Biomaterials and Biosystems 15 (2024) 100100

Contents lists available at ScienceDirect

Biomaterials and Biosystems

journal homepage: www.elsevier.com/locate/bbiosy

Biomaterials functionalized with magnetic nanoparticles for tissue engineering: Between advantages and challenges

V. Goranov

BioDevice Systems s.r.o., Bulharska 996/20, Praha 10, Czech Republic

ARTICLE INFO

Keywords:
Magnetically-responsive biomaterial
Magnetic scaffold
Magnetic nanoparticles
Biosystems
Tissue precursor
Cells

ABSTRACT

The integration of magnetic nanoparticles (MNPs) into biomaterials offers exciting opportunities for tissue engineering as they enable better control over cell guidance, release of bioactive factors and tissue maturation. Despite their potential, challenges such as the heterogeneity of MNPs, their cytotoxicity and the need for precise control of MNP`s properties hinder their widespread application. Overcoming these challenges will require new interdisciplinary efforts and technological advances, including the development of mathematical tools and additional elaborations to ensure the biocompatibility of MNPs.

1. Introduction

The incorporation of magnetic micro- and nano- particles (MNPs) into various materials has proven to be a promising approach for the creation of multifunctional and remotely-controlled biosystems [1-3]. Such a biosystem based on a magnetic scaffold (MS) can potentially be used for the in vitro formation of an implantable tissue precursor (TP) [3-5]. Furthermore, MS can attract magnetized host cells (MCs) and MNPs and retain them in the porous space (Fig. 1) under the influence of an external magnetic field (MF) [6]. Recent studies have confirmed that the structural and physical properties of such scaffolds can be controlled spatially and temporally by varying the gradient of MF strength [4,7]. This makes them useful for a variety of biomedical applications, including the creation of drug depots with a regulated release of active factors (AFs) upon implantation into an organism and development of tissue structures *in vitro* and even *in vivo* [6-8].

Functionalized MNPs may contain molecules [7] that are essential for the development of functionally adequate tissues. For example, MSs with immobilised "MNPs drug depots" that release AFs locally in vivo can be used to treat various diseases, especially tumours [6]. Magnetic nano-carriers containing a ^{68}Ga–DTPA complex have been proposed for the targeted delivery of the antitumor drug doxorubicin [9]. Another study proposes the use of functionalized MNPs for the treatment of inflammatory bowel disease [10]. These MNPs show potential in the fields of disease diagnostics, drug/gene delivery and multifunctional therapies. Recent studies [8] have demonstrated the development of TPs based on the three-dimensional (3D) assembly of magnetized stem cells into regular structures (such as chains, cylinders and filaments) under the influence of MF. These structures also have potential for the reconstruction of tubular and vascular tissues [11]. Moreover complexes with spatially patterned cell populations can be used to develop combined tissue constructs, such as osteochondral or meniscal TPs, with potential for efficient vascularisation [6].

On the other hand, the impregnation of various biomaterials with regular magnetic structures based on MNPs opens up the possibility of further attraction and regular patterning of MCs using MF [12,13]. Such composite biomaterials with controllable magnetic microarchitecture play an increasingly important role in tissue engineering and regenerative medicine. For example, a disk-shaped microstructure regulated by size of 7 to 23 μm can be developed by assembly of iron oxide nanoparticles inside hydrogel under the influence of rotating magnetic field [14]. These MNPs were synthesized in the same way as the techniques used for "Ferumoxytol" preparation that were chosen because only this inorganic nano-drug was approved by FDA for clinical applications [15]. The approaches used by other authors make it possible to assemble various spatial elements (chains, rings, etc.) that are composed by MNPs [16,17]. The developed structures can serve as "points of attraction" for MCs capturing. Moreover, multilayered structures with a mimetic architectures resembling native tissues [18] can be produced in special hydrogels (loaded with MNP) by applying MF to achieve regular alignment of collagen fibers. Another method proposes to assemble mosaic iron oxide nanoparticles into filaments under the influence of MF [19]. Within the gelatin-methacryloyl matrix, such filaments can stimulate the development of contractile tissue. Finally, magnetic hydrogels prepared using MNPs and different types of hydrogel matrices show tremendous potential for tissue engineering and other biomedical applications by taking advantage of their biocompatibility, controlled architectures and smart response to MF. In addition, MNPs incorporated into biomaterials can be used to induce thermogenic and/or mechanotransductive effects through the application of alternating MF [14,20].

https://doi.org/10.1016/j.bbiosy.2024.100100
Received 12 February 2024; Received in revised form 13 August 2024; Accepted 28 August 2024
Available online 31 August 2024

By combining various MNPs with different hydrogels and extracellular matrix, improved mechanical performance and structural fidelity were achieved [2,6]. The synergistic benefits of this combination have highlighted the prospects of organizing geometric elements that can be achieved with 3D bioprinting technology. Progress in this area is now moving towards four-dimensional (4D) magnetic bioprinting. Such approach supports the development of dynamic, patterned biological structures through the use of magnetically responsive biomaterials and advanced 3D bioprinting techniques [7]. These structures have the unique ability to change their shape and function in response to different stimuli. Despite these advances, there are still some challenges such as the inhomogeneous distribution of nanomaterials in MSs and technical problems in the fabrication of complex 3D structures.

