

# Magnetic Substrates for Tissue Engineering—A Review

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**Abstract:** Tissue engineering is based on combining cells with suitable scaffolds and growth factors. Recently, bone tissue engineering has been especially investigated deeply due to a large number of bone-related diseases. One approach to improve scaffolds is based on using piezoelectric materials as a way to influence the growing bone tissue by mechanical stress. Another method to stimulate tissue growth is by applying an external magnetic field to composites of magnetostrictive and piezoelectric materials, as well as the possibility to prepare oriented surfaces by orienting embedded magnetic fibers or nanoparticles. In addition, magnetic scaffolds without other special properties have also been reported to show improved properties for bone tissue and other tissue engineering. Here, we provide an overview of recent research on magnetic scaffolds for tissue engineering, differentiating between bone and other tissue engineering. We show the advantages of magnetic scaffolds, especially related to cell guidance and differentiation, and report recent progress in the production and application of such magnetic substrates for different areas of tissue engineering.

**Keywords:** tissue engineering; scaffold; bone tissue regeneration; stem cell differentiation

## 1. Introduction

Tissue engineering belongs to the recently heavily investigated field of research and development. Tissue engineering helps in treating bone defects and substituting damaged organs and tissue, such as cardiovascular tissue engineering, hard and connective tissue engineering and soft tissue engineering [1–5]. Generally, for tissue engineering, the optimum combination of cells with a suitable scaffold and corresponding growth factors is necessary [6]. Since the new tissue should replace the damaged or missing tissue, it should mimic the original tissue not only regarding its shape but also with respect to its function and mechanical properties [7–9].

These requirements pose some challenges for tissue engineering substrates. Often, scaffolds are used that mimic the extracellular matrix (ECM) regarding their surface morphology and also porosity, enabling the transport of growth factors and other necessary biomolecules, as well as stem cell differentiation [10–12]. In the last years, new methods like electrospinning and 3D printing have enabled the building of functional scaffolds with the required morphology and porosity [13–16], while freeze drying, as an example of an established technique, is still often being used [17,18].

Besides the methods used to prepare scaffolds, the scaffold materials are also highly important and vary depending on the planned application, such as bone, skin or soft tissue [19]. Generally, it is necessary to use biocompatible, non-cytotoxic materials, including the potential degradation products, which enable cell attachment, proliferation and differentiation [20]. For bone tissue engineering, hydroxyapatite (HAP) is a common ingredient since HAP is also a large part of the inorganic bone constituents [21]. Other inorganic materials often used in tissue engineering are titanium, bioactive glasses and glass-ceramics [22–24], while a broad range of natural and man-made polymers can be used,

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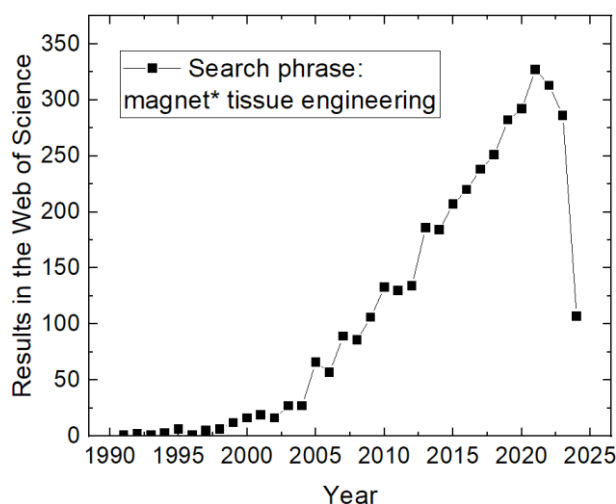


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such as gelatin, silk fibroin, alginate, poly(urethanes) (PUs) and poly(caprolactone) (PCL) [25–29]. To mimic the ECM and thus improve cell adhesion and proliferation, special gels can be coated on these tissues [30]. Another important factor is the already-mentioned mechanical properties of the tissue, which should also mimic those of the original tissue, making bioactive glass and porous bioceramics very interesting for bone tissue engineering [31].

Besides the pure morphology and biocompatibility, there are other factors influencing cell adhesion, proliferation and differentiation. Different functionalities can be integrated in polymers or hydrogels, such as antibacterial properties, drug or biomolecule delivery and biodegradability [32–34]. Among the physical properties that are investigated in detail are electro-conductivity, e.g., for neural tissue engineering [35], and magnetic properties of scaffolds, e.g., for stem cell differentiation [36].

Research on tissue engineering based on magnetic materials has intensified during the last two decades, as Figure 1 shows. Potential methods to prepare magnetic scaffolds with integrated magnetic nanoparticles or magnetic coatings for tissue engineering are discussed in the next section. Afterwards, we provide an overview of recent improvements in tissue engineering with magnetic materials, especially those related to bone and neural tissue engineering, focusing on magnetic hydrogels as well as additively manufactured and electrospun magnetic scaffolds.



**Figure 1.** Results for the search phrase “magnet\* tissue engineering” in the Web of Science. Data collected on 18 May 2024.

## 2. Integration of Magnetic Material in Tissue Engineering Systems—Methods and Outcomes

Several possibilities exist to integrate magnetic material in tissue engineering systems [37]. Most often, magnetic iron oxides such as  $\text{Fe}_3\text{O}_4$  (magnetite) or  $\gamma\text{-Fe}_2\text{O}_3$  (maghemite) are used in the form of nanoparticles. Both materials are actually ferrimagnetic but become superparamagnetic if their size is below the superparamagnetic limit, making them highly interesting for medical applications such as magnetic resonance imaging or targeted drug delivery since they can be accumulated at defined positions in the human body by a magnetic field [38,39].

