, endothelial progenitor cell (EPC)-induced graft was fabricated by the immobilization of bioactive peptides (WKYMVm and YIGSR) on the PCL/PGC nanofiber scaffolds for promoting vasculogenesis. This strategy achieved the successful immobilization and sustained release of bioactive dual peptides and directed the vascularized bone regeneration under the stimulation of EPCs.

Thus, these dual-peptide functionalized nanofiber-based scaffolds show excellent advantages in early osteogenesis and angiogenesis. For instance, the composite promoted calvarial defect repair. The in vitro study suggested that the new scaffold benefited the osteogenesis of MSCs.[133] Several fiber-based scaffolds for bone-tissue engineering are presented in Table 2.

2.4. Nanofibers for Dental Applications. Recent dietary trends have shown notable increases in the intake of sugary foods and beverages, which led to the proliferation of oral diseases among the population. There is a great need for novel and functional biomaterials that can interface with complex dental structures to treat these ailments. In recent years, nanofibers have risen as potential solutions, as they can form high surface area and microporous 3D frameworks and scaffolds that can easily imitate complex dental tissues and provide advantages in cell adhesion, proliferation, and differentiation. However, there are some shortcomings of nanofibers impeding the wide progress of nanofibers to clinical applications. Control of fabrication, physicochemical properties, and functioning of nanofibers is required to overcome these limitations. Advanced in vivo studies are certainly essential to appraise the biocompatibility of nanofiber scaffolds. Anti-inflammatory activity, or/and tissue regeneration of scaffolds should be controlled.[112] Furthermore, the mechanical properties of nanofibers scaffolds should be tolerable during tissue regeneration application. The objective of this subsection is to summarize the current advancement of nanofibers for dental applications. Besides, numerous aspects of nanofibers and their potential dental applications have been highlighted. As a consequence of the complexity of various oral infections, the dentistry industry has come up with different approaches to anti-infective nanotechnology. There has been a rise in the application of nanofibers and new techniques in the dentistry industry for the delivery of antimicrobial molecules. Nanofibers can be used for endodontic or periodontal therapy, or even on implant surfaces.[134]

A bioharmonious technique to eradicate bacteria from the root canal system after pulpal necrosis of immature permanent teeth is fundamental for regenerative endodontic procedures. Sousa and co-workers fabricated clindamycin-modified triple antibiotic polymer nanofibers. After synthesizing the clindamycin-modified triple antibiotic polymer, the data suggests that it might be a possible substitute for antibiotic pastes.[135] In another study, amoxicillin (AMX) encapsulated poly-DL-lactic acid (PDLLA) nanofibers were fabricated by electrospinning, and the cell viability, behavior of periodontal ligament cells, and antibacterial capabilities of the nanofibers were investigated. The experiment results showed that AMX was successfully encapsulated in the fabricated fibers, allowing a sustained release of the substance. After the initial attachment, it could be observed that the cells stretched out along the directions of the nanofibers. Moreover, the growth of *S. sanguinis* and *P. gingivalis* was significantly reduced by the

Table 2. List of Various Fiber-Based Scaffolds for Bone Tissue Engineering

types of nanofibers	cell lines	application	ref
cyroelectrospun PCL (CE) nanofibers surrounded by a macroporous gelatin/heparin cryogel (GH) or CECH nanofibrous scaffold	osteogenic cells	bone regeneration and osteogenic differentiation	122
GelMA/nHA/PLLA nanofibrous membrane	human bone marrow stromal cells (hBMSC)	bone regeneration	123
endothelial progenitor cell (EPC)-induced graft on the surface of PCL/PGC nanofibers	endothelial progenitor cell (EPC)	osteogenesis of MSCs and promotion of vasculogenesis	133
preosteoblastic cells on chitosan-based composite fibers	preosteoblastic cells	cell adhesion	124
PCL/whitlockite (WH) artificial periosteum	bone marrow stromal cells (BMSCs) and human umbilical vein endothelial cells (HUVECs)	regulate cell adhesion, proliferation, and osteogenesis differentiation	125
silk fibroin (SF)/PLGA coaxial nanofibers	bone marrow mesenchymal stem cells (BMSCs)	bone regeneration	126
silk fiber-based hydrogels	stem cells	bone regeneration and bone-tissue engineering	127
3D printed biodegradable PGSLP/gelatin fiber scaffold	endothelial cells and osteogenic cells	bone regeneration; angiogenesis and osteogenesis	128
DFO-loaded fiber membranes	human mesenchymal stem cells (hMSCs) and MC3T3-E1	promote osteogenic differentiation of hMSCs, MC3T3-E1, and rapid wound healing rate	129

https://doi.org/10.1021/acsbiomaterials.2c00786
ACS Biomater. Sci. Eng. 2022, 8, 3690−3716

PDLLA-AMX nanofibers. In addition, the fibers promoted the viability and mobility of periodontal ligament cells and reduced inflammation.[136] In yet another study, TCH-incorporated polylactic acid (PLA), PCL, and GL nanofibers and titanium (Ti) modified TCH-integrated nanofibers were developed for the evaluation of antimicrobial and osteogenic behavior.

The experimental results demonstrated that TCH-integrated nanofibers could be useful for Ti dental implants as an osteogenic inducer and antimicrobial surface modifier.[137] Besides efficient antibacterial activity, nanofibers have various other dental applications like tissue regeneration, endodontics application, and implant coatings.[139−141] A vast investigation has been performed to explore the potential of nanofibers for the repair and regeneration of different dental and oral tissues such as periodontal tissues, dentin, dental pulp, oral mucosa, and skeletal tissues. The process and purpose of electrospinning for biomedical and dental applications like tooth regeneration, wound healing, and prevention of dental caries are also extensively studied (Figure 9).[138,142−144] Hamidabadi

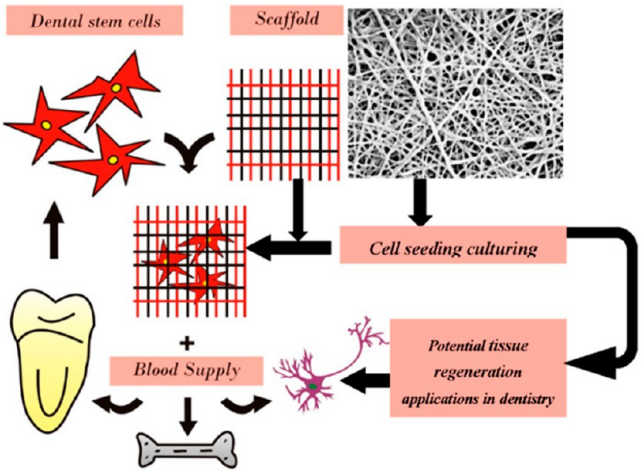


Figure 9. Schematic presentation of using electrospinning scaffolds for tissue engineering of various oral and dental issues. Reproduced with permission from ref 138. Copyright 2016 MDPI.

and co-workers developed chitosan intercalated montmorillonite (OMMT)/PVA nanofibers to guide the differentiation of human dental pulp stem cells (hDPSCs) toward neuronlike cells. The OMMT/PVA fiber scaffolds exhibited augmented mechanical properties and biocompatibility along with a homogeneous morphology.[145]

Similarly, PLA/PCL blend nanofibers containing both nanohydroxyapatite (nHA) and zeolite were manufactured for promoting the proliferation of hDPSCs with possible application in dental tissue engineering. The results exhibited that zeolite-loaded nanofibers are the best candidate scaffold for their application in bone and tooth tissue engineering (Figure 10).[146] Pankajakshan and co-workers described how periodontitis is one of the most aggressive diseases that weakens the integrity of tooth-supporting structures. Electrospinning was used to develop bioactive membranes for dental regeneration and nanofibers for antibiotic drug delivery to improve current endodontics.[147] Furthermore, nanofibrous materials applied for dental applications must possess adequate mechanical properties, because they will face vigorous mechanical loads over time. Borges and co-workers developed a composite resin filled with nylon-6 nanofibers and nylon-6

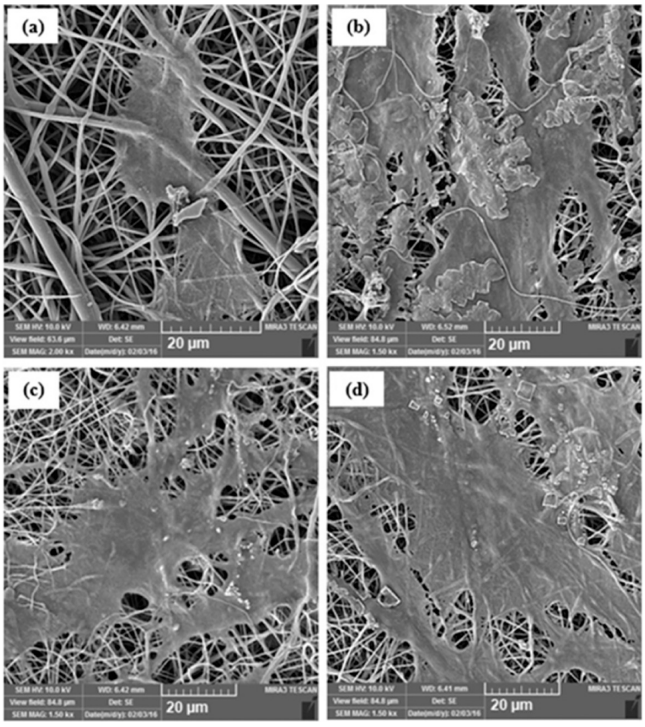


Figure 10. FE-SEM images of hDPSCs adhesion to designed nanofibers: (A) PCL-PLA, (B) PCL-PLA/Zeolite, (C) PCL-PLA/nHA, and (D) PCL-PLA/nHA/Zeolite. Reproduced with permission from ref 146. Copyright 2020 Elsevier.

nanofibers with multiwalled carbon nanotubes or with prepolymerized resin with different concentrations. They have investigated the composite film thickness, volumetric polymerization shrinkage, flexural strength, and elastic modulus of the composite resins. The experimental results revealed that the mechanical and physicochemical properties of composite resins were improved, and they estimated that the composites would be suitable for dental applications.[148] Amiri and co-workers engineered polyacrylonitrile (PAN) reinforced dental composites to investigate the enhanced interfacial adhesion between PAN fibers and dental resin matrix by surface modification of the fibers. Bisphenol A glycidyl methacrylate (Bis-GMA)/triethylene glycol dimethacrylate (TEGDMA) was used as the dental resin. Initially, pristine PAN electrospun fibers were prepared followed by the surface of the fibers being treated with a dental resin. The dental resin-coated PAN fibers exhibited improved properties.[149] Yancey and co-workers proposed a study to compare the properties of different nanofiber-reinforced hybrids. For instance, flexural strength/modulus, depth of cure, degree of conversion, and polymerization shrinkage of the composite nanofiber were compared to those of traditional hybrid composites, and improved properties were observed.[150] Poly(ether imide) fibers were fabricated and the properties and potential mechanical improvements for their application in dental materials were analyzed.[151] The aforementioned mechanical properties were also studied for dental applications by using zirconia and alumina nanofibers.[152] Similarly, bioceramic nanoparticle-embedded nanofibers have been used for dental regeneration due to their nanostructures, flexibility, and cell homing behavior.[153]

Another study focused on the dual delivery of calcium chelating bone therapeutics with mineralized nanofiber frag-

https://doi.org/10.1021/acsbiomaterials.2c00786
ACS Biomater. Sci. Eng. 2022, 8, 3690−3716

Table 3. Summary of Clinical Trials on the Use of Electrospun Nanofibers for Different Applications

nanofibers	clinical trial	results	ref
3D nanofibrous extracellular matrices (NF-ECMs).	test cellular behavior of human mesenchymal stem cells on NF-ECMs	3D NF-ECMs provide	161
3D nanofiber scaffolds cross-linked with hyaluronic	repair cartilage defects in rabbits	demonstrated elevated compressive strength, thicker new cartilage, and a remarkable deposition of type collagen II and aggrecan	162
mometasone furoate and poly(lactic-co-glycolic acid) nanofibers	insertion into the maxillary sinuses of rabbits to treat chronic rhinosinusitis	MF-PLGA nanofibers proved to be safe when applied on the Sino nasal mucosa, gave a sustained release of the drug, and reduced inflammation for a prolonged time	163
functionalized carbon nanofibers (CNFs) with docetaxel (DTX) and mitomycin C (MMC)	chemo sensitizing potential of CNFs with the conventional chemotherapeutics docetaxel and mitomycin C	resulted in additive inhibition of short- and long-term proliferation compared to the individual treatments; combination of MMC with CNFs showed more than twice the cell death rate mediated by apoptosis	164
carbon nanofiber reinforced within silk protein fibroin of nonmulberry tropical Tasar silkworm *Antheraea mylitta*	incubation in simulated body fluid for in vitro and in vivo bone regeneration	showed a sustained growth factor (TGF-β1 and BMP-2) release, therefore, supporting successful osseointegration	165
aligned PLLA nanofibers with a chitosan/collagen hydrogel layer	fabrication of a tendon	aligned PLLA nanofibers with a chitosan/collagen hydrogel layer	166
bacterial cellulose nanofiber sheets loaded with venlafaxine and doxycycline	20 subjects were chosen for diabetic foot ulcer examination	showed a new capillary bed formation and abundant chronic inflammatory cells (mostly polymorphonuclear cells), meaning it may be an option for diabetic foot ulcer management and ulcer size reduction	167
acyclovir nanofiber patches	efficiency of acyclovir nanofiber patch compared with acyclovir cream in 60 patients with recurrent labial herpes	acyclovir nanofiber patches are more effective in accelerating symptom relief in recurrent labial herpes, yet they are not effective in decreasing crusting or healing time	168
voriconazole (VCR) incorporated in composited polyvinyl alcohol (PVA)/hydroxypropyl-βcyclodextrin blended nanofibers	male New Zealand white rabbits were treated for ophthalmic drug delivery	accomplished a sustained release of VRC for 24 h; bioavailability of VRC was notably increased in rabbit tears, and very few tolerance problems were observed during 7 days of application	169
PCL/PGA/PLA fiber mesh	regeneration of patient-specific ear-shaped cartilage	clinical application for auricular reconstruction	159
PLLA/gelatin nanofiber membrane	chronic cutaneous wound healing	clinical case experiment showed around 93% of wound closing and 7% of recovery rate	160
poly(lactide-co-glycolide) biodegradable scaffolds seeded with neural stem cells	spinal cord injury	pilot study of clinical safety of the PLGA poly-L-lysine scaffold for the treatment of complete traumatic acute spinal cord injury	170
matrix comprising collagen and P4HB	soft tissue repair	BioFiber and BioFiber-CM absorbable biologic scaffold for soft tissue repair and reinforcement postmarket surveillance clinical study	170
isolated primary chondrocytes with autologous bone marrow cells seeded onto a polymeric scaffold	cartilage repair	prospective feasibility, nonrandomized, single-arm multicenter, multinational interventional clinical investigation using instruct therapy for the repair of knee cartilage defects	170

https://doi.org/10.1021/acsbiomaterials.2c00786
ACS Biomater. Sci. Eng. 2022, 8, 3690−3716

