ISSN: 2414-1895 DOI: 10.6919/ICJE.202201_8(1).0008

# Functional Nanomaterials and Their 2D and 3D Fabrications for Tissue Engineering and Drug Delivery Applications

Weifan Lee

Taipei Wego Senior High School,China

## Abstract

**This review paper provides an overview of the fabrication of the functional nanomaterials and their practical applications for tissue engineering (TE). The study of nanomaterials has been a coruscating field of research that has a huge impact on science, engineering, and medicine. In terms of applied science, it succeeded the limits of conventional materials, hence making the opt of the materials more multifaceted. Nanomaterials can be highly beneficial in TE because of their morphological properties-flexibility and thus they allowed the fibers to be formed in various shapes in accordance with the extracellular structure. Because of these benefits, further research on this topic is conducted as of now.**

## Keywords

**Tissue Engineering, Nanomaterials, Hydrogels, Electrospinning.**

## 1. Introduction

### 1.1 The Importance of Nanostructured Materials in Tissue Engineering

In the abstract, TE aims to create a temporary extracellular structure to temporarily serve the role of the original tissue to repair a wound or substitute a malfunctioning organ. Various fabrications methods now provide more options of materials for TE. Among the materials, porous polymer scaffold was found to be meeting the criteria of applicable artificial fibers, while the material in nanoscale, engineered nanofibers (NF), show higher applicability since their properties often surpass the limitation of the corresponding material in macroscales. NFs are beneficial because of their large surface area, the huge surface to volume ratio, and length to diameter aspect ratio. NFs' unique properties allowed the fabrication of porous extracellular matrix (ECM) to increase the similarity between the scaffold and membranes with spaces and large surface areas [1].

One criterion for TE would be whether it is bio-compatible or not. Since the study of TE usually deals with long-term defects in the tissues, it is vital that the scaffold is reconcilable with the tissues and has the capability of degrading along with the process of cells growing. On top of that, the degraded product should not be hazardous or be giving rise to immune responses [2].

There are many methods for fabricating nanofibers, including template synthesis, drawing, thermal-induced phase separation, self-assembly, and electrospinning [3]. Among the methods, electrospinning is significant because of its ability to produce two-dimensional and three-dimensional structures. However, its low productivity, use of toxic materials, and extra processes required to extract the fibers are considered defects of electrospinning. Despite the defects, electrospinning still holds its vitality since most of the applied scaffolds now are not bioresorbable, which implies the fact that they cannot serve as temporary templates that are similar to the properties of the membranes [1].

## 1.2 Human Skin Architecture, Skin Anatomy and Extracellular Matrix

### 1.2.1 Human Skin Architecture

Humans' skin and its annexation (e.g. nail, hair) form the largest organ of the human body, 2 m2 in terms of surface area. At the same time, the skin accounts for 15% of body weight [4]. The skin protects the internal tissue from either physical, chemical, or biological threats, and prevents the human body from excessive water loss [4]. With that being said, it is imperative to treat the wound on the skin if there is one.

When the structure of the skin is broken, a wound appears. Wounds may occur due to reasons like rupture of the tissue, congenital anomalies. As the previous paragraph demonstrated, skin is an essential organ in terms of protecting the human body, so it is imperative to treat a wound immediately after to ensure homeostasis, inflammation, cell migration, proliferation, and maturation [1].

### 1.2.2 Skin Anatomy

The skin is fundamentally composed of three different layers: epidermis, dermis, and hypodermis, as seen in Figure 1. The Epidermis, the outer level of the skin, is composed of a special cell, keratinocytes, in a special arrangement, which is the part that produces keratin, a specialized protein used for protection. Dermis, the middle level, is the layer that comprises fibrillar-structure proteins. Consequently, Dermis lies on the hypodermis, which is subcutaneous tissue, or panniculus. It consists of small lobes of fat, called lipocytes. The thickness of the epidermis can vary between 50 μm to 1550 μm regarding the location of the skin (e.g. eyelids, feet) [4].

In detail, the dermis holds several glands (e.g. adrenal, eccrine, apocrine, sebaceous). At the same time, it allows the circulation of blood and lymph of a specific skin area. The hypodermis serves as the connection between the skin and the bone, muscle, and tendon.