Although the applications of magnetized biomaterials described above have promising potential, several challenges hinder their widespread clinical application. Even when MNPs are embedded in a slowly degradable scaffold, there is still a risk that they may degrade or detach from this material in the body under the influence of various biological factors [21,22]. Therefore, a better understanding of the properties of MNPs is necessary to design them to be inherently safe for clinical application. For broad biomedical application, any new formulation of MNP-based biomaterial systems must be systematically tested for a number of essential parameters that characterize biocompatibility, surface chemistry, stability of the impregnated MNPs, etc. [23].

2. Advantages

The enhanced saturation of magnetic biomaterials with bioactive factors in combination with anisotropic patterning to mimic various functional tissue structures has paved the way for a novel direction in tissue engineering, termed “magnetic force-based tissue engineering” [24]. This involves the application of cells magnetized by MNPs to develop intricate tissue constructs. Further research has shown that the application of this principle in cell culture and co-culture techniques enables an ordered cell distribution (an approach known as “magnetic cell patterning”) [25]. Here, MF provides efficient positioning of the different cell populations in the MS. Furthermore, the concept of “stimuli (magneto)-responsive biomaterial” (MLB) introduces a new level of combined biosystems [6]. These systems serve as a structural framework that supports the attachment, proliferation and differentiation of MCs with the development of appropriate TPs [26]. This also includes the ability to deliver stimuli to cells or release growth factors and bioactive molecules “on demand” [7]. The development of functionally adequate tissue after the implantation of TPs can be promoted by stimulation with an alternating MF [27,28]. In addition, the release of AFs from functionalized MNPs under the influence of MF has great potential for clinical applications, especially to support the healthy state of the surrounding tissues after tumour surgery [6]. In this context, it is worth mentioning the extensively researched and validated approach proposed by researchers at the University of Dresden, which introduces feedback-controlled drug delivery systems for autoregulated triggering of the release of AFs tailored to the specific requirements of the microenvironment [29]. Magnetically triggered release could be a promising complementary method that offers an additional route to regulate drug delivery. For example, this approach shows potential in the treatment of rhythmic clinical disorders such as diabetes and heart disease [10]. In such systems, drugs are released in specific concentrations on demand in response to fluctuating metabolic needs.

Another physical phenomenon that can be achieved by the application of MNPs is local hyperthermia induced by alternating MF. For example, our research shows that specifically functionalized MNPs can release AFs when heated [30]. This experiment demonstrates the

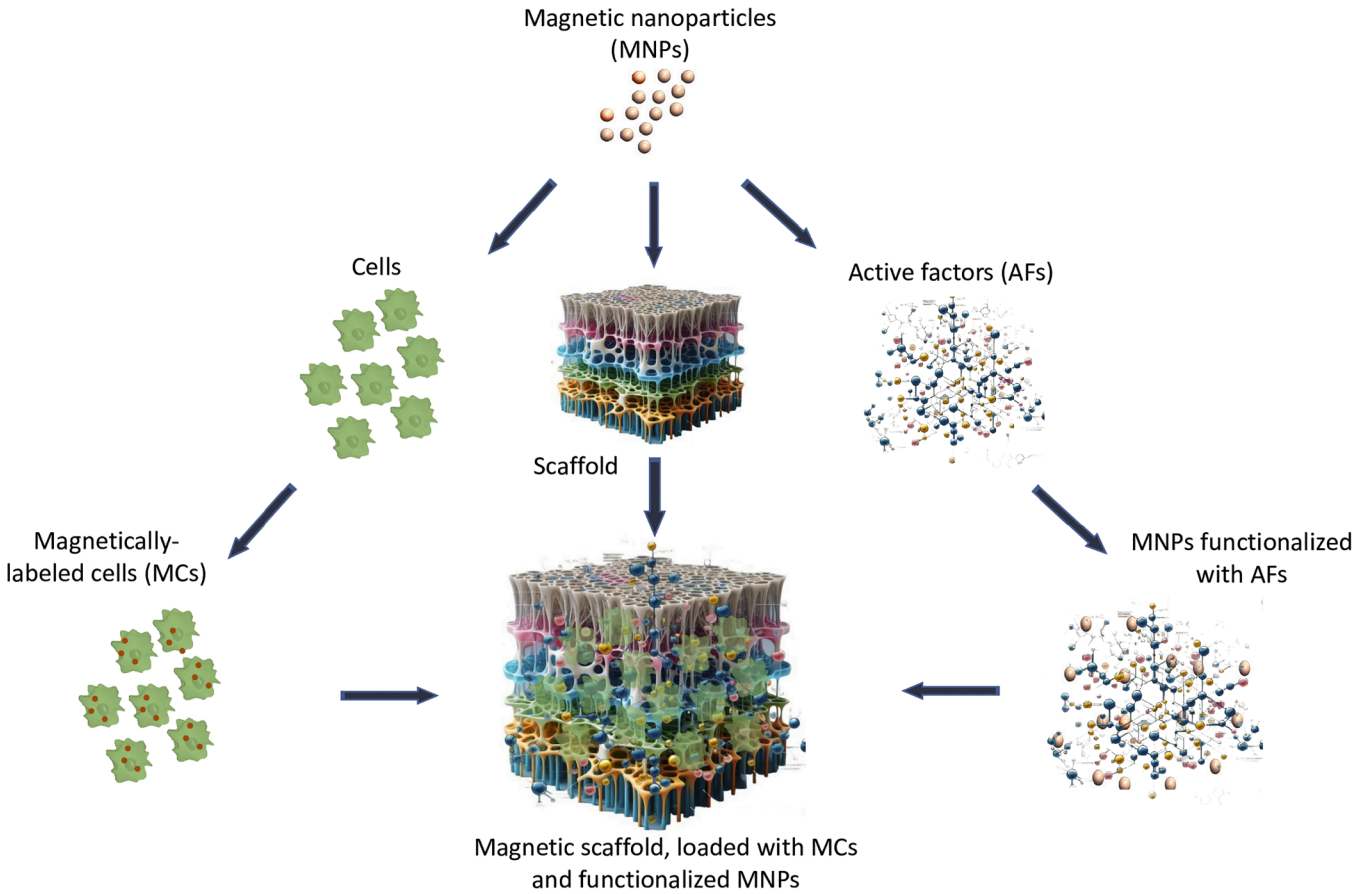

Fig. 1. Scheme of MNPs application for development of TP.