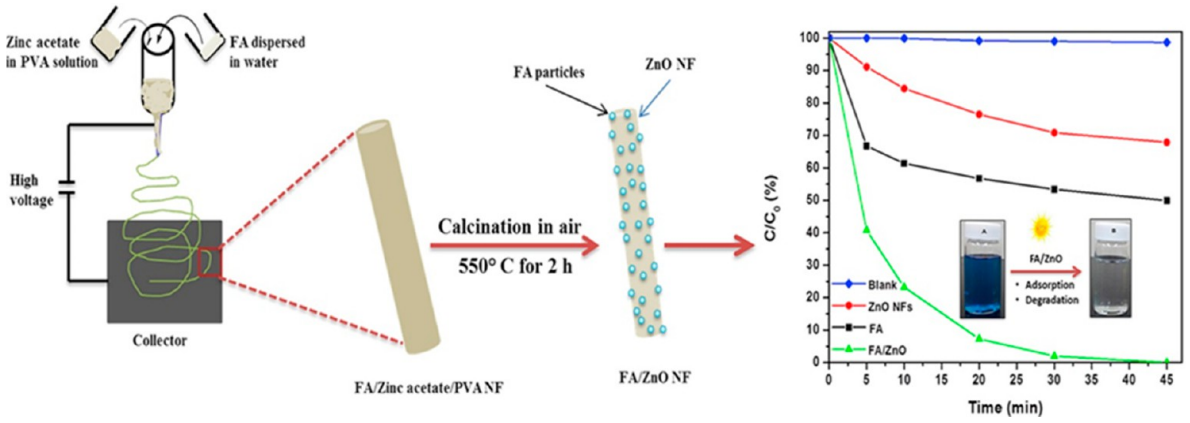


Figure 11. Demonstration of the electrospinning technique and posterior air calcination. Reproduced with permission from ref 175. Copyright 2018 Elsevier.

ments to regenerate alveolar bone in vivo. Alendronate (ALN) has been reported to induce osteonecrosis, therefore a low dose of ALN along with BMP-2 mimicking peptide conjugated to a heptaglutamate moiety (E7-BMP-2) was aggregated onto mineralized nanofiber fragments. The nanofiber fragments were composed of polylactide-*co*-glycolide-collagen-gelatin in ratios PCG 2:1:1. The method to incorporate the E7-BMP-2 into the fibers was via calcium coupling/chelation. The results showed that this technique could have potential applications in bone regeneration.[154]

2.5. Role of Nanofibers in Clinical Trials. A comprehensive assessment of registered preclinical and clinical trials was performed to ascertain the clinical ability of nanofibers in biomedical applications. Limited literature was found for clinical trials of nanofibers in wound healing, drug delivery, dentistry, tissue engineering, etc. The results were presented in Table 3. Several clinical and preclinical applications of nanofibers are currently being considered (Table 3). Preclinical tests revealed that various nanofibers displayed no inflammatory response, no toxicity toward living cells, loss of cell integrity, no cellular damage, etc. For instance, PCL fiber scaffolds were used in tendon repair and negligible inflammatory results were observed in the mice model, and reflection of cell infiltration into the fiber scaffold was also noticed.[155] In another study, polyurethane Tecophilic nanofiber textiles (NT) were submitted to a clinical trial as chronic wound healing entities.[156] In addition, clinical studies of metronidazole and doxycycline-loaded PCL fibers scaffolds explored in patients with chronic periodontitis have been reported.[157,158] PCL fiber mesh-based 3D printing scaffold has been exploited as patient-specific ear-shaped cartilage in the clinical application for auricular regeneration.[159] Similarly, PLLA/gelatin nanofibers were evaluated as biomimetic skin substitutes for chronic cutaneous wound healing. Clinical applications of nanofibers exhibited superior biological, physicochemical, and safety characteristics. Around 93.3% of wound closing and 6.7% of wound recovery were observed in clinical tests.[160] Several nanofibers applied in clinical trials are presented in Table 3.

Clinical trials provide valuable information about the level of efficiency that nanofibers have in certain applications. Table 3 demonstrates how nanofibers can be useful and efficient for specific circumstances, yet they can also be unnecessary for other uses, such as the acyclovir trial. Clinical trials can help us cover all the gray areas there still are in the nanofiber field and open new pathways for research.

3. NANOFIBERS FOR ENVIRONMENTAL REMEDIATION

Water is one of the vital entities for all lives to flourish and access to safe and potable water is one of the top priorities to measure the standard of living of a populace. However, agricultural waste, industrial pollution, and untreated wastewater contaminate the useable water. Traditional water remediation technologies are being modernized to augment the quantity of safe and useable water and avert the pollution of natural water resources. To date, activated carbon has been used as one of the potential adsorbents in the wastewater/water remediation process. However, it possesses greenhouse gas emissions, high levels of carbon footprints, high cost, and high energy consumption for production. Thus, the development of cost-effective alternative materials from sustainable, and renewable sources is imperative and biomaterials are attractive eco-friendly sources for water purification methods. For instance, chitosan, zein, protein nanofibrils, silk, cellulose nanofibers, etc., have been used as adsorbents for environmental remediation thanks to their nontoxic, ubiquitous, and excellent adsorbent characteristics.[171]

Therefore, due to the negative environmental impact provoked by mankind through its use of harmful products and chemicals, there is a great need for the development of environmentally friendly, low-cost, and renewable nanomaterials that will help in reversing the damages. It is expected that the development of these nanomaterials will provide a sustainable alternative and contribute to environmental remediation.[172] Perhaps one of the most researched and explored applications for nanofibers in the field of environmental remediation is the cleaning of water and air that has been polluted by dyes, heavy metal ions, and hydrocarbons, among other contaminants due to their excellent adsorption ability and high surface area.[173,174] For example, fly ash (FA) is a contaminant generated by the combustion of coal, leading to water and air pollution. It is normally seen as a residue in thermal power plants. Bishweshwar and co-workers developed FA-incorporated zin oxide (FA/ZnO) nanofibers for the removal of methylene blue (MB) from wastewater treatment. The FA/ZnO fibers exhibited excellent photocatalytic and MB adsorption of efficacy. Thus, the pollutant FA was used as an adsorbent for wastewater treatment (Figure 11).[175]

https://doi.org/10.1021/acsbiomaterials.2c00786
ACS Biomater. Sci. Eng. 2022, 8, 3690−3716

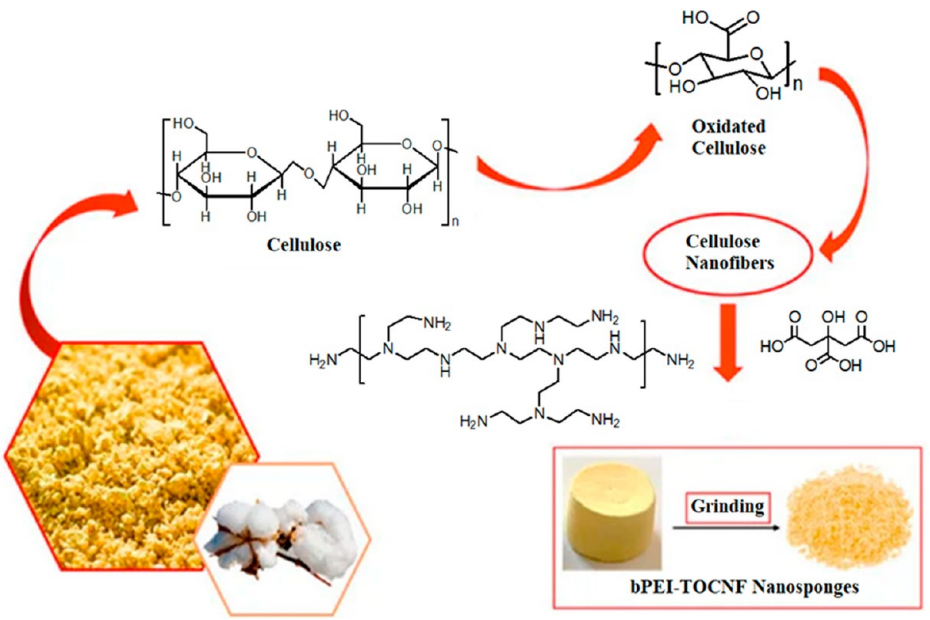


Figure 12. Production of cellulose-based nanomaterials. Reproduced with permission from ref 177. Copyright 2020 MDPI.

In another case, Gopinath and co-workers developed electrospun CuO-ZnO (CZ) nanofibers for simultaneous antibacterial properties and environmental remediation. The obtained CZ nanofibers successfully removed Congo red dye from wastewater. Besides, the CZ fibers exhibited excellent antibacterial activity against *Escherichia coli* (*E. coli*) and *Staphylococcus aureus* (*S. aureus*). Thus, CZ composite fibers are explored as a potent nanoplatform for the amputation of organic and biological contaminants.[176] Riva and co-workers developed cellulose-based materials for the efficient removal of organic dyes from wastewater. These nanofibers could be reusable due to the porous structure of cellulose fibers (Figure 12).[177]

It is reported that native cellulose nanofiber (CNF)-based pyrolysis products called char materials offer a wide range of favorable merits and possible applications. They are very accessible and eco-friendly and are used for the elimination of charged heavy metals, bacteria, and viruses, as well as the air purification of CO_2. Thus, cellulose nanofibers were produced by using slow pyrolysis from wood, bacteria, and Cladophora algae. The obtained nanofibers exhibited excellent surface area and porosity to investigate dye and oil adsorption from wastewater.[178] Nanofibers that are derived from biomass are ideal for environmental remediation uses because of their low toxicity and availability. For instance, TEMPO (2,2,6,6,-tetramethylpiperidine-1-oxyl radical)-promoted oxidized cellulose nanofibers (TOCNFs) are made from wood biomass and contain carboxyl groups. It is a strong green nanomaterial, and due to its functional groups of carboxylic acid and alcohols, these nanofibers are useful to remove heavy metal ions. This makes them ideal for wastewater treatments and water purification. The authors also identified their recyclability, which allows these nanofibers to be used for several cycles, making them suitable for industrial processes. The main properties of adsorption, strength, and low environmental impact of the nanofibers make them ideal for removing pollutants (Figure 13).[172]

Thus, eco-friendly, or/and sustainable biomaterials showed promising performance for environmental remediation. Specifically, multilayered biomaterials-based nanofibers exhibited superior filtration ability, considering they are eco-friendly with exceptional mechanical properties compared to single-layered nanofibers. Lastly, these nanofibers need to have tensile and degradation properties for industrial-scale use in rivers or lakes.[179]

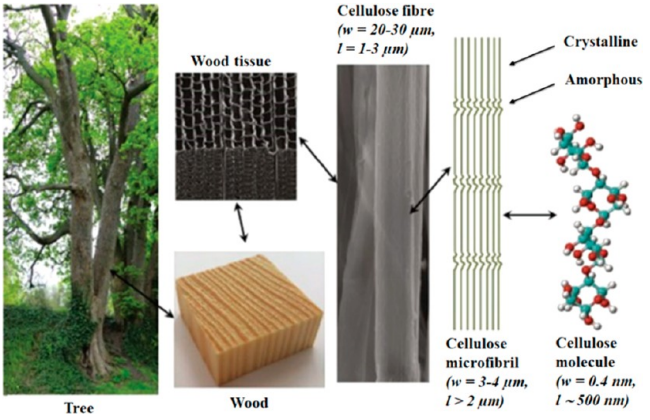


Figure 13. Demonstration of how nanofibers are made from wood biomass. Reproduced with permission from ref 172. Copyright 2021 Wiley−VCH.

