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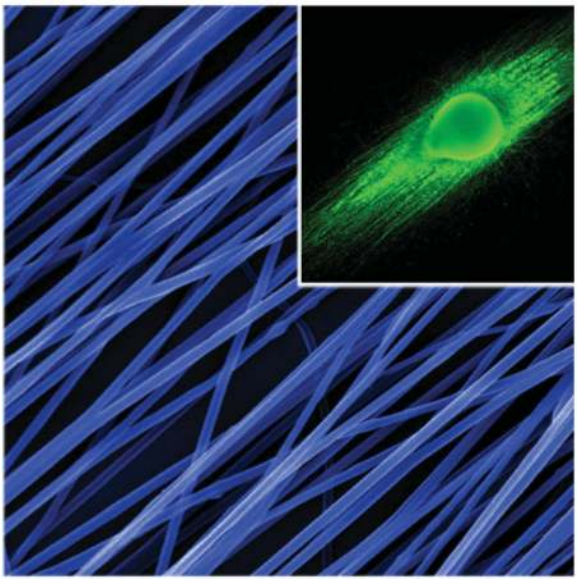
Putting Electrospun Nanofibers to Work for Biomedical Research

Jingwei Xie, **Xiaoran Li**, and **Younan Xia***
Department of Biomedical Engineering, Washington University in St. Louis, Saint Louis, Missouri 63130, USA

Abstract



Electrospinning has been exploited for almost one century to process polymers and related materials into nanofibers with controllable compositions, diameters, porosities, and porous structures for a variety of applications. Owing to its high porosity and large surface area, a non-woven mat of electrospun nanofibers can serve as an ideal scaffold to mimic the extracellular matrix for cell attachment and nutrient transportation. The nanofiber itself can also be functionalized through encapsulation or attachment of bioactive species such as extracellular matrix proteins, enzymes, and growth factors. In addition, the nanofibers can be further assembled into a variety of arrays or architectures by manipulating their alignment, stacking, or folding. All these attributes make electrospinning a powerful tool for generating nanostructured materials for a range of biomedical applications that include controlled release, drug delivery, and tissue engineering.

Keywords

biological applications of polymers; biomaterials; electrospinning; fibers

xia@biomed.wustl.edu.

Introduction

Electrospinning is a remarkably simple and versatile technique capable of generating continuous fibers directly from a variety of polymers and composite materials. Typically, the diameters of the electrospun fibers can be controlled in the range of tens of nanometers to micrometers, and the fibers can be deposited as nonwoven mats, or aligned into uniaxial arrays and further stacked into multilayered architectures.[1] This technique was demonstrated more than 100 years ago and was first patented in the 1930s.[2] However, it did not receive much attention till the early 1990s. Electrospun fibers have found widespread use in a broad range of applications owing to their intrinsic large surface areas. In the biomedical field, they have been demonstrated as carriers for controlled release and drug delivery, as scaffolds for tissue engineering, as barriers for the prevention of adhesion, as substrates for wound dressing, as supports for biocatalysis, and as active components for biosensing.[3]

Over the past decade, the use of electrospun nanofibers in biomedical applications has been drastically increased. When used as scaffolds, electrospun nanofibers offer a range of attractive features such as large surface areas, high porosities, and ease of construction into different shapes, making them ideal candidates for tissue or neural engineering. The composition of the electrospun fibers can also be tailored to fabricate functional scaffolds desired for guiding and/or controlling the proliferation of cells or neurons. Furthermore, the physical/chemical properties of the electrospun nanofibers can be readily modified by encapsulation and/or immobilization of bio-active species to elicit specific biological responses.

This article reviews some recent developments related to the electrospinning technique, with a focus on the control of composition, structure, and assembly of nano-fibers. We also illustrate two major biomedical applications of electrospun fibers in the context of drug encapsulation and tissue engineering.

The Setup and Mechanism

Figure 1 shows a typical setup for electrospinning, which consists of three major components: a high-voltage power supply, a spinneret, and an electrically conductive collector. A hypodermic needle (with a flat end) and a piece of aluminum foil serve well as the spinneret and collector, respectively. The liquid (a melt or solution) for electrospinning is loaded in a syringe and fed at a specific rate set by a syringe pump. In many cases, a well-controlled environment (e.g., humidity, temperature, and atmosphere) is also required in order to have a smooth, reproducible operation of electrospinning.[4]

Although the setup for electrospinning is incredibly simple, the mechanism of spinning fibers under the influence of an electric field is rather complicated. The essence of electrospinning is to generate a continuous jet by immobilizing charges onto the surface of a pendent droplet. In order to better understand the basic aspects, an electrospinning process can be divided into five major steps: i) charging of the pendent droplet; ii) formation of the cone-jet; iii) thinning of the steady jet; iv) onset and growth of jet stabilities that give rise to a diameter reduction into nanometer-scale sizes; and v) collection of the fibers in different forms.[5] It has recently been resolved that the spinning process is mainly driven by whipping rather than splaying of a jet.[6,7] Figure 2 shows a typical electrospinning jet captured using a high-speed camera.[8] The whipping instability originates from the electrostatic interactions between the external electric field and the surface charges on the jet. Formation of fibers with nanometer-scale diameters is achieved by stretching and acceleration of the unstable fluid filament until it has been solidified or it has been deposited on the collector. The liquid jet has to maintain a suitable viscoelasticity in order to survive

the whipping process. A jet can occasionally split into two jets that splay apart, with the axis of the thinner branch being positioned perpendicular to the primary jet.

In addition to experimental investigations, mathematic models have been developed to help gain insight into the electrospinning process. Reneker and co-workers simplified the charged liquid jet into a chain of connected, viscoelastic dumbbells in an effort to explain the occurrence of bending stability.[6,7] The three-dimensional trajectory of the jet could also be calculated using a linear Maxwell equation and the results agreed well with experimental observations. Rutledge and co-workers developed a model to describe the jet as a long, slender object to elucidate the electrospinning mechanism.[9,10] Their studies indicate that the whipping of a jet is predominant during an electrospinning process rather than splaying. This model was also used to predict the saturation of whipping amplitude and the diameter of an electrospun fiber.[11] All these modeling studies render a better understanding of the mechanistic details involved in an electrospinning process, which has been used to guide the optimal design of new setups and to achieve a better control over the size, alignment, and assembly of the electrospun fibers.

Requirements of the Polymers and Solvents

In the early days, electrospinning was mainly used to prepare polymeric nanofibers. So far it has been successfully applied to more than 100 types of natural and synthetic polymers.[12] There are already a number of recent review articles on electrospinning, especially those by Bowlin and co-workers and Chu and co-workers that specifically concentrate on polymeric materials.[13,14] The focus of this article is placed on the use of electrospinning to prepare polymeric nanofibers for biomedical applications. Table 1 shows a partial list of electrospinnable polymeric materials with immediate or potential applications in biomedical research. These materials can be divided into four major classes: natural polymers, synthetic polymers, polymer blends, and composites. In principle, proteins, DNAs and even viruses can all be directly electrospun into fibers. For example, Fang and Reneker fabricated fibers from calf thymus Na-DNA by electrospinning a water/ethanol (70/30) solution with DNA concentrations in the range of 0.3 to 1.5%.[28] Lee and Belcher prepared fibers from viruses by electrospinning liquid crystalline suspensions of viruses in a cross-linking solution of glutaraldehyde.[29] Most of the work on electrospinning involves the use of polymers with very high molecular weights. In a recent study, Long and coworkers demonstrated that the presence of sufficient intermolecular interactions (e.g., entanglement) rather than high molecular weight is the primary criterion for determining the electrospinnability of a solution. To this end, phospholipids lecithin fibers with diameters that range from 1 to 5 μm have been successfully prepared by electrospinning at concentrations above the critical concentration of entanglement, which offers a lot of potential applications in drug delivery and tissue engineering.[25]

The solvent also plays a critical role in controlling the physical properties of a polymer solution, including surface tension, electrical conductivity, and viscosity. The primary rule for choosing a solvent for electrospinning is that the solvent should be able to dissolve the polymer to form a solution with an appropriate concentration and viscosity. Secondly, the solvent should be sufficiently volatile so that it can evaporate to a large extent before the nanofibers hit the surface of a collector. However, if the solvent is too volatile, it may cause clogging at the tip of the spinneret during electrospinning. This problem can be partially solved by mixing with a solvent that has a high boiling point, for example, the case of dichloromethane (DCM)/dimethylformamide (DMF). Thirdly, the solvent (or more appropriately, the solution) is also required to have the ability to carry electrical charges.[69] This might require the addition of a salt or a surfactant. For example, the presence of lithium chloride has been proven to be useful in bridging the electrostatic interaction between the

solvent and the polymer. Some ionic surfactants (e.g., dodecyltrimethylammonium bromide, tetrabutylammonium chloride, or tetrabutylammonium tetraphenylborate) have also been used to eliminate the formation of beads and thus obtain ultra-fine fibers by increasing the conductivity of the polymer solution.[70,71] Table 1 also includes some commonly used solvents for electrospinning. In general, natural polymers like collagen, chitosan, and cellulose usually use hexafluoroisopropanol (HFIP) or tetrafluoropropanol (TFP) as a solvent for electrospinning; synthetic biodegradable polymers often require the use of solvents like DCM, acetone, DMF, and HFIP.

The residual solvent that remains in electrospun nanofibers should be as little as possible. This is particularly important for biomedical applications because organic solvents are usually used for electrospinning of polymeric materials and most of them are toxic to cells. After fabrication, the residual solvent inside fibers can be removed by freeze drying or drying under vacuum. The amount of residual solvent inside polymer matrices should be less than the exposure limits regulated by international health authorities and institutes: for example, tolerable daily intake by the International Program on Chemical Safety, acceptable daily intake by the World Health Organization, or permitted daily exposure by the Food and Drug Administration (USA).