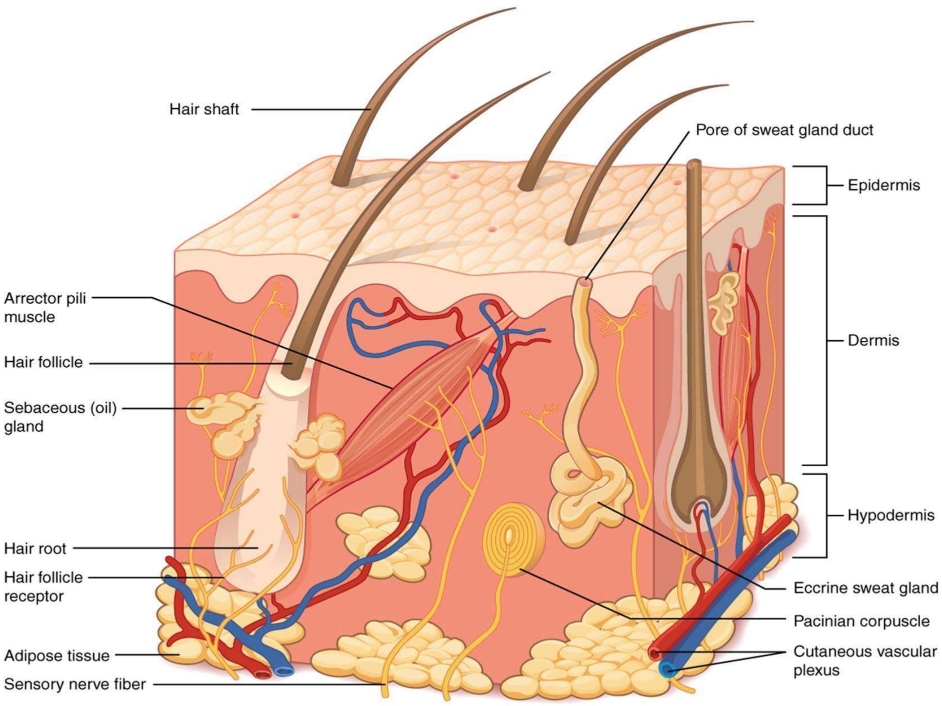


**Figure 1.** 3D visualization of skin structure [5].

### 1.2.3 Extracellular Matrix (ECM)

ECM has substantial importance when evaluating the healing process since it both affects the cellular and mechanical responses, both directly and indirectly [1]. It is a significant part of every organ since

ISSN: 2414-1895 DOI: 10.6919/ICJE.202201_8(1).0008

it is responsible for homeostasis and repairing. ECM provides mechanical stability by attaching the epithelium to the underlying tissues. On top of that, ECM allows the response to the milieu and the communication for the adaptation to the environment between the cells. Furthermore, it is also responsible for relaying the information. Doubtlessly, ECM is so significant that it would lead to disorder if the ECM is harmed.

## 2. Electrospinning as an Excellent Technique for Scaffold Building

### 2.1 2D Electrospinning for Skin Tissue Engineering

As aforementioned, when repairing the wound tissues, a scaffold should be temporary, biodegradable, and non-toxic. With regard to these protocols, 2D scaffold is one of the best choices among all the materials. Moreover, natural fibers have high compatibility with ECM because of their intrinsic properties [6]. Such being the case, it has a lower chance of causing an inflammatory reaction and immunotoxicity. At present, various kinds of NFs made out of natural polymers are being fabricated and applied.

Some of the polymers used in electrospinning even exist in ECM, polysaccharides (chitosan, cellulose, Aloe vera, hyaluronic acid), proteins (collagen, elastin, fibrin, sericin, gelatin), and polynucleotides (DNA, RNA); meanwhile, those polymers can be extracted from an organism. Polymers with different properties would also affect the healing process in different ways, which is a way used to manually control the process of healing [7]. This demonstrates the reason why natural polymers would have a lower chance of arousing inflammatory reactions. Natural polymers made up of ECM proteins are recognized to be ideal alternatives for wounded tissue. Examples include small intestinal submucosa, acellular dermis, the bladder acellular matrix graft, and the amniotic membrane. Additionally, it promotes the interaction between the tissues and speeds up angiogenesis [8].

