POLITECNICO DI TORINO
Repository ISTITUZIONALE

Innovative nanotechnology tools for the functional control and tracking of human stem cells

Original
Innovative nanotechnology tools for the functional control and tracking of human stem cells / Marino, Attilio; Battaglini, Matteo; Tapeinos, Christos; Larrañaga, Aitor; Ciofani, Gianni. - In: MATERIALS TODAY ADVANCES. - ISSN 2590-0498. - 16:(2022), p. 100298. [10.1016/j.mtadv.2022.100298]

Availability:
This version is available at: 11583/2971491 since: 2022-09-20T06:57:58Z

Publisher:
Elsevier

Published
DOI:10.1016/j.mtadv.2022.100298

Terms of use:

This article is made available under terms and conditions as specified in the corresponding bibliographic description in the repository

Publisher copyright

(Article begins on next page)

02 May 2024

Materials Today Advances 16 (2022) 100298

Contents lists available at ScienceDirect

Materials Today Advances

journal homepage: www.journals.elsevier.com/materials-today-advances/

Innovative nanotechnology tools for the functional control and tracking of human stem cells

Attilio Marino [a, 1, *], Matteo Battaglini [a, 1], Christos Tapeinos [b], Aitor Larrañaga [c], Gianni Ciofani [a, **]

[a] Istituto Italiano di Tecnologia, Smart Bio-Interfaces, Viale Rinaldo Piaggio 34, 56025 Pontedera, Italy
[b] University of Helsinki, Faculty of Pharmacy, Division of Pharmaceutical Chemistry and Technology, Drug Research Program, Viikinkaari 5, 00014, Helsinki, Finland
[c] University of the Basque Country (UPV/EHU), Department of Mining-Metallurgy Engineering and Materials Science, POLYMAT, Faculty of Engineering in Bilbao, Plaza Torres Quevedo 1, 48013 Bilbao, Spain

ARTICLE INFO

Article history:
Received 18 July 2022
Received in revised form
25 August 2022
Accepted 5 September 2022
Available online xxx

Keywords:
Smart nanomaterials
Nanostructured surfaces
Stem cells
Remote cell stimulation
Cell tracking

ABSTRACT

The precise control of stem cell behavior, including differentiation, transdifferentiation, and reprogramming, is fundamental for safely and efficiently using human stem cells in regenerative medicine. Thanks to recent innovations and developments in the field of nanomedicine, as well as its integration with advanced molecular biology approaches, the possibility of engineering and restoring functions of complex tissues become reality. Multifunctional nanotechnological tools allow to finely control the release of growth factors, mRNA, and other molecules, to promote cell fate conversion, and to perform long-term tracking *in vivo*. Furthermore, stimulation approaches based on smart and biocompatible nanotransducers promise to remotely modulate the stem cell activity, paving the way for the actual exploitation of these technologies in the internal tissues of large-sized animals. In this review, the most innovative nanotechnology tools applied to stem cell-based regenerative medicine are presented, and their implications for future research and clinics are discussed.

© 2022 The Authors. Published by Elsevier Ltd. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

1. Introduction

A plethora of chemico-physical cues guide stem cell behaviors from the quiescent to the proliferative and differentiative state. The complex gradients of biochemical, mechanical, and topographical signals from the specific stem cell niche to the differentiated tissues finely regulate proliferation, migratory behavior, morphology maturation, and differentiation of the stem cells and their progeny. The precise control of these phenomena is fundamental for tissue homeostasis, regeneration, and function [1]. The reconstruction of the chemico-physical microenvironment of the stem cell niches and the delivery of specific pro-differentiative cues to precisely manipulate cell fate and behavior represents a huge challenge to scientific research and technology, requiring competencies and tools from different disciplines including molecular biology, bioengineering, and material science. In this scenario, nanotechnology offers a multitude of smart and multifunctional platforms for the controlled delivery of nucleic acids [2], growth factors [3], and drugs [4], remote stimulation with physical cues (*e.g.*, electric, mechanical and thermal) [5], and nano-topographical reconstruction of the extracellular matrix (ECM) [6]. Moreover, nanotechnology also offers innovative tools for the multi-modal long-term tracking of transplanted stem cells in internal tissues [7]. Altogether, these nanotechnology-based approaches applied to stem cells allow for improved control in cell reprogramming, expansion, and differentiation, with unique capabilities for medical imaging and enhanced therapy performances. Therefore, the synergic combination of stem cell therapy approaches and nanoparticle technologies shows great promise for the investigation, diagnosis, and treatment of various degenerative and genetic diseases.

Concerning stem cell reprogramming, in 2013 the conversion of human umbilical cord mesenchymal stem cells (MSCs) into induced pluripotent stem cells (iPSCs) by nanomaterial-assisted delivery of four plasmids encoding for the Yamanaka factors (Oct4, Sox2, Klf4,

* Corresponding author.
** Corresponding author.
E-mail addresses: attilio.marino@iit.it (A. Marino), gianni.ciofani@iit.it (G. Ciofani).
[1] These authors equally contributed to this work.

https://doi.org/10.1016/j.mtadv.2022.100298
2590-0498/© 2022 The Authors. Published by Elsevier Ltd. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

and c-Myc) was demonstrated for the first time [8]. In this pioneering work, Cao et al. devised a simple and safe approach for generating virus-free iPSCs by using plasmid-encapsulated calcium phosphate nanoparticles. The iPSCs obtained with this technique showed both the expression of pluripotency markers and differentiation capability into the three germ layers. The recent developments in nanomaterial science and gene editing methods allowed for the improvement of reprogramming technologies. As an example, efficient cell reprogramming through the delivery of CRISPR/dCas9 ribonucleoproteins with magnetic peptide-imprinted chitosan nanoparticles was recently demonstrated [9]. This approach prevents the risks of the insertion of mutations into the genome of the target cells. Furthermore, recent nanotechnology and molecular biology tools addressed the issue of the scarce efficiency and slow kinetics of the somatic cell reprogramming into iPSCs. In this framework, Meng et al. took advantage of the mesenchymal-to-epithelial transition (MET) phenomenon for enhancing the conversion efficiency of fibroblasts into iPSCs [10]. To this aim, the authors nanoengineered gold nanoparticles with ADH-1, a cyclic pentapeptide that selectively and competitively binds to and blocks N-cadherin. Thanks to this nanoplatform, a 7-fold increase in reprogramming efficiency compared to the Yamanaka factors-based strategy was reached, with stemness and pluripotency of iPSCs demonstrated both *in vitro* and *in vivo*.