Such superparamagnetic iron oxide nanoparticles (SPIONs) are known to be biocompatible [38]. However, there have been reports that iron oxide freely released into a cell can cause a cytotoxic effect in some cases, e.g., when the cell is coated with dextran and the coating has opened due to cell membrane interactions [40]. On the other hand, dextran-coated SPIONs have been shown to be non-cytotoxic in other studies [41], similar to SPIONs conjugated with antibodies [42] or aptamer-coupled SPIONs [43]. A gold coating was shown to further reduce their cytotoxicity towards non-cancer cells [44]. SPIONs can

also be integrated in scaffolds, e.g., from hydrogels [45,46], to make them magneto-responsive. Besides SPIONs, other metallic or metal-oxidic nanoparticles, coated or pure, can be embedded to prepare magneto-responsive scaffolds [47,48]. Using poly(ethylene glycol) (PEG) microgels with embedded SPIONs via an in-mold polymerization process, Castro et al. showed partial collagen fiber alignment along magnetically aligned PEG microgels [49]. Similarly, Filippi et al. revealed more mineralization and faster vascularization using magnetically actuated PEG/magnetic nanoparticle composites with human adipose tissue-derived stromal vascular fraction cells [50]. Magnetic HAP composite hydrogels, prepared by adding SPIONs to a poly(vinyl alcohol) (PVA) solution, showed a significantly higher adhesion and proliferation of human osteoblasts with increasing SPION concentration in the hydrogel, connected to an increase in the hydrogel pore size, which enabled nutrient exchange [51]. Aligning collagen hydrogels with embedded magnetic nanoparticles using strong magnetic fields has also been reported by several other authors [52]. In the above-mentioned experiments, the applied magnetic field induction was in the range of 10 mT to about 400 mT.

By embedding carbonyl iron particles in a poly(acrylamide) (PAAM) hydrogel, Abdeen et al. showed the possibility to modulate the scaffold's elasticity reversibly using an alternating magnetic field [53] with a maximum amplitude of 1 T. Carbonyl iron particles have shown little toxicity in *in vivo* tests on rats, while *in vitro* studies revealed varying cytotoxicity, depending on the cell line [54]. This broad spectrum of potential responses may be attributed to the ability of nanoparticles to modify the medium composition in *in vitro* assays [55]. The photosensitizer hypericin, often used in photodynamic therapy, was even found to be less cytotoxic to normal cells when bound to SPIONs [56].

It should be mentioned that cytotoxicity towards tumor cells is a positive feature of magnetic nanoparticles, which can be supported, e.g., by using porous hollow nanoparticles, which can be filled with cisplatin for solid tumor treatment [57]. Cytotoxicity towards osteosarcoma cells could be supported by a spinning magnetic field [58].

Other researchers showed the degradation of a magnetic hydrogel under magnetic field stimulation [59], improved osteoblastic cell proliferation and mineralization on a magnetic hydrogel [60] and improved alkaline phosphatase (ALP) activity of mesenchymal stem cells when they grew on a magnetic hydrogel heated to 43 °C by magnetic hyperthermia [61]. Generally, the magnetic stimulation of musculoskeletal tissue engineering is often investigated [62]. Other research groups found positive effects of magnetic nanoparticles embedded in hydrogels for cartilage tissue engineering, neural tissue engineering and tissue engineering of other organs [63–66]. In addition to hydrogels, other diverse scaffolds have been investigated with respect to the effect of magnetic properties, such as 4D bioprinted scaffolds [67,68], nanocomposites [69] and electrospun nanofiber mats [70–72].

An important parameter of magnetic scaffolds that has not yet been mentioned is their degradation *in vivo* and *in vitro*. On the one hand, coupling growth factors to magnetic nanoparticles was found to decrease the enzymatic degradation of the growth factors [73,74]. On the other hand, many nonmagnetic matrix materials used in combination with magnetic nanoparticles, such as gelatin, degrade relatively fast *in vivo*, which is not significantly altered by the addition of magnetic nanoparticles [75]. Finally, SPIONs themselves can also be degraded by acids, leading to the release of free ionic iron, which may lead to an overload of iron if excessively high SPION doses are used [76–79]. The effect of such free iron ions varies for different cell types and has to be taken into account when the cytotoxicity of magnetic nanoparticles on normal cells is estimated [80–82].

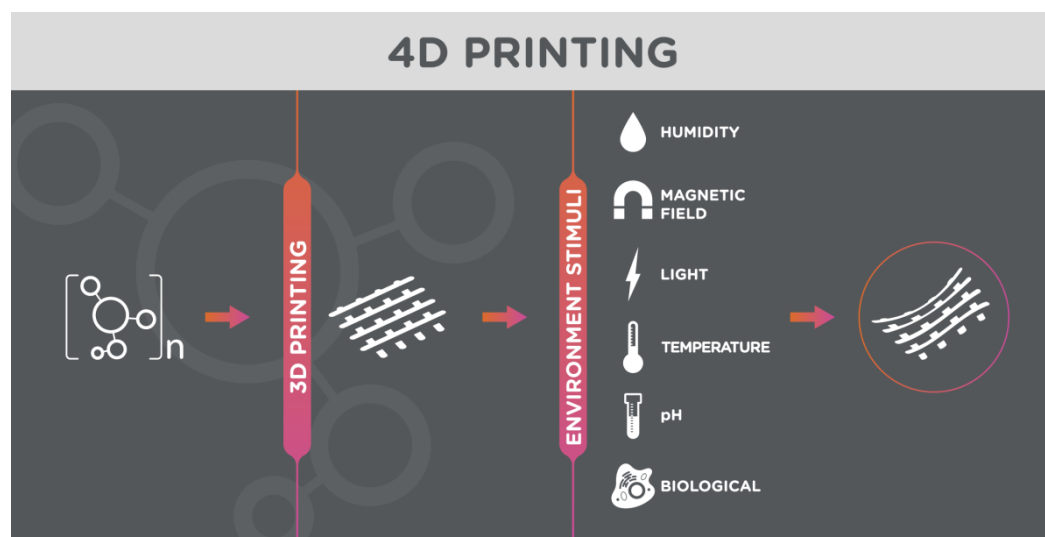
Besides the aforementioned effects of magnetic materials on scaffolds regarding the modification of morphological and mechanical properties of the scaffold, the response of cells to such magnetic scaffolds and magnetic stimulation regarding stem cell differentiation was reviewed in detail by Mocanu-Dobranici et al. [83], who explained that such reactions could be based on focal adhesion redistribution and assembly as well as changing their morphology, where focal adhesions contain structural and functional proteins.

Similar effects were reported by other researchers [84]. On the other hand, magnetic forces can also be used to manipulate magnetically labeled cells or cells suspended in a paramagnetic medium, enabling their positioning even without a scaffold [85–87]. These techniques, however, are not in the scope of this review. Instead, especially modern scaffold production methods such as the 3D/4D printing and electrospinning of magnetic scaffolds are described in the next section, followed by recent research on magnetic hydrogels.