Nanofiber-based meshes were prepared from a green and sustainable waste glass for the separation of oil/water mixtures. The meshes behaved as a multifunctional water purification system by removing concurrently water-soluble contaminants during the oil/water separation process. Organic dye removal is also a potential use for these nanofibers since they are superoleophobic.[180] Several other nanofiber-based sorption systems were also used for the purification of wastewater.[181] In another study, ethylenediamine (EDA)-functionalized carbon nanofibers (CNFs) containing porous carbon beads were fabricated to remove salicylic acid (SA) from the wastewater. These nanofibers could be applied to further pollutants in aqueous solutions because of their high adsorption capacity compared to resins or CNTs.[182] Nanocellulose (NC) exhibited a wide range of advantages for its use in nanofibrous materials

https://doi.org/10.1021/acsbiomaterials.2c00786
ACS Biomater. Sci. Eng. 2022, 8, 3690−3716

since it is a renewable natural polymer. For wastewater remediation treatments, NC together with other additives with different functional groups is being explored. NC has been used in food packaging aimed at environmental remediation since it is safe and degradable, and contains a wide surface area. In water treatment, NC adsorbs toxic materials like petroleum polymers and activated carbons. Nevertheless, even though NC is a potential candidate, there is still limited information regarding heavy metals that cannot apply to water.[183]

Magnetic zinc Ferrite ($ZnFe_2O_4$)@TiO_2 nanofibers were prepared by hydrothermal technique followed by an electrospinning technique. The obtained $ZnFe_2O_4$@TiO_2 nanofibers have been used simultaneously for both energy conversion and environmental remediation. Specifically, $ZnFe_2O_4$@TiO_2 nanofibers presented around 42% of incident photo-to-current conversion efficiency along with excellent photocatalytic efficiency toward dye removal.[184] In another study, nitrogen-enriched carbon nanofiber aerogels (NCNA-900) with ultrafine nanofiber network structures were made by using chitin nanofiber aerogels. The composite structure has a high surface area and displays potential as a dye adsorbent. It provides great adsorption of Congo red and rhodanine. It can also serve as energy storage without any corrosive or toxic substances since it used marine biomass. Chitin nanofiber aerogels contain a 3D structure and provide effective properties allowing them to adsorb dyes such as Congo red and rhodamine B.[185] A biomass (cotton) supported metal−organic frameworks (ZIF-67)-based catalyst precursor Cot@ZIF-67 was prepared from cobalt (Co) ions, cotton, and 2-methylimidazole. This catalyst proved that it could remove almost all bisphenol A from wastewater within five minutes. The catalyst removed the bisphenol A by degrading it since it is an organic pollutant. The nanofibers made of cotton are proven to be porous and environmentally friendly in a cost-effective way. Biomass-derived carbon shows a promising way to remove or degrade contaminants using biomass like banana peels, cotton, etc.[186] Similarly, a robust, reusable, and multifunctional Fe_3O_4@PAN/CS fiber membrane was primed via a facile and eco-friendly gas-spinning method. The obtained membranes removed contaminants from water and air, simultaneously.[187]

In another study, nonwoven polyimide nanofibers were shown to maintain superior air filtration performance at 370 °C. Real field testing validated that polyimide nanofibers could effectively remove all kinds of PMs from car exhaust at the temperature range of 50−80 °C, bringing down the content of PMs to 99.5%. The authors reported that these nanofibers can work individually or with other types of industrial dust collectors at the temperature range of 25−270 °C.[188] Electrospun nanofibers made with materials like aerogels have been used for oil spill treatments.[189,190] The fabrication of nanofibrous polymeric sorbents, which include capillary action, like polysulfone fibrous mats, are being considered as wastewater and oil spill treatments.[191−193] The sorbent can be altered depending on the water environment or oil type to meet specific chemical guidelines and make it more efficient. Hydrophobic-oleophilic polymer-based nanofibers, carbon-based fibers, and composite nanofibers are potential candidates for oil spill treatments.[194]

Another source of great concern is the pollution of water with heavy metal ions and even radioactive materials. Heavy metal ion pollutants are present in water and are difficult to remove. However, by using biomass polymers as a material, these contaminants can be eliminated by cellulose nanofibers (CNFs).[195] For instance, nitro-oxidized carboxy cellulose nanofibers (NOCNFs) are rich in nitric acid and are examples of biomass polymers capable of removing contaminants. These nanofibers have proven to remove very small particles of UO^{22+} from contaminated water.[196,197] The NOCNFs not only help in the removal of pollutants from water but can also help with solar cells.[198] It is also reported that hexavalent chromium (Cr^{6+}) is highly toxic and Cr^{6+}-polluted water causes possible health issues.[199,200] To solve this, researchers fabricated oxidized graphitic carbon nitride (Ox-g-C_3N_4) nanosheets decorated with polyaniline nanofiber (Ox-g-C_3N_4/PANI-NF) for the removal of Cr^{6+} ions from wastewater. The nanofibers were positively charged, which attracted negatively charged chromium ions.[201] It is important to mention that temperature and pH also play important roles in the adsorption process.[202,203] However, the sorption studies demonstrated that these nanofibers were ideal for the removal of hexavalent chromium.[201]

In many natural disasters, nuclear reactors can be damaged, and radionuclides are released, contaminating the seawater and soil. To clean up radionuclides, researchers have used ferric hexacyanoferrate, also known as Prussian blue (PB), o trap radioactive cesium ions, because it forms stable colloids in water. Therefore, cellulose nanofiber (CNF) backboned PB was prepared and found to be more stable in water. These CNF/PB fibers were successfully used to remove the radioactive cesium ions. The tests in contaminated soil with cesium have been made using CNF/PB encapsulated spongiform adsorbents, which demonstrated excellent results. These 3D porous nanofibers show a promising future for specific contaminant cleaning.[204] Looking at another facet of environmental remediation, new photocatalysts have been prepared using electrospinning methods with further calcination to develop nanofibers using a polyoxometalate (PMo_{12})/TiO_2 composite and platinum (Pt) nanoparticle. A photoreduction technique was also used to test the photocatalytic activity the nanofibers possessed. The fibers were proven to have high photocatalytic efficiency, no toxicity, and high oxidation. This demonstrated that the removal of methyl orange was indeed possible under the light. The morphological studies displayed that Pt nanoparticles were equally distributed within the PMo_{12}−TiO_2 nanofibers.[205]

Self-standing photocatalytic TiO_2 fibrous membranes are promising materials for environmental remediation but possess poor mechanical properties. In this case, scientists produced soft Zr-doped TiO_2 (ZT) nanofibrous membranes with augmented mechanical properties and better photocatalytic activity. They added Zr^{4+} because it could promote fewer surface defects and slow down grain growth. The ZT nanofibers are well interconnected and have small grain and pore sizes, which helps in having a better photocatalytic, and tensile strength. As a result, ZT membranes stimulated methylene blue to degrade better compared to P25 (a commercial catalyst) and are easily recycled.[206] A noble metal-based catalytic Pt/Al_2O_3 electrospun membrane was prepared and used for gas and water treatments or BPA degradation. The results revealed a complete elimination of bisphenol A and conversion from CO to CO_2.[207] Recyclable photocatalytic CNFs@I-doped $Bi_2O_2CO_3$−MoS_2 nanosheets were developed for water remediation under irradiation of visible light. These composite fibers can be reused, and they have a great potential for the removal and degradation of the rhodamine B contaminant under visible light.[208] In another

https://doi.org/10.1021/acsbiomaterials.2c00786
ACS Biomater. Sci. Eng. 2022, 8, 3690−3716

study, spiropyran-doped SF/PEO nanofibers were manufactured for acidic acid (AA) detection. The nanofibers are cost-effective and can accomplish multiple functions at the same time, which makes them effective. The AA detection mechanism is a progressive transition of the merocyanine to protonated merocyanine. This process occurs in a very short period, and the fibers can be reused several times.[209]

However, photocatalysts have gained popularity in colorant treatments because they use solar energy to degrade the colorants into CO_2 or mineral acids. Compared to TiO_2, CeO_2 catalysts are said to be potent because they last longer and are inexpensive, yet it lacks photocatalytic properties. By modifying CeO_2 into a crystal structure, its photocatalytic activity can be enhanced. CeO_2 nanofiber crystals were decomposed harmful colorants under both sunlight and solar light. For instance, CeO_2 nanofibers successfully degraded the methylene blue under sunlight. The nanofibers can also be reused for various cycles and the many oxygen atoms helped in the photocatalytic performance.[210] Apart from polymer-based nanofibers, protein nanofibrils have been used for water purification that can deliver clean water, reduce worldwide food waste, improve global health, minimize energy consumption without CO_2 emission, and lower the impact on climate change. Vegetable proteins from agricultural waste are attractive for protein nanofibril production (like soy, pea, or rice). In post-treatment residues of water purification, protein nanofibrils can reduce toxicity by providing one-step adsorption and a cutback of harmful metal ions to their elemental states on the nanofibril's outer layer due to the amino acids they have. Microorganism contamination, biofilm formation, and possible fouling affect the long-term use of protein nanofibrils in water treatments. Yet, amyloid oligomers could be used to make antifouling coatings. Also, silk nanofibrils are used for the removal of heavy metals with little degradation properties.[211]

4. CONCLUSIONS AND FUTURE PERSPECTIVE

The production and utilization of spun fibrous scaffolds derived from a wide range of materials, including natural and synthetic polymers, which can also serve as a reinforcement of ceramics, metals, carbonaceous materials, and organic/inorganic composites, have been discussed. By selecting suitable materials and fabrication methods, the surface characteristics of nanofiber scaffolds can be readily tuned to attain favorable biological, optical, electrical, chemical, and magnetic properties. Nanofibers incorporated as reinforcement also have shown a promising future. In this review, different spun fibrous scaffolds for a wide range of applications have been summarized. Thanks to their nanoscale size, high surface area to volume ratio, porous architecture, and tunable mechanical/thermal properties, nanofiber scaffolds can be utilized as (i) ultrafiltration fiber scaffolds for environmental remediation such as wastewater treatment, and air purification and (ii) fiber scaffolds for biomedical applications, drug delivery systems, tissue/bone-tissue engineering, wound dressing, and dental implants. Nanofiber scaffolds should bring major changes in the biomedical and healthcare sectors due to the large surface area that increases the interactions with tissues and the possibility to incorporate different features in scaffolds. However, before their widespread biomedical and health sector application, the major demerits associated with fibrous scaffolds' biocompatibility and physiochemical integrity must be remedied. For instance, leaching and/or disintegration of fiber scaffolds in body fluids may not be sustained due to their salvage. Despite several studies on spun fibrous scaffolds and applications in the past five years, the strategies for large-scale production of fiber scaffolds have emerged very slowly, which limits their widespread applications. Nonetheless, investigation of fiber scaffold functionality would eventually lead to the advancement of cost-effective, biocompatible, energy efficiency products, some of which could possess characteristics that are not available yet in conventional materials. Overall, some challenges of spun fibrous scaffolds for clinical, medical, and environmental remediation remain unsolved, and it is hypothesized that these structural scaffolds will become available commercially in the near future.

AUTHOR INFORMATION

Corresponding Author

Narsimha Mamidi − *Department of Chemistry and Nanotechnology, The School of Engineering and Science, Tecnologico de Monterrey, Monterrey, Nuevo Leon 64849, Mexico;* orcid.org/0000-0001-8842-4649; Email: nmamidi@tec.mx

Authors

Rubén Gutiérrez García − *Department of Chemical Engineering, The School of Engineering and Science, Tecnologico de Monterrey, Monterrey, Nuevo Leon 64988, Mexico*

José Daniel Hernández Martínez − *Department of Chemistry and Nanotechnology, The School of Engineering and Science, Tecnologico de Monterrey, Monterrey, Nuevo Leon 64849, Mexico*

Camila Martínez Briones − *Department of Chemistry and Nanotechnology, The School of Engineering and Science, Tecnologico de Monterrey, Monterrey, Nuevo Leon 64849, Mexico*

Andrea Michelle Martínez Ramos − *Department of Biotechnology, The School of Engineering and Science, Tecnologico de Monterrey, Monterrey, Nuevo Leon 64988, Mexico*

María Fernanda Leal Tamez − *Department of Chemistry and Nanotechnology, The School of Engineering and Science, Tecnologico de Monterrey, Monterrey, Nuevo Leon 64849, Mexico*

Braulio González Del Valle − *Department of Chemical Engineering, The School of Engineering and Science, Tecnologico de Monterrey, Monterrey, Nuevo Leon 64988, Mexico*

Francisco Javier Macias Segura − *Department of Chemistry and Nanotechnology, The School of Engineering and Science, Tecnologico de Monterrey, Monterrey, Nuevo Leon 64849, Mexico*

Complete contact information is available at: https://pubs.acs.org/10.1021/acsbiomaterials.2c00786

Notes

The authors declare no competing financial interest.

ACKNOWLEDGMENTS

We gratefully acknowledge Tecnológico de Monterrey, Consejo Nacional de Ciencia y Tecnología de México (CONACYT), and Sistema Nacional de Investigadores (SNI).

https://doi.org/10.1021/acsbiomaterials.2c00786
ACS Biomater. Sci. Eng. 2022, 8, 3690−3716

REFERENCES

(1) Liu, Y.; Nguyen, A.; Allen, A.; Zoldan, J.; Huang, Y.; Chen, J. Y. Regenerated Cellulose Micro-Nano Fiber Matrices for Transdermal Drug Release. *Mater. Sci. Eng. C Mater. Biol. Appl.* **2017**, *74*, 485−492.

(2) Semnani, D.; Afrashi, M.; Alihosseini, F.; Dehghan, P.; Maherolnaghsh, M. Investigating the Performance of Drug Delivery System of Fluconazole Made of Nano−Micro Fibers Coated on Cotton/Polyester Fabric. *J. Mater. Sci.: Mater. Med.* **2017**, *28* (11), 175.

(3) El-Okaily, M. S.; El-Rafei, A. M.; Basha, M.; Abdel Ghani, N. T.; El-Sayed, M. M. H.; Bhaumik, A.; Mostafa, A. A. Efficient Drug Delivery Vehicles of Environmentally Benign Nano-Fibers Comprising Bioactive Glass/Chitosan/Polyvinyl Alcohol Composites. *Int. J. Biol. Macromol.* **2021**, *182*, 1582−1589.

(4) Khalf, A.; Madihally, S. v. Recent Advances in Multiaxial Electrospinning for Drug Delivery. *Eur. J. Pharm. Biopharm* **2017**, *112*, 1−17.

(5) Preem, L.; Mahmoudzadeh, M.; Putrinš, M.; Meos, A.; Laidmäe, I.; Romann, T.; Aruväli, J.; Härmas, R.; Koivuniemi, A.; Bunker, A.; Tenson, T.; Kogermann, K. Interactions between Chloramphenicol, Carrier Polymers, and Bacteria−Implications for Designing Electrospun Drug Delivery Systems Countering Wound Infection. *Mol. Pharmaceutics* **2017**, *14* (12), 4417−4430.

(6) Thakkar, S.; Misra, M. Electrospun Polymeric Nanofibers: New Horizons in Drug Delivery. *European Journal of Pharmaceutical Sciences* **2017**, *107*, 148−167.

(7) Contreras-Cáceres, R.; Cabeza, L.; Perazzoli, G.; Díaz, A.; López-Romero, J. M.; Melguizo, C.; Prados, J. Electrospun Nanofibers: Recent Applications in Drug Delivery and Cancer Therapy. *Nanomaterials* **2019**, *9* (4), 656.