A series of smart nanotechnology tools have been developed to promote the proliferation of stem cells, as well as their differentiation and maturation towards specific cell fates. The main aim is to develop particular cell types and organoids *in vitro* and regenerate tissues *in vivo*. One approach involves the use of nanocarriers to deliver mRNA, siRNA, growth factors, and other biomolecules to control gene expression and cell behavior. A recent trend is to load the nanocarriers with chemically modified RNA (cmRNA), which allows for enhanced genetic stability and reduced immunogenicity [11,12]. Also, the use of smart nanosystems for the actuated release of the cargo enables a more precise temporal control of cell modulation [13,14]. Another approach regards the treatment of cells with active nanomaterials to chronically deliver thermal, electric, mechanical, and oxidative cues [15]. Piezoelectric, magnetothermal, magnetoelectric, photothermal, and photodynamic stimulations have been provided by such nanotransducers to further guide stem cell fate. This strategy consents after-transplant modulation of stem cell behavior in complex animals by exploiting sources of energy able to efficiently penetrate through the biological tissues (*e.g.*, ultrasounds and magnetic fields). Finally, a third strategy contemplates the engineering of surface nanotopographies to trigger specific mechanotransduction signaling pathways [16]. Although the mechanobiology phenomena regulating cell behavior still require to be fully elucidated, nanostructured surfaces with both deterministic and chaotic features demonstrated to efficiently regulate proliferation and cell fate promotion. In this regard, the engineering of surface topography is not only relevant for *in vitro* applications, but also when integrating prostheses/implants with stem cell therapy for tissue engineering [17,18].

2. Stem cells in research and clinics

Stem cells are a class of cells responsible for the development of organs and systems and are pivotal for the regeneration of tissues. Stem cells are characterized by the ability of constant self-renewal and by the potential to differentiate into many different cells when exposed to specific stimuli [19,20]. Given these abilities is of no surprise that stem cell analysis, characterization, and exploitation have been one of the main investigated approaches for regenerative medicine and tissue repair. Stem cells could potentially be used as a countermeasure for age-related diseases, injuries, neurodegenerative disorders, and congenital defects [19,20]. The study of stem cells holds also great promise in the field of cancer research due to the association of tumors with the so-called cancer stem cells (CSCs), a subpopulation of cancer cells that have been linked to tumor initiation and relapses [21]. Stem cells can be classified based on their “potency” and their biological origin. As we will discuss in the following paragraphs potency and tissue origins of stem cells are almost always linked. The term potency refers to the ability of stem cells to differentiate in different subsets of cells. In particular stem cells can be classified as totipotent, pluripotent, multipotent, oligopotent, and unipotent based on the number of different cell types in which they can be differentiated [22]. Totipotent stem cells are cells that can self-renew by dividing and developing into the three primary germ cell layers of the early embryo and extra-embryonic tissues such as the placenta [23]. A fertilized egg is a totipotent stem cell and as such can develop into any specialized cell of the organism. Only the zygote and the cells derived from the first few mitotic divisions after fertilization can differentiate into extra-embryonic tissues. Once the blastocyst stage is reached, the inner cell mass cells become pluripotent being able to differentiate into the three primary germ cell layers but not into extra-embryonic tissues [24]. Multipotent stem cells can differentiate in all the cell types of one particular lineage [25], for example, neural stem cells (NSCs) which can differentiate into neuronal cellular subtypes such as neurons, astrocytes, and oligodendrocytes [26]. Oligopotent stem cells can differentiate in a limited subset of cells of a specific tissue, for example, oligopotent stem cells have been identified in the pig cornea where they can differentiate into corneal and conjunctival cells [27]. Lastly, unipotent stem cells can self-renew and differentiate in only one subtype of cells for example the satellite cells of skeletal muscle [28]. As previously mentioned the potency of cells is strictly linked to their tissue of origins, with cells derived from early-stage embryos being the most potent, followed by pluripotent cells derived from later-stage embryos and multipotent, oligopotent, and unipotent cells derived from adult tissues. iPSCs represent an innovative class of stem cells obtained from somatic cells reprogrammed and de-differentiated through the expression of specific factors. In the following paragraphs, we will briefly discuss the various types of stem cells based on their origin (as shown in the scheme of Fig. 1) with particular attention to the potential applications and advantages/disadvantages of each type.

2.1. Embryonic, fetal, and umbilical cord-derived stem cells

Embryonic stem cells derived from the inner cell masses of mammalian blastocysts have longly been investigated both base studies of developmental biology and in regenerative medicine approaches. The main attraction of embryonic stem cells is associated to their ability to differentiate in cells of all three embryonic germ layers, which makes embryonic stem cells a very promising source of mature cells for transplant and regenerative medicine [29]. The main drawbacks connected to the use of embryonic stem cells are due to the ethical issues related to the obtainment of these cells and to the possibility of immune rejection and teratoma formation once implanted [29,30]. This phenomenon of teratoma formation has been linked to the presence of residual pluripotent stem cells in batches of mature cells obtained from the differentiation of embryonic stem cells [29]. To overcome these limitations other fetal sources of stem cells have been investigated such as umbilical cord blood, placenta, and amniotic fluid. Stem cells