Controlling the Composition and Structure

Homopolymers and Block Copolymers

Uniform nanofibers can be readily fabricated by electrospinning solutions of homopolymers with sufficient chain entanglement. With poly(methyl methacrylate) (PMMA) as an example, Wilkes and co-workers have studied the diameter of electrospun fibers as a function of molecular weight and viscosity.[72,73] It was observed that only polymer droplets were formed with solutions in the dilute regime due to insufficient chain entanglement. With increasing concentration, droplets and beaded fibers were observed in the semidilute, unentangled regime. With a further increase in concentration, beaded and uniform fibers were obtained in the semidilute, entangled regime. In addition to size, the internal structure of the electrospun fibers also has a strong dependence on the parameters used for electrospinning. Figure 3 shows scanning electron microscopy (SEM) images of fibers electrospun from poly(L-lactide) (PLLA) solutions under different conditions, where a range of different structures were observed. In general, for each polymer, one has to work out a set of parameters in order to obtain uniform nanofibers by electrospinning.

It is well-known that block copolymers can form microphase-separated structures including spheres, cylinders, gyroids, and lamellae in bulk, depending on the molecular weight, volume fraction of each block, and the degree of immiscibility between the different blocks.[74] Therefore, block copolymers may offer a good opportunity to form various internal structures in electrospun nanofibers by microphase separation. To this end, Joo and co-workers have investigated the formation of various domain structures (e.g., a cylindrical or lamellar morphology) in submicrometer scale fibers electrospun from poly(styrene-*block*-isoprene) (PS-*b*-PI).[75] Because of the short period of time and strong elongational deformation involved in an electrospinning process, the domain structures are not as well developed in electrospun fibers as those in films. In contrast, more uniform domain structures and an increase in *d*-spacing were observed for the fibers after an annealing process. In another demonstration, Rutledge and co-workers fabricated microphase-separated fibers by electrospinning a solution of a poly(dimethyl siloxane)-polystyrene (PDMS-PS) block copolymer blended with homopolymer PS.[76] It was observed that the PDMS blocks tend to segregate to the surface of the fibers because of the lower surface tension of the PDMS component. The same group also applied electrospinning to prepare polymeric fibers with periodic structures (e.g., concentric layers and spherical micro-

domains) by taking advantage of the microphase separation of cylindrically confined block copolymers.[77] They employed a two-fluid coaxial electrospinning technique to encapsulate the desired block copolymers such as poly(styrene-*block*-isoprene-*block*-styrene) (the core) with another, protective polymer such as poly[(methyl methacrylate)-*co*-(methacrylic acid)] (the sheath). They achieved microphase separation with a long-rang order by annealing the core-sheath fibers in an oven under vacuum.

Polymer Blends

Electrospinning of polymer blends offers the potential to prepare functional nanofibers for use in a variety of applications.[14] For example, blends of natural polymers can provide a simple way to combine different bioactivities for biomedical applications in contrast to the difficulties of modifying the chemical structures of monomers; blends of natural and synthetic polymers can enhance both physical properties (e.g., mechanical strength and duration of usage) and biological functionality (e.g., cell adhesion); blends of synthetic polymers can tailor the hydrophobicity, degradation rate, shrinking behavior, and mechanical properties for specific biomedical applications.

Two situations may occur for electrospinning of a polymer blend. One is that the polymers are miscible with each other and can form a homogeneous mixture. After electrospinning, the fibers consist of phases homogeneously mixed at the molecular level. In another situation, the polymers contained in the electrospinning solution may separate into different phases to generate a specific phase-separated morphology as the solvent evaporates rapidly. Normally, an incompatibility or large solubility difference of the two polymers is desired for phase separation.[78,79] By selective removal of one component after electrospinning, porous fibers will be obtained. In addition, Mead and co-workers demonstrated that nanofibers with a core–sheath structure can be formed as a result of phase separation during the electrospinning of a polymer blend, and the formation of a core–sheath structure was found to be dependent on both thermodynamic and kinetic factors.[79,80] In general, polymer blends with lower molecular weights tend to form core–sheath structures rather than co-continuous structures owing to the high molecular mobility.[79,80] Nanofibers electrospun from an poly[2-methoxy-5-(2-ethylhexoxy)-1,4-phenylenevinylene] and poly(9,9-dioctylfluorene) (MEH-PPV/PFO) blend were found to exhibit a co-continuous or core–sheath structure.[81] In a separate study, Yuan and co-workers examined electrospinning a blend of chitosan and poly(ethylene oxide) (PEO) in acetic acid and they obtained both ultrafine fibers and micro-fibers that were mainly made of PEO and chitosan, respectively, probably caused by phase separation.[82]

Porous Nanofibers

Porous nanofibers can be fabricated by inducing phase separation between two polymers during the electrospinning of a polymer blend, followed by selective removal of one component through thermal degradation or solvent extraction.[78,83–88] For a single polymer system, it is also possible to induce phase separation between the polymer and the solvent through temperature reduction, followed by solvent evaporation under freeze-drying. In this case, the liquid jet can be directly electrospun into a cryogenic liquid to induce a phase separation between the polymer and the solvent.[89] By adjusting the distance between the spinneret and the collector, one can control the amount of solvent trapped in the nanofibers and thus the porosity. Figure 4A shows an SEM image of porous PS fibers prepared by electrospinning the solution into liquid nitrogen, followed by drying under vacuum. The inset shows a higher magnification SEM image taken from the broken end of a fiber, which implies that the fiber was porous throughout. Figure 4B shows a transmission electron microscopy (TEM) image of the porous fibers, with the inset taken at a higher

magnification. This approach has been extended to a number of polymers, including poly(ε-caprolactone) (PCL), poly(acrylonitrile) (PAN), and poly(vinylidene fluoride) (PVDF).

Core–Sheath Tubular Nanofibers

The conventional setup for electrospinning has been modified in a number of ways to generate fibers that have a variety of secondary structures such as core–sheath and microtubes with single or multiple channels. Notable examples include co-axial, microfluid manifold, triple-layer co-axial, and multiple channels.[90–95] Figure 5A shows a setup with a coaxial capillary spinneret that was used to fabricate a core–sheath tubular structure. Figure 5B shows a TEM image of TiO_2/poly(vinyl pyrrolidone) (PVP) composite tubular nanofibers fabricated by electrospinning with a coaxial capillary spinneret, with the core liquid being mineral oil and the sheath liquid being a mixture of PVP and $Ti(OiPr)_4$ in alcohol. Figure 5C shows an SEM image of tubular nanofibers. Similar approaches have been widely employed to generate core–sheath structured fibers. Jiang and co-workers developed gelatin-coated PCL fibers by coaxial electrospinning, showing favorable mechanical characteristics and capacity of supporting cell proliferation.[96] Wendorff and co-workers demonstrated production of PCL microtubes using one-step co-axial electrospinning of PCL in chloroform/DMF (80: 20, w/w) as the sheath and PEO in a mixture of water and ethanol (40: 60, w/w) as the core. The transformation of the core–sheath structure into microtubes is primarily based on the evaporation of the core solution through the sheath.[97] Interestingly, a recent study demonstrated the production of core–sheath PMMA–PAN fibers using a single-nozzle electrospinning technique.[98] The aforementioned approaches for the control of compositions and structures by electrospinning, which may not be limited to the examples we described here, could also be suited for other materials.

Controlling the Assembly

Uniaxial Alignment

Electrospun fibers are usually deposited on the surface of a collector as a non-woven mat where the fibers have a random orientation. They can be aligned into a uniaxial array through the use of an electrostatic force or a rotational mechanical mandrel. Several studies have demonstrated that electrospun fibers can be aligned parallel to each other when a drum (or a wheel-like bobbin) rotating at a high speed or a static metal frame was used as the collector.[99,100] This approach is capable of generating well-aligned fibers, which can be easily transferred onto various substrates for device fabrication. Our group has developed a simple and versatile method for generating nanofibers as uniaxially aligned arrays over large areas by stretching/collecting the fibers across the void gap formed between a pair of conductive substrates.[101] Figure 6A shows a dark-field optical micrograph of aligned nanofibers of PVP deposited across a gap formed between two conductive silicon stripes. Figure 6B shows an SEM image of the same sample, which confirms that the nanofibers deposited across the gap were uniaxially aligned. We also studied the effect of the area and geometric shape of the insulating gap on the alignment of fibers.[102] The results showed that the fibers tended to oriented along a direction such that the net torque of electrostatic forces applied to the two ends of a discrete segment of the fiber were minimized. By varying the design of the patterned electrode, it was possible to control both alignment and assembly of the electrospun nanofibers. Recently, Jiang and coworkers developed a method for aligning fibers into a parallel array by electrospinning a polymer solution doped with magnetic nanoparticles in magnetic field.[103] In related work, Lin and coworkers developed the concept of “near-field” electrospinning, which can be use to deposit nanofibers in a direct, continuous, and controllable manner.[104] The detailed description of

other setups for controlling nanofiber assemblies can be found in the review article by Teo and Ramakrishan.[105]

Stacked Arrays

There has been some success in stacking electrospun nanofibers into controllable architectures. As discussed in Section 5.1, our group has obtained nanofibers as uniaxially aligned arrays over large areas by using a collector that consisted of two pieces of conductive substrates separated by a void gap.[101] The uniaxially aligned nanofibers could be easily stacked into a multilayered film with a controllable, hierarchically porous structure.[106] This concept has also been extended to replace the void gap with a highly insulating substrate such as quartz or polystyrene. By patterning the collector into an array of electrodes on an insulating solid support, we could easily direct the deposition of nanofibers into a multilayered film by alternating the scheme for applying the high voltage. Figure 7A shows a four-electrode pattern and Figure 7B shows a double-layered mesh of PVP nanofibers obtained by alternately grounding the electrode pairs. Figure 7C shows another test pattern consisting of six electrodes and Figure 7D shows an SEM image of a tri-layered thin film of PVP nanofibers that were deposited across the three pairs of electrodes by alternately grounding each pair of electrodes. Note that the nanofibers in each layer were uniaxially aligned, with their long axes rotated by 60 degrees between adjacent layers. By controlling the electrode pattern and/or the sequence for grounding the pair of electrodes it is also feasible to generate more complex architectures that consist of well-aligned nanofibers. Similarly, electrospinning of a magnetizable solution in a magnetic field also allows the construction of nanofibers into a stacked array such as a grid.[103] Teo and Ramakrishna demonstrated that uniaxially aligned nanofibers between two fixed points could be twisted to form bundles and other types of constructs (e.g., a micrometer-sized yarn by braiding three nanofiber bundles manually).[107] In related work, the continuous yarns consisting of aligned nanofibers were further woven into textiles for various applications.[108]