Furthermore, natural polymers (collagen, glycosaminoglycan, chitosan, starch, hyaluronic acid, and alginate) are relatively weaker and softer compared to other polymers. This could be advantageous because of its flexibility [7]. Flexibility can be an important factor of a scaffold since it can adapt itself to the shape of the wound.

### 2.2 3D Electrospinning for Skin Tissue Engineering

Just as 2D structures, 3D nanomaterial emerged because of its special properties, even superior to 2D structures. Differ from 2D nanomaterials, 3D nanomaterials have a 3rd axis that allowed cell interactions, cell migration, and other functions that are essential for the cell cycle [9]. Simultaneously, it serves as a better substitution to the wounded tissue since it is more similar to the tissues of the human body.

The fabrication of 3D nanomaterials has the advantage of alterable morphological properties, porosity, and size of the fiber. Duan et al mentioned that ultralight-weight 3D nanomaterials with 2.7 mg/cm3 with 99.6% porosity can now be fabricated through a particular manufacturing method [10]. This is significantly beneficial in terms of TE since the porous structure allows the surrounding cells to seed in the pores and replicate to cure the particular location. Compared with 2D structures, 3D structures have more benefits than 2D structures in terms of cell implanting.

## 3. Conductive Hydrogels (Injectable and 3D Printing) for Tissue Engineering

Hydrogel is one of the ideal materials applied to TE because it is soft, porous, water-bearing, and its structure is similar to ECM. In general, hydrogels are able to conduct ionic currents dissolved in the water. However, it lacks electron conductivity so it may be a hindrance to the communication between the cells which use electric signals. The most feasible and common way to fabricate conductive hydrogels is to install nano-conductive fillers. To further enhance productivity, multiple-phase composite hydrogels have been introduced.

ISSN: 2414-1895 DOI: 10.6919/ICJE.202201_8(1).0008

### 3.1 Nanocomposite Conductive Hydrogels

Nano-conductive fillers like CNTs and graphene tend to gather into clumps after the installment. To solve this, there are several particular methods to manufacture conductive hydrogels to prevent the fillers from aggregating [11]. Here, conductive hydrogels can be divided into several kinds: nanocomposite conductive hydrogels, conductive polymer hydrogels, self-assembled graphene hydrogels, and multi conductive phase composite conductive hydrogels.

In this paper, we will only be examining some of the examples of conductive hydrogels that are applied to the field of TE.

#### 3.1.1 Carbon-Based Nanocomposite Conductive Hydrogels

Carbon-based nanocomposite conductive hydrogels are hydrogels that include carbon nanomaterials (e.g. carbon nanotube (CNT), graphene, fullerene (C60), nano-diamonds). CNT and graphene are especially used to enhance conductivity. Due to their special properties, it is widely used when constructing conductive tissues like nerves, muscles, or cardiac tissues [12].

CNT's hydrophobic feature hinders the reaction between it and the hydrophilic hydrogels. In this case, CNT should be appended with particular kinds of polarity groups (e.g. amines (NH2), hydroxyl (OH), carboxyl (COOH)) or combined with polymers to achieve more even dispersion. (Figure 2).

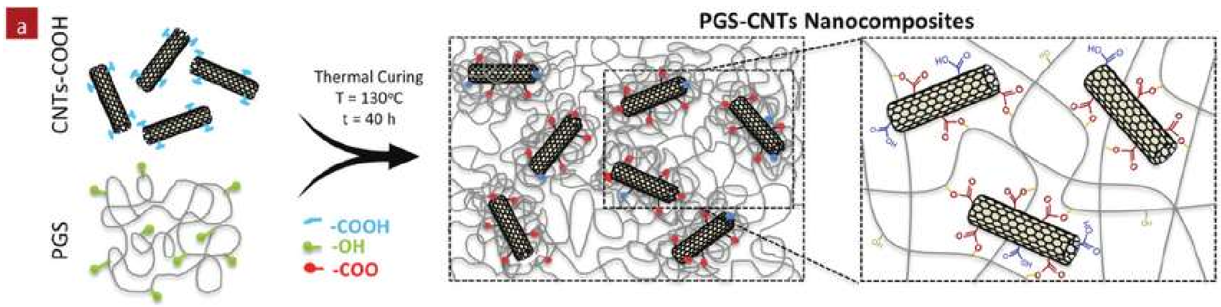


**Figure 2.** Synthesis of PGS-CNT. Reproduced from [13].

During the process, the hydroxyl group on PGS will esterify with the carboxyl groups attached to CNT. Here, CNT in PGS (polyglycerol sebacate)-CNT serves as both covalent and physical crosslinkers. The crosslinking then enhances the both tensile and compression modulus, while not reducing the elasticity of the hydrogel.