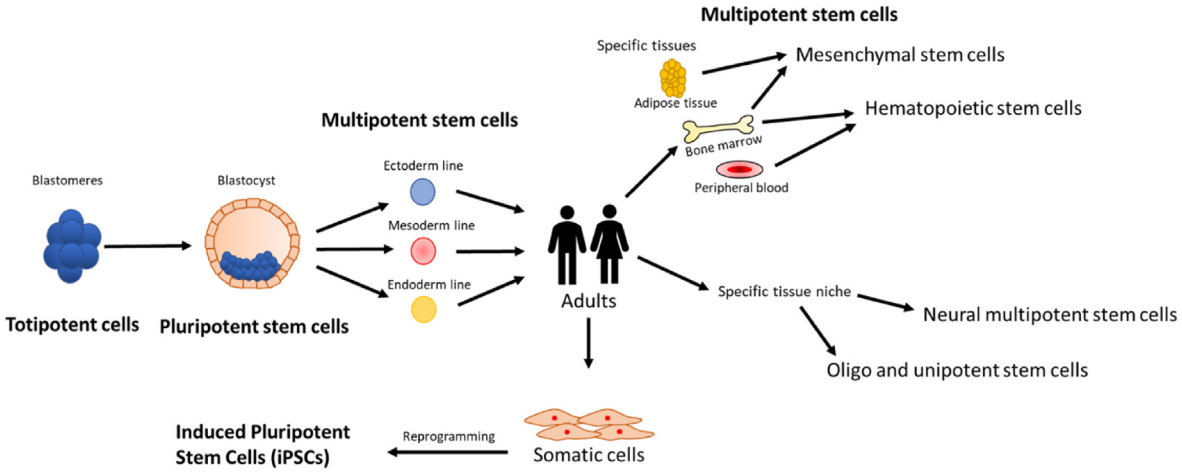

Fig. 1. A schematic representation of various sources of stem cells and their relative potency. From left to right, totipotent represent the earliest stage of embryo development and can differentiate in any cells (including extra-embryonic structures). With the successive development stages, the potency is gradually lost with totipotent cells becoming pluripotent (inner cells of the blastocyst), multipotent (cells derived from the three main embryo sheets), and unipotent (*e.g.*, germ line stem cells and epidermal stem cells). In adults, multipotent stem cells can still be found in different locations (adipose tissue, bone marrow, peripheral blood, central nervous system) and oligo/unipotent cells can be found in specific tissue niches. Adult somatic cells can be harvested and reprogrammed to express specific molecular markers to obtain iPSCs.

derived from fetal tissue have shown low immunogenic response and the ability to differentiate into a large variety of adult cells. Moreover, cells derived from amniotic fluid, placenta, and umbilical blood did not show significant induction of teratoma formation once transplanted to a recipient [29].

2.2. Adult stem cells

Adult stem cells have been recently identified in many adult tissues including bone marrow, adipose tissue, dental tissues, endometrium, skin, heart, liver, and brain [29,31]. Stem cells in adult tissues play a pivotal role in maintaining and repairing the homeostasis of tissues by replenishing mature cell types [29]. Stem cells resident in tissue can alternate between a quiescent or an activate proliferating and differentiating state depending on the signaling present in the surrounding microenvironment niche [29]. The main advantage of adult stem cells over embryonic stem cells is due to the relative lack of ethical issues connected to their use, and the possibility to employ these cells in autologous transplant-based approaches to overcoming some of the immune rejection problems related to the use of other stem cells types [29,32]. The main drawbacks related to the use of adult stem cells are mainly related to their potency, in particular, the differentiative possibilities of adult stem cells are limited by their tissue of origins and most adult stem cells are multipotent, being able to differentiate only into one lineage subset of adult cells [28,29,33]. Due to the differentiation limitations of adult stem cells, subsets of stem cells derived from specific tissues need to be harvested (mostly by surgical approach) for tissue-specific transplant approaches. *In vitro* culturing of adult stem cells is also fairly hard and complicated, with adult stem cells being limited in terms of proliferation rates when compared to embryonic stem cells [32]. Despite these drawbacks, adult stem cells are still a very promising tool being currently investigated in a large variety of potential clinical approaches including treatment of cardiovascular disease, injuries, degeneration of tissues, neurological disorders, liver diseases, lung disorders, and even diabetes [29,34–41]. As previously described, adult stem cells have a lower differentiation potency compared to embryonic stem cells (ESCs). In particular, adult stem cells are classified as multipotent or unipotent cells. A subclass of adult stem cells is represented by progenitor cells. Progenitors are a class of cells present in various organs, they are able to self-renew and differentiate. Their role is mainly associated with the repair of organs after injuries [42].

2.3. Induced pluripotent stem cells (iPSCs)

iPSCs are pluripotent cells derived from the differentiation of adult somatic cells. The procedure for the obtainment of iPSCs was first described by Kazutoshi Takahashi and Shinya Yamanaka in 2006 in a work where somatic mouse cells were re-programmed by forcing the expression of the transcription factors Oct4, Sox2, Klf4, and c-Myc [43,44]. In terms of differentiation potency iPSCs are comparable to embryonic stem cells, being pluripotent cells able to differentiate in any adult cells of the three main germ layers. However, iPSCs present several advantages over other embryonic stem cells: First of all iPSCs can be potentially obtained from adult tissues overcoming the ethical and methodological limitations posed by embryonic tissues. Moreover, iPSCs represent a very promising and unmatched tool for personalized medicine approaches. Despite the great potential of iPSCs, there are still several obstacles that need to be addressed concerning their potential clinical application. First of all, from a methodological point of view, the obtainment of iPSCs from somatic cells is a relatively slow process and with a high variability mainly due to the low reprogramming efficiency [44]. Then, iPSCs tend to accumulate mutations and genome instability compromising their differentiation and proliferation efficiency [44].

3. Nanoparticle-assisted active stimulation of stem cells

With the recent development of a new generation of stimuli-responsive active nanomaterials able to finely interact with cells and locally deliver physical and chemical cues, precise spatiotemporal control of stem cell behavior is now possible. In this section, the magnetic, photothermal, piezoelectric, and antioxidant nanomaterials used to modulate stem cell behavior (Fig. 2) have been described.