(8) Ghafoor, B.; Aleem, A.; Najabat Ali, M.; Mir, M. Review of the Fabrication Techniques and Applications of Polymeric Electrospun Nanofibers for Drug Delivery Systems. *Journal of Drug Delivery Science and Technology* **2018**, *48*, 82−87.

(9) Li, J.-J.; Yang, Y.-Y.; Yu, D.-G.; Du, Q.; Yang, X.-L. Fast Dissolving Drug Delivery Membrane Based on the Ultra-Thin Shell of Electrospun Core-Shell Nanofibers. *European Journal of Pharmaceutical Sciences* **2018**, *122*, 195−204.

(10) Göttel, B.; de Souza e Silva, J. M.; Santos de Oliveira, C.; Syrowatka, F.; Fiorentzis, M.; Viestenz, A.; Viestenz, A.; Mäder, K. Electrospun Nanofibers − A Promising Solid in-Situ Gelling Alternative for Ocular Drug Delivery. *Eur. J. Pharm. Biopharm.* **2020**, *146*, 125−132.

(11) Sofi, H. S.; Ashraf, R.; Khan, A. H.; Beigh, M. A.; Majeed, S.; Sheikh, F. A. Reconstructing Nanofibers from Natural Polymers Using Surface Functionalization Approaches for Applications in Tissue Engineering, Drug Delivery and Biosensing Devices. *Materials Science and Engineering: C* **2019**, *94*, 1102−1124.

(12) Hadjianfar, M.; Semnani, D.; Varshosaz, J. Polycaprolactone/Chitosan Blend Nanofibers Loaded by 5-Fluorouracil: An Approach to Anticancer Drug Delivery System. *Polym. Adv. Technol.* **2018**, *29* (12), 2972−2981.

(13) Gugulothu, D.; Barhoum, A.; Afzal, S. M.; Venkateshwarlu, B.; Uludag, H. Structural Multifunctional Nanofibers and Their Emerging Applications BT. *Handbook of Nanofibers*; Barhoum, A., Bechelany, M., Makhlouf, A. S. H., Eds.; Springer International Publishing: Cham, 2019; pp 693−732. DOI: 10.1007/978-3-319-53655-2_16

(14) Li, D.; Tao, L.; Shen, Y.; Sun, B.; Xie, X.; Ke, Q.; Mo, X.; Deng, B. Fabrication of Multilayered Nanofiber Scaffolds with a Highly Aligned Nanofiber Yarn for Anisotropic Tissue Regeneration. *ACS Omega* **2020**, *5* (38), 24340−24350.

(15) Dadras Chomachayi, M.; Solouk, A.; Akbari, S.; Sadeghi, D.; Mirahmadi, F.; Mirzadeh, H. Electrospun Nanofibers Comprising of Silk Fibroin/Gelatin for Drug Delivery Applications: Thyme Essential Oil and Doxycycline Monohydrate Release Study. *J. Biomed. Mater. Res., Part A* **2018**, *106* (4), 1092−1103.

(16) Bakhsheshi-Rad, H. R.; Hadisi, Z.; Hamzah, E.; Ismail, A. F.; Aziz, M.; Kashefian, M. Drug Delivery and Cytocompatibility of Ciprofloxacin Loaded Gelatin Nanofibers-Coated Mg Alloy. *Mater. Lett.* **2017**, *207*, 179−182.

(17) Kamble, P.; Sadarani, B.; Majumdar, A.; Bhullar, S. Nanofiber Based Drug Delivery Systems for Skin: A Promising Therapeutic Approach. *Journal of Drug Delivery Science and Technology* **2017**, *41*, 124−133.

(18) Singh, A.; Rath, G.; Singh, R.; Goyal, A. K. Nanofibers: An Effective Tool for Controlled and Sustained Drug Delivery. *Curr. Drug Delivery* **2018**, *15* (2), 155−166.

(19) Wsoo, M. A.; Shahir, S.; Mohd Bohari, S. P.; Nayan, N. H. M.; Razak, S. I. A. A Review on the Properties of Electrospun Cellulose Acetate and Its Application in Drug Delivery Systems: A New Perspective. *Carbohydr. Res.* **2020**, *491*, 107978.

(20) Irani, M.; Mir Mohamad Sadeghi, G.; Haririan, I. A Novel Biocompatible Drug Delivery System of Chitosan/Temozolomide Nanoparticles Loaded PCL-PU Nanofibers for Sustained Delivery of Temozolomide. *Int. J. Biol. Macromol.* **2017**, *97*, 744−751.

(21) Li, J.; Xu, W.; Li, D.; Liu, T.; Zhang, Y. S.; Ding, J.; Chen, X. Locally Deployable Nanofiber Patch for Sequential Drug Delivery in Treatment of Primary and Advanced Orthotopic Hepatomas. *ACS Nano* **2018**, *12* (7), 6685−6699.

(22) Bhandari, J.; Mishra, H.; Mishra, P. K.; Wimmer, R.; Ahmad, F. J.; Talegaonkar, S. Cellulose Nanofiber Aerogel as a Promising Biomaterial for Customized Oral Drug Delivery. *Int. J. Nanomedicine* **2017**, *12*, 2021−2031.

(23) Hosseinkhani, H.; Hong, P.-D.; Yu, D.-S. Self-Assembled Proteins and Peptides for Regenerative Medicine. *Chem. Rev.* **2013**, *113* (7), 4837−4861.

(24) Cui, H.; Webber, M. J.; Stupp, S. I. Self-Assembly of Peptide Amphiphiles: From Molecules to Nanostructures to Biomaterials. *Peptide Science* **2010**, *94* (1), 1−18.

(25) Arnon, Z.; Vitalis, A.; Levin, A.; Michaels, T.; Caflisch, A.; Knowles, T.; Adler-Abramovich, L.; Gazit, E. Dynamic Microfluidic Control of Supramolecular Peptide Self-Assembly. *Nat. Commun.* **2016**, *7*, 13190.

(26) Webber, M.; Matson, J.; Tamboli, V.; Stupp, S. Controlled Release of Dexamethasone from Peptide Nanofiber Gels to Modulate Inflammatory Response. *Biomaterials* **2012**, *33*, 6823−6832.

(27) Fleming, S.; Ulijn, R. Design of Nanostructures Based on Aromatic Peptide Amphiphiles. *Chem. Soc. Rev.* **2014**, *43*, 8150−8177.

(28) Kalafatovic, D.; Nobis, M.; Son, J.; Anderson, K. I.; Ulijn, R. v. MMP-9 Triggered Self-Assembly of Doxorubicin Nanofiber Depots Halts Tumor Growth. *Biomaterials* **2016**, *98*, 192−202.

(29) Adler-Abramovich, L.; Vaks, L.; Carny, O.; Trudler, D.; Magno, A.; Caflisch, A.; Frenkel, D.; Gazit, E. Phenylalanine Assembly into Toxic Fibrils Suggests Amyloid Etiology in Phenylketonuria. *Nat. Chem. Biol.* **2012**, *8* (8), 701−706.

(30) Webber, M. J.; Newcomb, C. J.; Bitton, R.; Stupp, S. I. Switching of Self-Assembly in a Peptide Nanostructure with a Specific Enzyme. *Soft Matter* **2011**, *7* (20), 9665−9672.

(31) Williams, R. J.; Smith, A. M.; Collins, R.; Hodson, N.; Das, A. K.; Ulijn, R. v. Enzyme-Assisted Self-Assembly under Thermodynamic Control. *Nat. Nanotechnol.* **2009**, *4* (1), 19−24.

(32) Toledano, S.; Williams, R. J.; Jayawarna, V.; Ulijn, R. V. Enzyme-Triggered Self-Assembly of Peptide Hydrogels via Reversed Hydrolysis. *J. Am. Chem. Soc.* **2006**, *128* (4), 1070−1071.

(33) Li, T.; Lu, X.-M.; Zhang, M.-R.; Hu, K.; Li, Z. Peptide-Based Nanomaterials: Self-Assembly, Properties and Applications. *Bioactive Materials* **2022**, *11*, 268−282.

(34) Liu, W.; Liu, K.; Du, H.; Zheng, T.; Zhang, N.; Xu, T.; Pang, B.; Zhang, X.; Si, C.; Zhang, K. Cellulose Nanopaper: Fabrication, Functionalization, and Applications. *Nano-Micro Letters* **2022**, *14* (1), 104.

(35) Ansar, R.; Saqib, S.; Mukhtar, A.; Niazi, M. B. K.; Shahid, M.; Jahan, Z.; Kakar, S. J.; Uzair, B.; Mubashir, M.; Ullah, S.; Khoo, K. S.; Lim, H. R.; Show, P. L. Challenges and Recent Trends with the Development of Hydrogel Fiber for Biomedical Applications. *Chemosphere* **2022**, *287*, 131956.

https://doi.org/10.1021/acsbiomaterials.2c00786
ACS Biomater. Sci. Eng. 2022, 8, 3690−3716