Examples of Biomedical Applications

Non-woven mats of electrospun nanofibers can serve as ideal scaffolds for tissue engineering because they can mimic the extracellular matrix (ECM) in that the architecture of nanofibers is similar to the collagen structure of the ECM—a 3D network of collagen fibers 50–500 nm in diameter. Furthermore, electrospun nanofibers have several advantages for tissue regeneration: desirable topography (e.g., 3D porosity, nanometer-scale size, and alignment), encapsulation and local sustained release of growth factors, and surface functionalization (e.g., surface immobilization of bioactive molecules or functional groups). Scaffold materials used for tissue engineering have to be biocompatible and notable examples include natural or synthetic biodegradable polymers, biocompatible polymers, and composites with bioactive inorganic solids such as hydroxyapatite (HA). Here we only illustrate two examples of applications for electrospun nanofibers including encapsulation and tissue engineering.

Encapsulation of Bioactive Materials

Encapsulation of bioactive materials is usually used to functionalize electrospun fibers for various applications (e.g., sustained delivery of therapeutic agents, immobilization of bioactive species, and release of growth factors for enhancement of cells proliferation and functions). For encapsulation of bioactive species in polymeric fibers, a simple mixture of oil and water phases or a water/oil emulsion is usually used as long as one can achieve a uniform distribution for the materials loaded into the nanofibers. The bioactivity of biomacromolecules has to be carefully examined during this process due to their tendency to denature and thus lose the function.

Antibiotic-loaded electrospun fibers for topical sustained release have desirable utility in biomedical applications, particularly in the prevention of post-surgical adhesions and infections. Several antibiotics have been encapsulated in electrospun fibers. Wnek and co-workers pioneered the use of electrospinning to encapsulate tetracycline hydrochloride (used as a model drug) inside electrospun fibers of poly(ethylene-*co*-vinylacetate) (EVA), poly(lactic acid) (PLA), and a blend of these polymers, and then examined the release of the drug from the fibers.[109] The fibers were electrospun from polymer solutions in chloroform, which also contained a small amount of methanol to solubilize the drug. Jing and co-workers encapsulated rifampin in PLLA fibers using electrospinning and examined its release *in vitro*. It was found that the release of rifampin in the presence of proteinase K followed nearly zero-order kinetics due to the gradual degradation of the PLLA fibers.[110] Chu and co-workers demonstrated the successful encapsulation and sustained release of a hydrophilic antibiotic drug, cefoxitin sodium.[111]

Electrospun fibers encapsulated with anticancer drugs have attracted much attention in recent years as implants for sustained chemotherapy, particularly as an alternative for the commercial products in the treatment of brain tumors. Although commercial implants like the Gliadel Wafer that delivers BCNU (or Carmustine) have been demonstrated with some success to improve the survival rate of patients with brain tumors, its potential is limited by the resistance of many brain tumors to BCNU. In this case, AGT, a DNA-repair protein found in the majority of brain tumors, is responsible for much of the resistance.[112,113] Several studies have demonstrated the possibility of using fibers electrospun from biodegradable polymers as a vehicle for chemotherapeutic drugs. Jing and co-workers encapsulated paclitaxel, doxorubicin hydrochloride, and doxorubicin base as model drugs in electrospun PLLA fibers.[114] It was demonstrated that the burst release of the drugs could be prevented through the use of polymers compatible with drugs and the degradation of PLLA fibers in the presence of proteinase K can tailor *in vitro* release profiles. However, the loading of doxorubicin was low because of its limited solubility in chloroform, which was used as the solvent for electrospinning. In order to solve this problem, they dissolved doxorubicin and the polymers PLLA and PEG in an aqueous phase and oil phase, respectively, and then formulated them into a water-in-oil (W/O) emulsion for electrospinning.[115] The doxorubicin was encapsulated inside the electrospun fibers and the released doxorubicin had the same chemical structure and showed the same antitumor activity against C6 glioma cells. In related work, Xie and Wang developed paclitaxel-encapsulated PLGA micro- and nanofibers by electrospinning PLGA and paclitaxel in DCM.[71] Thermal analysis results confirmed that paclitaxel was in an amorphous or a molecular dispersion state after the electrospinning process, which is more favorable for diffusion through the polymer matrix. The cumulative release of paclitaxel was linear to the square root of time and the sustained release could endure more than two months. They also examined cisplatin encapsulation in PLLA nanofibers by electrospinning a mixture of PLLA in DCM and cisplatin in water or dimethyl sulfoxide (DMSO).[116] More than 75 d sustained release could be achieved using the fibrous formulation without a large initial burst. It was also observed that the cytotoxicity of cisplatin encapsulated in nanofibers was about four times higher than that of the free drug based on the actual amount of drug released. The same group recently reported electrospun biodegradable micro- and nanofiber implants that could be used to deliver paclitaxel for post-surgical chemotherapy against malignant glioma.[117] An *in vivo* tumor inhibition study against subcutaneous C6 glioma in BALB/c nude mice indicate that animals treated with discs or sheets of paclitaxel-loaded electrospun fibers had much smaller tumors on day 24 and day 32 post-tumor inoculation when compared to placebo control and Taxol control groups, which confirmed the sustained release of paclitaxel and improved tumor inhibition. Encapsulation of other anticancer drugs such as BCNU and curcumin in electrospun fibers has also been reported.[118,119] These studies indicate that electrospun fibers loaded with anticancer drugs could become a class of

promising implants to treat brain tumors. For clinical applications, surgery will be required to implant micro- or nanofiber flat mats that can be either fabricated or modified to almost any size. This approach represents an attractive form for local delivery applications with a variety of shapes (e.g., tubes) constructed using different target geometries.[109]

Continuous nanofibers loaded with proteins may synergistically provide topographical and biochemical signals to cells. The sustained release of proteins from aligned polymeric fibers has great potential in applications such as tissue engineering. Leong and co-workers demonstrated the feasibility of encapsulating human β-nerve growth factor (NGF) stabilized by a carrier protein bovine serum albumin (BSA) in a copolymer of ε-caprolactone and ethyl ethylene phosphate (PCLEEP) by electrospinning a mixture of the protein and polymer solution.[120] They obtained partially aligned protein encapsulated fibers and found that the protein was randomly dispersed throughout the fibrous mesh in an aggregated form. The sustained release of NGF could endure for at least three months by a diffusion process. A PC12 neurite outgrowth assay confirmed that the bioactivity of NGF after release from electrospun fibers was maintained at least partially. The same group also investigated human glia cell-derived neurotrophic factor (GDNF) encapsulated inside aligned PCLEEP fibers using the same approach as their previous study.[121] The protein was also randomly dispersed throughout the polymer matrix in an aggregated form. Figure 8A shows the *in vitro* release profiles of GDNF from fibrous matrices, indicating a sustained manner for up to two months after an initial burst release of about 30%. In another study, Wang and co-workers encapsulated bone morphogenetic protein 2 (BMP-2) in three-dimensional fibrous PLGA/HA composite scaffolds by electrospinning a W/O emulsion that contained a mixture of BMP-2 water solution, HA water suspension, and PLGA DCM solution.[68] Figure 8B shows the *in vitro* release profiles for BMP-2 from the fibrous scaffolds. In this study, the amount of PLGA used for electrospinning was 3 g. There was no HA in sample s1. Samples s2 and s3 contain 150 and 300 mg of HA. Sample s4 also contained 150 mg of HA. For samples s1–s3, the BMP-2 solution was added into an aqueous phase to form an emulsion for electrospinning. For sample s4, fibrous scaffolds were treated with a BMP-2 solution after electrospinning. It was found that the more HA nanoparticles added the higher percentage of BMP-2 released from the fiber matrices, which might be due to the hydrophilicity of HA. Also, the released BMP-2 protein maintained its integrity and natural conformations after the electrospinning process. A similar sustained release property *in vivo* was also confirmed by measuring the BMP-2 concentration in serum for 1, 2, 4, and 6 week(s) after implantation of the fibrous scaffolds. The *in vivo* data indicates that the bioactivity of BMP-2 released from the PLGA/HA/BMP-2 composite was well preserved. [122] Coaxial electrospinning was also employed to encapsulate various bioactive materials in the core. It was demonstrated that encapsulation of a model protein, BSA, along with a water soluble polymer PEG within PCL using coaxial electrospinning could eliminate the key issue faced by the conventional setup for protein encapsulation—the primary emulsion being a major cause for protein denaturation and aggregation.[123,124] Alternatively, BSA-PCL core—shell nanofibers were fabricated by electrospinning with BSA in distilled water (at 10 $mg \cdot mL^{-1}$) as the core solution and 10% w/v PCL in a 60: 40 (v/v) mixture of DCM and ethanol as the sheath solution, respectively.[125] The release kinetics could be controlled by incorporation of PEG as a porogen in the sheath of the nanofibers. These studies clearly demonstrate that electrospinning is a versatile technique for achieving the delivery of biochemical stimuli in a controlled manner for regenerative medicine applications.

