ADVANCED FUNCTIONAL MATERIALS
www.afm-journal.de

Magnetic Systems for Regenerative Medicine

Manuela E. Gomes and Rui M. A. Domingues**

Over the last decade, magnetic-based systems have made remarkable breakthroughs in the field of tissue engineering and regenerative medicine. The ability for contactless manipulation of magnetic responsive biomaterials, or even living cells, has been leveraged to devise innovative concepts that are widening the available bioengineering design space that can be explored in this multidisciplinary field. From the fabrication of cellular constructs with bioinspired patterns and hierarchical structures up to the concepts of levitational bioassembly, magnetic systems are enabling to engineer 3D tissues that better recapitulate the complex biophysical and biological cues of their native counterparts. Moreover, the inherent magnetic responsiveness of this living systems is being explored as mechanical and electrical nanotransducers to further stimulate cell functions, not only in vitro but also in vivo. Remarkably, recent advances in the convergence of microfabrication technologies with magnetic materials is also opening prospects to further fabricate advanced living microrobots and microphysiological systems with new added functionalities. Due to their good track record of biological tolerance and biodegradability, iron oxide-based nanoparticles remain the first choice of (superpara)magnetic nanomaterials, but new variants and combinations of nanomaterial are being increasingly explored in this field. Altogether, magnetic systems are contributing in multiple ways to boost the regenerative potential of bioengineered constructs and may lead to the development of in vitro tissue/organ models with improved physiological relevance.

In this Special Issue we invited world experts to report their latest findings and revise recent advances on the field of Magnetic Systems for Regenerative Medicine. This collection of 12 articles highlight how different magnetic systems are being explored for cell manipulation and tracking and directly interact with its specific receptors. Moreover, particular focus is dedicated to the convergence of magnetic systems with other interface technologies for the fabrication of living tissue engineered constructs, 3D in vitro tissue/organ models and biohybrid microrobots.

Most human tissue have ordered cellular and extracellular matrix (ECM) patterns that are key for organ function. However, recreating tissue-specific anisotropic patterns and gradients in bioengineered tissues has been a major challenge. In article number 202202468, Laura De Laporte and co-workers use high aspect-ratio and magneto-responsive microgels that can be oriented within hydrogel matrices (Anisogel) by external magnetic fields to recapitulate the complex and anisotropic architecture of native ECM. In this study, the authors explore in detail how different local physical, biochemical, and mechanical properties of Anisogel affect oriented nerve cell growth. Jerome Crassous and co-workers (article number 202202430) further demonstrate how the angle of microgel alignment in Anisogel under static external magnetic field can be pre-programmed depending on the alignment of ellipsoidal maghemite nanoparticles, integrated as responsive fillers within the microgels. This approach allows to fabricate hydrogel-based constructs with both parallel and orthogonal microgel orientation, broadening the potential of bioengineering tools to recreate the architectural complexity of living tissues.

The induction of specific cellular patterns can be promoted not only by controlling the biochemical and biophysical properties of the encapsulating material, but also by manipulating the organisation and bioassembly of cells itself. The contactless implementation of this concept can be achieved by the prior "magnetization" of cells for their subsequent manipulation with magnetic fields. Christina Janko and her team (article number 202203672) compare the cellular labelling efficiency of superparamagnetic iron oxide nanoparticles (SPIONs) with different coatings, and evaluate their respective magnetic control potential for induction of 2D patterns and 3D spheroid aggregates. Claire Wilhelm and colleagues (article number 202204850) applied a similar concept to produce magnetic muscle cells spheroids. These magnetic muscle microunits were then aligned by magnetic fields within collagen hydrogels, creating spheroid stings that fuse into 3D fiber-like muscle structures during in vitro culture time. A different approach was proposed by Orit Shefi and co-workers (article number 202204925) that used SPIONs labelled nerve cells to produce 3D cell clusters within collagen-based hydrogels controlled by the applied magnetic fields. These patterned hydrogel units can be assembled into multi-layered constructs, creating functional 3D microarchitectures of neural networks. While the fabrication of defined 3D cellular structures with magnetic manipulation often relies on their labelling with magnetic nanoparticles (MNPs), diamagnetic levitation, a method where cells are made susceptible to magnetic manipulation by contact with paramagnetic media (e.g. gadolinium based solutions), is an attractive alternative for cell manipulation in 3D space. In article 202204092, Gozde Durmus and co-workers demonstrate