### 3. Production Methods of Magnetic Scaffolds

#### 3.1. 3D/4D Printing

Different 3D-printing techniques enable the production of scaffolds for tissue engineering from diverse materials in nearly any shape [88–90]. While tissue-like materials, such as hydrogels, can also be 3D printed [91], there is still a large difference between simple 3D-printed shapes and materials that can transform due to external stimuli, such as humidity, light, temperature, pH value, biological parameters or, as discussed here, magnetic fields, as shown in Figure 2 [92]. This process is called 4D printing, with time as the fourth dimension.



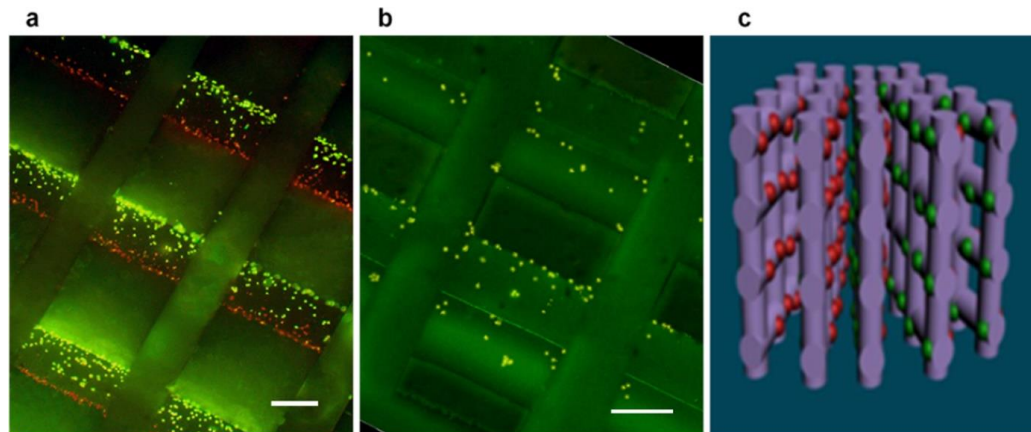
**Figure 2.** The idea of 4D printing—environmental stimuli change 3D printed objects with time. From [92], originally published under a CC-BY license.

Diverse biocompatible and bioresorbable polymers can be used to produce stimuli-responsive hydrogels, such as agarose, alginate, chitosan, collagen, gelatin, hyaluronic acid, poly(ethylene glycol) (PEG), poly(lactic acid) (PLA), poly(lactic-co-glycolic acid) (PLGA), polycaprolactone (PCL) and pluronic acid (poloxamer) [92]. Among the thermoresponsive materials, poly(*N*-isopropylacrylamide) (PNIPAM) can be 3D printed and shows reversible folding/unfolding near the human body temperature, while polydopamine (PDA) show a photothermal effect [92]. Diverse biopolymers show pH responsiveness, while cellulose, polyurethane copolymers and other materials swell or shrink upon humidity variations [92].

The 4D printing of magnetic materials has been investigated deeply in the last years, not only for tissue engineering but also regarding magnetically controlled bionic robots [93], magneto-electronic devices [94], electromagnetic shielding, technical permanent magnets and diverse medical applications [95]. One important parameter of all magnetic 3D-printed objects, independent of the printing technique, is the magnetic anisotropy imposed by the printing process, which may be advantageous or disadvantageous for the specific application. As a possibility to decouple the magnetic anisotropy from the 3D printing process, Pardo et al. reported a combination of magnetically and matrix-assisted bioprinting methods [96]. They used low-viscosity magnetic bioinks, which were not

crosslinked during printing, so that the embedded magnetic microfibers could be arranged as required after printing, before the 3D print was solidified. The resulting anisotropic fibrous microstructure was found to be advantageous for tendon tissue engineering, especially in combination with remote magneto-mechanical stimulation, which enabled the differentiation of encapsulated human adipose-derived stem cells towards the tenogenic phenotype [96].

In several studies, cells were loaded with magnetic nanoparticles so that they could be moved by magnetic forces [97–99]. Going one step further, Goranov et al. reported the use of magnetic scaffolds with short-scale magnetic gradients that could orient and trap magnetized cells in different positions on the scaffold [100]. They produced a magnetic osteogenic scaffold from bioresorbable Fe-doped hydroxyapatite with PCL using a 3D bioprinter, while mesenchymal stem cells (MSCs) and human umbilical vein endothelial cells (HUVECs) were magnetically labeled using commercial fluorescent magnetic nanoparticles. The idea of combining these two types of cells in bone healing is based on the finding that the combination of osteogenic and vasculogenic cells was found to improve bone healing in comparison with that in single-cell populations [101]. Goranov et al. investigated the cell motility in an applied magnetic field and found a magnetic nanoparticle concentration of 100 pg/cell to be ideal regarding motility and cell viability [100]. Applying a static magnetic field firstly in one direction, dragging MSCs onto the scaffold in this direction, seeding HUVECs on the scaffold and then dragging them using a reversed static magnetic field in the other direction resulted in the separation of both cell populations, as depicted in Figure 3 [100]. Also for bone tissue engineering, Ksouri et al. produced 3D magnetic and nonmagnetic PLA porous structures using fused deposition modeling (FDM) printing and showed that the embedded magnetic particles stimulated cell activity control and promoted  $\text{Ca}^{2+}$  accumulation as well as cell growth and proliferation [102].



**Figure 3.** Micro-spatial patterning of magnetically labeled cells in magnetized scaffolds (scale bars 200  $\mu\text{m}$ ): (a) magnetic PCL/Fe-hydroxyapatite (HA) scaffold; (b) nonmagnetic PCL/HA scaffold; (c) schematic illustration of magnetically assembled 3D cellular architectures. From [100], originally published under a CC-BY license.

In 3D-printed alginate hollow-fiber scaffolds, drugs as well as living cells could be locally released; this was magnetically driven by the extrusion of drugs and cells from the fiber cores after the scaffolds were deformed under the impact of an external magnetic field [103].

Najafabadi et al. used the liquid deposition modeling (LDM) of sol-gel synthesized magnetic bioactive glass with alumina nanowires in PCL [104]. Such magnetic bioactive glass composites are mainly used to repair bone defects caused by bone tumors. They found that the composite improved the mechanical strength, contact angle, degradation, bioactivity and finally cell viability and proliferation of MG-63 cells as compared to pure PCL/magnetic bioactive glass scaffolds, making this material blend interesting for bone

tissue engineering [104]. Mechanical properties and biodegradation were also investigated for shape memory property composites from  $\text{Fe}_3\text{O}_4$  nanoparticles in PCL 3D printed by material extrusion [105]. Here, the authors found an increase in tensile properties due to the magnetic nanofiller.