Hadjiargyrou and co-workers loaded DNA plasmid in electrospun PLGA and PLA-PEG nanofibers for sustained gene delivery.[126] They demonstrated that nanostructured DNA/polymer scaffolds could be fabricated by electrospinning a plasmid DNA polymer solution, and the plasmid DNA released from the fibers was structurally intact and capable of cell

transfection. In their follow-up studies, they developed a strategy for encapsulating plasmid DNA as shown in Figure 9.[127,128] In a typical process, core–shell DNA nanoparticles were formed through solvent-induced condensation of plasmid DNA in a mixture of DMF and TE buffer (10×10^{-3} M tris(hydroxymethyl)aminomethane (Tris) and 1×10^{-3} M ethylenediaminetetraacetic acid (EDTA)) and subsequent loading of the condensed DNA globule into PLA-PEG-PLA. The PLA shell protects the encapsulated DNA from degradation during electrospinning of a mixture of encapsulated DNA nanoparticles and PLGA into a fibrous non-woven scaffold. The bioactive plasmid DNA could then be released in an intact form from the scaffold with a controlled rate and transfected cells *in vitro*. In a different study, Nie and Wang fabricated PLGA/HA composite fibers loaded with BMP-2 plasmid DNA.[129] Three different ways were used to incorporate plasmid DNA into fibrous scaffolds, including encapsulation of naked DNA, adsorption of DNA/chitosan nanoparticles onto fibers, and encapsulation of DNA/chitosan nanoparticles into a scaffold during the electrospinning process. DNA/chitosan nanoparticles were first formed as a result of an electrostatic interaction between plasmid DNA and chitosan and DNA/chitosan nanoparticle-loaded PLGA/HA composite fibers were generated by electrospinning a mixture of a DNA/chitosan nanoparticle suspension and PLGA/HA solution. This study demonstrated that BMP-2 plasmid DNA/chitosan nanoparticles could be encapsulated into fibers using electrospinning without losing its integrity. It was shown that the use of HA as an additive could aid the release of DNA from fibrous matrices and enhance human mesenchymal stem cells (hMSC) attachment without decreasing cell viability. In addition, the DNA/chitosan nanoparticles showed the highest transfection efficiency and cell viability. In another work, Craighead and co-workers demonstrated the production of polymeric nanofibers that contained isolated stretched λ bacteriophage DNA molecules, and showed the first direct observation of orientation and elongation of individual polymer molecules in an electrospun nanofiber.[130]

Bacteria or virus-loaded electrospun fibers are of great interest as living membranes for a variety of applications including biofiltration, biosensors, and biocatalysis. Lee and Belcher demonstrated the encapsulation of M13 viruses in PVP fibers.[29] It was shown that virus-loaded PVP electrospun fibers retained the ability to infect bacterial hosts after resuspending in a buffer solution. Zussman and co-workers investigated the encapsulation of bacteria (*Escherichia coli, Staphylococcus albus*) and viruses (T7, T4, λ) in electrospun nanofibers by electrospinning a mixture of bacteria and viruses suspension and poly(vinyl alcohol) (PVA) aqueous solution.[131] It was demonstrated that the encapsulated bacteria and viruses could survive the electrospinning process and maintain their viability at relatively high levels. Furthermore, the bacteria and viruses were still viable after three months stored at −20 and −55 °C. The results demonstrate the potential of electrospinning for the encapsulation and immobilization of living organisms. Greiner and co-workers also examined the encapsulation of living bacteria in PEO fibers.[44] They chose *Micrococcus (M.) luteus* (capable of adapting for life at low water activities and to survive rapid changes in osmotic pressure) and *Escherichia (E.) coli* (much more fragile) as two model bacteria for encapsulation studies. Suspensions of living bacteria in 4.5% of PEO in water were electrospun into fibers. When measured 1 h after electrospinning, 74% of *M. luteus* were found to survive the electrospinning process. In contrast, only 0.1% of *E. coli* survived the electrospinning process. Co-axial electrospinning was also used to encapsulate living organisms in fibers. Wownsend-Nicholson and Jaya-singhe developed a method based on a coaxial spinneret, where a concentrated living biosuspension flows through the inner needle and a medical grade PDMS medium flows through the outer needle.[132] They identified the operational conditions under which the finest cell-bearing composite microfibers were generated. Cells after the electrospinning process were viable and no cellular damage occurred. This study demonstrated the feasibility of using coaxial electrospinning for

biomedical applications through the encapsulation of living cells in composite microfibers for producing bioactive scaffolds.

Tissue Engineering

Neural Tissue Engineering—Uniaxially aligned nanofibers can be used to guide the growth of neurons owing to its intrinsic anisotropic features as compared to other systems such as hydrogels and films. Ramakrishna and co-workers found that aligned nanofibrous scaffolds were better suited for culturing nerve stem cells *in vitro* than random microfibrous scaffolds in a mixture of Dulbecco's modified Eagle medium (DMEM)/F12 with 1:1 ratio (Gibco, USA) containing N-2 supplement.[133] It has also been demonstrated that only aligned electrospun nanofibers without any surface modification could specify the direction of dorsal root ganglia (DRG) neurite growth and even guide axonal growth and glial cell migration in the presence of neurobasal medium with B27 supplements or growth medium consisting of DMEM/F12 and 10% fetal calf serum (FCS).[134–136]

Neurites extension or nerve functional recovery can be further enhanced by immobilizing extracellular matrix proteins and neurotrophins on the surface of electrospun nanofibers or encapsulating neurotrophic factors inside nanofibers for sustained release. Meiners and co-workers reported that the polyamide nanofibers covalently modified with neuroactive peptides derived from human tenascin-C could significantly enhance the ability of the nanofibers to facilitate neuronal attachment, neurite generation, and neurite extension *in vitro*.[137] Li and co-workers modified the surface of electrospun nanofibers with extracellular matrix proteins and neurotrophic factors and then used them for nerve tissue engineering by promoting and specifically directing neurite outgrowth from nerve tissue.[138] Figure 10A indicates that there was no neurite outgrowth from the DRG tissue at all on untreated, randomly oriented nanofibers. In comparison, there was significant neurite outgrowth from DRG tissue on untreated, aligned nanofibers and the neuritis extended along the direction parallel to the long axes of the fibers (see Figure 10B). The same group also examined whether biochemical cues from immobilized basic fibroblast growth factor (bFGF) induced or enhanced neurite extension on aligned nanofibers. Figure 10C shows that the longest and most dense neurite extension was observed on aligned nanofibers with immobilized bFGF. The authors claimed that surface immobilization of bFGF has a great advantage owing to that fact that only a relatively small amount of bFGF is conjugated to the nanofibers and that the new system can be used to topically deliver bFGF without side effects.

Leong and co-workers reported that aligned poly[(ε-caprolactone)-*co*-(ethyl ethylene phosphate)] (PCLEEP) nanofibers loaded with glia cell line-derived neurotrophic factors (GDNF) showed a sustained release of proteins for up to two months *in vitro*. The synergistic effect of encapsulated proteins could promote a more significant recovery from injured peripheral nerve tissue.[121] Figure 11A shows a cross-sectional view of a nerve conduit constructed from longitudinally aligned electrospun fibers. The tubes were fabricated by rolling the fibers into a tube and sealing the front edge of the mat to the tube with 8 wt.-% of PCLEEP-DCM solution, with the electrospun fibers aligned longitudinally or circumferentially. Figure 11B shows an SEM image of the PCLEEP fibers aligned along the long axis of a nerve conduit. These nerve conduits were then examined for sciatic nerve regeneration across 15-mm critical defects in rats. Figure 11C–F show optical micrographs of the cross sections of the regenerated sciatic nerves. All rats that received nerve guides from electrospun fibers (with or without GDNF) had regenerated sciatic nerves at 15 mm from the proximal end. Only 4 out of 6 rats in the empty nerve guide group (tubes composed of PCLEEP film) had a regenerated sciatic nerve at 8–10 mm from the proximal end, of which only 2 rats had myelinated axons at the same location. Voids circled in Figure 11D

were observed in the nerve cross sections from longitudinally aligned fibers. These voids could be the bundles of electrospun fibers that were present at the site of injury but dissolved during histological processing. Figure 11E shows similar voids that were observed in the nerve cross sections from the group of circumferentially aligned fibers. However, GDNF-loaded fibers were not found in any of the sciatic nerves from the group of longitudinally aligned fibers with GDNF. Regarding either longitudinally or circumferentially aligned fibers but without GDNF, the total number of myelinated axons and the nerve cross-sectional areas were significantly larger as compared to the empty conduits composed of PCLEEP film. However, there was no significant difference between the two different orientations for the aligned fibers. The incorporation of exogenous growth factor significantly enhanced nerve regeneration. This study demonstrated the feasibility of combining biochemical and topographic cues into a single implant to enhance peripheral nerve tissue regeneration.

Encapsulation of neurotrophin factors for sustained release and functionalization with species for promoting cell adhesion and differentiation are two general methods of decorating aligned electrospun fibers for nerve tissue regeneration. Other physical factors could also be incorporated to further facilitate nerve regeneration. Shin and co-workers introduced mechanical stimuli and substrates micropatterned with electrospun microfibers to investigate their effects on neurite outgrowth and guidance.[139] It was demonstrated that microfiber-based substrates combined with an appropriate fluid-induced shear stress resulted in promotion of neurite extension and highly controlled alignments. Specifically, neurons were most highly aligned with the microfibers at a shear stress of 0.50 Pa and the average length of neurite outgrowth was the longest at a shear stress of 0.25 Pa. In a different demonstration, the application of an external electrical stimulus through a conductive film made of polypyrrole (PPy) was shown to significantly improve the extension of neurites.[140] Hence, it seems to be an interesting idea to fabricate conductive nanofibers encapsulated with neurotrophin factors to further promote neural tissue regeneration and functional recovery by combining a set of different cues. In principle, all these factors aforementioned could be combined into one system to design optimal nerve conduits for nerve regeneration in animal or clinical studies.