3.1. Magnetic nanomaterials

Magnetic nanomaterials are one of the main classes of nanomaterials currently used and studied as a tool to manipulate stem

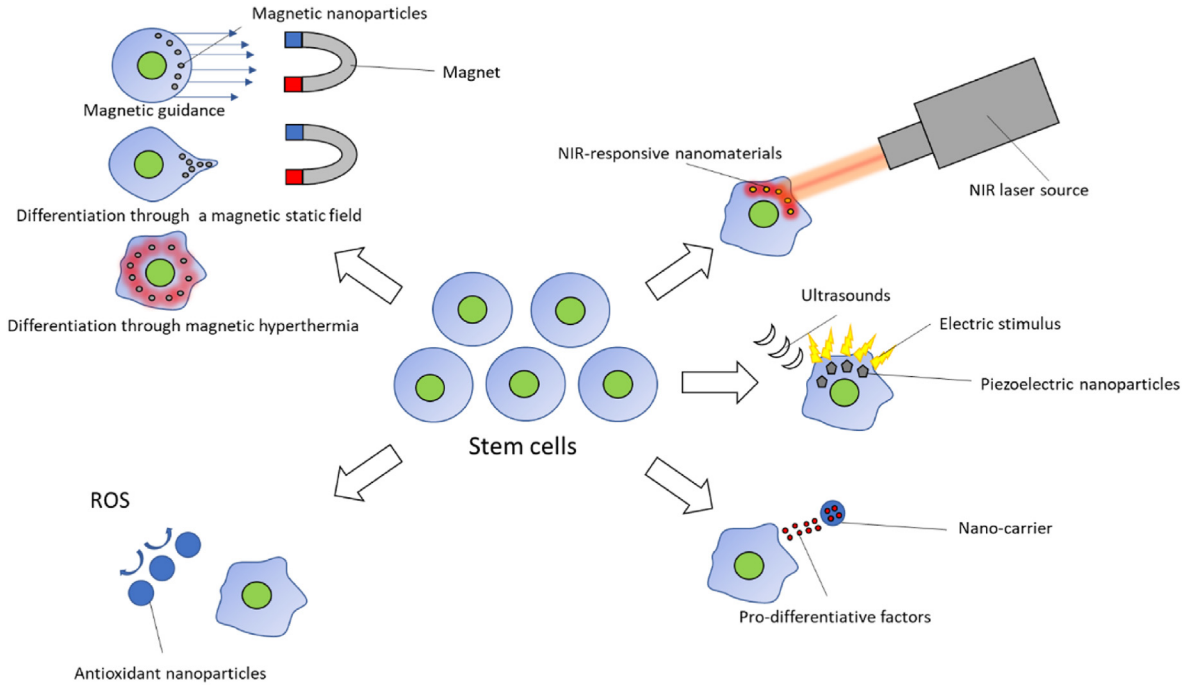

Fig. 2. The scheme summarizes the active nanomaterials-based approaches to control the differentiative fate of stem cells. From top left in clockwise order: stimulation through magnetic nanomaterials, photothermal activation with NIR-responsive nanostructures, local delivery of electrical cues through piezoelectric nanoparticles, use of nanomaterials as carriers of pro-differentiative factors and agents, and lastly antioxidant nanomaterials.

cells. In particular, thanks to the relatively high penetrability and lack of harmful effects, remote stimulation of magnetic nanomaterials through the application of a magnetic external field represents a very promising tool in the stem cells field. The applications of magnetic nanomaterials for stem cells manipulation can be classified into three main groups: 1) use of magnetic nanomaterials in conjunction with an external magnetic field to move stem cells and guide them in specific sites of interest; 2) use of magnetic nanomaterials in conjunction with a static magnetic field to control stem cell functions, in particular, their differentiation levels and fate; 3) use of an alternating magnetic field combined with magnetic nanoparticles to achieve localized hyperthermia effects and stimulate stem cells differentiation. Magnetic guidance of stem cells has been investigated as a delivery system to guide stem cells into damaged tissue for regenerative approaches [45]. For magnetic guidance, stem cells are usually treated with magnetic nanoparticles and then guided to the desired site through the application of an external magnetic field. In one such approach, MSCs were labeled with Fe_3O_4@polydopamine (PDA) nanoparticles and were guided through the application of an external magnetic field to the spinal cord of a rat model of sciatic nerve injury. The guided MSCs were able to reduce microglial and astrocyte activation and act on neuropathic pain with no evident adverse effects on other organs of the animals [45]. In a similar approach adipose-derived mesenchymal stem cells (AdMSCs) were treated with citric acid-coated superparamagnetic iron oxide nanoparticles (SPIONs) and guided to the sciatic nerve of an *in vivo* Wallerian degeneration model [46]. The guided cells showed regenerative processes, effects on remyelination processes, and effects on functional recovery [46]. Magnetic guidance of stem cells has been investigated also as a potential treatment for central nervous system disorders such as Alzheimer's disease [47], stroke [48], Parkinson's disease [49], and models of auditory cell damage [50]. The application of a static magnetic field has also been used to regulate the proliferation and differentiation of stem cells. For example, Li and colleagues demonstrate that the treatment of NSCs with SPIONs was able to promote cellular proliferation, while the combination of SPIONs with a static magnetic field had the opposite effects and inhibited NSCs expansion [51]. The combinatory effects of magnetic nanostructures and static magnetic fields seem to be cell-specific and highly dependent on the cellular state. For example, it has been shown that the treatment with magnetic nanoparticles and a static magnetic field of AdMSC can reduce senescence and induce chondrogenesis [52]. Lastly, the ability of SPIONs to induce heating when exposed to an alternating magnetic field has been exploited to control the differentiative fate of stem cells. In particular, Walker and colleagues developed a nanostructure composed of SPIONs coated with a thermo-responsive polymer (poly(N-isopropylacrylamide) (PNIPAM)) and functionalized with the WNT3a growth factor [53]. The developed nanostructures were tested upon MSCs. The authors were able to show that the Wnt3a conjugated to the nanostructures was inactive until the application of an alternating magnetic field. The application of an alternating magnetic field was able to induce an increment in temperature thanks to the presence of SPIONs and, consequently, trigger the Wnt3a release from the thermo-responsive coating. The released Wnt3a was then able to interact with MSCs and induce their proliferation. As commented by the authors this very promising approach could potentially be used in combination with other proteins and growth factors to finely tune the proliferation and differentiation fate of stem cells [53].

3.2. Photothermal nanotransducers

Another nanotechnology-based approach for inducing thermal stress and modulating differentiation of stem cells consists of the use of photothermal nanotransducers. Depending on the specific light wavelengths that such nanotransducers absorb and convert into heat, it is possible to distinguish nanomaterials operating in the visible/UV light and the near-infrared (NIR) ranges [54].

Compared to the visible/UV range, irradiation in the NIR (800−1700 nm), especially in the NIR-II (1000−1350 nm) and NIR-III biological windows (1500−1700 nm), is preferable for *in vivo* application due to the better penetrability through the biological tissues [55]. Nanomaterials for NIR photothermal conversions include gold nanoshells/nanorods/nanocages, carbon nanotubes, graphene nanostructures, iron oxide nanoparticles, upconversion nanoparticles, rare earth-based nanomaterials, organic dye-based nanoparticles, and polymeric nanostructures [56].