Besides FDM and LDM techniques, 3D printing with a bioprinter or in general with a syringe and a needle is often applied to print magnetic hydrogels. Choi et al. used this technique to print a combination of a self-healing hydrogel and a self-healing ferrogel, the latter defined as a hydrogel containing superparamagnetic iron oxide nanoparticles, and reported dimensional changes in the tissue scaffold under an external magnetic field [106]. A self-healing ferrogel from glycol chitosan, oxidized hyaluronate and  $\text{Fe}_3\text{O}_4$  nanoparticles was used as a 3D printing ink for scaffolds with mechanical properties that could be adjusted by the polymer ratio and overall content [107]. A porous hydrogel scaffold of polyvinyl alcohol/sodium alginate/hydroxyapatite (PVA/SA/HAP) loaded with graphene oxide (GO)@ $\text{Fe}_3\text{O}_4$  nanoparticles was prepared by extrusion through a nozzle and subsequent crosslinking in  $\text{CaCl}_2$  solution and showed improved physical properties and magnetothermal conversion efficiency, as well as bone mesenchymal stem cell (BMSC) differentiation in vitro [108]. Monks et al. used heat induction in magnetic hydrogels, 3D printed by extrusion, for the spatiotemporally controlled release of molecules [109].

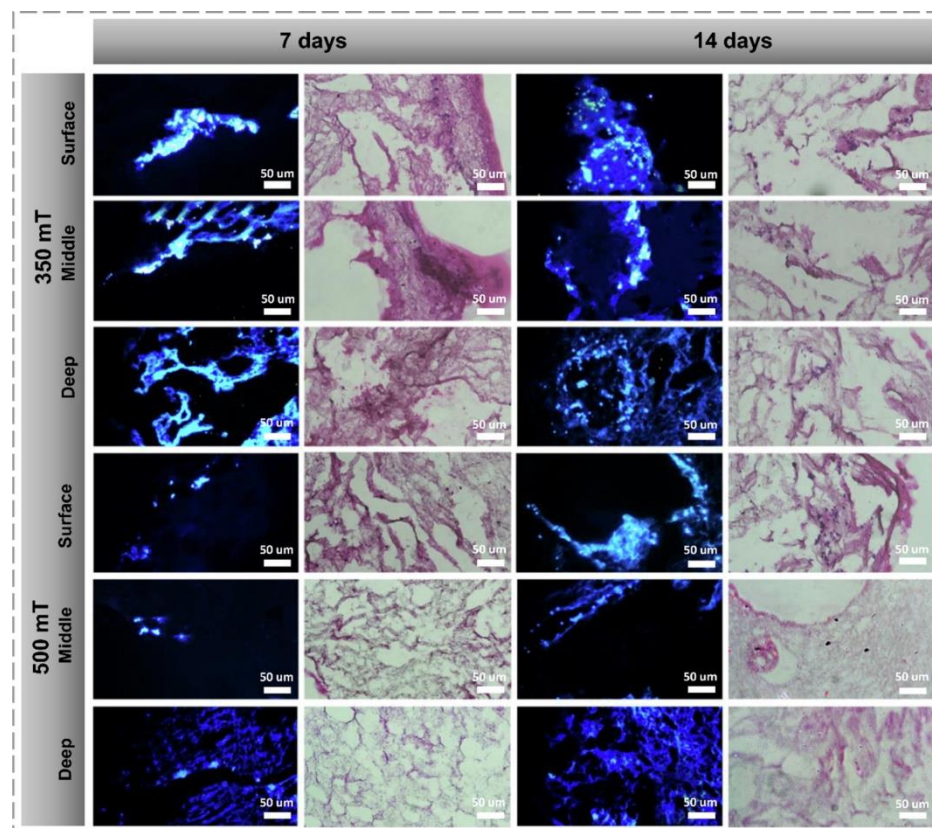
Another relatively new technique, besides 3D printing, is electrospinning. The use of this technology to produce magnetic scaffolds for tissue engineering is described in the next section.

### 3.2. Electrospinning

Electrospinning is a technique that enables the production of nanofiber mats from diverse polymers or polymer blends in which metallic, ceramic or other nanoparticles can be embedded [110]. Such electrospun nanofiber mats can be used for batteries and other energy applications [111,112], food packaging [113,114], filtration [115,116], biotechnology and biomedicine [117–119]. The introduction of magnetic nanoparticles enables the production of polymer/magnet hybrid nanofibers, as well as the possibility to produce pure magnetic nanofibers by calcinating the polymer after the electrospinning process [120]. Such magnetic nanofibers can be used as freestanding membrane or as coatings on stents, 3D printed scaffolds or other substrates [121–123].

Using magnetically assisted wet electrospinning, Bakhtiary et al. produced a 3D magnetic nanofibrous scaffold from gelatin/PCL/iron oxide that showed good mechanical properties and porosity as well as biodegradability and the absorption of phosphate buffer solution (PBS) [124]. Comparing scaffolds spun in different magnetic fields, the 350 mT scaffolds revealed higher cell proliferation and infiltration of the inner part than 500 mT scaffolds, as depicted in Figure 4, as well as high stem cell neural differentiation [124].

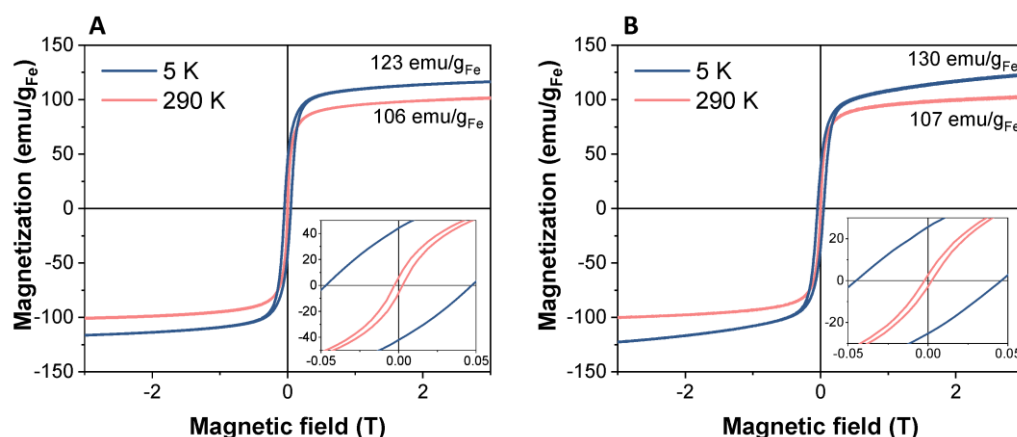




**Figure 4.** Cryosection images of olfactory ecto-mesenchymal stem cells seeded on scaffolds produced at 350 mT and 500 mT, respectively, taken at different depths of scaffolds. Optical and fluorescence microscopy after staining with 4,6-diamidino-2-phenylindole (DAPI) and hematoxylin and eosin (H&E), respectively. From [124], copyright (2022), with permission from Elsevier.