Bone Regeneration—Current bone grafts have serious limitations,[141,142] making bone tissue engineering a promising alternative. The major components of the bone family of materials include carbonated apatite crystals, type I collagen fibrils, and water. Small amounts of nano-collagenous proteins (<10% of the total proteins) also exist.[143] Some studies have shown that electrospun fibers of a polymer alone can serve as bone tissue engineering scaffolds and enhance bone regeneration to a certain extent. For example, a membrane made of silk fibroin nanofibers was shown to possess good biocompatibility with enhanced bone regeneration in a rat and no evidence of any inflammatory reaction was observed.[144] More often, a biodegradable polymer is combined with a bioactive inorganic material before or after the electrospinning process to mimic the composition of bone and provide high mechanical strength for bone regeneration. In other cases, the electrospun fibers are loaded with bone morphogenic proteins to facilitate bone regeneration.

Much attention has been given to HA as the inorganic phase owing to the similarity of its crystallographic structure to inorganic materials found in natural bones and its biocompatibility and osteoconductivity. The organic phase is usually made of a synthetic biodegradable polymer (e.g., PCL, PLA, or PLGA) or natural polymer (e.g., gelatin or collagen). Ramakrishna and co-workers developed bone regeneration membranes made of PCL/calcium carbonate composite nanofibers by electrospinning $CaCO_3$ nanoparticles and PCL in a mixture of 75 wt.-% chloroform and 25 wt.-% methanol.[61] The membrane displayed better osteoconductivity and barrier effect against soft tissue invasion as compared

to conventional membranes for bone regeneration. However, a further study of osteoblast function including secretion of osteonection and osteocalcin proteins and alkaline phosphatase activity still needs to be conducted. Kim and co-workers generated PLA/HA nanocomposite fibers by electrospinning a mixture of HA fine particles and PLA in chloroform.[60] Hydroxysteric acid was introduced as a surfactant between the hydrophilic HA powders and the hydrophobic PLA dissolved in chloroform to keep the HA suspension stable. Preliminary cellular assays showed good cell attachment and proliferation and also enhancement of expression of alkaline phosphatase, which indicates its potential applications as a three-dimensional scaffold for bone regeneration. The same group also fabricated electrospun nanofibers of gelatin-hydroxyapatite biomimetics for guided tissue regeneration.[64] They started with the preparation of a gelatin-HA composite sol from gelatin, calcium nitrate, and ammonium hydrogen phosphate. The sample was then frozen, followed by drying under vacuum. Finally, the freeze-dried powders were dispersed in HFIP and electrospun into composite nanofibers. It was observed that the HA nanoparticles were uniformly distributed in the gelatin matrix and the nanocomposite fibrous mesh showed much higher osteoblastic cellular activity than the pure gelatin equivalent. Ramakrishna and co-workers also developed PCL/HA/collagen biocomposite fibrous scaffolds, which can provide mechanical support and direct the growth of human fetal osteoblasts for tissue engineering of bone.[145] PCL in this composite fibrous scaffold can provide mechanical stability, while collagen can support cell proliferation and HA can enhance the mineralization of osteoblasts for bone regeneration. Recently, the same group also investigated the mineralization of osteoblasts with collagen/HA nanofibers which are the two major solid components of human bone.[146] The crystalline HA (29±7.5 nm in size) was encapsulated inside the collagen nanofibers. It was observed that osteoblasts on the composite fibrous scaffolds showed an insignificant level of proliferation but a much higher level of mineralization (56% in collagen/HA nanofibrous scaffolds) as compared to collagen. Alternatively, nanofibrous scaffolds could even be directly mineralized by incorporating P-containing anionic functional groups into the backbone of the polymers or as side groups to help initiate rapid nucleation and deposition of HA.[147,148]

Other than calcium-containing ceramics, siloxane was also incorporated in nanofibers to form hybridized nanofibers for bone tissue engineering applications. Kim and co-workers fabricated hybrid nanofibers that consisted of gelatin-siloxane for use as bone regeneration matrices. In this case, gelatin and siloxane were dissolved in an acidic solvent of acetic acid, ethyl acetate, and distilled water and then used as a precursor solution for electrospinning.[66] Owing to the cross-linking effect of the siloxane with the gelatin chains, the hybrid nanofibers had better chemical stability in a saline solution as compared to the pure gelatin nanofibers. It was observed that osteoblastic cells could adhere, migrate, and proliferate on the hybridized nanofiber scaffold. Furthermore, it was demonstrated that osteoblastic activity (e.g., alkaline phosphatase) of osteoblasts on the hybridized nanofibers was better than that on the pure gelatin.

Wang and co-workers developed three-dimensional fibrous PLGA/HA composite scaffolds encapsulated with BMP-2 for sustained delivery.[68] Two approaches were used to load BMP-2 into three-dimensional fibrous scaffolds: encapsulation inside the fibers and coating on the fiber surface. It was shown that the released BMP-2 protein maintained its integrity and natural conformations after the electrospinning process. In addition, loading with HA could enhance cell attachment to the scaffolds. In order to investigate whether the PLGA/HA composite fibrous scaffolds loaded with BMP-2 through electrospinning improve bone regeneration, the performance of PLGA/HA/BMP-2 scaffolds was characterized in a nude mouse model.[122] Figure 12 shows soft X-ray photographs of nude mice tibia fractures after 1, 2, 4, and 6 week(s) of implantation of composite scaffolds as well as control (without implantation of any scaffold). It is evident that bone ends from the control were

sharp as the postoperation case. No significant bone regeneration was observed after 4 weeks and the delayed union of bone fractures was clearly seen as indicated by white arrows in the images. Interestingly, BMP-2 loaded samples show wide and dull bone ends, suggesting new bone formation after 4 weeks. All bone defects were healed perfectly at 6 weeks for BMP-2 loaded scaffolds, while the control group is still only partially repaired.

Alternatively, electrospun nanofibers can be combined with gene therapy or stem cell biology to provide a new route to bone regeneration. Wang and co-workers fabricated PLGA/HA composite fibrous scaffolds by electrospinning, with DNA being incorporated into the scaffolds.[129] The authors concluded that the fibrous scaffolds loaded with HA and DNA/chitosan nanoparticles are promising as gene delivery devices for bone regeneration. Lee and co-workers electrospun nanofibers from type I collagen and investigated the morphology, growth, adhesion, cell motility, and osteogenic differentiation of human bone marrow-derived mesenchymal stem cells on the fibrous scaffolds.[149] It was found that focal adhesion formation quantified by staining the area of the cytoplasmic protein vinculin for fiber matrices was much less as compared with PS. The distance of cell migration was 37.3 to 56.7% of those on polystyrene. Alkaline phosphatase activity showed no differences after 12 d of osteogenic differentiation and reverse transcription polymerase chain reaction (RT-PCR) results showed comparable osteogenic gene expression of osteocalcin, osteonectin, and ostepontin between cells differentiated on PS and nanofiber surfaces. This difference could be due to lack of inorganic phase of bone materials. Furthermore, single-cell RT-PCR of type I collagen gene expression demonstrated higher expression in cells seeded on the nanofibers than that on the PS surface. It was concluded that type I collagen nanofibers support the growth of mesenchymal stem cells (MSCs) without compromising their osteogenic differentiation capability and can be used as a scaffold for bone tissue engineering to facilitate intramembranous bone formation.

Conclusion

Electrospinning is a remarkably simple technique well-suited for manufacturing nanofibers with a broad range of functionality. The composition, morphology, and pore structures of electrospun nanofibers could all be tailored using a number of physical and/or chemical methods. Although some progress has been achieved using electrospun fibers for biomedical applications such as drug delivery and tissue engineering, currently most of these studies are based upon *in vitro* experiments and their use for *in vivo* applications is still in a rudimental stage. We believe that electrospun nanofibers and related materials will continue to grow strongly in biomedical applications through multidisciplinary collaborations that may involve scientists from materials science, chemistry, biology, and medicine.

Biographies

Jingwei Xie was born in Anhui province, China in 1977. He received his B.S. and M.S. degrees (with Prof. Xiaohua Lu) in 1999 and 2002, respectively, from the Department of Chemical Engineering, Nanjing University of Technology. He then continued his Ph.D. study (with Prof. Chi-Hwa Wang) in the Department of Chemical and Biomolecular Engineering, National University of Singapore. His doctoral thesis was mainly focused on the development of biomedical devices using electrohydrodynamic atomization. He received

his Ph.D. in June, 2007, and immediately joined Prof. Younan Xia's group as a postdoctoral research associate at Washington University in St. Louis, where his research centers on the development of electrospinning for fabrication of nanofiber scaffolds, with a focus on their biomedical applications. His research interests include micro- and nanofabrication, neural tissue engineering, stem cell therapy, tendon repair, and controlled release formulations. He has published more than 20 peer-reviewed papers.

Xiaoran Li was born in Hebei province, China in 1980. She received her B.S. degree in polymer materials from Hebei University of Technology in 2004. She then entered the Department of Polymer Materials, Tianjin University, and is pursuing her Ph.D. degree under the supervision of Prof. Xiaoyan Yuan. She joined the Xia group at Washington University in St. Louis in the fall of 2007 as a jointly supervised student. Her research interest includes the preparation of nanofibers with multifunctions for use in tissue engineering and drug delivery.

Younan Xia was born in Jiangsu, China, in 1965. He received a B.S. degree in chemical physics from the University of Science and Technology of China (USTC) in 1987 and then worked as a graduate student on nonlinear optical crystals for four years at the Fujian Institute of Research on the Structure of Matter, Chinese Academy of Sciences. He came to the United States in 1991, received a M.S. degree in inorganic chemistry from the University of Pennsylvania (with the late Professor Alan G. MacDiarmid) in 1993 and a Ph.D. degree in physical chemistry from Harvard University (with Professor George M. Whitesides) in 1996. After a postdoctoral stint with Professors George M. Whitesides and Mara Prentiss at Harvard University, he started as an Assistant Professor of Chemistry at the University of Washington in Seattle in 1997. He was promoted to Associate Professor and Professor in 2002 and 2004, respectively. In the fall of 2007, he relocated to Washington University in

St. Louis to take the position of James M. McKelvey Professor for Advanced Materials in the Department of Biomedical Engineering. He also holds joint appointments in the Departments of Energy, Environmental and Chemical Engineering, Biochemistry and Molecular Biophysics, Radiology, and Chemistry. Currently, his research centers on the design and synthesis of nanostructured materials with controlled properties for applications in imaging, sensing, drug delivery, cancer treatment, tissue engineering, catalysis, energy conversion, photonics, and electronics.