The cell response to a moderate heat shock (HS) treatment is known to increase the expression of HS proteins (hsp) with chaperone functions, which in turn activate protective mechanisms promoting survival, while excessive HS induces cell death. In NSCs and neural progenitors, the overexpression of *hsp* genes and the increase in reactive oxygen species (ROS) levels induced by moderate HS are associated with enhanced neural differentiation [57]. Hsp have an essential regulatory role during embryonic and postnatal neurodevelopment. As an example, the spatio-temporal expression of hsp27 correlates with neural differentiation [58]. However, it is important to specify as the upregulation of hsp27 expression is observed in human embryonic stem cell-derived differentiating motor neurons, while downregulation of this chaperone is reported during neural maturation [59]. In the literature, it has been demonstrated that not only hsp expression is modulated during neural differentiation, but also hsp regulates neural differentiation. A possible molecular cascade involved in the promotion of neural differentiation is triggered by the interactions of hsp27 with the protein kinase B, which in turn regulates cell growth and differentiation [58]. In addition to hsp and ROS, calcium waves and cell membrane depolarizations *via* capacitative currents may also be involved in the HS-induced neural differentiation mechanisms [60]. Concerning photothermal activation of neural differentiation, gold nanocage-coated surfaces were demonstrated to recreate a pro-differentiative environment for neural stem cells, with a significantly higher neural differentiation yield compared to the coated flat substrates (45% and 28% of post-mitotic neurons, respectively). Photothermal stimulation in the NIR induced the expression of 27, 70, and 90α hsp in cells, further promoted the neural differentiation efficiency (56% of post-mitotic neurons), and enhanced neuronal maturation in terms of dendrite sprouting with thermal dose-dependency. Gold nanocage photothermal stimulation also improved the functionality of the differentiated neurons, which exhibited action potentials and superior levels of Na^+ voltage-gated channels compared to controls [61].

As an alternative application, nanoparticle-assisted photothermal stimulation has been exploited for promoting MSC-based wound healing. In the work of Yao et al., ultrasmall CuS@BSA nanoparticles showing good photothermal conversion at 980 nm were used for the thermal treatment of MSCs to promote their differentiation into fibroblasts [62]. The regenerative mechanism was also tested *in vivo* in an injured wound model where the CuS@BSA-mediated thermal treatment was able to efficiently improve the closure of a wound. However, further details of the molecular mechanisms involved in photothermal-induced fibroblast differentiation remain to be explored.

Finally, magnetic photothermal nanoparticles have been recently exploited as a smart multifunctional nanotool to reprogram suspension cells, which are difficult to transfect by using nonviral vectors. Specifically, human peripheral blood mononuclear cells have been treated with iron oxide nanoparticle-decorated graphene oxide complexed with polyethylenimine and irradiated in the NIR to induce membrane permeabilization and enhanced their transfection with episomal plasmids for reprogramming [63]. Furthermore, the pre-treatment of the suspension cells with magnetic stirring and nanoparticles promoted the interface of the nano-complexes to the floating cells, therefore allowing efficient photothermal permeation of the cell membrane and enhanced internalization of the plasmids.

3.3. Piezoelectric nanomaterials

Electrical stimuli have been shown to have effects on the control of the differentiation fate of stem cells [64]. The proposed mechanism of action for this phenomenon involves the activation of voltage dependant membrane channels (such as Ca^{2+} voltage dependant channels), changes in cellular orientation, and cytoskeletal organization [65]. Piezoelectric nanomaterials represent a relatively innovative tool to achieve remote electrical stimulations of tissues and biological structures, thanks to their ability to transduce physical stimulation to an electrical signal. Deep physical stimulation of piezoelectric nanomaterials is commonly achieved through ultrasounds due to the high tissue penetrability of ultrasounds. Thanks to their properties, piezoelectric nanomaterials have been investigated to remotely control the differentiation potential and fate of stem cells. Ceramic piezoelectric nanomaterials such as barium titanate nanoparticles (BTNPs) represent one of the most investigated classes of piezoelectric nanostructures for stem cell-based approaches. For example, *Spirulina platensis* (*S. platensis*) derived magnetic and piezoelectric micromotors have been investigated as a tool to control the differentiative fate of NSCs. *S. platensis* is a well know microalgae commonly used in nutritional supplements and studied for its 3D helical structure. By coating *S. platensis* with superparamagnetic Fe_3O_4 nanoparticles and piezoelectric BTNPs Liu and colleagues were able to obtain a helical-shaped micromotor with magnetic and piezoelectric properties [66,67]. The helical shape combined with the magnetic properties granted the authors the possibility to finely control the micromotors' movements utilizing a rotating magnetic field, while the piezoelectric properties of BTNPs were used to convert an ultrasound physical stimulation into an electrical stimulus [66]. In particular, by tuning the applied ultrasounds stimulus the authors were able to control the differentiative fate of NSCs towards astrocytes, different types of neurons, or oligodendrocytes [66]. In another work randomly orientated poly-(l-lactic acid) (PLLA) fibrous scaffolds doped with BTNPs were investigated to stimulate osteogenic differentiation. As commented by the authors, the combination of the random orientation of the fiber composing the scaffold with the electric properties of BTNPs stimulate the early osteogenic differentiation of bone marrow-derived mesenchymal stem cells (BM-MSCs), making these scaffold a promising candidate for tissue engineering approaches [68]. It is worth mentioning that BTNPs seem to have pro-differentiative effects even without ultrasound stimulation, for example in a work from our group we demonstrated how glycol-chitosan-coated BTNPs were well tolerated by rat MSCs and were able to induce a pro-osteogenic differentiation highlighted by an increment in hydroxyapatite deposition [69]. Nylon-11 piezoelectric nanoparticles have also been for the remote stimulation of stem cell differentiation. In particular, it has been shown that nylon-11 piezoelectric nanoparticles (size around 50 nm) can be internalized by e dental pulp stem cells (DPSCs), and ultrasound stimulation of DPSCs cells treated with nylon-11 cells can induce osteogenic differentiation thanks to the piezoelectric properties of the nanomaterial [70]. Lastly, a novel approach based on the combination of magnetostrictive nanostructures, piezoelectric materials, and graphene oxide has been proposed for the design of magnetoelectric nanocomposite able to stimulate hMSC differentiation. In particular, Esmaeili et al. proposed a scaffold composed of graphene oxide (GO) magnetostrictive $CoFe_2O_4$ nanoparticles (CFO), and the piezoelectric polymer polyvinylidene difluoride (PVDF) for culturing and differentiating hMSCs. The

obtained nanocomposite was able to transduce a magnetic stimulation exerted through an external field into a physical deformation of the scaffold caused by the presence of CFO nanoparticles. The generated physical deformation was then transduced into a localized electric charge by PVDF, that in turn was able to stimulate the neural differentiation of MSCs growth on the scaffold [71].