Electrospun nanofiber mats loaded with melatonin and magnetite nanoparticles were used as a nerve guidance conduit scaffold for peripheral nerve repair [125]. Chen et al. showed that these scaffolds enabled sequential as well as sustainable drug release, which produced a suitable micro-environment for nerve regeneration while at the same time having sufficient mechanical properties and biocompatibility. In this way, the electrophysiological recovery of regenerated sciatic nerves was promoted *in vivo*, making this approach interesting for long-term nerve defect treatment [125]. Funnell et al. embedded SPIONs in aligned electrospun nanofibers [126]. They investigated neurite outgrowth due to contact guidance by the aligned fibers as well as mechanical stimulation by the SPIONs in an external magnetic field and showed that an alternating magnetic field could increase the neurite length by 40% as compared to that under a static magnetic field. In comparison with untethered SPIONs in the culture medium, the magnetic nanofibers increased the neurite length by 30% and the neurite area by 62%, showing the positive impact of SPION-grafted nanofiber mats in alternating magnetic fields on the stimulation of neurite outgrowth [126].

By embedding SPIONs in type-I collagen, 3D electrospun scaffolds were prepared for seeding with human bone marrow-derived mesenchymal stem cells (hBM-MSCs) [127]. The 3D structure of the needle-electrospun scaffolds was reached by spinning for 3 h before crosslinking. The magnetic properties of these scaffolds were nearly identical to those of the pure magnetite nanoparticles (Figure 5) [127].



**Figure 5.** Magnetization curves of (A) Fe<sub>3</sub>O<sub>4</sub> nanoparticles with dimercaptosuccinic acid (DMSA) coating; (B) 20% collagen/2% SPIONs scaffold normalized to grams of iron. Magnification of curves at low fields is shown in insets. From [127], originally published under a CC-BY license.

Using a silk fibroin electrospun scaffold filled with cobalt ferrite nanoparticles, Reizabal et al. showed improved cell viability upon magneto-mechanical stimulation as well as high pre-osteoblast proliferation, indicating the importance of magnetoactive biocompatible scaffolds for the remote stimulation of bones for their regeneration [128]. The addition of cobalt–zinc ferrite nanoparticles to PCL nanofiber mats resulted in reduced nanofiber diameter, improved mechanical properties and biodegradation, as well as strongly increased biocompatibility and cell adhesion inside an electromagnetic field [129].

Core–shell electrospinning was used to produce poly(3-hydroxybutyrate) (PHB), PHB/gelatin and PHB/magnetite/gelatin scaffolds, with slightly increased fiber diameters with the addition of gelatin and a strong further increase upon the addition of magnetite [130]. The resulting core–shell structures led to a decreased crystallinity of the PHB phase, as compared to that of pure PHB fibers, and were not cytotoxic; however, no significant differences were found regarding cell adhesion and growth [130]. Nanofiber mats were also electrospun from PHB/magnetite particles, the latter partly citric acid-coated [131]. Pryadko et al. showed that, on the one hand, that magnetite nanoparticles were prone to magnetite–maghemite phase transitions during the preparation of the scaffold, which could be impeded by citric acid functionalization, while no such phase transition occurred in micron-sized magnetite particles. On the other hand, all nanofiber mats were stable in lipase solution and PBS for one month, were biocompatible and could support angiogenesis in vivo 30 days after they were implanted in rats, and the scaffolds including magnetite nanoparticles showed faster proliferation of rat MECs [131].

A combination of electrospun nanofiber segments inside a hydrogel was investigated by Hiraki et al., who aligned these SPION-containing segments magnetically, with the degree of alignment being dependent on SPION density and magnetic field strength [132]. The authors functionalized the fiber segments with peptides, resulting in fibroblasts growing aligned with them and multicellular migrated cell spheroids breaking up into single cells and clusters [132]. Another short magnetic nanofiber/hydrogel composite scaffold was prepared by Wang et al., who oriented the magnetic nanofibers inside a magnetic field, resulting in a scaffold that could guide the 3D cell alignment of muscle fibers [133].

Besides composites with nanofibers and 3D printed structures, hydrogels have been used as scaffolds for a long time. The next section provides a brief overview of recent developments in this research area.

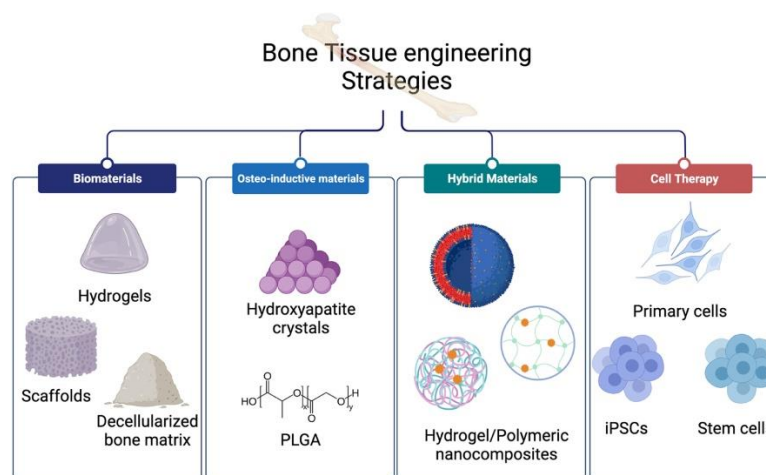
### 3.3. Hydrogels

Hydrogels are used as scaffolds for diverse tissue engineering applications. They can serve as a matrix mimicking the ECM and deliver drugs to support tissue formation. In bone tissue engineering, they are often used in the form of “smart”, i.e., stimuli-



responsive, hydrogels [134]. This can mean that the hydrogels react on varying temperature, pH, chemicals, electric or magnetic fields, biological events, etc.