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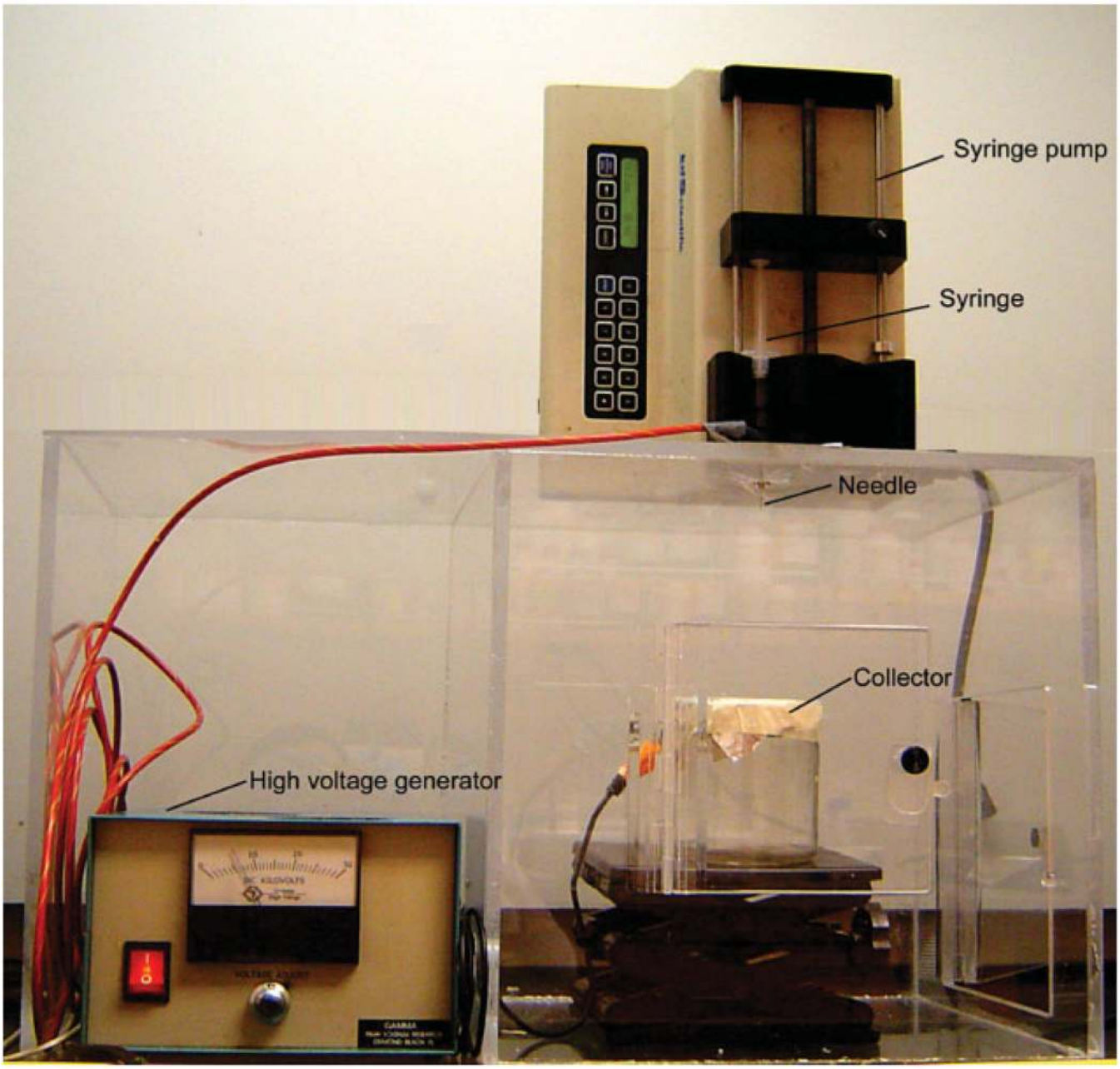

Figure 1.
A typical setup for electrospinning, which includes three major components: a high voltage generator, a spinneret (in this case, a flat-end needle), and a collector (in this case, a piece of aluminum foil).

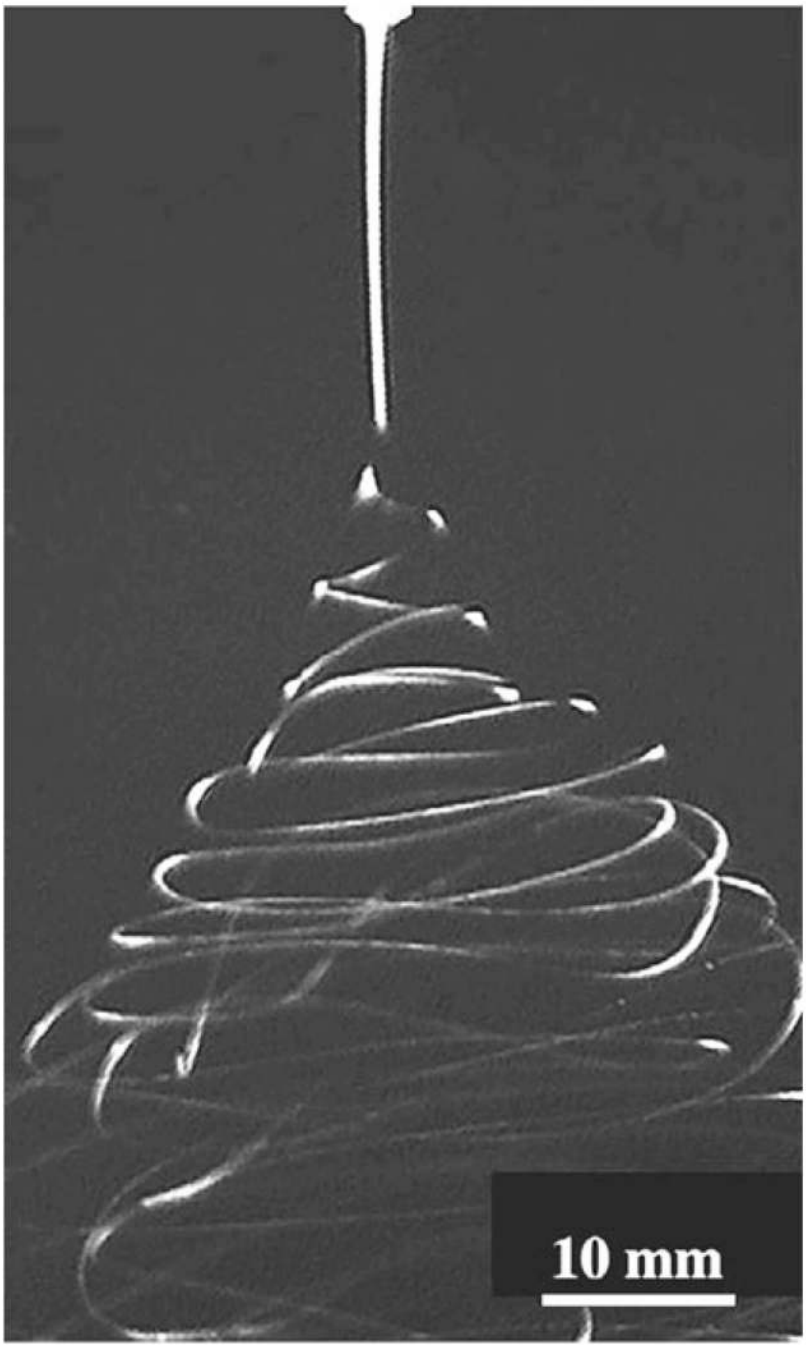

Figure 2.
Photographs of typical electrospinning jets captured using a high-speed camera showing the electrically driven bending instability. Reproduced with permission from ref.[8], Copyright 2007 Elsevier.

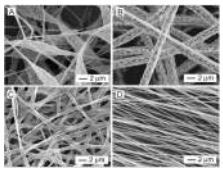

Figure 3.

Electrospun poly(L-lactide) (PLA) fibers having various structures: A) beaded porous fibers; B) highly porous, uniform fibers; C) belt-shaped solid fibers; and D) uniform solid fibers with a circular cross section. In the preparation of samples A and B, the feeding rate for the polymer solution was 0.8 and 0.5 mL · h^{-1}, respectively, and the concentrations of PLA in DCM was 0.8 and 1.3%, respectively. In the preparation of sample C, the feeding rate for the polymer solution was 0.8 mL · h^{-1} and the concentration of PLA in DCM/DMF (80: 20) was 1.3%. In the preparation of sample D, the feeding rate was 0.5 mL · h^{-1} and the concentration of PLA in DCM was 0.8%, together with 5×10^{-3} M TCAB.

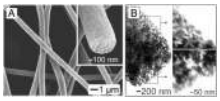

Figure 4.

A) SEM image of PS porous fibers prepared by electrospinning into liquid nitrogen, followed by drying under vacuum. The inset gives an SEM image of the broken end of a fiber at a higher magnification, indicating the fiber was porous throughout. B) TEM of the porous PS fibers shown in (A) with insets at higher magnifications. Reproduced with permission from ref.[89] Copyright 2006 American Chemical Society.

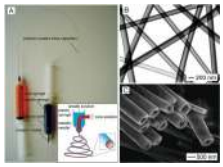

Figure 5.

A) Schematic illustrating fabrication of tubular nanofibers by electrospinning with a coaxial spinneret. Reproduced with permission from ref.[91] Copyright 2005 The Royal Society of Chemistry. B) TEM and C) SEM images of TiO_2/poly(vinyl pyrrolidone) (PVP) composite tubular nanofibers prepared by electrospinning with a coaxial spinneret, where the inner liquid was mineral oil and the outer liquid was an alcohol solution of PVP and $Ti(O\textit{i}Pr)_4$. Reproduced with permission from ref.[92] Copyright 2004 American Chemical Society.