(36) Ahmadi-Aghkand, F.; Gholizadeh-Ghaleh Aziz, S.; Panahi, Y.; Daraee, H.; Gorjikhah, F.; Gholizadeh-Ghaleh Aziz, S.; Hsanzadeh, A.; Akbarzadeh, A. Recent Prospective of Nanofiber Scaffolds Fabrication Approaches for Skin Regeneration. *Artificial Cells, Nanomedicine, and Biotechnology* **2016**, *44* (7), 1635−1641.
(37) Jiang, J.; Chen, S.; Wang, H.; Carlson, M. A.; Gombart, A. F.; Xie, J. CO2-Expanded Nanofiber Scaffolds Maintain Activity of Encapsulated Bioactive Materials and Promote Cellular Infiltration and Positive Host Response. *Acta Biomaterialia* **2018**, *68*, 237−248.
(38) Ghorbani, M.; Mahmoodzadeh, F.; Yavari Maroufi, L.; Nezhad-Mokhtari, P. Electrospun Tetracycline Hydrochloride Loaded Zein/Gum Tragacanth/Poly Lactic Acid Nanofibers for Biomedical Application. *Int. J. Biol. Macromol.* **2020**, *165*, 1312−1322.
(39) Zhao, X.; Sun, X.; Yildirimer, L.; Lang, Q.; Lin, Z. Y.; Zheng, R.; Zhang, Y.; Cui, W.; Annabi, N.; Khademhosseini, A. Cell Infiltrative Hydrogel Fibrous Scaffolds for Accelerated Wound Healing. *Acta Biomaterialia* **2017**, *49*, 66−77.
(40) Chen, W.; Chen, S.; Morsi, Y.; El-Hamshary, H.; El-Newhy, M.; Fan, C.; Mo, X. Superabsorbent 3D Scaffold Based on Electrospun Nanofibers for Cartilage Tissue Engineering. *ACS Appl. Mater. Interfaces* **2016**, *8* (37), 24415−24425.
(41) Li, B.; Liu, Y.; Wei, S.; Huang, Y.; Yang, S.; Xue, Y.; Xuan, H.; Yuan, H. A Solvent System Involved Fabricating Electrospun Polyurethane Nanofibers for Biomedical Applications. *Polymers (Basel)* **2020**, *12* (12), 3038.
(42) Kajdič, S.; Planinšek, O.; Gašperlin, M.; Kocbek, P. Electrospun Nanofibers for Customized Drug-Delivery Systems. *Journal of Drug Delivery Science and Technology. Editions de Sante* **2019**, *51*, 672−681.
(43) Akpan, U. M.; Pellegrini, M.; Obayemi, J. D.; Ezenwafor, T.; Browl, D.; Ani, C. J.; Yiporo, D.; Salifu, A.; Dozie-Nwachukwu, S.; Odusanya, S.; Freeman, J.; Soboyejo, W. O. Prodigiosin-Loaded Electrospun Nanofibers Scaffold for Localized Treatment of Triple Negative Breast Cancer. *Materials Science and Engineering: C* **2020**, *114*, 110976.
(44) Sarkar, K.; Gomez, C.; Zambrano, S.; Ramirez, M.; de Hoyos, E.; Vasquez, H.; Lozano, K. Electrospinning to ForcespinningTM. *Mater. Today* **2010**, *13* (11), 12−14.
(45) Mamidi, N.; Zuníga, A. E.; Villela-Castrejón, J. Engineering and Evaluation of Forcespun Functionalized Carbon Nano-Onions Reinforced Poly (ε-Caprolactone) Composite Nanofibers for PH-Responsive Drug Release. *Materials Science and Engineering: C* **2020**, *112*, 110928.
(46) Mamidi, N.; Delgadillo, R. M. V.; González-Ortiz, A. Engineering of Carbon Nano-Onion Bioconjugates for Biomedical Applications. *Materials Science and Engineering: C* **2021**, *120*, 111698.
(47) Mamidi, N.; Delgadillo, R. M. V.; Castrejón, J. V. Unconventional and Facile Production of a Stimuli-Responsive Multifunctional System for Simultaneous Drug Delivery and Environmental Remediation. *Environmental Science: Nano* **2021**, *8* (7), 2081−2097.
(48) Weng, B.; Xu, F.; Alcoutlabi, M.; Mao, Y.; Lozano, K. Fibrous Cellulose Membrane Mass Produced via Forcespinning® for Lithium-Ion Battery Separators. *Cellulose* **2015**, *22* (2), 1311−1320.
(49) García-Valderrama, E. J.; Mamidi, N.; Antunes-Ricardo, M.; Gutiérrez-Uribe, J. A.; del Angel-Sanchez, K.; Elías-Zúñiga, A. Engineering and Evaluation of Forcespun Gelatin Nanofibers as an Isorhamnetin Glycosides Delivery System. *Pharmaceutics* **2022**, *14* (6), 1116.
(50) Webber, M.; Matson, J.; Tamboli, V.; Stupp, S. Controlled Release of Dexamethasone from Peptide Nanofiber Gels to Modulate Inflammatory Response. *Biomaterials* **2012**, *33*, 6823−6832.
(51) Zhang, P.; Cheetham, A. G.; Lin, Y.-a.; Cui, H. Self-Assembled Tat Nanofibers as Effective Drug Carrier and Transporter. *ACS Nano* **2013**, *7* (7), 5965−5977.
(52) Soukasene, S.; Toft, D. J.; Moyer, T. J.; Lu, H.; Lee, H.-K.; Standley, S. M.; Cryns, V. L.; Stupp, S. I. Antitumor Activity of Peptide Amphiphile Nanofiber-Encapsulated Camptothecin. *ACS Nano* **2011**, *5* (11), 9113−9121.
(53) Kalafatovic, D.; Nobis, M.; Javid, N.; Frederix, P. W. J. M.; Anderson, K. I.; Saunders, B. R.; Ulijn, R. v. MMP-9 Triggered Micelle-to-Fibre Transitions for Slow Release of Doxorubicin. *Biomater. Sci.* **2015**, *3* (2), 246−249.
(54) Yan, G.; He, S.; Chen, G.; Ma, S.; Zeng, A.; Chen, B.; Yang, S.; Tang, X.; Sun, Y.; Xu, F.; Lin, L.; Zeng, X. Highly Flexible and Broad-Range Mechanically Tunable All-Wood Hydrogels with Nanoscale Channels via the Hofmeister Effect for Human Motion Monitoring. *Nano-Micro Letters* **2022**, *14* (1), DOI: 10.1007/s40820-022-00827-3.
(55) Keirouz, A.; Chung, M.; Kwon, J.; Fortunato, G.; Radacsi, N. 2D and 3D Electrospinning Technologies for the Fabrication of Nanofibrous Scaffolds for Skin Tissue Engineering: A Review. *WIREs Nanomedicine and Nanobiotechnology* **2020**, *12* (4), e1626.
(56) Liu, J.-X.; Dong, W.-H.; Mou, X.-J.; Liu, G.-S.; Huang, X.-W.; Yan, X.; Zhou, C.-F.; Jiang, S.; Long, Y.-Z. In Situ Electrospun Zein/Thyme Essential Oil-Based Membranes as an Effective Antibacterial Wound Dressing. *ACS Applied Bio Materials* **2020**, *3* (1), 302−307.
(57) Chantre, C. O.; Gonzalez, G. M.; Ahn, S.; Cera, L.; Campbell, P. H.; Hoerstrup, S. P.; Parker, K. K. Porous Biomimetic Hyaluronic Acid and Extracellular Matrix Protein Nanofiber Scaffolds for Accelerated Cutaneous Tissue Repair. *ACS Appl. Mater. Interfaces* **2019**, *11* (49), 45498−45510.
(58) Mamidi, N.; Gutierrez, H. M. L.; Villela-Castrejon, J.; Isenhart, L.; Barrera, E. V.; Elias-Zuniga, A. Fabrication of Gelatin-Poly-(Epichlorohydrin-Co-Ethylene Oxide) Fiber Scaffolds by Force-spinning® for Tissue Engineering and Drug Release. *MRS Commun.* **2017**, *7* (4), 913−921.
(59) Sun, L.; Gao, W.; Fu, X.; Shi, M.; Xie, W.; Zhang, W.; Zhao, F.; Chen, X. Enhanced Wound Healing in Diabetic Rats by Nanofibrous Scaffolds Mimicking the Basketweave Pattern of Collagen Fibrils in Native Skin. *Biomater Sci.* **2018**, *6* (2), 340−349.
(60) Wu, T.; Xue, J.; Li, H.; Zhu, C.; Mo, X.; Xia, Y. General Method for Generating Circular Gradients of Active Proteins on Nanofiber Scaffolds Sought for Wound Closure and Related Applications. *ACS Appl. Mater. Interfaces* **2018**, *10* (10), 8536−8545.
(61) Cui, W.; Cheng, L.; Hu, C.; Li, H.; Zhang, Y.; Chang, J. Electrospun Poly(L-Lactide) Fiber with Ginsenoside Rg3 for Inhibiting Scar Hyperplasia of Skin. *PLoS One* **2013**, *8* (7), e68771.
(62) Zhu, Y.; Liao, Y.; Zhang, Y.; Shekh, M. I.; Zhang, J.; You, Z.; Du, B.; Lian, C.; He, Q. Novel Nanofibrous Membrane-Supporting Stem Cell Sheets for Plasmid Delivery and Cell Activation to Accelerate Wound Healing. *Bioengineering & Translational Medicine* **2021**, *7* (1), e10244.
(63) Abolghasemzade, S.; Pourmadadi, M.; Rashedi, H.; Yazdian, F.; Kianbakht, S.; Navaei-Nigjeh, M. PVA Based Nanofiber Containing CQDs Modified with Silica NPs and Silk Fibroin Accelerates Wound Healing in a Rat Model. *J. Mater. Chem. B* **2021**, *9* (3), 658−676.
(64) Hu, W.; Wang, Z.; Xu, Y.; Wang, X.; Xiao, Y.; Zhang, S.; Wang, J. Remodeling of Inherent Antimicrobial Nanofiber Dressings with Melamine-Modified Fibroin into Neoskin. *J. Mater. Chem. B* **2019**, *7* (21), 3412−3423.
(65) Pham-Nguyen, O.-V.; Shin, J. U.; Kim, H.; Yoo, H. S. Self-Assembled Cell Sheets Composed of Mesenchymal Stem Cells and Gelatin Nanofibers for the Treatment of Full-Thickness Wounds. *Biomaterials Science* **2020**, *8* (16), 4535−4544.
(66) Sever-Bahcekapili, M.; Yilmaz, C.; Demirel, A.; Kilinc, M. C.; Dogan, I.; Caglar, Y. S.; Guler, M. O.; Tekinay, A. B. Neuroactive Peptide Nanofibers for Regeneration of Spinal Cord after Injury. *Macromol. Biosci.* **2021**, *21* (1), 2000234.
(67) Wang, R.; Wang, Z.; Guo, Y.; Li, H.; Chen, Z. Design of a RADA16-Based Self-Assembling Peptide Nanofiber Scaffold for Biomedical Applications. *J. Biomater Sci. Polym. Ed* **2019**, *30* (9), 713−736.
(68) Tang, J. D.; Mura, C.; Lampe, K. J. Stimuli-Responsive, Pentapeptide, Nanofiber Hydrogel for Tissue Engineering. *J. Am. Chem. Soc.* **2019**, *141* (12), 4886−4899.
(69) Yang, S.; Li, X.; Liu, P.; Zhang, M.; Wang, C.; Zhang, B. Multifunctional Chitosan/Polycaprolactone Nanofiber Scaffolds with Varied Dual-Drug Release for Wound-Healing Applications. *ACS Biomaterials Science & Engineering* **2020**, *6* (8), 4666−4676.

https://doi.org/10.1021/acsbiomaterials.2c00786
ACS Biomater. Sci. Eng. 2022, 8, 3690−3716

(70) Li, N.; Xue, F.; Zhang, H.; Sanyour, H. J.; Rickel, A. P.; Uttecht, A.; Fanta, B.; Hu, J.; Hong, Z. Fabrication and Characterization of Pectin Hydrogel Nanofiber Scaffolds for Differentiation of Mesenchymal Stem Cells into Vascular Cells. *ACS Biomaterials Science & Engineering* **2019**, *5* (12), 6511−6519.
(71) Mamidi, N.; Romo, I. L.; Leija Gutiérrez, H. M.; Barrera, E. v; Elías-Zúñiga, A. Development of Forcespun Fiber-Aligned Scaffolds from Gelatin−Zein Composites for Potential Use in Tissue Engineering and Drug Release. *MRS Commun.* **2018**, *8* (3), 885−892.
(72) Mamidi, N.; Romo, I. L.; Barrera, E. v; Elías-Zúñiga, A. High Throughput Fabrication of Curcumin Embedded Gelatin-Polylactic Acid Forcespun Fiber-Aligned Scaffolds for the Controlled Release of Curcumin. *MRS Commun.* **2018**, *8* (4), 1395−1403.
(73) Roy, S.; Kuddannaya, S.; Das, T.; Lee, H. Y.; Lim, J.; Hu, X.; Chee Yoon, Y.; Kim, J. A Novel Approach for Fabricating Highly Tunable and Fluffy Bioinspired 3D Poly(Vinyl Alcohol) (PVA) Fiber Scaffolds. *Nanoscale* **2017**, *9* (21), 7081−7093.
(74) Cai, J.; Xie, X.; Li, D.; Wang, L.; Jiang, J.; Mo, X.; Zhao, J. A Novel Knitted Scaffold Made of Microfiber/Nanofiber Core−Sheath Yarns for Tendon Tissue Engineering. *Biomaterials Science* **2020**, *8* (16), 4413−4425.
(75) Xu, Y.; Shi, G.; Tang, J.; Cheng, R.; Shen, X.; Gu, Y.; Wu, L.; Xi, K.; Zhao, Y.; Cui, W.; Chen, L. ECM-Inspired Micro/Nanofibers for Modulating Cell Function and Tissue Generation. *Science Advances* **2020**, *6* (48), eabc2036.
(76) Nasajpour, A.; Mostafavi, A.; Chlanda, A.; Rinoldi, C.; Sharifi, S.; Ji, M. S.; Ye, M.; Jonas, S. J.; Swieszkowski, W.; Weiss, P. S.; Khademhosseini, A.; Tamayol, A. Cholesteryl Ester Liquid Crystal Nanofibers for Tissue Engineering Applications. *ACS Materials Letters* **2020**, *2* (9), 1067−1073.
(77) Ogueri, K. S.; Laurencin, C. T. Nanofiber Technology for Regenerative Engineering. *ACS Nano* **2020**, *14* (8), 9347−9363.
(78) Li, X.; Cho, B.; Martin, R.; Seu, M.; Zhang, C.; Zhou, Z.; Choi, J. S.; Jiang, X.; Chen, L.; Walia, G.; et al. Nanofiber-Hydrogel Composite–Mediated Angiogenesis for Soft Tissue Reconstruction. *Science Translational Medicine* **2019**, *11* (490), eaau6210.
(79) Niu, Y.; Liu, G.; Chen, C.; Fu, M.; Fu, W.; Zhao, Z.; Xia, H.; Stadler, F. J. Urethral Reconstruction Using an Amphiphilic Tissue-Engineered Autologous Polyurethane Nanofiber Scaffold with Rapid Vascularization Function. *Biomaterials Science* **2020**, *8* (8), 2164−2174.
(80) Qiu, Z.; Zhao, J.; Huang, F.; Bao, L.; Chen, Y.; Yang, K.; Cui, W.; Jin, W. Myocardial Fibrosis Reversion via RhACE2-Electrospun Fibrous Patch for Ventricular Remodeling Prevention. *npj Regenerative Medicine* **2021**, *6* (1), 44.
(81) Xi, K.; Gu, Y.; Tang, J.; Chen, H.; Xu, Y.; Wu, L.; Cai, F.; Deng, L.; Yang, H.; Shi, Q.; Cui, W.; Chen, L. Microenvironment-Responsive Immunoregulatory Electrospun Fibers for Promoting Nerve Function Recovery. *Nat. Commun.* **2020**, *11* (1), 4504.
(82) Wang, J.; Xiong, H.; Zhu, T.; Liu, Y.; Pan, H.; Fan, C.; Zhao, X.; Lu, W. W. Bioinspired Multichannel Nerve Guidance Conduit Based on Shape Memory Nanofibers for Potential Application in Peripheral Nerve Repair. *ACS Nano* **2020**, *14* (10), 12579−12595.
(83) Fang, X.; Guo, H.; Zhang, W.; Fang, H.; Li, Q.; Bai, S.; Zhang, P. Reduced Graphene Oxide−GelMA−PCL Hybrid Nanofibers for Peripheral Nerve Regeneration. *J. Mater. Chem. B* **2020**, *8* (46), 10593−10601.
(84) Lee, S.-J.; Asheghali, D.; Blevins, B.; Timsina, R.; Esworthy, T.; Zhou, X.; Cui, H.; Hann, S. Y.; Qiu, X.; Tokarev, A.; Minko, S.; Zhang, L. G. Touch-Spun Nanofibers for Nerve Regeneration. *ACS Appl. Mater. Interfaces* **2020**, *12* (2), 2067−2075.
(85) Asadian, M.; Chan, K. V.; Norouzi, M.; Grande, S.; Cools, P.; Morent, R.; de Geyter, N. Fabrication and Plasma Modification of Nanofibrous Tissue Engineering Scaffolds. *Nanomaterials* **2020**, *10* (1), 119.
(86) Jin, G.; He, R.; Sha, B.; Li, W.; Qing, H.; Teng, R.; Xu, F. Electrospun Three-Dimensional Aligned Nanofibrous Scaffolds for Tissue Engineering. *Materials Science and Engineering: C* **2018**, *92*, 995−1005.
(87) Hatamzadeh, M.; Najafi-Moghadam, P.; Beygi-Khosrowshahi, Y.; Massoumi, B.; Jaymand, M. Electrically Conductive Nanofibrous Scaffolds Based on Poly(Ethylene Glycol)s-Modified Polyaniline and Poly(ε-Caprolactone) for Tissue Engineering Applications. *RSC Adv.* **2016**, *6* (107), 105371−105386.
(88) Kim, J. I.; Kim, J. Y.; Park, C. H. Fabrication of Transparent Hemispherical 3D Nanofibrous Scaffolds with Radially Aligned Patterns via a Novel Electrospinning Method. *Sci. Rep.* **2018**, *8* (1), 3424.
(89) Shah Hosseini, N.; Simon, B.; Messaoud, T.; Khenoussi, N.; Schacher, L.; Adolphe, D. Quantitative Approaches of Nanofibers Organization for Biomedical Patterned Nanofibrous Scaffold by Image Analysis. *J. Biomed Mater. Res. A* **2018**, *106* (11), 2963−2972.
(90) Stocco, T. D.; Bassous, N. J.; Zhao, S.; Granato, A. E. C.; Webster, T. J.; Lobo, A. O. Nanofibrous Scaffolds for Biomedical Applications. *Nanoscale* **2018**, *10* (26), 12228−12255.
(91) Wu, S.; Duan, B.; Liu, P.; Zhang, C.; Qin, X.; Butcher, J. T. Fabrication of Aligned Nanofiber Polymer Yarn Networks for Anisotropic Soft Tissue Scaffolds. *ACS Appl. Mater. Interfaces* **2016**, *8* (26), 16950−16960.
(92) Zhang, K.; Bai, X.; Yuan, Z.; Cao, X.; Jiao, X.; Qin, Y.; Wen, Y.; Zhang, X. Cellular Nanofiber Structure with Secretory Activity-Promoting Characteristics for Multicellular Spheroid Formation and Hair Follicle Regeneration. *ACS Appl. Mater. Interfaces* **2020**, *12* (7), 7931−7941.
(93) Afewerki, S.; Bassous, N.; Harb, S. V.; Corat, M. A. F.; Maharjan, S.; Ruiz-Esparza, G. U.; de Paula, M. M. M.; Webster, T. J.; Tim, C. R.; Viana, B. C.; Wang, D.; Wang, X.; Marciano, F. R.; Lobo, A. O. Engineering Multifunctional Bactericidal Nanofibers for Abdominal Hernia Repair. *Communications Biology* **2021**, *4* (1), 233.
(94) Zarei, M.; Samimi, A.; Khorram, M.; Abdi, M. M.; Golestaneh, S. I. Fabrication and Characterization of Conductive Polypyrrole/Chitosan/Collagen Electrospun Nanofiber Scaffold for Tissue Engineering Application. *Int. J. Biol. Macromol.* **2021**, *168*, 175−186.
(95) Yan, J.; Wang, Y.; Li, X.; Guo, D.; Zhou, Z.; Bai, G.; Li, J.; Huang, N.; Diao, J.; Li, Y.; He, W.; Liu, W.; Tao, K. A Bionic Nano-Band-Aid Constructed by the Three-Stage Self-Assembly of Peptides for Rapid Liver Hemostasis. *Nano Lett.* **2021**, *21* (17), 7166−7174.
(96) Porrelli, D.; Mardirossian, M.; Musciacchio, L.; Pacor, M.; Berton, F.; Crosera, M.; Turco, G. Antibacterial Electrospun Polycaprolactone Membranes Coated with Polysaccharides and Silver Nanoparticles for Guided Bone and Tissue Regeneration. *ACS Appl. Mater. Interfaces* **2021**, *13* (15), 17255−17267.
(97) Ramalingam, R.; Dhand, C.; Mayandi, V.; Leung, C. M.; Ezhilarasu, H.; Karuppannan, S. K.; Prasannan, P.; Ong, S. T.; Sunderasan, N.; Kaliappan, I.; Kamruddin, M.; Barathi, V. A.; Verma, N. K.; Ramakrishna, S.; Lakshminarayanan, R.; Arunachalam, K. D. Core-Shell Structured Antimicrobial Nanofiber Dressings Containing Herbal Extract and Antibiotics Combination for the Prevention of Biofilms and Promotion of Cutaneous Wound Healing. *ACS Appl. Mater. Interfaces* **2021**, *13* (21), 24356−24369.
(98) Shahriari-Khalaji, M.; Hu, G.; Chen, L.; Cao, Z.; Andreeva, T.; Xiong, X.; Krastev, R.; Hong, F. F. Functionalization of Amino-alkylsilane-Grafted Bacterial Nanocellulose with ZnO-NPs-Doped Pullulan Electrospun Nanofibers for Multifunctional Wound Dressing. *ACS Biomaterials Science & Engineering* **2021**, *7* (8), 3933−3946.
(99) Jirofti, N.; Golandi, M.; Movaffagh, J.; Ahmadi, F. S.; Kalalinia, F. Improvement of the Wound-Healing Process by Curcumin-Loaded Chitosan/Collagen Blend Electrospun Nanofibers: In Vitro and In Vivo Studies. *ACS Biomaterials Science & Engineering* **2021**, *7* (8), 3886−3897.
(100) Ding, Z.; Zhang, Y.; Guo, P.; Duan, T.; Cheng, W.; Guo, Y.; Zheng, X.; Lu, G.; Lu, Q.; Kaplan, D. L. Injectable Desferrioxamine-Laden Silk Nanofiber Hydrogels for Accelerating Diabetic Wound Healing. *ACS Biomaterials Science & Engineering* **2021**, *7* (3), 1147−1158.
(101) Chen, S.; Carlson, M. A.; Li, X.; Siddique, A.; Zhu, W.; Xie, J. Minimally Invasive Delivery of 3D Shape Recoverable Constructs