Typical bone tissue engineering hydrogel materials are PVA, collagen, gelatin and PEG [134]. The main strategies for bone tissue engineering are depicted in Figure 6 [134]. Here, magneto-responsive hydrogels can be produced by integrating metallic or metal-oxide nanoparticles, such as iron oxide, cobalt, iron and nickel [134]. Additionally, nanoclays have been reported to be useful as crosslinkers for alginate or methacrylated hyaluronic acid, which improves the structural formability of such hydrogels for bone tissue engineering [135]. Other methods of crosslinking include photoinitiators and molecular agents such as genipin, dopamine, caffeic acid, tannic acid and others [136].



**Figure 6.** Different strategies are employed for bone tissue engineering. From [134], copyright (2022), with permission from Elsevier.

Hydrogels are also applied in other fields of tissue engineering. Bonhome-Espinosa et al. reported a magnetic fibrin-agarose hydrogel developed for cartilage tissue engineering [137]. The authors embedded magnetic nanoparticles as well as human hyaline chondrocytes in fibrin-agarose hydrogels and found that with the addition of the magnetic nanoparticles, the viscoelastic moduli of the hydrogels were improved, and the embedded cells stabilized the biomechanical properties since they compensated for the minor polymer degradation during cell cultivation. Nevertheless, these scaffolds were weaker than original human articular cartilage tissue by several orders of magnitude, impeding the direct substitution. Both scaffolds, with and without magnetic nanoparticles, showed good biocompatibility and cell proliferation [137].

Gelatin methacryloyl is a photo-crosslinkable hydrogel that has been investigated for bone tissue engineering and also for cardiac and neural regeneration [138]. Many more hydrogels from the aforementioned and other materials are used in tissue engineering, e.g., for skeletal—bone and cartilage—tissues, electroactive—nerve tissues, cardiac tissues, muscle tissues—and other tissues, such as skin and vascular tissues [139]. The next section provides an overview of the most frequently used applications of magnetic scaffolds for bone, nerve and other tissue engineering applications.

Generally, all fabrication techniques mentioned here have different advantages, such as hydrogel production (a well-known technique leading to lightweight, open-pore materials), 3D printing (free choice of shapes and broad availability of materials for different additive manufacturing techniques) and electrospinning (relatively simple technique, enabling the spinning of a broad range of materials in nanofibrous shape) but also disadvantages (toxic solvents or crosslinking agents necessary for some electrospinning materials, 3D printing with inexpensive equipment allows only for using a limited set of materials). As in most areas of research, choosing the optimum technique for the required scaffold material, shape, porosity, heat resistance, mechanical properties, etc. is necessary. In

addition, potential cytotoxicity as well as the degradation of the used materials have to be taken into account and fitted to the corresponding application.

To conclude this section, Table 1 presents the most important production methods of magnetic scaffolds.

**Table 1.** Typical production methods of magnetic scaffolds.

Method	Materials	Ref.
4D-printed hydrogels	Agarose, alginate, chitosan, collagen, gelatin, hyaluronic acid, PEG, PLA, PLGA, PCL, poloxamer with magnetic nanoparticles, ferrogel	[92,106–109]
4D-printed polymers	PNIPAM, PDA	[92]
3D-printed anisotropic fibrous microstructures	Low-viscosity magnetic bioinks	[96]
3D bioprinting	PCL/Fe-doped HAP	[100]
FDM printing	Magnetic PLA	[102]
LDM printing	Magnetic bioactive glass	[104]
FDM printing	PCL/Fe <sub>3</sub> O <sub>4</sub>	[105]
Electrospinning on 3D-printed scaffolds	Magnetic nanofibers	[121–123]
Magnetically assisted wet electrospinning	Gelatin/PCL/iron oxide	[124]
Electrospinning	Melatonin/magnetite-loaded fibers	[125]
Electrospinning-aligned fibers	SPIONs in nanofibers	[126]
Needle electrospinning	SPIONs in collagen nanofibers	[127]
Electrospinning	Cobalt–zinc ferrite/PCL	[129]
Core–shell electrospinning	PHB/magnetite/gelatin	[130]
Hydrogel	PVA, collagen, gelatin, PEG, agarose and other polymers with magnetic nanoparticles	[134,137,139]