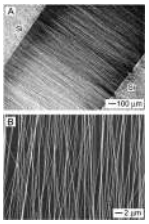

Figure 6.
Micrographs showing the alignment of poly(vinyl pyrrolidone) (PVP) nanofibers across a void gap between two pieces of conductive silicon substrates: A) dark-field optical micrograph; and B) SEM image from the same sample. Reproduced with the permission from ref.[101] Copyright 2003 American Chemical Society.

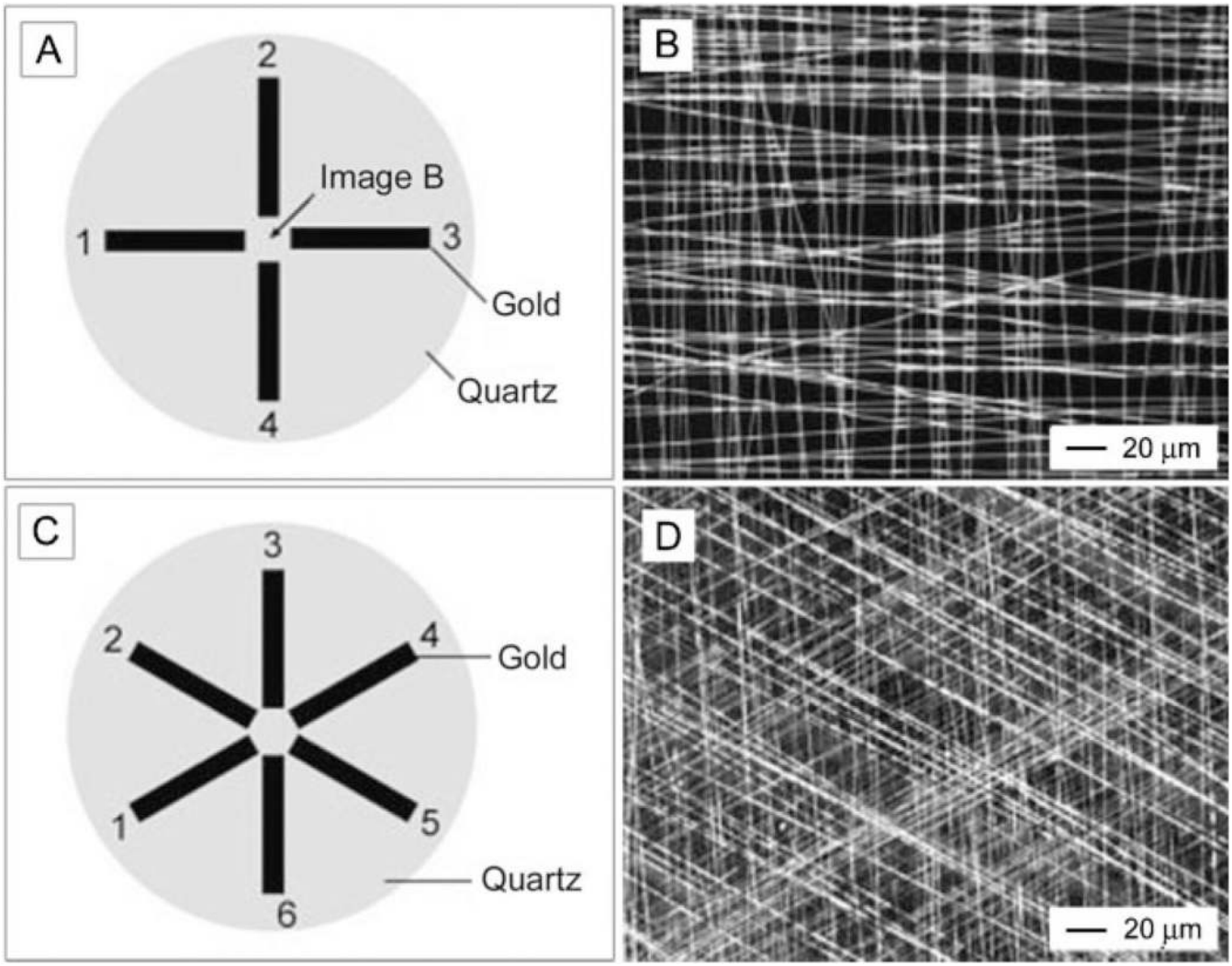

Figure 7.

A) Schematic illustrations of patterns composed of two pairs of electrodes. B) Optical micrograph of poly(vinyl pyrrolidone) (PVP) nanofibers collected in the center area of the electrodes shown in (A). During collection, the electrode pairs of 1,3 and 2,4 were alternatively grounded for ≈5 s. C) Schematic illustrations of patterns composed of three pairs of electrodes. D) Optical micrograph of a tri-layer mesh of PVP nanofibers which were collected in the center area of the electrodes shown in (C). The electrode pairs of 1,4, 2,5, and 3,6 were sequentially grounded for ≈ 5 s to collect alternating layers with orientations of their fibers rotated by around 60°. Reproduced with permission from ref.[106] Copyright 2004 Wiley InterScience.

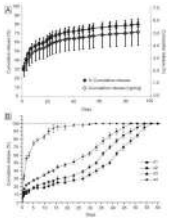

Figure 8.
In vitro release profiles: A) Glia cell-derived neurotrophic factor from electrospun poly[(ε-caprolactone)-*co*-(ethyl ethylene phosphate)] fibers; B) Bone morphogenic protein 2 (BMP-2) release from poly(lactide-*co*-glycolide)/hydroxyapatite fibrous scaffold. s1–s3: the BMP-2 solution was added directly into the aqueous fabrication solution for electrospinning which contains different amounts of hydroxylapatite nanoparticles; s4: the BMP-2 protein was added to each fibrous scaffold sample of s4 after scaffold was fabricated and dried for 3 d using a freeze drier. Reproduced with permission from ref.[121,122] Copyright 2007 and 2008 Wiley InterScience.

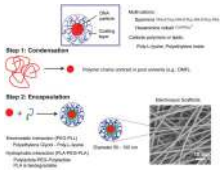

Figure 9.
Illustration of encapsulation of DNA inside electrospun fibers. Reproduced with permission from ref.[127] Copyright 2006 Institute of Physics and IOP publishing.

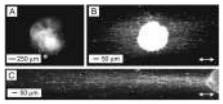

Figure 10.
Neurite outgrowth from dorsal root ganglia tissue on nanofibers. Immunofluorescent staining of neurofilaments was used to visualize neurite outgrowth from dorsal root ganglia tissue on (A) untreated random poly(L-lactide) (PLLA) nanofibers, (B) untreated aligned PLLA nanofibers, and (C) immobilized-basic fibroblast growth factor on aligned PLLA nanofibers after 6 d of *ex vivo* culture. Reproduced with permission from ref.[138] Copyright 2007 the American Chemical Society.