3.4. Antioxidant nanomaterials

Reactive oxygen species (ROS) are of pivotal importance for several physiological functions including stem cell differentiation processes. The equilibrium between ROS production and scavenging activity of antioxidant moieties seems to be at the base of several stem cells related processes, such as in the modulation of NSCs differentiation fate [72]. Therefore nanostructures with promising antioxidant properties have been studied and employed as a tool to control the proliferation and differentiation fate of stem cells. For example, commercially available selenium nanoparticles (5−50 nm in diameter) were used to reduce ROS production in human embryonic stem cells and induce differentiation. In particular, the balance change in ROS production caused by the treatment with selenium nanoparticles induced osteogenic differentiation with an increment in JNK and FOXO3a expression, increment of mineralization, and inhibition of adipogenic differentiation [73]. In another example, antioxidant lycopene nanostructures demonstrate different effects on stem cells depending on the cell culture media used for the culture procedure. In particular, poly lactic-co-glycolic acid nanoparticles loaded with lycopene showed the ability to enhance osteoblast differentiation in rat BM-MSCs cultured in osteogenic media, but they also inhibited adipocyte differentiation of the same cells when administrated in an adipogenic media [74]. Similarly, gold nanostructures functionalized with PEG and 2,2,6,6-tetramethylpiperidine-N-oxyl (Au-PEG-TEMPO NPs, 40 nm in diameter) have been investigated as tools to reduce ROS in stem cells and guide their differentiation fate. In particular, Au-PEG-TEMPO-NPs showed the ability to reduce ROS in human MSCs and promote their differentiation towards osteogenic fate [75]. Slightly different results were obtained using astaxanthin-encapsulated polymeric micelles (average size 112.3 ± 16.6 nm) as antioxidant agents in hMSCs. In the case of astaxanthin-loaded nanostructures, the treatment of human MSCs and the consequent reduction of ROS enhanced the osteogenic, chondrogenic, and adipogenic differentiation when combined with the appropriate medium [76]. Cerium oxide nanoparticles (nanoceria) have also been proposed as an antioxidant tool to control stem cell differentiation, for example in a work from our group we demonstrated how the treatment of MSCs with nanoceria was able to reduce adipogenesis, suggesting the potential of cerium oxide nanoparticles as an anti-obesity tool [77]. However, it has also been reported that nanoceria treatment can reduce the differentiation levels of neural progenitor cells (C17.2 murine cell line), by acting both on molecular pathways involved in neuronal differentiation and cytoskeletal organization [78].

4. Non-viral nanovectors and nanocarriers for cell fate regulation

The field of tissue engineering and regenerative medicine can be benefited from the efficient delivery of active biomolecules capable of modulating the behavior of stem cells intracellularly. Considering the intrinsic susceptibility of these molecules to undergo protease- and nuclease-induced degradation, the use of nanovehicles that can protect the integrity of the encapsulated/entrapped biomolecules while ensuring that they reach their target site in their active form is of vital importance. These nanovehicles can be further engineered to promote their internalization by the target cells/organs *via* functionalization with targeting motifs (*e.g.*, antibodies, aptamers, cell-penetrating peptides) on their surface [79] or by tuning their physico-chemical and morphological properties (*e.g.*, size, surface charge, shape, stiffness). Moreover, their small size and morphology at the nanoscale can be exploited to promote their passive accumulation in tumors through the enhanced permeation and retention (EPR) effect [80].

The delivery of genetic material is of particular importance in this context considering its potential to modulate cellular functions by replacing, silencing, or promoting the expression of specific genes. Viral vectors (*e.g.*, adeno-associated virus (AAVs), lentivirus (LVs)) have been traditionally considered for the delivery of genetic material to a plethora of cell lines, thanks to their high transfection efficiency. However, the use of viral vectors raises concerns regarding their safety and immunogenicity in humans, which hampers their clinical translation. Moreover, the development of viral vectors is associated with time-consuming and costly protocols that further limit their use as a biological tool for the development of novel clinical and investigational therapies [81]. Physical approaches, including, among others, electroporation, hydrodynamic injection, and microinjection, have been also regularly used for delivering genetic material into cells. However, they still represent suboptimal approaches for the safe and efficient delivery of genetic material both *in vitro* and *in vivo* [82]. For example, electroporation, which relies on the transient permeabilization of the cell membrane by means of an applied electrical field, can have detrimental effects on cell viability. Besides, electroporation cannot be applied to selectively deliver the genetic material to specific cell types from a heterogeneous pool due to its lack of specificity, thus requiring a preliminary cell purification process.

For all these reasons, the development of non-viral nanovectors and nanocarriers has attracted a great deal of attention in this field. In principle, non-viral approaches represent a better alternative in terms of safety and require a more facile formulation. Ideally, nanovectors and nanocarriers should protect the encapsulated genetic material (e.g., DNA or RNA) or biomolecules (*e.g.*, growth factor) from degradation/denaturation, while facilitating the cellular uptake and subsequent release at the target subcellular compartment (e.g., cytosol, nucleus) [83]. Despite some solutions are already available in the market (*e.g.*, lipofectamine, polyethylenimine (PEI)), their transfection efficiencies are remarkably lower than their viral counterparts. Therefore, inorganic, polymeric, and lipid-like nanostructures with improved transfection efficiencies and lower toxicity with respect to commercial delivery systems are continuously under investigation [81,84].