M. E. Gomes, R. M. A. Domingues
3B's Research Group
I3Bs - Research Institute on Biomaterials
Biodegradables and Biomimetics
University of Minho
Headquarters of the European Institute of Excellence on issue
Engineering and Regenerative Medicine
AvePark - Parque de Ciência e Tecnologia ona Industrial da Gandra
Barco, 4805-017 Guimarães, Portugal
E-mail: megomes@i3bs.uminho.pt; rui.domingues@i3bs.uminho.pt
M. E. Gomes, R. M. A. Domingues
ICVS/3B's - PT Government Associate Laboratory Braga
Guimarães, Portugal
The ORCID identification number(s) for the author(s) of this article can be found under https://doi.org/10.1002/adfm.202211925.

DOI: 10.1002/adfm.202211925

the application of this levitational biofabrication technique for the 3D bioassembly and density-based spatial coding of multicellular constructions, termed “Levitoids”. The biofabrication potential of this technique was further demonstrated on the manipulation and self-assembly of “levitospheres” (cell spheroid units) within a hydrogel matrix, allowing to create heterogeneous 3D living constructs with defined architecture within an ECM-like microenvironment. Overall, these bioinspired living systems fabricated by direct magnetic cell manipulation might lead to bioengineered tissues with improved regenerative potential, but can also be leveraged as advanced miniaturized microphysiological systems for in vitro research.

The convergence of magnetic cell patterning systems with automated 3D biofabrication technologies is broadening the design space available for fabricating living artificial constructs recreating complex tissue hierarchical architectures and gradients. In article number 202208940, Manuela Gomes and colleagues propose a magnetically-assisted 3D bioprinting system to fabricate anisotropic constructs based on composite hydrogel bioinks incorporating magnetic microfibers. To enable the control over magnetic microfibers organization while preserving the fidelity of printed multilayer constructs, the concepts of magnetically- and matrix-assisted 3D bioprinting were combined. The biofabrication potential of this extrusion-based system was demonstrated for tendon tissue engineering, a high anisotropic and hierarchical fibrous tissue. This study further demonstrates that beyond control of the hierarchical cell pattering, magnetic biomaterials can also be leveraged as remote actuators for magneto-mechanical stimulation of mechanosensitive cells during in vitro maturation steps. In fact, 3D printing of materials that can be remotely actuated via external stimuli is generally known as 4D printing. These systems are particularly interesting in the context of regenerative medicine because it can be explored to produce shape morphing biomaterials that e.g. facilitate the implantation of medical devices or be triggered to apply mechanical stimuli to host cells. In article numbers 202202539, Lorenzo Moroni and co-workers propose the 4D printing of shape morphing biomaterials by digital light processing (DLP) based on nanocomposite inks incorporating anisotropic magnetite nanoparticles. This study shows that the alignment of ferromagnetic nanoparticles in printed nanocomposite hydrogels can be controlled to induce complex scaffold movements depending on the direction of applied magnetic fields. The proposed strategy demonstrates potential to pattern and control movements in 3D structures to be used, for instance, in tissue engineering applications.