effective release of vascular endothelial growth factor from a thermo-responsive magnetic material (PNIPAM) upon transition to near physiological temperatures (39°C). Such a biocompatible system can be used in particular for the controlled release of AFs that can stimulate cells inside MSs. Another strategy involves thermally sensitive liposomes based on MNPs [31]. When exposed to an alternative MF, the magnetic nanoparticles initiate the release of the liposomal content during the heating. The authors describe CD90-targeted magneto-liposomes that encapsulate the antitumor complex 17-AAG.

The use of MNPs may be an alternative to certain mechano-transduction methods in which mechanical forces transmitted directly from an actuator to target cells [6]. MNPs enable the generation of mechanical oscillations under the influence of remotely applied alternating MF [32]. These oscillations can exert forces on cell membranes, thereby activating mechanotransductive pathways and biochemical cues for cell/tissue development [33]. Such an approach is increasingly applied in tissue engineering and regenerative medicine [34]. Mechanical stimuli play a crucial role in promoting extracellular matrix production. A scaffold impregnated with MNPs demonstrates an enhanced effect on the development of some tissues (especially contractile) [33,35]. For example, the differentiation of mesenchymal stem cells into bone, cartilage, muscle, vascular or connective tissues is particularly influenced by mechanical stimuli. The direct application of mechanical stimuli can significantly improve the in vitro maturation of tissue-engineered constructs designed for the regeneration of various mechanosensitive tissues such as tendon, skeletal muscle, cartilage and bone [36].

As early as 2007, a group of researchers [1] pioneered the development of tubular structures in vitro using magnetized liposomes, cells and MF. Several recent studies have focused on processes related to the assembly/patterning of MCs in MS using mesenchymal stem cells, vascular cells and fibroblasts. [5,37]. Furthermore, some authors investigated the creation of tubular structures by 3D-assembling of MCs into complex, multilayered biomaterial that demonstrated the potential to generate urinary or vascular TPs [38]. In certain cases, the patterning of single cells alone is not sufficient to develop physiologically relevant tissue constructs. Therefore, the use of cell spheroids is a promising approach to improve cell-scaffold interactions and to develop fully-fledged tissue [39]. As an alternative to dispersed cells, spheroids are 3D cell aggregates that preserve crucial aspects of the cellular microenvironment. These include cell-cell interactions, interactions with an endogenous extracellular matrix secreted by the cells, and signalling gradients leading to a heterogeneous distribution of nutrients more closely resemble native tissue. MNPs can be successfully incorporated into cellular spheroids to facilitate magnetic manipulation of desired shapes, patterns and 3D tissue constructs by MF [40].

Among the various MNPs, those developed using superparamagnetic iron oxide cores (SPIONs) have revealed particular promise for biocompatibility and efficient manipulation by MFs. Endothelial cell spheroids containing SPIONs showed high viability and phenotypic stability during in vitro culture [41-43]. Researchers also utilized microfluidic synthesis to produce spherical Janus hydrogel particles that exhibit superparamagnetic properties and have the ability to assemble into stable chain-like microstructures under the influence of MF. [44]. Despite the problems with regulatory obstacles related to the approval of MNPs for clinical use, experiments with FDA-approved SPIONs (ferumoxytol) have confirmed the prospects for the development of some TPs that may be closer to clinical application [45]. These experiments show that ferumoxytol-labeled magnetic spheroids can be imaged in vitro and monitored in vivo using magnetic resonance imaging (MRI) [46].

Further experiments in which different cell types were magnetically patterned in an additively manufactured MS show the potential for the development of vascularized osteogenic TPs [25,47]. Thus, MS in combination with spatially patterned cell populations can be used for the development of 3D tissue structures such as osteochondral or meniscal TPs, which are preconditioned for efficient vascularization. Finally, the development of tissue constructs using MLBs holds immense potential for optimizing the timing and delivery of magnetized cells and active factors as well as for spatio-temporal cell patterning and dynamic stimulation of tissue development at different stages of TP maturation.

3. Challenges

Despite the considerable potential of MLBs to facilitate the development of tissue constructs, there are numerous challenges associated with the physical and chemical properties of MNPs and magnetically

Table 1
The main challenges related to the physical and chemical properties of MNPs used for the development of MLBs and possible solutions.