The property of inorganic nanomaterials to passively promote the differentiation of stem cells to a specific cell lineage has been reviewed elsewhere [85,86]. Herein, their capacity to act as carriers of genetic material and biomolecules and modulate cellular functions will be highlighted. As an example, mesoporous silica nanoparticles (MSNs) were used to deliver hepatocyte nuclear factor 3β (HNF3β) plasmid DNA (pDNA) to induce the differentiation of iPSCs into hepatocyte-like cells with mature functions [87]. The synthesized MSNs had a size of about 150 nm and a positive surface charge thanks to the presence of quaternary ammonium groups on their surface. This facilitated the uptake of the nanoparticles by an endocytic pathway without causing any cytotoxic effect on iPSCs at concentrations up to 200 μg/ml and without disturbing their stemness. Other promising inorganic nanomaterials that have shown high transfection efficiencies and low cytotoxicity are those based on calcium carbonate (*e.g.*, amorphous calcium carbonate -ACC- spheres, and vaterite nanoparticles) [88,89]. Their therapeutic potential was demonstrated by forming a complex between

ACC and small interfering RNA (siRNA) targeting the amplified in breast cancer 1 (AIB1). The resulting nanoparticles were able to attenuate tumor growth both *in vitro* and *in vivo*, and represent a promising approach for gene delivery [88], that can be adopted also for stem cell modification. Similarly, carbon-based materials such as graphene, carbon nanotubes, and carbon dots (CDs) have shown improved efficiencies and lower cytotoxicity than commercially available lipofectamine and PEI. For this reason, they have been considered for gene delivery applications in "hard-to-transfect" stem cells and for cell reprogramming [90–92]. For example, graphene oxide-PEI (GO-PEI) complexes were used as mRNA delivery nanovehicles for iPSCs production without the need for repetitive daily transfection due to mRNA degradation [91]. The GO-PEI-RNA complexes showed improved stability against RNase treatment and, more importantly, allowed reprogramming iPSCs while excluding the risk of genomic integration and insertional mutagenesis associated with DNA-based approaches. These "footprint-free" iPSCs could accordingly pave the way toward their safe clinical use. In a different example, CDs of small size (<10 nm), spherical shape, uniform distribution, and positive surface charge were used as non-viral gene delivery vehicles to induce the neuronal differentiation of ectodermal MSCs (EMSCs) [92]. The synthesized CDs showed an excellent capacity in condensing pDNA encoding Ascl1, Brn2, and Sox2, and demonstrated higher transfection efficiency than PEI and lipofectamine with very low cytotoxicity. According to the morphological and PCR analysis, CDs were able to efficiently induce a neuron-like morphology and expression of neuronal markers (Tuj1, Map2, and Tau) in EMSCs.

A wide variety of polymer-based delivery vehicles have been designed to act as nanovectors and nanocarriers for active biomolecules. The polymeric nanoparticles based on poly(β-amino esters), a family of polymers that undergo hydrolytic degradation, have been successfully used to induce the overexpression of vascular endothelial growth factor (VEGF) in hMSCs and human embryonic stem cell-derived cells (hESdCs) [93]. After subcutaneous implantation of the transfected cells, angiogenesis was significantly promoted in mice, showing higher vessel density as well as reduced muscle degeneration and tissue fibrosis compared to cells transfected with lipofectamine. Dendrimers have been also studied for the delivery of active biomolecules. In this regard, amine-terminated high molecular weight dendrimers (e.g., poly(amidoamine) (PAMAM)) shows high transfection efficiencies but are usually cytotoxic. Thus, several strategies have been proposed to overcome the scarce biocompatibility, including the modification of low molecular weight dendrimers with hydrophobic chains to create self-assembled dendrimers [83] or grafting natural-based and biocompatible polymers to obtain novel architectures [94,95]. The latter approach was followed to engineer nanoparticles based on carboxymethylchitosan-modified PAMAM that were subsequently used to intracellularly deliver dexamethasone to rat bone marrow stromal cells to induce osteogenic differentiation [95]. More sophisticated polymer-based nanocarriers and nanovectors, such as the layer-by-layer (LbL) capsules, polymersomes, and bioengineered nanoparticles have been designed to provide a more efficient and safer delivery platform. The LbL approach relies on the sequential deposition of building blocks on colloidal nano- or microparticles that act as a template. This method is highly versatile and allows the fabrication of polymer-based capsules and particles with multiple functionalities [96]. In this method, the active biomolecules, including genetic material, can be loaded either in the cavity or in the multilayer membrane. Polymer nanoparticles fabricated via the LbL methodology were successfully used to silence B-cell lymphoma 2 (BCL-2) in lymphoma and leukemia cells, hampering the proliferation of blood cancer cells both *in vitro* and *in vivo* [97]. LbL carriers have been also investigated to modulate the response of stem cells (*e.g.*, iPSCs and embryonic stem cells) with promising results in terms of biocompatibility, cell uptake, and cell differentiation both *in vitro* and *in vivo* [98,99]. Polymersomes, which can be considered the synthetic alternative to liposomes, are also potential candidates as polymer-based non-viral carriers. Recent advances in polymer chemistry allow now the design of smart polymersomes with a heterogeneous membrane that can be exploited to encapsulate and release genetic material (*e.g.*, siRNA and pDNA) in response to temperature and pH changes [100]. These dually gated polymersomes were able to efficiently transfect cells *in vitro* and *in vivo* with a green fluorescent protein (GFP)-encoding plasmid. Another example highlighting the enormous potential of polymeric materials to deliver genetic material into different cell types was reported by Moffett et al. [101]. In their bioengineered approach, polymeric nanoparticles were carefully designed to include surface-anchored targeting ligands to promote receptor-mediated endocytosis, a polyglutamic acid coating to avoid off-target binding, and a biodegradable core based on poly(β-amino ester) to condense and protect the cargo (*i.e.*, nucleic acids). These nanoparticles have been exploited in three different scenarios: *i*) to knock-out target genes in anti-cancer T-cells, *ii*) to enhance the self-renewal properties in hematopoietic stem cells, and *iii*) to improve the antitumor activity of T-cells by mRNA transfection. It is expected from the aforementioned examples that the field of non-viral nanovehicles will provide safer and more efficient nanovectors and nanocarriers in the near future that could overcome the limitations of the currently available solutions.