Graphene and graphene oxide (GO) are also widely used for constructing carbon-based nanocomposite conductive hydrogels. Compared with graphene, GO is more hydrophilic but less conductive. In particular, GOs can more efficiently deliver genes when it is bonded to cationic polymers (e.g. polyethyleneimine (PEI)). At the same time, with its low molecular weight, branched PEI has low cytotoxicity.

#### 3.1.2 Metal Nanocomposite Conductive Hydrogels

One of the most feasible ways for the fabrication of nanocomposite conductive hydrogels is to add metal NPs into the matrix regarding their capability of conducting. However, the applicability may be affected because of the metal's high tendency to corrosion in wet environments. To solve this, noble metals would be applied (e.g. Au, Ag, Pt). In particular, research on gold as conductive fillers has been carried out due to its biocompatibility.

To fabricate a matrix that would not arouse a negative immune response, Dvir et al, combined AuNPs with the decellularized matrix. The experiment results showed that AuNPs are able to dramatically increase the conductivity while not affecting the intrinsic properties [14]. To achieve uniform

ISSN: 2414-1895 DOI: 10.6919/ICJE.202201_8(1).0008

dispersion of AuNPs, Auguste and colleagues submerged mercapto-2-hydroxyethyl into potassium tetrachloroaurate (KAuCl4 (aq)) solution, reduced by sodium borohydride (NaBH4). The experiment conducted by the group had successfully produced even dispersed AuNPs, which indicates that this may be a feasible method of fabrication [15].

### 3.2 Multi-Conductive Phase Composite Conductive Hydrogels

Research done previously has demonstrated that single conductive phase hydrogels do not have sufficient mechanical properties and electrical conductivity. Research done by Yadavalli et al. and Ahmad et al has successfully conveyed that multi-conductive phase hydrogels are better in terms of physical properties (e.g. strength) [16,17]. Consequently, the research marked the outset of a new era for the research in multi-conductive phase composite conductive hydrogels.

### 3.3 TE Application of Conductive Hydrogel

#### 3.3.1 Myocardial Tissue Engineering

The myocardium is an electricity-responsive tissue, which relays messages between the cells. Meanwhile, a myocardial tissue wound may eventually result in the formation of scar tissue, a hindrance to signal transmission, declination in cardiac function, and heart failure [11].

Fortunately, Auguste et al [15], Khorshidi and Karkhanch [18], Khademhosseini et al [19], had successfully shown that hydrogel can be applied in myocardial TE to construct scaffolds that can relay electrical signals. This promoted further research on conductive hydrogel-based myocardial TE.

In the field of myocardial TE, hydrogels can be used to serve as temporary cardiac tissue without the use of cells. PNIPAAM (Poly N-isopropylacrylamide), a kind of temperature-sensitive material, was utilized for it to be delivered to the MI area of a rat model. To achieve this, several groups (e.g. hydroxyethyl methacrylate-poly(trimethylene carbonate), acrylic acid (AAc)) is attached to PNIPAAM [20]. (Figure 3).