#	Issue.	Approaches to solving the problem.
1.	Standardization of MNPs	Given the current variability of MNPs, standardization is essential to ensure reproducibility and comparability of results in different MLBs. Standardization of MNPs properties, including surface functionalization and encapsulation, to ensure consistent and predictable effects on AFs release or tissue development.
2.	Optimization of surface functionalization techniques for MNPs	The improvement and standardization of techniques for surface functionalization of MNPs is necessary to control their interactions with cells and tissues. The development of robust methods for consistent surface modification will help to minimize unintended effects on cell behavior and tissue development.
3.	Biocompatibility of MLBs	Establishing standardized protocols to assess the effects of MNPs on cell behavior, including cytotoxicity, inflammation, and long-term effects, is crucial for ensuring the safety of magneto-responsive biomaterials.
4.	Optimizing spatio-temporal control of dynamic metabolic conditions in developing tissues	Development of strategies for precise spatio-temporal control of the availability of oxygen, nutrients and other essential molecules during the development cycle of tissue precursors, taking into account the dynamic nature of tissue development.
5.	Mechanical properties	Ensuring adequate mechanical properties of tissue-specific extracellular matrices and minimizing negative effects on cell behavior and tissue development in MLBs.
6.	Attenuation of cytotoxicity and inflammation	Addressing the potential cytotoxicity and inflammation caused by MNPs, with a focus on predicting and minimizing these effects for implanted MLBs.
7.	Long-term experiments in controlled environments	Development of materials science and engineering to support long-term experiments conducted in tightly controlled environments (e.g. using a suitable flow-through bioreactor in vitro) to meet the need for durable and reliable experimental conditions for magneto-responsive biosystems.
8.	Development of predictive mathematical models	Development of mathematical tools for the prediction and optimization of parameters related to the saturation and structuring of MLBs with magnetized cells using magnetic fields and considering trophic conditions.

responsive biomaterial systems containing these nanoparticles. Table 1 lists just a few of the most important of these.

These challenges contribute to the complexity of using MLBs in tissue engineering and emphasize the need for interdisciplinary efforts and technological advances to overcome obstacles and fully exploit the potential of this innovative approach. The diversity of MNPs, each with different surface functionalization or encapsulation in polymers, can have a direct impact on seeded cells and tissue development [6,43]. Even minor alterations in hydrodynamic size, surface charge, and surface chemistry can significantly affect MNP agglomeration, protein corona formation, accumulation in cells and extracellular space, as well as cytotoxicity and inflammation when applied in vivo.

On the other hand, it remains a challenge to provide MLBs with specific physiological properties, such as suitable tissue-tissue interfaces and appropriate mechanical properties of tissue-specific extracellular matrices. Furthermore, spatio-temporal control over the availability of oxygen, nutrients and AFs throughout the whole development cycle of TPs in vitro is a major challenge. To overcome these limitations, advances in materials science and engineering are crucial for performing the required long-term experiments in precisely controlled environments.

Another important prerequisite for the development of tissue engineering based on MLBs is the creation of mathematical tools to predict the parameters of MLB saturation/patterning with MCs in routine practice.

4. Conclusion and future perspectives

MNPs and magnetized cells incorporated into various biomaterials enable 3D tissue development that can be remotely controlled by external MF. MLBs produced using such an approach have the potential to be cost-effective tools for controlling the delivery and release of AFs both in vitro and even in vivo. Furthermore, MLB/MS could additionally be efficiently loaded with external magnetized objects (magnetized cells or/and functionalized MNPs), benefiting the delivery of AFs and TP development. Such MLBs can provide additional functionalities to TPs by either directly influencing the interaction of the scaffold with cells (affecting adhesion, proliferation and differentiation) or by serving as smart systems for AFs` delivery and/or tissue regeneration.

Some important points regarding complementary studies that have the potential to improve the production and applicability of MLBs should be noted. While the direction described above focuses on MNP-based constructs, other magnetically activated biomaterials offer additional possibilities. For example, an active soft porous scaffold containing a macroporous ferrogel can undergo significant deformation under the influence of a pulsed MF, changing its volume by more than 70% [48]. This property enhances the scaffold's ability to magnetically trigger the release of drugs or stimulate the development of contractile cells [49]. Researchers have also demonstrated a technique to fabricate and assemble 3D magnetic microblocks that mimic repetitive cellular functional units typical of tissues in vivo [50]. Several papers have explored the use of different types of magnetic hydrogels for remote activation and assembly of cells using microfluidic devices [51]. These studies demonstrate methods for the magnetic assembly of millions of cells in a 3D construct [25,37].

The transition from magnetic 3D to 4D bioprinting represents a significant advance in the development of biomaterials with new properties. This approach allows 3D constructs to be manipulated remotely by physical forces, allowing them to change their shape or behavior in response to different stimuli. Impressive results have been achieved by using multilayer printing to develop magnetic actuators with different patterns [41]. Some studies are moving towards 4D materials by combining biopolymers with anisotropic particles [42].

In this context, MNPs with multimodal magneto-electric properties have a number of advantages. Such MNPs enable wireless sensing and control of electric fields anywhere in vitro and in the human body via magnetic fields at the nanoscale level [52]. This approach opens up possibilities for the stimulation of neurons and the development of new nanomedical methods for the non-invasive diagnostics and treatment of brain diseases.

Minimizing the potential toxic effects of MNPs is another important prerequisite for the successful development of TPs. Recently, promising studies on the cytotoxicity of MNPs have been performed [55]. The authors showed the gradual decrease of magnetization, indicating the degradation of most nanoparticles in the population of mesenchymal stem cells loaded with MNPs. This process was almost complete one month after exposure to the nanoparticles, with no effect on cell differentiation. It should be noted that this was observed at low doses of internalized nanoparticles (on average 1 pg of iron per cell).