Non-invasive approaches using remotely controllable MNPs have demonstrated their potential ability to enhance treatment efficacy in regenerative medicine and tissue repair. Alicia El Aj and co-workers (Article number 202201311) explored the possibility of expanding the capabilities of such systems adding electrical properties. For that purpose, they have developed MNPs incorporated Graphene Oxide (GO) based nanocomposites (GOMNPs) and functionalised it with TREK1 and Piezo1 antibodies to specifically target the respective mechanosensitive ion channels. This approach showed significant upregulation in osteogenic markers expression and enhanced bone formation. In article number 202204558, remotely controlled MNPs were used for thermal activation of a heat sensitive ion channel TRPV1 that promotes axonal growth in a calcium-dependent manner. Using this approach, Polina Anikeeva and co-workers observed accelerated axonal growth through elongation of neurofilaments and increased Schwann cell migration following magnetothermal stimulation, demonstrating the potential of this technology as a minimally invasive therapy to accelerate nerve regeneration.

The most well studied and wider application of MNPs, in particular SPIONs, in the medical field is by far in magnetic resonance imaging (MRI), where they have been used for over 30 years. In the article 202207626, the only review manuscript in this issue, Jeff Bulte and colleagues provided an overview of reports on the tolerance of cells to magnetic labelling versus unlabelled cells. Now that magnetic particle imaging (MPI) cell tracking is emerging as a new in vivo cellular imaging modality, there has been a renaissance in SPIONs formulation based on lessons learned from the occasional past pitfalls encountered with SPION-labelling of cells for MRI, which is expected to expedite possible future clinical translation of (combined) MRI/MPI cell tracking.

More importantly, the convergence of magnetic particle systems for precision imaging with their possible manipulation as cell containing magnetic microrobots, may open numerous possibilities as theragnostic tools with very broad bioengineering applications. As so, biohybrid microrobotics have been exploited, for example, as delivery vehicles to actively transport therapeutic payload to tumours. However, biohybrid microrobotics design has been mainly focused on the living organisms’ motility and biocompatibility, while the unique biological function of the natural organism is often overlooked. Utkan Demerci and co-workers (article number 202201800) have developed an all-in-one self-propelled volvox-based multifunctional robot, i.e. Volbot, with built-in capabilities of fluid mixing, multimode imaging, and photosynthesis mediated in situ oxygen generation. Combined with MNPs, Volbots motion can be controlled by magnetic fields, while red-light irradiation enhances Volbot’s locomotive behaviour, mixing of biofluids and modulate oxygen production to improve the efficacy of photodynamic therapy. Because Volbots can absorb near-infrared irradiation and produce localized hyperthermia, this high-yield oxygen-producing biohybrid “microfactory” revealed effective on the suppression of subcutaneous tumours in a photodynamic/photothermal-synergistic therapy. The impressive Volbots functional toolbox also includes multimode imaging capabilities, making it a promising multifunctional microrobotics-based theranostic approach for precision cancer treatment.

Altogether, this special issue is an outstanding collection of expert contributions covering the multiple directions in which magnetic systems are being explored for advancing the multidisciplinary filed of regenerative medicine. Our hope is that this state-of-the-art topics and research papers will serve as an inspiration to foster the surge of new transformative ideas for the development of the next generation of advanced regenerative magnetic systems.

Conflict of Interest

The authors declare no conflict of interest.

Manuela E. Gomes is Associate Professor with Habilitation and Vice-President of the I3Bs Research Institute of the University of Minho, Portugal. Her research interests currently focus on tendon tissue engineering strategies, in particular using magnetic systems to remotely modulate cells and tissue responses. She currently coordinates a Consolidator Grant from the European Research Council (ERC) in this research area, among other projects. She is a Fellow of the Tissue Engineering and Regenerative Medicine International Society (TERMIS) and presently Chair-Elect of the European Chapter (TERMIS-EU).

Rui Domingues is a senior Researcher at I3Bs – Research Institute for Biomaterials, Biodegradables and Biomimetics, University of Minho, Portugal. He received his PhD in Chemical Engineering from the University of Aveiro. His research focuses on the development of functional biomaterials and biofabrication concepts for tissue engineering and regenerative medicine applications. He has particular interest on nanostructured and nanocomposite biomaterials with biomimetic features and how it can be explored to control cell fate in tissue engineered systems.