with Ordered Structures for Tissue Repair. *ACS Biomater Sci. Eng.* **2021**, *7* (6), 2204−2211.
(102) Chu, B.; He, J.-M.; Liu, L.-L.; Wu, C.-X.; You, L.-L.; Li, X.-L.; Wang, S.; Chen, C.-S.; Tu, M. Proangiogenic Peptide Nanofiber Hydrogels for Wound Healing. *ACS Biomaterials Science & Engineering* **2021**, *7* (3), 1100−1110.
(103) Guo, W.; Feng, W.; Huang, J.; Zhang, J.; Fan, X.; Ma, S.; Li, M.; Zhan, J.; Cai, Y.; Chen, M. Supramolecular Self-Assembled Nanofibers Efficiently Activate the Precursor of Hepatocyte Growth Factor for Angiogenesis in Myocardial Infarction Therapy. *ACS Appl. Mater. Interfaces* **2021**, *13* (19), 22131−22141.
(104) Maggay, I. V.; Venault, A.; Fang, C.-Y.; Yang, C.-C.; Hsu, C.-H.; Chou, C.-Y.; Ishihara, K.; Chang, Y. Zwitterionized Nanofibrous Poly(Vinylidene Fluoride) Membranes for Improving the Healing of Diabetic Wounds. *ACS Biomaterials Science & Engineering* **2021**, *7* (2), 562−576.
(105) Sadeghzadeh, H.; Mehdipour, A.; Dianat-Moghadam, H.; Salehi, R.; Khoshfetrat, A. B.; Hassani, A.; Mohammadnejad, D. PCL/Col I-Based Magnetic Nanocomposite Scaffold Provides an Osteoinductive Environment for ADSCs in Osteogenic Cues-Free Media Conditions. *Stem Cell Research & Therapy* **2022**, *13* (1), 143.
(106) Wang, L.; Qiu, Y.; Guo, Y.; Si, Y.; Liu, L.; Cao, J.; Yu, J.; Li, X.; Zhang, Q.; Ding, B. Smart, Elastic, and Nanofiber-Based 3D Scaffolds with Self-Deploying Capability for Osteoporotic Bone Regeneration. *Nano Lett.* **2019**, *19* (12), 9112−9120.
(107) Wang, D.; Jang, J.; Kim, K.; Kim, J.; Park, C. B. Tree to Bone": Lignin/Polycaprolactone Nanofibers for Hydroxyapatite Biomineralization. *Biomacromolecules* **2019**, *20* (7), 2684−2693.
(108) Nifant'ev, I.; Gavrilov, D.; Tavtorkin, A.; Chinova, M.; Besprozvannykh, V.; Komarov, P.; Zaitsev, V.; Podoprigora, I.; Ivchenko, P. Antibacterial Poly(ε-CL)/Hydroxyapatite Electrospun Fibers Reinforced by Poly(ε-CL)-b-Poly(Ethylene Phosphoric Acid). *International Journal of Molecular Sciences* **2021**, *22* (14), 7690.
(109) Li, R.; Wang, H.; John, J. v; Song, H.; Teusink, M. J.; Xie, J. 3D Hybrid Nanofiber Aerogels Combining with Nanoparticles Made of a Biocleavable and Targeting Polycation and MiR-26a for Bone Repair. *Adv. Funct Mater.* **2020**, *30* (49), 2005531.
(110) Zhang, Y.; Wang, T.; Li, J.; Cui, X.; Jiang, M.; Zhang, M.; Wang, X.; Zhang, W.; Liu, Z. Bilayer Membrane Composed of Mineralized Collagen and Chitosan Cast Film Coated With Berberine-Loaded PCL/PVP Electrospun Nanofiber Promotes Bone Regeneration. *Frontiers in Bioengineering and Biotechnology* **2021**, *19*, 9.
(111) Cheng, L.; Chen, Z.; Cai, Z.; Zhao, J.; Lu, M.; Liang, J.; Wang, F.; Qi, J.; Cui, W.; Deng, L. Bioinspired Functional Black Phosphorus Electrospun Fibers Achieving Recruitment and Biomineralization for Staged Bone Regeneration. *Small* **2020**, *16* (50), 2005433.
(112) Abouzeid, R. E.; Khiari, R.; Beneventi, D.; Dufresne, A. Biomimetic Mineralization of Three-Dimensional Printed Alginate/TEMPO-Oxidized Cellulose Nanofibril Scaffolds for Bone Tissue Engineering. *Biomacromolecules* **2018**, *19* (11), 4442−4452.
(113) Cheng, Z.; Ye, Z.; Natan, A.; Ma, Y.; Li, H.; Chen, Y.; Wan, L.; Aparicio, C.; Zhu, H. Bone-Inspired Mineralization with Highly Aligned Cellulose Nanofibers as Template. *ACS Appl. Mater. Interfaces* **2019**, *11* (45), 42486−42495.
(114) Cheng, G.; Yin, C.; Tu, H.; Jiang, S.; Wang, Q.; Zhou, X.; Xing, X.; Xie, C.; Shi, X.; Du, Y.; Deng, H.; Li, Z. Controlled Co-Delivery of Growth Factors through Layer-by-Layer Assembly of Core−Shell Nanofibers for Improving Bone Regeneration. *ACS Nano* **2019**, *13* (6), 6372−6382.
(115) Jin, S.; Sun, F.; Zou, Q.; Huang, J.; Zuo, Y.; Li, Y.; Wang, S.; Cheng, L.; Man, Y.; Yang, F.; Li, J. Fish Collagen and Hydroxyapatite Reinforced Poly(Lactide-Co-Glycolide) Fibrous Membrane for Guided Bone Regeneration. *Biomacromolecules* **2019**, *20* (5), 2058−2067.
(116) Wang, R.; Shi, M.; Xu, F.; Qiu, Y.; Zhang, P.; Shen, K.; Zhao, Q.; Yu, J.; Zhang, Y. Graphdiyne-Modified TiO2 Nanofibers with Osteoinductive and Enhanced Photocatalytic Antibacterial Activities to Prevent Implant Infection. *Nat. Commun.* **2020**, *11* (1), 4465.
(117) Hwang, T. I.; Kim, J. I.; Lee, J.; Moon, J. Y.; Lee, J. C.; Joshi, M. K.; Park, C. H.; Kim, C. S. In Situ Biological Transmutation of Catalytic Lactic Acid Waste into Calcium Lactate in a Readily Processable Three-Dimensional Fibrillar Structure for Bone Tissue Engineering. *ACS Appl. Mater. Interfaces* **2020**, *12* (16), 18197−18210.
(118) Chang, B.; Ma, C.; Liu, X. Nanofibers Regulate Single Bone Marrow Stem Cell Osteogenesis via FAK/RhoA/YAP1 Pathway. *ACS Appl. Mater. Interfaces* **2018**, *10* (39), 33022−33031.
(119) Yahia, S.; Khalil, I. A.; El-Sherbiny, I. M. Sandwich-Like Nanofibrous Scaffolds for Bone Tissue Regeneration. *ACS Appl. Mater. Interfaces* **2019**, *11* (32), 28610−28620.
(120) Zhai, Y.; Schilling, K.; Wang, T.; el Khatib, M.; Vinogradov, S.; Brown, E. B.; Zhang, X. Spatiotemporal Blood Vessel Specification at the Osteogenesis and Angiogenesis Interface of Biomimetic Nanofiber-Enabled Bone Tissue Engineering. *Biomaterials* **2021**, *276*, 121041.
(121) Mi, X.; Gupte, M. J.; Zhang, Z.; Swanson, W. B.; McCauley, L. K.; Ma, P. X. Three-Dimensional Electrodeposition of Calcium Phosphates on Porous Nanofibrous Scaffolds and Their Controlled Release of Calcium for Bone Regeneration. *ACS Appl. Mater. Interfaces* **2020**, *12* (29), 32503−32513.
(122) Lee, S. S.; Santschi, M.; Ferguson, S. J. A Biomimetic Macroporous Hybrid Scaffold with Sustained Drug Delivery for Enhanced Bone Regeneration. *Biomacromolecules* **2021**, *22* (6), 2460−2471.
(123) Li, B.; Chen, Y.; He, J.; Zhang, J.; Wang, S.; Xiao, W.; Liu, Z.; Liao, X. Biomimetic Membranes of Methacrylated Gelatin/Nano-hydroxyapatite/Poly(l-Lactic Acid) for Enhanced Bone Regeneration. *ACS Biomaterials Science & Engineering* **2020**, *6* (12), 6737−6747.
(124) Zhang, S.; Zhao, G.; Wang, J.; Xie, C.; Liang, W.; Chen, K.; Wen, Y.; Li, X. Organic Solvent-Free Preparation of Chitosan Nanofibers with High Specific Surface Charge and Their Application in Biomaterials. *ACS Appl. Mater. Interfaces* **2021**, *13* (10), 12347−12358.
(125) Zhang, X.; Liu, W.; Liu, J.; Hu, Y.; Dai, H. Poly-ε-Caprolactone/Whitlockite Electrospun Bionic Membrane with an Osteogenic−Angiogenic Coupling Effect for Periosteal Regeneration. *ACS Biomaterials Science & Engineering* **2021**, *7* (7), 3321−3331.
(126) Yao, J.; Liu, Z.; Ma, W.; Dong, W.; Wang, Y.; Zhang, H.; Zhang, M.; Sun, D. Three-Dimensional Coating of SF/PLGA Coaxial Nanofiber Membranes on Surfaces of Calcium Phosphate Cement for Enhanced Bone Regeneration. *ACS Biomaterials Science & Engineering* **2020**, *6* (5), 2970−2984.
(127) Ding, Z.; Lu, G.; Cheng, W.; Xu, G.; Zuo, B.; Lu, Q.; Kaplan, D. L. Tough Anisotropic Silk Nanofiber Hydrogels with Osteoinductive Capacity. *ACS Biomaterials Science & Engineering* **2020**, *6* (4), 2357−2367.
(128) Geng, M.; Zhang, Q.; Gu, J.; Yang, J.; Du, H.; Jia, Y.; Zhou, X.; He, C. Construction of a Nanofiber Network within 3D Printed Scaffolds for Vascularized Bone Regeneration. *Biomaterials Science* **2021**, *9* (7), 2631−2646.
(129) Shi, R.; Zhang, J.; Niu, K.; Li, W.; Jiang, N.; Li, J.; Yu, Q.; Wu, C. Electrospun Artificial Periosteum Loaded with DFO Contributes to Osteogenesis via the TGF-B1/Smad2 Pathway. *Biomaterials Science* **2021**, *9* (6), 2090−2102.
(130) Zhang, Y.; Li, J.; Soleimani, M.; Giacomini, F.; Friedrich, H.; Truckenmüller, R.; Habibovic, P. Biodegradable Elastic Sponge from Nanofibrous Biphasic Calcium Phosphate Ceramic as an Advanced Material for Regenerative Medicine. *Adv. Funct. Mater.* **2021**, *31* (40), 2102911.
(131) Du, Z.; Zhao, Z.; Liu, H.; Liu, X.; Zhang, X.; Huang, Y.; Leng, H.; Cai, Q.; Yang, X. Macroporous Scaffolds Developed from CaSiO3 Nanofibers Regulating Bone Regeneration via Controlled Calcination. *Materials Science and Engineering: C* **2020**, *113*, 111005.
(132) He, B.; Zhao, J.; Ou, Y.; Jiang, D. Biofunctionalized Peptide Nanofiber-Based Composite Scaffolds for Bone Regeneration. *Materials Science and Engineering: C* **2018**, *90*, 728−738.