Currently, there are few mathematical and numerical models in the literature that describe the physical properties of MLBs and the processes involved in the positioning of magnetized AFs and cells in the context of TP development. Our attempts to address this issue include multiparametric analyzes that consider both the spatiotemporal characteristics of MLB loaded with magnetised cells and the evaluation of parameters for sufficient oxygen/nutrient transport to support the maintenance of favorable conditions for tissue development [53,54].

Our attempts to predict and evaluate the cytotoxic potential of various MLBs and MNPs involve the development of specific mathematical approaches based on time-dependent multi-readout simulations. They have been used for the selection of functionalized MNPs (in this case nanoliposomes) with minimal cytotoxic potential and minimal ability to trigger immune cell activation [56,57]. In particular, these models use a previously proposed approach [58] to predict different parameters characterizing the cytotoxic effects, taking into account spatial and temporal features of the toxicodynamic processes. In particular, this model takes into account the accumulation of nanoparticles in cells, the release of toxic metabolites and the maintenance of proliferation potential.

Although numerous studies are being conducted to explore the potential of MNPs and MLBs for both in vitro and in vivo applications, it is important to point out that in vivo experiments are significantly less common. The main challenge in conducting in vivo experiments is the fact that the biocompatibility of MLBs and MNPs is crucial for clinical applications. Although most of the recently produced MNPs do not exhibit significant cytotoxicity in vitro, they may cause adverse effects such as inflammation or toxicity to surrounding tissues in vivo [59]. Furthermore, the precise delivery of MNPs to specific tissues or cells in a living organism remains a major challenge [60]. The lack of targeted delivery may lead to off-target effects and reduced therapeutic efficacy. In addition, the regulatory landscape for the use of MNPs and MLBs in the clinical setting can be complex and difficult to navigate. Regulatory authorities require extensive safety and efficacy data before approving the use of MNPs and MNP-containing biomaterials in humans [61]. The basic approach to mitigate these issues is largely the same as in the case of the in vitro study and described above. Furthermore, the use of in vivo imaging techniques such as MRI can facilitate the tracking of MNPs in the body in real time (and even partially assess their biodegradation from the implanted MLB) [62]. This capability allows researchers to monitor the distribution and behavior of MNPs and provides valuable insights for optimizing their design and application in therapeutic contexts. In addition, immobilization of MNPs in biomaterials during the development of MLBs may help to alleviate some of these concerns by reducing the risk of uncontrolled release or migration of MNPs in the body. Moreover, recent approaches to in vitro evaluation of MNP transport across hysto-hematic barriers with and without facilitation of this transport by MF give hope for improving the delivery properties of these nanoparticles [63,64]. In particular, this methodology involves in vitro experiments with mathematical analysis using Artificial Intelligence in order to properly evaluate large data-sets obtained by fluorescence microscopy, toxicological tests and MNPs detectors [64].

In the future, novel computational approaches may facilitate the

development of new MLBs and corresponding technologies for magnetic bioprinting. These technologies are expected to overcome the challenges associated with the interactions of different cell types and meet the growing demand for high-throughput and high-precision systems. For example, machine learning and artificial intelligence algorithms provide powerful tools for monitoring and analyzing biosystems, taking into account the interactions between cells and biomaterials at the molecular level [65]. Such mathematical tools could be used for real-time analysis of data from bioreactors with MLBs and enable AI-based control systems for fine-tuning nutrient/oxygen delivery and remote activation of AF` release.

In addition, advances in complementary technologies could significantly increase the efficiency of MLB development and application. In particular, organ-on-chip systems, microfluidic biofabrication and the use of patient-derived induced pluripotent stem cells offer the potential to expand the scope of application of TPs based on magnetically responsive biomaterial systems [66].

CRediT authorship contribution statement

V. Goranov: Writing – review & editing, Writing – original draft, Validation, Resources, Project administration, Formal analysis, Data curation, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

No data was used for the research described in the article.

Acknowledgments

This publication was supported by the EU project “BOW” ID: 214685. It was also partially supported by the company Biodevice Systems s.r.o. I am especially grateful to V. Alek Dediu, who pioneered the research of magnetic scaffolds and was the inspirer of this publication. Special thanks to Andrey Goranov and Jaroslav Kostal for constructive criticism.