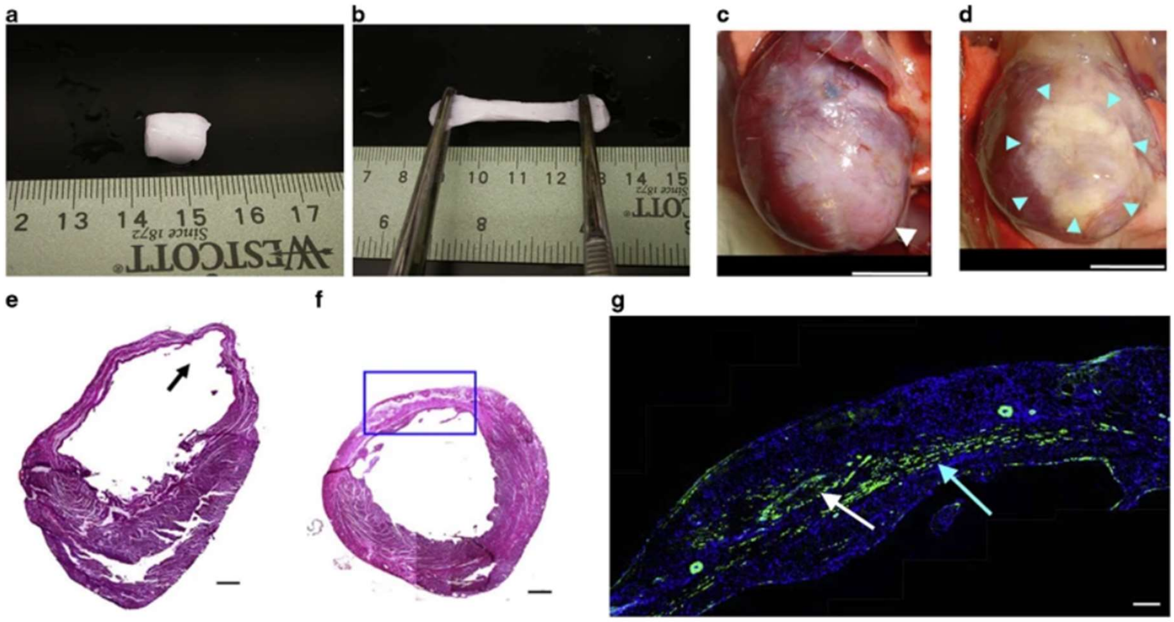


**Figure 3.** (a) composition of the material is NIPAAm-co-AAc-co-HEMAPTMC hybrid hydrogel (b) it is highly elastic (c) control experiment with rat heart injected with phosphate-buffered saline (PBS) solution (d) rat heart injected with conductive hydrogel (e) histological analysis by staining the heart injected with PBS (f) histological analysis by staining the heart

injected with conductive hydrogel (g) demonstration of tissue ingrowth. Reproduced from [20].

### 3.3.2 Neural Tissue Engineering (NTE)

Neural is one of the most vital tissues inside human body. It would surely be a burden if one loses the functions of neural tissue. Therefore, it is imperative to come up with a solution to cure the neurological tissue wound.

Although peripheral nerve does have the capability of regenerating itself, large area of peripheral nerve wound cannot be healed spontaneously by the neural tissue. As of now, autologous transplantation is the majority among the methods of therapy. However, the applicability and availability of this method can be limited due to limited autograft availability and other factors [11].

When searching for the applicable material, it must have the characteristic of being able to transmit electric signals in order to substitute the neural tissues temporarily. Yuan et al [21] [22], and Xu et al [23], had successfully demonstrated that conductive hydrogels might be one of the ideal material to NTE because of its ability to transmit electric signals, and allow nerve tissue regeneration. This stimulated the research in hydrogel-based NTE [24-26]. The chart below analyzes the contents of each research conducted related to hydrogel-based NTE.

**Table 1.** Contents of each research conducted related to hydrogel-based NTE

| Research group & References | Research content | Result |
|---|---|---|
| Zhou et al. [27-30] | Pure conductive PPy hydrogel processed by crosslinking and doping by TA | • Enhanced the differentiation of neural stem cells<br>• Stimulated the nerve tissue regeneration |
| Liu et al. [31] | 2-(methacryloxy) ethyltrimethy-lammonium chloride (MTAC) with positive charge combined with GO acrylate (GOa) and CNTpega-OPF to acquire CNTpega-OPF-MTAC (with hydroconductivity and surface electrical charge) | • Enhanced the proliferation and differentiation.<br>• Improved the conductivity and positive charge<br>• May be a potential material for NTE |
| Zhou et al. [32,33] | PPy conductive nanofibers | Decent biocompatibility with both Schwann cells and human cells (human umbilical cord mesenchymal stem cells (huMSC). Direct current was able to promote differentiation. |

### 3.3.3 Bone Tissue Engineering

In the case of large defects, bone tissue engineering can hinder the growth of scar tissue and stimulates the regeneration of bone tissue. Regarding the fact that bone tissue is electricity-conductive, materials used in bone tissue engineering should have the same property. As mentioned before, conductive hydrogel can be one of the ideal choices because of its distinct conductivity and high biocompatibility. However, hydrogel does not have the required mechanical strength for the substitution of bone tissue [11].