https://doi.org/10.1021/acsbiomaterials.2c00786
ACS Biomater. Sci. Eng. 2022, 8, 3690−3716

(133) Li, L.; Liu, W.; Zhao, Y.; Ma, P.; Zha, S.; Chen, P.; Lu, H.; Jiang, X.; Wan, S.; Luo, J.; Dai, Q.; Hu, J.; Utomo, Y. K. S.; Han, X.; Yang, Z.; Yang, L.; He, Q. Dual-Peptide-Functionalized Nanofibrous Scaffolds Recruit Host Endothelial Progenitor Cells for Vasculogenesis to Repair Calvarial Defects. *ACS Appl. Mater. Interfaces* **2020**, *12* (3), 3474−3493.
(134) Sousa, M. G. C.; Maximiano, M. R.; Costa, R. A.; Rezende, T. M. B.; Franco, O. L. Nanofibers as Drug-Delivery Systems for Infection Control in Dentistry. *Expert Opinion on Drug Delivery* **2020**, *17* (7), 919−930.
(135) Karczewski, A.; Feitosa, S. A.; Hamer, E. I.; Pankajakshan, D.; Gregory, R. L.; Spolnik, K. J.; Bottino, M. C. Clindamycin-Modified Triple Antibiotic Nanofibers: A Stain-Free Antimicrobial Intracanal Drug Delivery System. *Journal of Endodontics* **2018**, *44* (1), 155−162.
(136) Ho, M. H.; Claudia, J. C.; Tai, W. C.; Huang, K. Y.; Lai, C. H.; Chang, C. H.; Chang, Y. C.; Wu, Y. C.; Kuo, M. Y.; Chang, P. C. The Treatment Response of Barrier Membrane with Amoxicillin-Loaded Nanofibers in Experimental Periodontitis. *J. Periodontol* **2021**, *92* (6), 886−895.
(137) Bottino, M. C.; Münchow, E. A.; Albuquerque, M. T. P.; Kamocki, K.; Shahi, R.; Gregory, R. L.; Chu, T.-M. G.; Pankajakshan, D. Tetracycline-Incorporated Polymer Nanofibers as a Potential Dental Implant Surface Modifier. *Journal of Biomedical Materials Research Part B: Applied Biomaterials* **2017**, *105* (7), 2085−2092.
(138) Zafar, M.; Najeeb, S.; Khurshid, Z.; Vazirzadeh, M.; Zohaib, S.; Najeeb, B.; Sefat, F. Potential of Electrospun Nanofibers for Biomedical and Dental Applications. *Materials (Basel)* **2016**, *9* (2), 73.
(139) Panchbhai, A. 12 - Nanotechnology in Dentistry. In *Applications of Nanocomposite Materials in Dentistry*; Asiri, A. M., Inamuddin, Mohammad, A., Eds.; Woodhead Publishing, 2019; pp 191−203.
(140) Ye, K.; Kuang, H.; You, Z.; Morsi, Y.; Mo, X. Electrospun Nanofibers for Tissue Engineering with Drug Loading and Release. *Pharmaceutics* **2019**, *11* (4), 182.
(141) Zafar, M. S.; Alnazzawi, A. A.; Alrahabi, M.; Fareed, M. A.; Najeeb, S.; Khurshid, Z. 18 - Nanotechnology and Nanomaterials in Dentistry. In *Advanced Dental Biomaterials*; Khurshid, Z., Najeeb, S., Zafar, M. S., Sefat, F., Eds.; Woodhead Publishing, 2019; pp 477−505.
(142) Sihivahanan, D.; Nandini, V.; Rajesh, E.; Anitha, N. Goethite Nanofibers as Bio-Fillers in Dental Composite Resin. *Indian Journal of Forensic Medicine & Toxicology* **2020**, *14* (4), 1488−1491.
(143) Berton, F.; Porrelli, D.; di Lenarda, R.; Turco, G. A Critical Review on the Production of Electrospun Nanofibres for Guided Bone Regeneration in Oral Surgery. *Nanomaterials (Basel)* **2020**, *10* (1), 16.
(144) Bako, J.; Daroczi, L.; Csaba Hegedus, F. K. Biodegradable Polymer Based Electrospun Nanofibers for Dental Applications. *J Biotechnol. Biomater.* **2018**, *8*, 95−96.
(145) Ghasemi Hamidabadi, H.; Rezvani, Z.; Nazm Bojnordi, M.; Shirinzadeh, H.; Seifalian, A. M.; Joghataei, M. T.; Razaghpour, M.; Alibakhshi, A.; Yazdanpanah, A.; Salimi, M.; Mozafari, M.; Urbanska, A. M.; Reis, R. L.; Kundu, S. C.; Gholipourmalekabadi, M. Chitosan-Intercalated Montmorillonite/Poly(Vinyl Alcohol) Nanofibers as a Platform to Guide Neuronlike Differentiation of Human Dental Pulp Stem Cells. *ACS Appl. Mater. Interfaces* **2017**, *9* (13), 11392−11404.
(146) Mohandesnezhad, S.; Pilehvar-Soltanahmadi, Y.; Alizadeh, E.; Goodarzi, A.; Davaran, S.; Khatamian, M.; Zarghami, N.; Samiei, M.; Aghazadeh, M.; Akbarzadeh, A. In Vitro Evaluation of Zeolite-NHA Blended PCL/PLA Nanofibers for Dental Tissue Engineering. *Mater. Chem. Phys.* **2020**, *252*, 123152.
(147) Pankajakshan, D.; Albuquerque, M. T. P.; Bottino, M. C. 16 - Electrospun Nanofibers for Regenerative Dentistry. In *Electrospun Materials for Tissue Engineering and Biomedical Applications*; Uyar, T., Kny, E., Eds.; Woodhead Publishing, 2017; pp 357−384.
(148) Borges, A. L. S.; Tribst, J. P. M.; Dal Piva, A. M. O.; Souza, A. C. O. In Vitro Evaluation of Multi-Walled Carbon Nanotube Reinforced Nanofibers Composites for Dental Application. *International Journal of Polymeric Materials and Polymeric Biomaterials* **2020**, *69* (16), 1015−1022.
(149) Amiri, P.; Talebi, Z.; Semnani, D.; Bagheri, R.; Fashandi, H. Improved Performance of Bis-GMA Dental Composites Reinforced with Surface-Modified PAN Nanofibers. *J. Mater. Sci.: Mater. Med.* **2021**, *32* (7), 82.
(150) Yancey, E. M.; Lien, W.; Nuttall, C. S.; Brewster, J. A.; Roberts, H. W.; Vandewalle, K. S. Properties of a New Nanofiber Restorative Composite. *Operative Dentistry* **2019**, *44* (1), 34−41.
(151) Kukulka, E. C.; Archangelo, K. C.; Santos, J. D.; de Souza, J. R.; Borges, A. L. S. Development of Electrospun-Based Polyetherimide Fibers and Diameter Analysis for Potential Use in Dental Materials. *Brazilian Dental Science* **2021**, *24* (2), DOI: 10.14295/bds.2021.v24i2.2107.
(152) El-Saadany, A.; El-Safty, S.; Abdel Karim, U.; Kenawy, E.-R. Reinforcing Experimental Resin-Composites with Synthesized Zirconia and Alumina Nanofibers: Evaluation of Cuspal Flexure, Flexural Strength, Flexural Modulus and Fracture Toughness. *Tanta Dental Journal* **2019**, *16* (3), 149−162.
(153) Seo, S.-J.; Kim, H.-W.; Lee, J.-H. Electrospun Nanofibers Applications in Dentistry. *J. Nanomater.* **2016**, *2016*, 5931946.
(154) Boda, S. K.; Wang, H.; John, J. v; Reinhardt, R. A.; Xie, J. Dual Delivery of Alendronate and E7-BMP-2 Peptide via Calcium Chelation to Mineralized Nanofiber Fragments for Alveolar Bone Regeneration. *ACS Biomaterials Science & Engineering* **2020**, *6* (4), 2368−2375.
(155) Bosworth, L. Travelling along the Clinical Roadmap: Developing Electrospun Scaffolds for Tendon Repair. *Conference Papers in Science* **2014**, *2014*, 1−6.
(156) Arenbergerova, M.; Arenberger, P.; Bednar, M.; Kubat, P.; Mosinger, J. Light-Activated Nanofibre Textiles Exert Antibacterial Effects in the Setting of Chronic Wound Healing. *Experimental Dermatology* **2012**, *21* (8), 619−624.
(157) Chaturvedi, T.; Srivastava, R.; Srivastava, A.; Gupta, V.; Verma, P. Evaluation of Metronidazole Nanofibers in Patients with Chronic Periodontitis: A Clinical Study. *Int. J. Pharm. Investig* **2012**, *2*, 213−217.
(158) Chaturvedi, T. Doxycycline Poly E-Caprolactone Nanofibers in Patients with Chronic Periodontitis − A Clinical Evaluation. *J. Clin. Diagn. Res.* **2013**, DOI: 10.7860/JCDR/2013/5858.3519.
(159) Zhou, G.; Jiang, H.; Yin, Z.; Liu, Y.; Zhang, Q.; Zhang, C.; Pan, B.; Zhou, J.; Zhou, X.; Sun, H.; Li, D.; He, A.; Zhang, Z.; Zhang, W.; Liu, W.; Cao, Y. In Vitro Regeneration of Patient-Specific Ear-Shaped Cartilage and Its First Clinical Application for Auricular Reconstruction. *EBioMedicine* **2018**, *28*, 287−302.
(160) He, R.; Wang, K.; Ren, J.; Zhang, W.; Wang, Z.; Deng, K.; Shi, Y.; Luo, Y.; Yuan, Y.; Xu, T.; Zhu, L. Efficacy of a Synthetic Biomimetic Skin Substitute of PLLA/Gelatin Nanofiber Membrane in Facilitating Chronic Cutaneous Wound Healing. *Materials Technology* **2020**, *35*, 872−880.
(161) Alamein, M. A.; Liu, Q.; Stephens, S.; Skabo, S.; Warnke, F.; Bourke, R.; Heiner, P.; Warnke, P. H. Nanospiderwebs: Artificial 3D Extracellular Matrix from Nanofibers by Novel Clinical Grade Electrospinning for Stem Cell Delivery. *Adv. Healthcare Mater.* **2013**, *2* (5), 702−717.
(162) Chen, W.; Chen, S.; Morsi, Y.; El-Hamshary, H.; El-Newhy, M.; Fan, C.; Mo, X. Superabsorbent 3D Scaffold Based on Electrospun Nanofibers for Cartilage Tissue Engineering. *ACS Appl. Mater. Interfaces* **2016**, *8* (37), 24415−24425.
(163) Rivelli, G. G.; Perez, A. C.; Silva, P. H. R.; Gomes, E. C.; de, L.; Moreira, C. P.; de, S.; Tamashiro, E.; Valera, F. C. P.; Anselmo-Lima, W. T.; Pianetti, G. A.; Silva-Cunha, A.; et al. Biodegradable Electrospun Nanofibers: A New Approach For Rhinosinusitis Treatment. *European Journal of Pharmaceutical Sciences* **2021**, *163*, 105852.
(164) Erdmann, K.; Ringel, J.; Hampel, S.; Wirth, M. P.; Fuessel, S. Carbon Nanomaterials Sensitize Prostate Cancer Cells to Docetaxel and Mitomycin C via Induction of Apoptosis and Inhibition of Proliferation. *Beilstein Journal of Nanotechnology* **2017**, *8*, 1307−1317.