References

[1] Ito A, Ino K, Hayashida M, Kobayashi T, Matsunuma H, Kagami H, Ueda M, Honda H. Novel methodology for fabrication of tissue-engineered tubular constructs using magnetite nanoparticles and magnetic force. Tissue Eng 2005;11 (9-10):1553–61.
[2] Ceylan H, Yasa IC, Yasa O, Tabak AF, Giltinan J, Sitti M. 3D-printed biodegradable microswimmer for theranostic cargo delivery and release. ACS Nano 2019;13(3): 3353–62.
[3] Tolouei AE, Dülger N, Ghatee R, Kennedy S. A magnetically responsive biomaterial system for flexibly regulating the duration between pro- and anti-inflammatory cytokine deliveries. Adv Healthc Mater 2018;7(12):1800227.
[4] Gloria A, Russo T, d'Amora U, Zeppetelli S, d'Alessandro T, Sandri M, De Santis R. Magnetic poly(ε-caprolactone)/iron-doped hydroxyapatite nanocomposite substrates for advanced bone tissue engineering. J R Soc Interface 2013;10(80): 20120833.
[5] Bock N, Riminucci A, Dionigi C, Russo A, Tampieri A, Landi E, Dediu V. A novel route in bone tissue engineering: magnetic biomimetic scaffolds. Acta Biomater 2010;6(3):786–96.
[6] Biomedical applications of biomaterials functionalized with magnetic nanoparticles. In: Lodi MB, Fanti A, editors. Smart Nanosystems for Biomedicine, Optoelectronics and Catalysis; 2019. https://doi.org/10.5772/intechopen.89199.
[7] editors. In: Mousa SA, Bawa R, Audette GF, editors. The road from nanomedicine to precision medicine. CRC Press; 2020. https://doi.org/10.1201/9780429295010.
[8] Chen H, Sun J, Wang Z, Zhou Y, Lou Z, Chen B, Zhang F. Magnetic cell–scaffold interface constructed by superparamagnetic IONP enhanced osteogenesis of adipose-derived stem cells. ACS Appl Mater Interfaces 2018;10(51):44279–89.
[9] Pourmanouchehri Z, Jafarzadeh M, Kakaei S, Khameneh ES. Magnetic nanocarrier containing 68Ga–DTPA complex for targeted delivery of doxorubicin. J Inorgan Organometal Polym Mater 2018;28:1980–90. https://doi.org/10.1007/s10904-018-0826-7.
[10] Prakash M, Chandraprabha MN, Krishna RH, Satish H, Kumar SG. Iron oxide nanoparticles for inflammatory bowel disease: Recent advances in diagnosis and targeted drug therapy. Appl Surf Sci Adv 2024;19:203–17. https://doi.org/10.1016/j.apsadv.2023.100540.
[11] Demri N, Dumas S, Nguyen ML, Gropplero G, Abou-Hassan A, Descroix S, Wilhelm C. Remote magnetic microengineering and alignment of spheroids into 3D cellular fibers. Adv Funct Mater 2022;32(50):2204850.
[12] Bharti B, Fameau AL, Rubinstein M, Velev OD. Nanocapillarity-mediated magnetic assembly of nanoparticles into ultraflexible filaments and reconfigurable networks. Nat Mater 2015;14(11):1104–9.
[13] Hu K, Sun J, Guo Z, Wang P, Chen Q, Ma M, Gu N. A novel magnetic hydrogel with aligned magnetic colloidal assemblies showing controllable enhancement of magnetothermal effect in the presence of alternating magnetic field. Adv Mater 2015;27(15):2507–14.
[14] Fan F, Sun J, Chen B, Li Y, Hu K, Wang P, Gu N. Rotating magnetic field-controlled fabrication of magnetic hydrogel with spatially disk-like microstructures. Sci China Mater 2018;61(8):1112–22.
[15] Lu M, Cohen MH, Rieves D, report Pazdur RFDA. Ferumoxytol for intravenous iron therapy in adult patients with chronic kidney disease. Am J Hematol 2010;85(5): 315–9. https://doi.org/10.1002/ajh.21656.
[16] Saliba AE, Saias L, Psychari E, Minc N, Simon D, Bidard FC, Viovy JL. Microfluidic sorting and multimodal typing of cancer cells in self-assembled magnetic arrays. Proc Natl Acad Sci 2010;107(33):14524–9.
[17] Kralj S, Makovec D. Magnetic assembly of superparamagnetic iron oxide nanoparticle clusters into nanochains and nanobundles. ACS Nano 2015;9(10): 9700–7.
[18] Betsch M, Cristian C, Lin Y Y, Blaeser A, Schöneberg J, Vogt M, Buhl EM, Fischer H, Duarte Campos DF. Incorporating 4D into bioprinting: Real-time magnetically directed collagen fiber alignment for generating complex multilayered tissues. Adv Healthc Mater 2018;7(21):1800894.