To solve this, Karkhaneh et al [34] introduced hydrogel/fiber conductive scaffolds to enhance its mechanical strength by adding oxidized polysaccharides, gelatin, graphene for scaffolds and polyaniline electrospun fibers. Analysis of the experimental results conveyed that the introduction of conductive fibers had successfully enhanced the hydrogel's conductivity, elastic modulus, and roughness [34]. Furthermore, the hydrogel/fiber conductive scaffolds had performed superior human osteoblast-like proliferation, morphology, and cell adhesion than the conventional hydrogel conductive scaffolds itself [34].

### 3.4 Injectable Conductive Hydrogels

Injectable hydrogel can be fabricated through the process of physical or chemical crosslinking, which is able to turn into any shape to match the shape of the wound. Chemical crosslinking, despite being stable, often includes cytotoxic crosslinkers. Hydrogel processed through physical crosslinking (e.g. injectable hydrogel with electrostatic interaction, supramolecular self-injectable hydrogels), on the other hand, would not include cytotoxic substances, but it can be less stable.

Recently, utilization of injectable conductive hydrogels for TE has increased. Nih et al [35], introduced HA with vascular endothelial growth factor (VEGF) into the wounded tissues. Results had conveyed that it boosted angiogenesis, and the growth of axonal network along the blood vessels.

Injectable conductive hydrogel is a potential material for TE because it combines the benefits of both injectable hydrogel and conductive hydrogel. Research conducted by Ma et al. [36], and Wei et al. [37], conveyed the fact that injectable conductive hydrogel have the ability of boosting tissue regeneration.

On top of that, to maximize the effect of injectable conductive hydrogels, injectable conductive hydrogels can be associated with cell or gene therapy. Conventional cell implantation has the defect of having poor cell feasibility, which can result in the failure of cell therapy. Luckily, some research found out that injectable conductive hydrogels mixed with cells as well as biologically active molecules can prevent wound or cell’s death [11].

## 4. Conclusion

The article aforementioned had arranged the organized the recent research in functional nanomaterials and their 2D and 3D fabrications for TE. From these topics, one can analyze the vital attributes for nanomaterials to be applied in biotechnology include distinct biocompatibility, biodegradability, non-cytotoxicity.

As of now, nanomaterials have been paving a path for research in many fields. For TE, nanomaterials are rising materials to be researched furthermore because of their superior attributes. However, current progress of research does not bring an end to the journey of researching nanomaterials. There are still issues and challenges pending to be solved and explored for further applicable usage.

## References

[1] Keirouz, Antonios, et al. “2D And 3D Electrospinning Technologies for the Fabrication of Nanofibrous Scaffolds for Skin Tissue Engineering: A Review.” WIREs Nanomedicine and Nanobiotechnology, vol. 12, no. 4, 2020, doi:10.1002/wnan.1626.

[2] Lu, Lichun, and Antonios G. Mikos. "The importance of new processing techniques in tissue engineering." Mrs Bulletin 21.11 (1996): 28-32.

[3] Gundloori, Rathna VN, Amarnath Singam, and Naresh Killi. "Nanobased intravenous and transdermal drug delivery systems." Applications of Targeted Nano Drugs and Delivery Systems. Elsevier, 2019. 551-594.

[4] Kolarsick, Paul A. J. BS; Kolarsick, Maria Ann MSN, ARHP-C; Goodwin, Carolyn APRN-BC, FNP Anatomy and Physiology of the Skin, Journal of the Dermatology Nurses' Association: July 2011 - Volume 3 - Issue 4 - p 203-213 doi: 10.1097/JDN.0b013e3182274a98.