(165) Naskar, D.; Ghosh, A. K.; Mandal, M.; Das, P.; Nandi, S. K.; Kundu, S. C. Dual Growth Factor Loaded Nonmulberry Silk Fibroin/Carbon Nanofiber Composite 3D Scaffolds for in Vitro and in Vivo Bone Regeneration. *Biomaterials* **2017**, *136*, 67−85.
(166) Deepthi, S.; Nivedhitha Sundaram, M.; Deepti Kadavan, J.; Jayakumar, R. Layered Chitosan-Collagen Hydrogel/Aligned PLLA Nanofiber Construct for Flexor Tendon Regeneration. *Carbohydr. Polym.* **2016**, *153*, 492−500.
(167) Meamar, R.; Chegini, S.; Varshosaz, J.; Aminorroaya, A.; Amini, M.; Siavosh, M. Alleviating Neuropathy of Diabetic Foot Ulcer by Co-Delivery of Venlafaxine and Matrix Metalloproteinase Drug-Loaded Cellulose Nanofiber Sheets: Production, in Vitro Characterization and Clinical Trial. *Pharmacological Reports* **2021**, *73* (3), 806−819.
(168) Golestannejad, Z.; Khozeimeh, F.; Mehrasa, M.; Mirzaeei, S.; Sarfaraz, D. A Novel Drug Delivery System Using Acyclovir Nanofiber Patch for Topical Treatment of Recurrent Herpes Labialis: A Randomized Clinical Trial. *Clinical and Experimental Dental Research* **2022**, *8* (1), 184−190.
(169) Sun, X.; Yu, Z.; Cai, Z.; Yu, L.; Lv, Y. Voriconazole Composited Polyvinyl Alcohol/Hydroxypropyl-β-Cyclodextrin Nanofibers for Ophthalmic Delivery. *PLoS One* **2016**, *11* (12), e0167961.
(170) Goonoo, N.; Bhaw-Luximon, A.; Jhurry, D. In Vitro and in Vivo Cytocompatibility of Electrospun Nanofiber Scaffolds for Tissue Engineering Applications. *RSC Adv.* **2014**, *4* (60), 31618−31642.
(171) Kumar, A.; Sharma, G.; Naushad, M.; Al-Muhtaseb, A. H.; García-Peñas, A.; Mola, G. T.; Si, C.; Stadler, F. J. Bio-Inspired and Biomaterials-Based Hybrid Photocatalysts for Environmental Detoxification: A Review. *Chemical Engineering Journal* **2020**, *382*, 122937.
(172) Liu, S.; Low, Z.-X.; Xie, Z.; Wang, H. TEMPO-Oxidized Cellulose Nanofibers: A Renewable Nanomaterial for Environmental and Energy Applications. *Advanced Materials Technologies* **2021**, *6* (7), 2001180.
(173) Wang, M.; Wang, K.; Yang, Y.; Liu, Y.; Yu, D.-G. Electrospun Environment Remediation Nanofibers Using Unspinnable Liquids as the Sheath Fluids: A Review. *Polymers (Basel)* **2020**, *12* (1), 103.
(174) Aldalbahi, A.; El-Naggar, M. E.; El-Newehy, M. H.; Rahaman, M.; Hatshan, M. R.; Khattab, T. A. Effects of Technical Textiles and Synthetic Nanofibers on Environmental Pollution. *Polymers (Basel)* **2021**, *13* (1), 155.
(175) Pant, B.; Ojha, G. P.; Kim, H.-Y.; Park, M.; Park, S.-J. Fly-Ash-Incorporated Electrospun Zinc Oxide Nanofibers: Potential Material for Environmental Remediation. *Environ. Pollut.* **2019**, *245*, 163−172.
(176) Malwal, D.; Gopinath, P. Efficient Adsorption and Antibacterial Properties of Electrospun CuO-ZnO Composite Nanofibers for Water Remediation. *Journal of Hazardous Materials* **2017**, *321*, 611−621.
(177) Riva, L.; Pastori, N.; Panozzo, A.; Antonelli, M.; Punta, C. Nanostructured Cellulose-Based Sorbent Materials for Water Decontamination from Organic Dyes. *Nanomaterials* **2020**, *10* (8), 1570.
(178) Stefelova, J.; Slovak, V.; Siqueira, G.; Olsson, R. T.; Tingaut, P.; Zimmermann, T.; Sehaqui, H. Drying and Pyrolysis of Cellulose Nanofibers from Wood, Bacteria, and Algae for Char Application in Oil Absorption and Dye Adsorption. *ACS Sustainable Chemistry & Engineering* **2017**, *5* (3), 2679−2692.
(179) Gandavadi, D.; Sundarrajan, S.; Ramakrishna, S. Bio-Based Nanofibers Involved in Wastewater Treatment. *Macromol. Mater. Eng.* **2019**, *304* (11), 1900345.
(180) Ma, Q.; Cheng, H.; Yu, Y.; Huang, Y.; Lu, Q.; Han, S.; Chen, J.; Wang, R.; Fane, A. G.; Zhang, H. Preparation of Superhydrophilic and Underwater Superoleophobic Nanofiber-Based Meshes from Waste Glass for Multifunctional Oil/Water Separation. *Small* **2017**, *13* (19), 1700391.
(181) Attia, H.; Alexander, S.; Wright, C. J.; Hilal, N. Superhydrophobic Electrospun Membrane for Heavy Metals Removal by Air Gap Membrane Distillation (AGMD). *Desalination* **2017**, *420*, 318−329.
(182) Talreja, N.; Verma, N.; Kumar, D. Carbon Bead-Supported Ethylene Diamine-Functionalized Carbon Nanofibers: An Efficient Adsorbent for Salicylic Acid. *CLEAN Soil, Air, Water* **2016**, *44* (11), 1461−1470.
(183) Xu, Q.; Wang, Y.; Jin, L.; Wang, Y.; Qin, M. Adsorption of Cu (II), Pb (II) and Cr (VI) from Aqueous Solutions Using Black Wattle Tannin-Immobilized Nanocellulose. *Journal of Hazardous Materials* **2017**, *339*, 91−99.
(184) Al-Meer, S.; Ghouri, Z. K.; Elsaid, K.; Easa, A.; Al-Qahtani, M. T.; Shaheer Akhtar, M. Engineering of Magnetically Separable ZnFe2O4@ TiO2 Nanofibers for Dye-Sensitized Solar Cells and Removal of Pollutant from Water. *J. Alloys Compd.* **2017**, *723*, 477−483.
(185) Ding, B.; Huang, S.; Pang, K.; Duan, Y.; Zhang, J. Nitrogen-Enriched Carbon Nanofiber Aerogels Derived from Marine Chitin for Energy Storage and Environmental Remediation. *ACS Sustainable Chemistry & Engineering* **2018**, *6* (1), 177−185.
(186) Zhang, M.; Xiao, C.; Zhang, C.; Qi, J.; Wang, C.; Sun, X.; Wang, L.; Xu, Q.; Li, J. Large-Scale Synthesis of Biomass@MOF-Derived Porous Carbon/Cobalt Nanofiber for Environmental Remediation by Advanced Oxidation Processes. *ACS ES&T Engineering* **2021**, *1* (2), 249−260.
(187) Lv, D.; Tang, G.; Chen, L.; Zhang, M.; Cui, J.; Xiong, R.; Huang, C. Multifunctional Gas-Spinning Hierarchical Architecture: A Robust and Efficient Nanofiber Membrane for Simultaneous Air and Water Contaminant Remediation. *ACS Applied Polymer Materials* **2020**, *2* (12), 5686−5697.
(188) Zhang, R.; Liu, C.; Hsu, P.-C.; Zhang, C.; Liu, N.; Zhang, J.; Lee, H. R.; Lu, Y.; Qiu, Y.; Chu, S.; Cui, Y. Nanofiber Air Filters with High-Temperature Stability for Efficient PM2.5 Removal from the Pollution Sources. *Nano Lett.* **2016**, *16* (6), 3642−3649.
(189) Si, Y.; Yu, J.; Tang, X.; Ge, J.; Ding, B. Ultralight Nanofibre-Assembled Cellular Aerogels with Superelasticity and Multifunctionality. *Nat. Commun.* **2014**, *5* (1), 5802.
(190) Si, Y.; Fu, Q.; Wang, X.; Zhu, J.; Yu, J.; Sun, G.; Ding, B. Superelastic and Superhydrophobic Nanofiber-Assembled Cellular Aerogels for Effective Separation of Oil/Water Emulsions. *ACS Nano* **2015**, *9* (4), 3791−3799.
(191) Liu, L.; Lin, Z.; Niu, J.; Tian, D.; He, J. Electrospun Polysulfone/Poly(Lactic Acid) Nanoporous Fibrous Mats for Oil Removal from Water. *Adsorption Science & Technology* **2019**, *37* (5−6), 438−450.
(192) Singh, V.; Kendall, R. J.; Hake, K.; Ramkumar, S. Crude Oil Sorption by Raw Cotton. *Industrial & Engineering Chemistry Research* **2013**, *52* (18), 6277−6281.
(193) Zhu, H.; Qiu, S.; Jiang, W.; Wu, D.; Zhang, C. Evaluation of Electrospun Polyvinyl Chloride/Polystyrene Fibers As Sorbent Materials for Oil Spill Cleanup. *Environmental Science & Technology* **2011**, *45* (10), 4527−4531.
(194) Blinovskaya, Y. Y. Efficiency Sorbents Comparative Analysis for Heavy Oil Products in the Conditions of Low Temperatures. *IOP Conference Series: Earth and Environmental Science* **2019**, *272* (3), 032116.
(195) Kardam, A.; Raj, K.; Srivastava, S.; Srivastava, M. Nanocellulose Fibers for Biosorption of Cadmium, Nickel, and Lead Ions from Aqueous Solution. *Clean Technologies and Environmental Policy* **2014**, *16*, 385−393.
(196) Yang, R.; Aubrecht, K. B.; Ma, H.; Wang, R.; Grubbs, R. B.; Hsiao, B. S.; Chu, B. Thiol-Modified Cellulose Nanofibrous Composite Membranes for Chromium (VI) and Lead (II) Adsorption. *Polymer (Guildf)* **2014**, *55* (5), 1167−1176.
(197) Sharma, P. R.; Joshi, R.; Sharma, S. K.; Hsiao, B. S. A Simple Approach to Prepare Carboxycellulose Nanofibers from Untreated Biomass. *Biomacromolecules* **2017**, *18* (8), 2333−2342.
(198) Sharma, P. R.; Chattopadhyay, A.; Sharma, S. K.; Hsiao, B. S. Efficient Removal of UO22+ from Water Using Carboxycellulose Nanofibers Prepared by the Nitro-Oxidation Method. *Industrial & Engineering Chemistry Research* **2017**, *56* (46), 13885−13893.

https://doi.org/10.1021/acsbiomaterials.2c00786
ACS Biomater. Sci. Eng. 2022, 8, 3690−3716

(199) Ding, D.; Ma, X.; Shi, W.; Lei, Z.; Zhang, Z. Insights into Mechanisms of Hexavalent Chromium Removal from Aqueous Solution by Using Rice Husk Pretreated Using Hydrothermal Carbonization Technology. *RSC Adv.* **2016**, *6* (78), 74675−74682.
(200) Chen, G.; Feng, J.; Wang, W.; Yin, Y.; Liu, H. Photocatalytic Removal of Hexavalent Chromium by Newly Designed and Highly Reductive TiO2 Nanocrystals. *Water Res.* **2017**, *108*, 383−390.
(201) Kumar, R.; Barakat, M. A.; Alseroury, F. A. Oxidized G-C3N4/Polyaniline Nanofiber Composite for the Selective Removal of Hexavalent Chromium. *Sci. Rep.* **2017**, *7* (1), 12850.
(202) Tan, L.; Xue, X.; Lou, Z.; Zhu, J.; Baig, S.; Xu, X. Multifunctional Nanocomposite Fe3O4@SiO2-MPD/SP for Selective Removal of Pb(II) and Cr(VI) from Aqueous Solutions. *RSC Adv.* **2014**, *4* (86), 45920.
(203) Zhao, D.; Gao, X.; Wu, C.; Xie, R.; Feng, S.; Chen, C. Facile Preparation of Amino Functionalized Graphene Oxide Decorated with Fe3O4 Nanoparticles for the Adsorption of Cr(VI). *Appl. Surf. Sci.* **2016**, *384*, 1−9.
(204) Vipin, A. K.; Fugetsu, B.; Sakata, I.; Isogai, A.; Endo, M.; Li, M.; Dresselhaus, M. S. Cellulose Nanofiber Backboned Prussian Blue Nanoparticles as Powerful Adsorbents for the Selective Elimination of Radioactive Cesium. *Sci. Rep.* **2016**, *6* (1), 37009.
(205) Shi, H.; Zhao, T.; Zhang, Y.; Tan, H.; Shen, W.; Wang, W.; Li, Y.; Wang, E. Pt/POMs/TiO2 Composite Nanofibers with an Enhanced Visible-Light Photocatalytic Performance for Environmental Remediation. *Dalton Transactions* **2019**, *48* (35), 13353−13359.
(206) Song, J.; Wang, X.; Yan, J.; Yu, J.; Sun, G.; Ding, B. Soft Zr-Doped TiO2 Nanofibrous Membranes with Enhanced Photocatalytic Activity for Water Purification. *Sci. Rep.* **2017**, *7* (1), 1636.
(207) Wang, Y.; Zhan, S.; Di, S.; Zhao, X. Novel Flexible Self-Standing Pt/Al2O3 Nanofibrous Membranes: Synthesis and Multifunctionality for Environmental Remediation. *ACS Appl. Mater. Interfaces* **2018**, *10* (31), 26396−26404.
(208) Hu, J.; Chen, D.; Li, N.; Xu, Q.; Li, H.; He, J.; Lu, J. Recyclable Carbon Nanofibers@Hierarchical I-Doped Bi2O2CO3−MoS2Membranes for Highly Efficient Water Remediation under Visible-Light Irradiation. *ACS Sustainable Chem. Eng.* **2018**, *6* (2), 2676−2683.
(209) Genovese, M. E.; Caputo, G.; Nanni, G.; Setti, C.; Bustreo, M.; Perotto, G.; Athanassiou, A.; Fragouli, D. Light Responsive Silk Nanofibers: An Optochemical Platform for Environmental Applications. *ACS Appl. Mater. Interfaces* **2017**, *9* (46), 40707−40715.
(210) Murray, S.; Wei, W.; Hart, R.; Fan, J.; Chen, W.; Lu, P. Solar Degradation of Toxic Colorants in Polluted Water by Thermally Tuned Ceria Nanocrystal-Based Nanofibers. *ACS Applied Nano Materials* **2020**, *3* (11), 11194−11202.
(211) Peydayesh, M.; Mezzenga, R. Protein Nanofibrils for next Generation Sustainable Water Purification. *Nat. Commun.* **2021**, *12* (1), 3248.

https://doi.org/10.1021/acsbiomaterials.2c00786
ACS Biomater. Sci. Eng. 2022, 8, 3690−3716