[19] Tognato R, Armiento AR, Bonfrate V, Levato R, Malda J, Alini M, Eglin D, Giancane G, Serra T. A stimuli-responsive nanocomposite for 3D anisotropic cell-guidance and magnetic soft robotics. Adv Funct Mater 2019;29(9):1804647.
[20] Sun J, Fan F, Wang P, Ma S, Song L, Gu N. Orientation-Dependent Thermogenesis of Assembled Magnetic Nanoparticles in the Presence of an Alternating Magnetic Field. ChemPhysChem 2016;17(21):3377–84.
[21] Yang D, Xiao J, Wang B, Li L, Kong X, Liao J. The immune reaction and degradation fate of scaffold in cartilage/bone tissue engineering. Mater Sci Eng C 2019;104: 109927.
[22] Hanot CC, Choi YS, Anani TB, Soundarrajan D, David AE. Effects of iron-oxide nanoparticle surface chemistry on uptake kinetics and cytotoxicity in CHO-K1 cells. Int J Mol Sci 2015;17(1):54.
[23] Chen K, Han H, Tuguntaev RG, Wang P, Guo W, Huang J, Gong X, Liang XJ. Applications and regulatory of nanotechnology-based innovative in vitro diagnostics. View 2021;2(2):20200091.
[24] Ito A, Hayashida M, Honda H, Hata KI, Kagami H, Ueda M, Kobayashi T. Construction and harvest of multilayered keratinocyte sheets using magnetite nanoparticles and magnetic force. Tissue Eng 2004;10:873.
[25] Goranov V, Shelyakova T, De Santis R, Haranava Y, Makhaniok A, Gloria A, Tampieri A, Russo A, Kon E, Marcacci M, Ambrosio L, Dediu VA. 3D Patterning of cells in magnetic scaffolds for tissue engineering. . Sci Rep. 2020;10:2289. https://doi.org/10.1038/s41598-020-58738-5.
[26] Garello F, Svenskaya Y, Parakhonskiy B, Filippi M. Micro/nanosystems for magnetic targeted delivery of bioagents. Pharmaceutics 2022;14(6):1132.
[27] Zhao Y, Fan T, Chen J, Su J, Zhi X, Pan P, Zou L, Zhang Q. Magnetic bioinspired micro/nanostructured composite scaffold for bone regeneration. Colloids Surf B Biointerfaces 2019;174:70–9.
[28] Eslami P, Albino M, Scavone F, Chiellini F, Morelli A, Baldi G, Cappiello L, Doumett S, Lorenzi G, Ravagli C, Caneschi A, Laurenzana A, Sangregorio C. Smart magnetic nanocarriers for multi-stimuli on-demand drug delivery. Nanomaterials 2022;12(3):303.
[29] Maitz MF, Freudenberg U, Tsurkan MV, Fischer M, Beyrich T, Werner C. Bio-responsive polymer hydrogels homeostatically regulate blood coagulation. Nat Commun 2013;4:2168.
[30] Dionigi C, Lungaro L, Goranov V, Riminucci A, Pineiro-Redondo Y, Bañobre-López M, Rivas J, Dediu V. Smart magnetic poly(N-isopropylacrylamide) to control the release of bio-active molecules. J Mater Sci Mater Med 2014;25:2365–71.
[31] An Y, Yang R, Wang X, Han Y, Jia G, Hu C, Zhang Z, Liu D, Tang Q. Facile assembly of thermosensitive liposomes for active targeting imaging and synergetic chemo-/magnetic hyperthermia therapy. Front Bioeng Biotechnol 2021;9:691091.
[32] Labusca L, Herea DD, Danceanu CM, Minuti AE, Stavila C, Grigoras M, Gherca D, Stoian G, Ababei G, Chiriac H, Lupu N. The effect of magnetic field exposure on differentiation of magnetite nanoparticle-loaded adipose-derived stem cells. Mater Sci Eng C 2020;109:110652.
[33] Dobson J, Cartmell SH, Keramane A, El Haj AJ. Principles and design of a novel magnetic force mechanical conditioning bioreactor for tissue engineering, stem cell conditioning, and dynamic in vitro screening. IEEE Trans Nanobiosci 2006;5(3): 173–7.
[34] Seo D, Southard KM, Kim JW, Lee HJ, Farlow J, Lee JU, Litt DB, Haas T, Alivisatos AP, Cheon J, Gartner ZJ. Jun YW. A mechanogenetic toolkit for interrogating cell signaling in space and time. Cell 2016;165(6):1507–18.
[35] Sapir-Lekhovitser Y, Rotenberg MY, Jopp J, Friedman G, Polyak B, Cohen S. Magnetically actuated tissue engineered scaffold: Insights into mechanism of physical stimulation. Nanoscale 2016;8(6):3386–99.