## 4. Applications of Magnetic Scaffolds

### 4.1. Bone Tissue Engineering

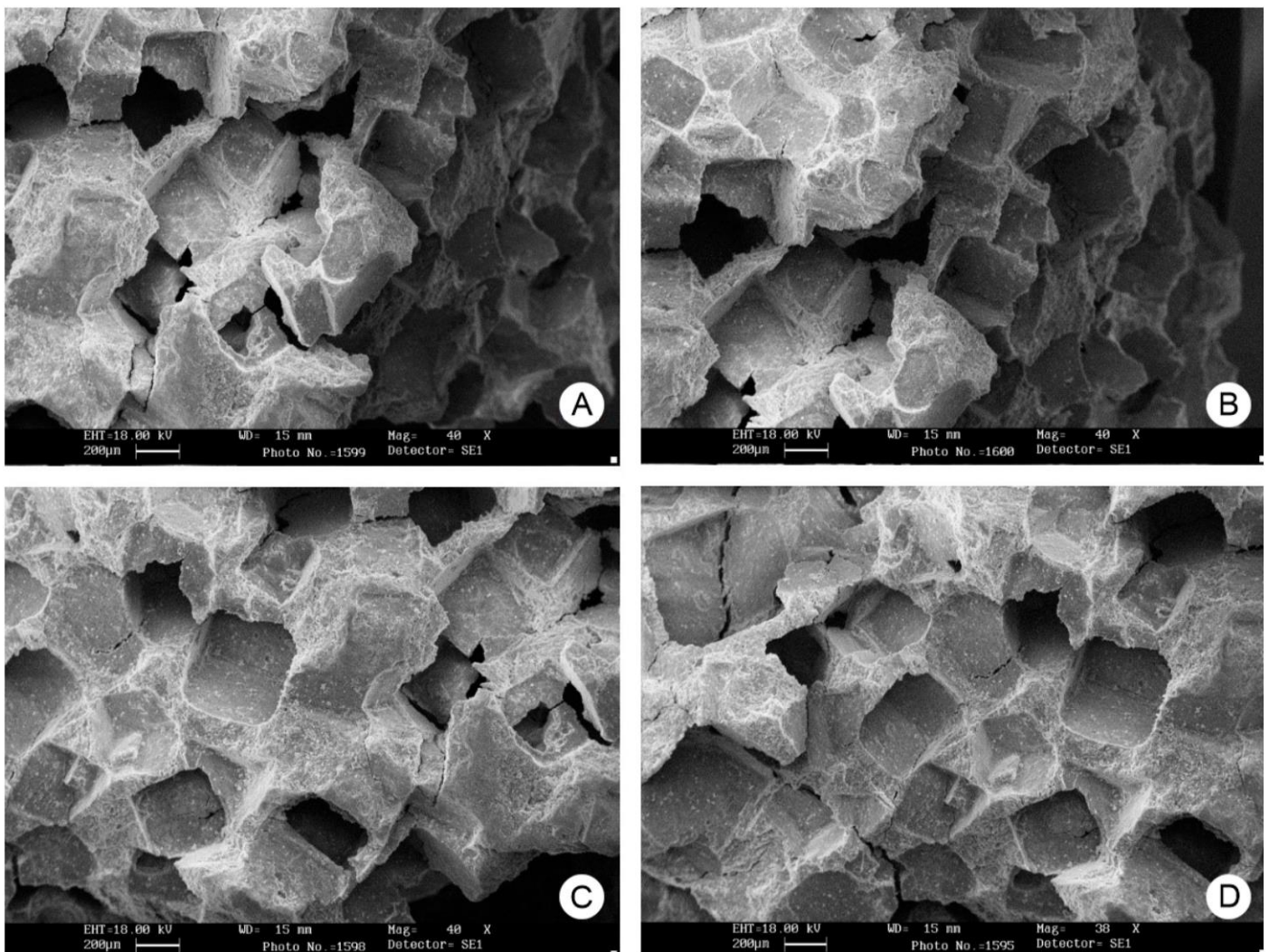
As mentioned before, different mechanisms have been reported that can explain the positive influence of magnetic scaffolds for bone tissue engineering [140]. On the one hand, small static magnetic fields of different field strengths have been shown to support the differentiation of progenitor cells, which has been attributed to the magnetic opening of cation channels and subsequent production of reactive oxygen species, as well as an increase in the concentration of metal ions, which both support cellular differentiation [141,142]. On the other hand, small static magnetic fields can also support cell proliferation, again due to an increase in calcium influx [143]. Large, static magnetic fields can even impact the ultrastructure of the cell, which also improves cell proliferation [144]. In addition, endothelial cells, which are necessary for diverse processes in bone healing, were found to be stimulated by small static or magnetic fields [145,146].

Several studies exist about electrospun magnetic nanofiber mats for bone tissue engineering [147]. Li et al. prepared PCL/magnetite/icariin magnetic membranes by electrospinning [148], where icariin is a Chinese traditional medicine and was previously shown to support bone tissue engineering through angiogenesis, anti-osteoporosis and anti-inflammatory properties [149]. An originally two-dimensional electrospun membrane was expanded into a 3D composite layered fibrous scaffold by the depressurization of supercritical CO<sub>2</sub> fluid [148]. In this way, a highly porous magnetic 3D scaffold was produced, with magnetic properties tailorable by the Fe<sub>3</sub>O<sub>4</sub> content.

Furthermore, 3D printing is also used for bone tissue engineering. Petretta et al. used extrusion-based bioprinting to produce PCL/HAP scaffolds with SPIONs at different SPION concentrations and found a 1% SPION concentration to be the most efficient for

cell entrapment and adhesion [150]. Moreover, these scaffolds were not cytotoxic to fibroblasts or mesenchymal stromal cells and showed higher osteogenic differentiation of the latter on the PCL/HA/SPION scaffolds in a magnetic field than on nonmagnetic PCL/HA scaffolds [150]. The osteogenic differentiation of preosteoblast MC3T3-E1 cells was also evaluated for HAP bone-mimicking bioceramics decorated with magnetic nanoparticles, produced by wet chemical co-precipitation [151]. The authors reported a concentration of 5  $\mu\text{g/mL}$  of HAP-decorated magnetic nanoparticles to be the optimum value regarding high osteogenic differentiation potential without cell toxicity.

A porous zirconia–calcium bio-composite with different amounts of magnetite nanoparticles was prepared by adding sodium chloride to reach the desired porosity, as shown in Figure 7 [152]. Here, the cubic morphology of the pores left by the dissolved NaCl is visible, resulting in pores with more than 20  $\mu\text{m}$  dimensions. These pores were found to significantly improve cell growth and the activation of ossification. Furthermore, the authors found higher apatite formation and a reduced degradation rate for scaffolds with higher amounts of magnetic nanoparticles. In addition, higher amounts of magnetic nanoparticles enabled the generation of more heat to prevent cancer cells from growing and support the healing of damaged bone tissue [152].



**Figure 7.** Scanning electron microscope (SEM) images of porous zirconia–calcium bio-composites in dry condition with different magnifications (A–D). From [152], copyright (2022), with permission from Elsevier.

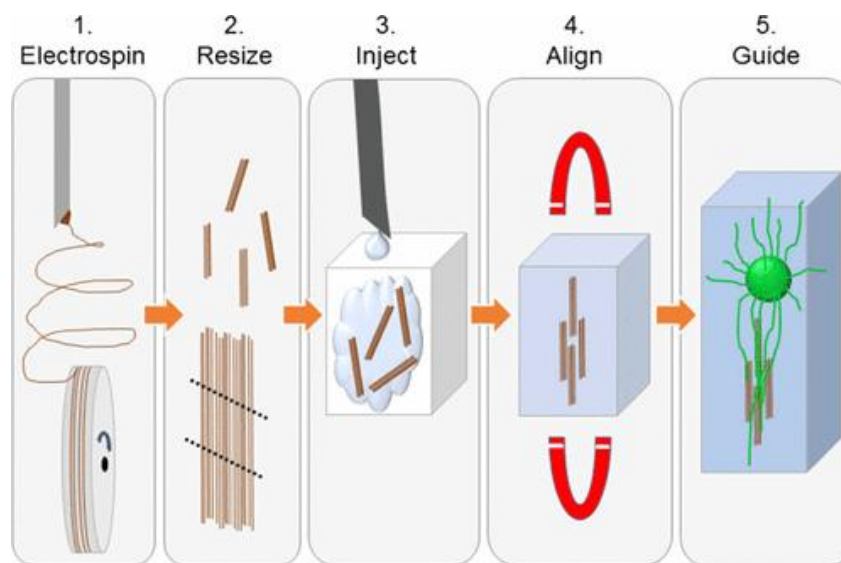
Wu et al. showed that the integration of magnetic nanoparticles improved bone regeneration due to enhanced osteogenesis and angiogenesis, which they investigated *in vitro* as well as *in vivo* [153]. This effect could be increased by combining a low concentration of  $\text{Fe}_3\text{O}_4$  with a static magnetic field. The positive impact of magnetic nanoparticles was also observed when they were dispersed in biopolymers [154], while most studies embedded magnetic nanoparticles in common bone tissue engineering materials such as PCL, poly-L-lactic acid (PLLA), HAP or alumina [155].