[5] “Biology for Majors II.” Structure and Function of Skin | Biology for Majors II, courses. lumenlearning. com/suny-wmopen-biology2/chapter/structure-and-function-of-skin/.

[6] Ige, Oladeji O., et al. “Natural Products: A Minefield of Biomaterials.” International Scholarly Research Network, 5 Jan. 2012.

[7] Asti, Annalia, and Luciana Gioglio. “Natural and Synthetic Biodegradable Polymers: Different Scaffolds for Cell Expansion and Tissue Formation.” The International Journal of Artificial Organs, vol. 37, no. 3, Mar. 2014, pp. 187–205, doi:10.5301/ijao.5000307.

[8] Matthias W. Laschke, Yves Harder, Michaela Amon, Ivan Martin, Jian Farhadi, Andrej Ring, Nestor Torio-Padron, René Schramm, Martin Rücker, Dominic Junker, Jörg M. Häufel, Carlos Carvalho, Michael Heberer, Günter Germann, Brigitte Vollmar, and Michael D. Menger.Tissue Engineering.Aug 2006.2093-2104.http://doi.org/10.1089/ten.2006.12.2093.

[9] Sun, B., Long, Y. Z., Zhang, H. D., Li, M. M., Duvail, J. L., Jiang, X. Y., & Yin, H. L. (2014). Advances in three-dimensional nanofibrous macrostructures via electrospinning. Progress in Polymer Science, 39(5), 862–890.

[10] Duan, G., Jiang, S., Jérôme, V., Wendorff, J. H., Fathi, A., Uhm, J., Altstädt, V., Herling, M., Breu, J., Freitag, R., Agarwal, S., & Greiner, A. (2015, March 30). Ultralight, soft polymer sponges by self-assembly of short electrospun fibers in colloidal dispersions. Wiley Online Library. Retrieved October 15, 2021, from https://onlinelibrary.wiley.com/doi/full/10.1002/adfm.201500001.

[11] Jiang L, Wang Y, Liu Z, Ma C, Yan H, Xu N, Gang F, Wang X, Zhao L, Sun X. Three-Dimensional Printing and Injectable Conductive Hydrogels for Tissue Engineering Application. Tissue Eng Part B Rev. 2019 Oct;25(5):398-411. doi: 10.1089/ten.TEB.2019.0100. Epub 2019 Sep 11. PMID: 31115274.

[12] Rafieian, Shirin, Mirzadeh, Hamid, Mahdavi, Hamid and Masoumi, Mir Esmaeil. "A review on nanocomposite hydrogels and their biomedical applications" Science and Engineering of Composite Materials, vol. 26, no. 1, 2019, pp. 154-174. https://doi.org/10.1515/secm-2017-0161.

[13] Elastomeric nanocomposite scaffolds made from poly(glycerol sebacate) chemically crosslinked with carbon nanotubes - Scientific Figure on ResearchGate. Available from: https://www. researchgate. net/ figure/Synthesis-and-fabrication-of-PGS-CNT-nanocomposites-a-Schematic-representation-of_fig1_265208629 [accessed 19 Oct, 2021].

[14] Dvir, T., Timko, B.P., Brigham, M.D., et al. Nanowired three-dimensional cardiac patches. Nat Nanotechnol 6, 720, 2011.

[15] You, J.O., Rafat, M., Ye, G.J.C., et al. Nanoengineering the heart: conductive scaffolds enhance connexin 43 expression. Nano Lett 11, 3643, 2011.

[16] Pal, R.K., Turner, E.E., Chalfant, B.H., et al. Mechanically robust, photopatternable conductive hydrogel composites. React Funct Polym 120, 66, 2017.

[17] Baniasadi, H., Ramazani, S.A.A., and Mashayekhan, S. Fabrication and characterization of conductive chitosan/ gelatin-based scaffolds for nerve tissue engineering. Int J Biol Macromol 74, 360, 2015.

[18] Khorshidi, S., and Karkhaneh, A. Hydrogel/fiber conductive scaffold for bone tissue engineering. J Biomed Mater Res A 106, 718, 2018.

[19] Shin, S.R., Bae, H., Cha, J.M., et al. Carbon nanotube reinforced hybrid microgels as scaffold materials for cell encapsulation. ACS Nano 6, 362, 2011.