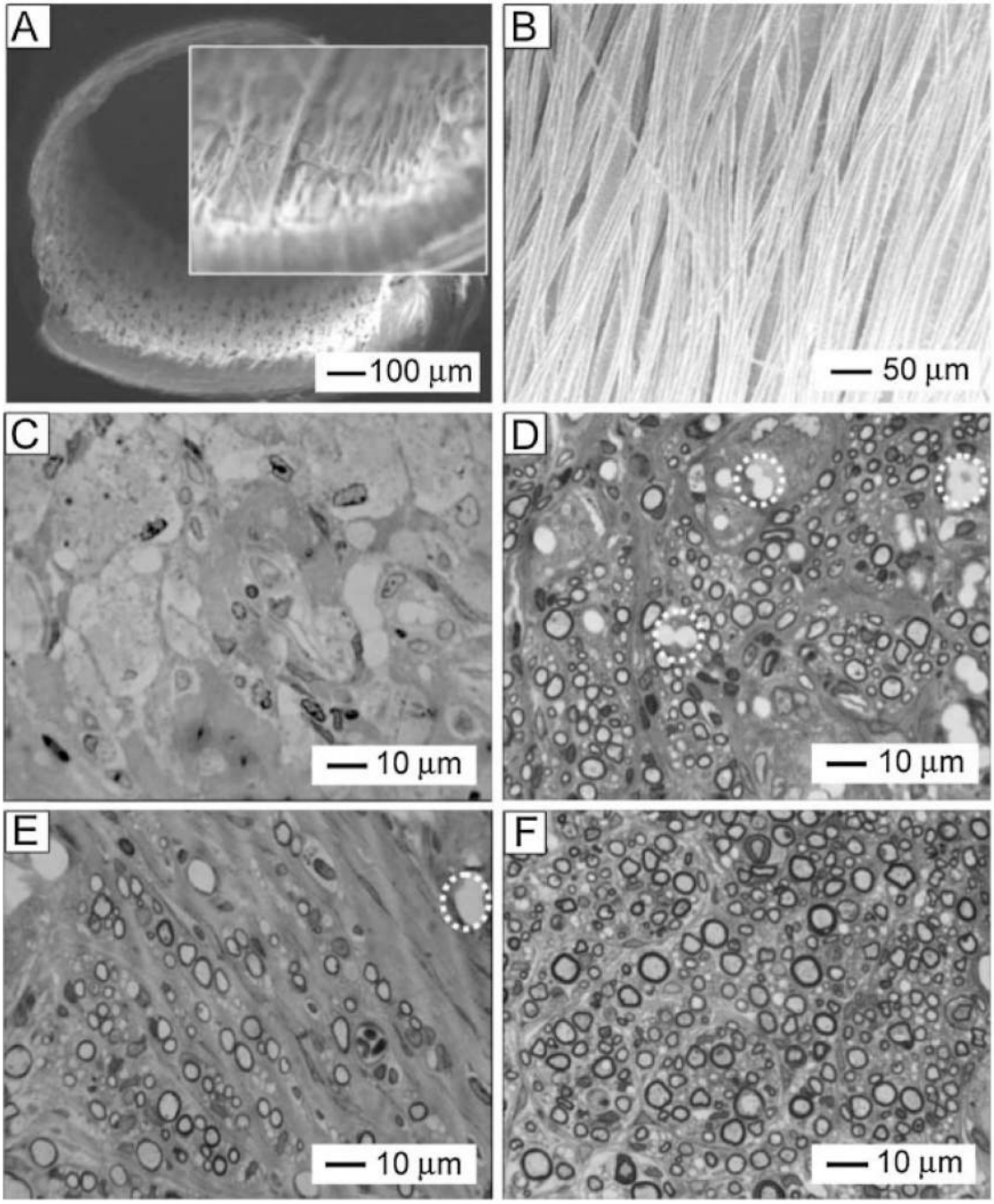

Figure 11.
A) Cross-sectional view of nerve conduits with aligned electrospun fibers; B) aligned poly[(ε-caprolactone)-*co*-(ethyl ethylene phosphate)] (PCL-EEP) fibers in nerve conduits; (C–F) optical micrographs of the cross sections of regenerated sciatic nerves and tubes were composed of: C) PCL-EEP film; D) plain PCL-EEP electrospun fibers aligned longitudinally; E) plain PCL-EEP electrospun fibers aligned circumferentially; F) glia-derived nerve factors loaded-PCL-EEP fibers aligned longitudinally. Dashed circles indicate voids left over by PCL-EEP electrospun fibers. Reproduced with the permission from ref. [121] Copyright 2007 Wiley InterScience.

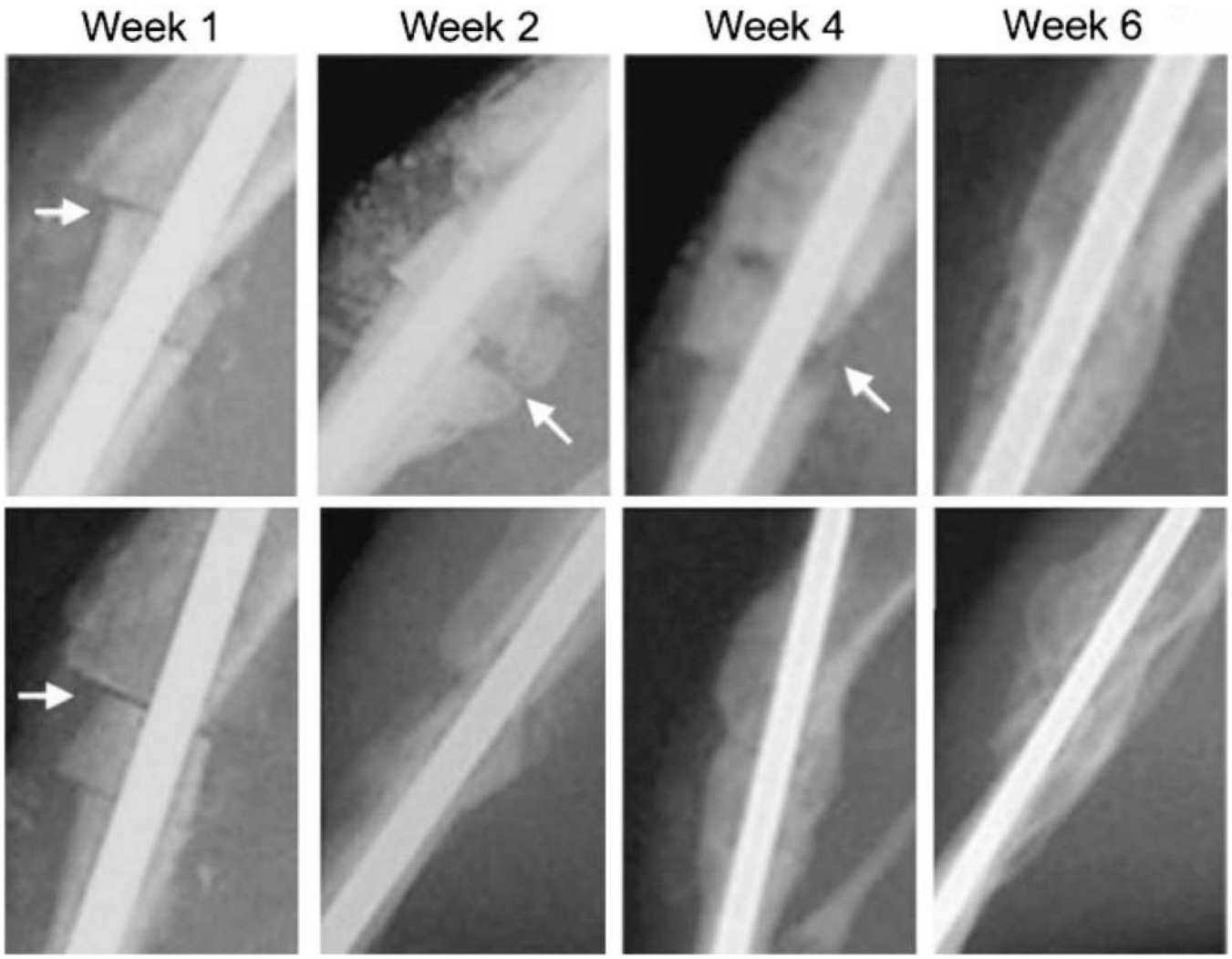

Figure 12.
Nude mice tibia bone regeneration experiments with the electrospun poly(lactide-*co*-glycolide)/hydroxyapatite (PLGA/HA) composite fibers as scaffolds: (top panel) control (without any implantation); and (bottom panel) the PLGA/HA fibrous scaffolds which were added in bone morphogenic protein 2 solution after electrospinning for adsorption. White arrows indicate the delayed-union of bone fractures. Reproduced with permission from ref. [122] Copyright 2008 Wiley InterScience.

Table 1

List of useful biomedical materials and solvents for electrospinning.

Materials[a)]	Solvent	Refs
Natural polymers		
Chitosan	90% Acetic acid	[15]
Gelatin	Formic acid	[16]
Gelatin	TFE	[17]
Collagen Type I, II, and III	HFIP	[18]
Collagen Type I, II, and III	HFIP	[19]
Collagen Type I, II, and III	HFIP	[20]
Elastin	HFIP	[21]
Hyaluronic acid	DMF/water	[22]
Cellulose	NMMO/water	[23]
Silk fibroin	Methanol	[24]
Phospholipids (Lecithin)	Chloroform/DMF	[25]
Fibrinogen	HFIP/10× minimal essential medium	[26]
Hemoglobin	TFE	[27]
Fibrous calf thymus Na-DNA	Water/ethanol	[28]
Virus M13 viruses	THF	[29]
Synthetic polymers		
PLGA	TFE/DMF	[30]
PLA	HFIP	[31]
PLA	DCM	[32]
PLA	DCM/DMF	[32]
PLA	DCM/pyridine	[32]
PCL	DCM/methanol	[33]
PHBV	Chloroform/DMF	[34]
PDO	HFIP	[35]
PGA	HFIP	[36]
PLCL	Acetone	[37]
PLCL	DCM	[32]
PLLA-DLA	Chloroform	[38]
PEUU	HFIP	[39]
Cellulose acetate	Acetic acid/water	[40]
PEG-*b*-PLA	Chloroform	[41]
EVOH	70% propan-2-ol/water	[42]
PVA	Water	[43]
PEO	Water	[44]
PVP	Ethanol/water	[45]
Blended		
PLA/PCL	Chloroform	[46]
Gelatin/PVA	Formic acid	[47]

Materials[a)]	Solvent	Refs
PCL/collagen	HFIP	[48]
Sodium aliginate/PEO	Water	[49]
Chitosan/PEO	Acetic acid/DMSO	[50]
Chitosan/PVA	Acetic acid	[51]
Gelatin/elastin/PLGA	HFIP	[52]
Silk/PEO	Water	[53]
Silk fibroin/chitosan	Formic acid	[54]
PDO/elastin	HFIP	[55]
PHBV/collagen	HFIP	[56]
Hyaluronic acid/gelatin	DMF/water	[57]
Collagen/chondroitin sulfate	TFE/water	[58]
Collagen/chitosan	HFIP/TFA	[59]
Composites		
PDLA/HA	Chloroform	[60]
PCL/$CaCO_3$	Chloroform/methanol	[61]
PCL/$CaCO_3$	DCM/DMF	[62]
PCL/HA	DCM/DMF	[62]
PLLA/HA	Chloroform	[63]
Gelatin/HA	HFIP	[64]
PCL/collagen/HA	HFIP	[65]
Collagen/HA	HFIP	[65]
Gelatin/siloxane	Acetic acid/ethyl acetate/water	[66]
PLLA/MWNTs/HA	1,4-dioxane/DCM	[67]
PLGA/HA	DCM/water	[68]

[a)]Abbreviations: PLGA, poly[(lactic-*co*-(glycolic acid)]; PLA, poly(lactic acid); PCL, poly(ε-caprolactone); PHBV, poly[(3-hydroxybutyrate)-*co*-(3-hydroxyvalerate)]; PDO, polydioxanone; PGA, poly(glycolic acid); PLCL, poly[(L-lactide)-*co*-(ε-caprolactone)]; PEUU, poly(esterurethane) urea; PLLA-DLA, poly[(L-lactide)-*co*-(D-lactide)]; EVOH, poly[ethylene-*co*-(vinyl alcohol)]; PVA, poly(vinyl alcohol); PEO, poly(ethylene oxide); PVP, poly(vinyl pyrrolidone); TFE, trifluoroethanol; HFIP, hexafluoroisopropanol; DMF, dimethylformamide; NMMO, *N*-methylmorpholine-*N*-oxide; THF, tetrahydrofuran; DCM, dichloromethane.