[36] Markides H, McLaren JS, El Haj AJ. Overcoming translational challenges–The delivery of mechanical stimuli in vivo. Int J Biochem Cell Biol 2015;69:162–72.
[37] Samal SK, Goranov V, Dash V, Russo A, Shelyakova T, Graziosi P, Lungaro L, Riminucci A, Uhlarz M, Bañobre-López M, Rivas J, Herrmannsdörfer T, Rajadas J, De Smedt S, Braeckmans K, Kaplan DL, Dediu VA. Multilayered magnetic gelatin membrane scaffolds. ACS Appl Mater Interfaces 2015;7(41):23098–109.
[38] Park S, Kim J, Lee MK, Park C, Jung HD, Kim HE, Jang TS. Fabrication of strong, bioactive vascular grafts with PCL/collagen and PCL/silica bilayers for small-diameter vascular applications. Mater Des 2019;181:108079.
[39] Ramos-Rodriguez H, Leach JK. Biomaterials are the key to unlock spheroid function and therapeutic potential. Biomater Biosyst 2023:100080.
[40] Mattix A, Olsen TR, Gu Y, Casco M, Herbst A, Simionescu DT, Visconti RP, Kornev KG, Alexis F. Biological magnetic cellular spheroids as building blocks for tissue engineering. Acta Biomater 2014;10(2):623–9.
[41] Simińska-Stanny J, Nizioł M, Szymczyk-Ziółkowska P, Brożyna M, Junka A, Shavandi A, Podstawczyk D. 4D printing of patterned multimaterial magnetic hydrogel actuators. Addit Manuf 2022;49:102506.
[42] Van de Walle A, Perez JE, Wilhelm C. Magnetic bioprinting of stem cell-based tissues. Bioprinting 2023:e00265.
[43] Teijeiro-Valiño C, Gómez MG, Yáñez S, Acevedo PG, Prieto AA, Belderbos S, Gsell W, Himmelreich U, Piñeiro Y, Rivas J. Biocompatible magnetic gelatin nanoparticles with enhanced MRI contrast performance prepared by single-step desolvation method. Nano Express 2021;2(2):020011.
[44] Yuet KP, Hwang DK, Haghgooie R, Doyle PS. Multifunctional superparamagnetic Janus particles. Langmuir 2010;26:4281–7.
[45] Ragelle H, Danhier F, Préat V, Langer R, Anderson DG. Nanoparticle-based drug delivery systems: a commercial and regulatory outlook as the field matures. Expert Opin Drug Deliv 2017;14(7):851–64.
[46] Yan S, Hu K, Zhang M, Sheng J, Xu X, Tang S, Li Y, Yang S, Si G, Mao Y, Zhang Y, Zhang F, Gu N. Extracellular magnetic labeling of biomimetic hydrogel-induced human mesenchymal stem cell spheroids with ferumoxytol for MRI tracking. Bioact Mater 2023;19:418–28.
[47] Petretta M, Gambardella A, Desando G, Cavallo C, Bartolotti I, Shelyakova T, Goranov V, Brucale M, Dediu VA, Fini M, Grigolo B. Multifunctional 3D-printed magnetic polycaprolactone/hydroxyapatite scaffolds for bone tissue engineering. Polymers 2021;13(21):3825.
[48] Zhao X, Kim J, Cezar CA, Huebsch N, Lee K, Bouhadir K, Mooney DJ. Active scaffolds for on-demand drug and cell delivery. Proc Natl Acad Sci U S A 2011;108 (1):67–72. https://doi.org/10.1073/pnas.1007862108.
[49] Emi TT, Barnes T, Orton E, Reisch A, Tolouei AE, Madani SZM, Kennedy SM. Pulsatile chemotherapeutic delivery profiles using magnetically responsive hydrogels. ACS Biomater Sci Eng 2018;4(7):2412–23. https://doi.org/10.1021/acsbiomaterials.8b00372.
[50] Xue L, Sun J. Magnetic hydrogels with ordered structure for biomedical applications. Front Chem 2022;10:1040492. https://doi.org/10.3389/fchem.2022.1040492.
[51] Feng Q, Li D, Li Q, Cao X, Dong H. Microgel assembly: Fabrication, characteristics and application in tissue engineering and regenerative medicine. Bioact Mater 2022;9:105–19. https://doi.org/10.1016/j.bioactmat.2022.01.001.
[52] Yue K, Guduru R, Hong J, Liang P, Nair M, Khizroev S. Magneto-electric nano-particles for non-invasive brain stimulation. PLoS One 2012;7(9):e44040.
[53] Makhaniok A, Haranava Y, Goranov V, Panseri S, Semerikhina S, Russo A, Marcacci M, Dediu V. In silico prediction of the cell proliferation in porous scaffold using model of effective pore. Biosystems 2013;114(3):227–37. https://doi.org/10.1016/j.biosystems2013-07-002.
[54] Makhaniok A, Goranov V, Dediu V. Determination of the protein layer thickness on the surface of polydisperse nanoparticles from the distribution of their concentration along a measuring channel. J Eng Phys Thermophys 2019;92:19–28. https://doi.org/10.1007/s10891-019-0203-4.
[55] Van de Walle A, Kolosnjaj-Tabi J, Lalatonne Y, Wilhelm C. Ever-evolving identity of magnetic nanoparticles within human cells: The interplay of endosomal confinement, degradation, storage, and neocrystallization. Acc Chem Res 2020;53 (10):2212–24. https://doi.org/10.1021/acs.accounts0c00123.
[56] Makhaniok A, Siutsou I, Vrana E, Goranov V. Mathematical model for estimation biomaterial toxicity in cell systems. In: Materials of 11th World Biomaterials Congress; 2020. p. 3968. 11th–15th December.
[57] Goranov V, Makhaniok A. Software for evaluation of immune cell activation (Application note). Biosystems 2024:235. https://doi.org/10.1016/j.biosystems.2023.105092.
[58] Byrne HJ, Maher MA. Numerically modelling time and dose dependent cytotoxicity. Comput. Toxicol. 2019;12:100090.
[59] Ma W, Wang X, Zhang D, Mu X. Research Progress of Disulfide Bond Based Tumor Microenvironment Targeted Drug Delivery System. Int J Nanomed 2024:7547–66.
[60] Rashidi L. Chapter 21: Functionalized Magnetic Nanoparticles (MNPs): Toxicity, Safety and Legal Aspects of Functionalized MNPs. Analytical Applications of Functionalized Magnetic Nanoparticles. 2021. https://doi.org/10.1039/9781839162756-00527.
[61] Rarokar N, Yadav S, Saoji S, Bramhe P, Agade R, Gurav S, Kumarasamy V. Magnetic nanosystem a tool for targeted delivery and diagnostic application: Current challenges and recent advancement. Int J Pharmac: X 2024:100231.
[62] Zhang W, Zhang S, Xu W, Zhang M, Zhou Q, Chen W. The function and magnetic resonance imaging of immature dendritic cells under ultrasmall superparamagnetic iron oxide (USPIO)-labeling. Biotechnol Lett 2017;39:1079–89.
[63] Polo E, Collado M, Pelaz B, Del Pino P. Advances toward more efficient targeted delivery of nanoparticles in vivo: understanding interactions between nanoparticles and cells. ACS Nano 2017;11(3):2397–402.
[64] Goranov V, Kostal Y. Evaluation of hysto-hematic barriers permeability for magnetic nanoparticles. Proce Nat. Acad. Sci. Belarus. Biol Series 2024;70(4): 217–31. in press.
[65] Elsen R, Nayak S. Artificial intelligence-based 3d printing strategies for bone scaffold fabrication and its application in preclinical and clinical investigations. ACS Biomater Sci Eng 2024. https://doi.org/10.1021/acsbiomaterials.3c01368.
[66] Materón M, Miyazaki CM, Carr O, Joshi N, Picciani PHS, Dalmaschio CJ, Davis F, Shimizu FM. Magnetic nanoparticles in biomedical applications: A review. Appl Surf Sci Adv 2021;6:100163. https://doi.org/10.1016/j.apsusc.2021.100163.