[20] Camci-Unal, G., Annabi, N., Dokmeci, M. et al. Hydrogels for cardiac tissue engineering. NPG Asia Mater 6, e99 (2014). https://doi.org/10.1038/am.2014.19.

[21] Qian, Y., Zhao, X., Han, Q., et al. An integrated multilayer 3D-fabrication of PDA/RGD coated graphene loaded PCL nanoscaffold for peripheral nerve restoration. Nat Commun 9, 323, 2018.

[22] Qian, Y., Song, J., Zhao, X., et al. 3D fabrication with integration molding of a graphene oxide/ polycaprolactone nanoscaffold for neurite regeneration and angiogenesis. Adv Sci 5, 1700499, 2018.

[23] Xu, C., Guan, S., Wang, S., et al. Biodegradable and electroconductive poly(3,4-ethylenedoixythiophene)/ carboxymethyl chitosan hydrogels for neural tissue engineering. Mater Sci Eng C Bio Sci 84, 32, 2017.

[24] Pyarasani, R.D., Jayaramudu, T., and John, A. Polyanilinebased conducting hydrogels. J Mater Sci 54, 974, 2019.

[25] Wang, S., Sun, C., Guan, S., et al. Chitosan/gelatin porous scaffolds assembled with conductive poly (3, 4- ethylenedioxythiophene) nanoparticles for neural tissue engineering. J Mater Chem B 5, 4774, 2017.

[26] Xu, C., Guan, S., Wang, S., et al. Biodegradable and electroconductive poly (3, 4-ethylenedioxythiophene)/ carboxymethyl chitosan hydrogels for neural tissue engineering. Mater Sci Eng C 84, 32, 2018.

[27] Zhou, L., Fan, L., Yi, X., et al. Soft conducting polymer hydrogels cross-linked and doped by tannic acid for spinal cord injury repair. ACS Nano 12, 10957, 2018.

[28] Navaei, A., Moore, N., Sullivan, R.T., et al. Electrically conductive hydrogel-based micro-topographies for the development of organized cardiac tissues. RSC Adv 7, 3302, 2017.

[29] Dillon, G.P., Yu, X., and Bellamkonda, R.V. The polarity and magnitude of ambient charge influences three dimensional neurite extension from DRGs. J Biomed Mater Res 51, 510, 2000.

[30] Makohliso, S.A., Valentini, R.F., and Aebischer, P. Magnitude and polarity of a fluoroethylene propylene electret substrate charge influences neurite outgrowth in vitro. J Biomed Mater Res 27, 1075, 1993.

[31] Liu, X., Miller, A.L., Park, S., et al. Functionalized carbon nanotube and graphene oxide embedded electrically conductive hydrogel synergistically stimulates nerve cell differentiation. ACS Appl Mater Interfaces 9, 14677, 2017.

[32] Zhou, J., Wang, Y., Cheng, L., et al. Preparation of polypyrrole-embedded electrospun poly (lactic acid) nanofibrous scaffolds for nerve tissue engineering. Neural Regen Res 11, 1644, 2016.

[33] Zhou, J., Cheng, L., Sun, X., et al. Neurogenic differentiation of human umbilical cord mesenchymal stem cells on aligned electrospun polypyrrole/polylactide composite nanofibers with electrical stimulation. Front Mater Sci 10, 260, 2016.

[34] Qian, Y., Zhao, X., Han, Q., et al. An integrated multilayer 3D-fabrication of PDA/RGD coated graphene loaded PCL nanoscaffold for peripheral nerve restoration. Nat Commun 9, 323, 2018.

[35] Nih, L.R., Gojgini, S., Carmichael, S.T., et al. Dualfunction injectable angiogenic biomaterial for the repair of brain tissue following stroke. Nat Mater 17, 642, 2018.

[36] Wu, Y., Guo, B., and Ma, P.X. Injectable electroactive hydrogels formed via host–guest interactions. ACS Macro Lett 3, 1145, 2014.

[37] Cui, H., Shao, J., Wang, Y., et al. PLA-PEG-PLA and its electroactive tetraaniline copolymer as multi-interactive injectable hydrogels for tissue engineering. Biomacromolecules 14, 1904, 2013.