#### 4.2. Nerve Tissue Engineering

The positive effect of magnetic scaffolds on nerve tissue engineering is mostly related to magnetic stimulation during nerve regeneration [156–158]. Low-frequency alternating magnetic fields were shown to influence the direction of neuron growth, which has been attributed to the mechanical impact on the particles and macromolecules in neurons [159]. Scaffolds containing magnetic nanoparticles were also found to increase bioelectric transmission and thus to support neuronal growth without an additional external magnetic field [160]. In many cases, however, the combination of a magnetic scaffold with an external magnetic field was shown to promote neuron growth and axon extension optimally [161–163].

One of the materials often used for neural tissue engineering is PLLA. PLLA scaffolds can mimic neural tissue ECM, reduce inflammatory responses, form 3D structures and be tailored for controlled drug release [164]. Adding SPIONs also enables magnetic stimulation inside a magnetic field to improve neurite outgrowth and neurogenesis [164]. While some authors found a static magnetic field to be sufficient for magnetic stimulation [162], others reported specific effects due to alternating magnetic fields [127]. In addition to the pure magnetic effect, functionalizing the SPIONs or other magnetic nanoparticles with a coating, e.g., a growth factor, further supports neurite outgrowth and neural differentiation [165].

An important factor in neural tissue engineering is the possibility to add anisotropic structures, mimicking the ECM and thus guiding neural orientation [166]. Such structures can be prepared not only by engraving or etching [167] but also by forming magnetic materials in a magnetic field, as depicted in Figure 8 [162]. This approach was also reported by Ghaderinejad et al., who injected short magnetic PCL/SPION nanofibers into an alginate hydrogel, where they were oriented inside a magnetic field to improve the storage and loss moduli of the hydrogel and to support the viability and neural differentiation of olfactory ecto-mesenchymal stem cells (OE-MSCs) [168]. Alternatively, Lacko et al. injected dissolvable magnetic alginate microparticles, which were aligned in a magnetic field and afterwards removed, so that a tubular microstructured template remained for nerve repair applications [169]. Another reason to introduce magnetic nanoparticles is for the delivery of drugs or genes [170,171].



**Figure 8.** Aligning electrospun short magnetic nanofibers, injected in hydrogel solution, to guide neurite alignment. Reprinted with permission from [162]. Copyright 2019 American Chemical Society.

#### 4.3. Other Tissue Engineering Scaffolds

Besides bone and nerve tissue engineering, there are other directions of tissue engineering for which magnetic tissues were found supportive. Vinhas et al. described magnetically assisted cell-sheet construction [172]. This technique enables the production of a tissue-like assembly by combining a confluent cell monolayer with magnetic nanoparticles and cultivation in a static magnetic field. The resulting magnetic cell sheet can show a tendon-like ECM with good mechano-elastic properties and responsiveness, making these living tissues useful for tendon therapy [172].

Several studies report magnetic scaffolds that may be used for more than one application in tissue engineering. Magnetic polysaccharide hydrogels were suggested for skin, cartilage, muscle and connective tissue engineering [173]. With patterned magnetic fields, cell arrays can grow at defined positions on different scaffolds [174]. On the other hand, heating SPIONs in a magnetic scaffold using an alternating magnetic field can generally be used to induce thermal drug release or to ablate pathological cells [47]. Magnetic fillers can increase the wettability and thus the bioactivity of magnetic scaffolds for diverse tissue engineering purposes [175] or generally be used to support cell differentiation for various cell types [176].

Table 2 provides a short overview of typical materials and techniques used for bone, nerve and other tissue engineering.

**Table 2.** Exemplary applications for different production methods and materials.

Application	Production	Materials	Ref.
Bone tissue engineering	Electrospinning	PCL/magnetite/icariin	[148]
Bone tissue engineering	Bioprinting	PCL/HAP/SPIONs	[150]
Bone tissue engineering	Wet chemical co-precipitation	HAP/magnetic nanoparticles	[151]
Nerve tissue engineering	Electrospinning	PLA/oleic acid-coated iron oxide nanoparticles	[162]
Nerve tissue engineering	Hydrogel	Injected short PCL/SPION nanofibers	[168]
Nerve tissue engineering	Hydrogel	Aligned magnetic alginate microparticles	[169]



Tendon therapy	Cultivation in static magnetic field	Confluent cell monolayer with magnetic nanoparticles	[172]
Skin, cartilage, muscle or connective tissue engineering	Hydrogel	Magnetic polysaccharides	[173]
Diverse tissues	Filling scaffolds	Magnetic nanoparticles	[175,176]

## 5. Conclusions

Generally, magnetic scaffolds for tissue engineering can be produced by combining a common tissue material, often biopolymers and other biocompatible polymers, with magnetic nanoparticles, such as iron oxides. New production methods for such magnetic scaffolds include 3D/4D printing and electrospinning, while hydrogel formation and wet chemical methods have been investigated for longer. Many studies concentrate on magnetic scaffolds for bone or neural tissue engineering, mostly taking into account the possibility to guide cells using magnetically structured surfaces, while magnetic tissue in general provides additional advantages such a potential for heating the scaffold, improved wettability and the possibility of magnetically triggered drug release.

As this brief review shows, magnetic tissue engineering scaffolds offer a broad range of advantages, can be prepared with common or novel production methods and thus are promising for future tissue engineering research.

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