5. Nanoparticles for tracking stem cells after transplant

5.1. Magnetic resonance imaging (MRI)

MRI is a non-invasive imaging modality allowing the three-dimensional visualization of various body tissues and organs using a strong magnetic field and tunable radio frequencies. The energy released from the water protons is finally detected by specialized MRI sensors to reconstruct the image [102,103]. Concerning stem cells, MRI offers a non-invasive, real-time, and high-resolution monitoring of cell location and migration after being administered to the body. To increase the imaging contrast and improve stem cell tracking, various nanoagents in the form of nanocomplexes or nanoparticles have been used. These nanoagents can be categorized as superparamagnetic contrast agents like SPIONs, paramagnetic contrast agents like gadolinium complexes or manganese nanoparticles, chemical exchange saturation transfer (CEST) agents like lanthanide complexes, and non-proton contrast agents like Fluorine-19 (^{19}F) [104,105].

In the following sections, we will describe, through some examples of the various reported studies of the last five years, the role of these nanoagents in stem cell tracking. Additional literature extended to a time frame longer than five years can be found in the works of Ma et al. [105] and Huang et al. [106].

Iron oxide-based nanoagents, specifically SPIONs, are the nanoagents that have been used the most in MRI, along with Gadolinium (Gd). Their tunable size, geometry, biocompatible character, and cell labeling efficiency make them an attractive option for stem cell dynamic monitoring. However, not all SPIONs present biocompatibility and high labeling efficiency. In fact, some of the produced SPIONs can be potentially toxic, present low labeling efficiency or low contrast enhancement, and/or may affect the properties (self-renewal and multi-differentiation) of the tracked stem cells. To overcome these limitations, most of the synthesized SPIONs are surface modified or coated with other materials like polymers. For example, Liao et al. used polydopamine to coat SPION clusters (SPIONs cluster@PDA) and subsequently

label ADSCs [107]. Their work showed that the SPIONs cluster@PDA-labeled ADSCs could accumulate to an injured liver after intravenous tail injection and repair it. Additionally, using an excisional skin wound mouse model, they could show that this accumulation could be enhanced with an external magnetic field. Polyglucose sorbitol carboxymethyl ether (PSC) [108] is another polymer used as a coating for SPIONs and subsequent cell tracking. In this study, Jiang et al. used PSC-SPIONs to label BM-MSCs and demonstrated that these cells reversed lung fibrosis *in vivo* by targeting endothelial-mesenchymal transition. Furthermore, they showed that the PSC-SPION-labeled BM-MSCs could be tracked in the lungs for 14 days. In another study, Gu et al. modified the surface of SPIONs using a self-assembled lipopeptide containing the neurite-promoting laminin ligand, IKVAV (Ile-Lys-Val-Ala-Val). It was shown that the peptide-modified SPIONs improved cell labeling, boosted the negative enhancement, and prolonged the T2 relaxation rate *in vivo* [109].

Gd-based nanocomplexes or nanoparticles have been robustly used as T1-contrast agents. Compared to T2-contrast agents like SPIONs, they generate a bright, positive signal, making them capable of distinguishing low intrinsic signals deriving from tissues [106]. Gd-based nanoagents are composed of gadolinium ions (Gd^{+3}) and a chelating agent, usually diethylenetriamine pentaacetic acid (DTPA). However, these complexes demonstrate low targeting ability towards MSCs and low labeling efficiency resulting in low MRI signals. As in the case of SPIONs, Gd-based nanoagents are modified to overcome these restraints. For example, Cai et al. used melanin-based Gd^{+3} nanoparticles to label bone MSCs showing shorter T1 relaxation time, higher stability, better cell-labeling efficiency, and lower cytotoxicity compared to the commercial Gd-DTPA. Moreover, the nanoparticles could be tracked up to four weeks after intramuscular administration. It should be noted that the size of the gadolinium complex affects the signal intensity with higher intensities deriving from the larger complexes, such as Gd hexanedione NPs [110], Gd-conjugated peptide dendrimers [111], polyethylene imine-conjugated Gd-DTPA [112] and Gd-hyaluronic acid [113].

An alternative approach to T1-weighted Gd-based contrast nanoagents is the Manganese (Mn)-based ones. Mn, in the form of Manganese Chloride, is already a Food and Drug Administration (FDA)-approved contrast agent. Compared to Gd, Mn is a naturally occurring element inside the body, making it more 'biocompatible' compared to Gd. Moreover, Mn has been robustly used as an MRI contrast agent for various diseases [114,115]. Nevertheless, the works reporting its use in stem cell tracking are limited. In one of these reported works, Venter et al. fabricated a manganese porphyrin-based nanoagent modified with an amine for enhanced cellular uptake. The Mn-based nanoagent demonstrated enhanced relaxation properties compared to clinically-used Gd-based ones and improved cell labeling of endothelial stem cells. Its localization was also studied and found to accumulate in the nucleus and the boundaries among cells [116].

CEST functionality is based on the chemical exchange of protons between the endogenous and exogenous (nanoagents) compounds and water molecules, leading to a buildup of magnetic saturation in the water and subsequent imaging through the nanoagent water signals [117,118]. One of the main advantages of the CEST approach is the imaging of different cell populations through their labeling with different CEST nanoagents [119]. Recently, Yuan et al. detected *in vivo* label-free MSCs through the overexpressed high-mannose N-linked glycans on the surface of these MSCs, demonstrating that using reporter genes of exogenous agents is unnecessary [120]. Additionally, the authors showed a higher intensity of CEST signal *in vivo* than *in vitro,* which they attributed to the reduced expression of mannose under the *in vitro* conditions.

The last category of nanoagent used in MRI is the non-proton ones. These nanoagents containing heteronuclei such as ^{13}C, ^{23}Na, ^{31}P, and ^{19}F can also be detected through MRI. However, the high concentrations needed limit their use [121]. Among these nanoagents, ^{19}F compounds show improved biocompatibility and ability to provide quantifiable data. Considering this, Quang et al. developed a nanoagent consisting of a perfluorooctylbromide (PFOB) core and a poly (lactic-co-glycolic acid) (PLGA) shell subsequently coated by polystyrene sulfonate (PSS) (Fig. 3). The nanoagent was successfully uptaken by hMSCs through a caveolae-mediated mechanism without affecting their differentiation and proliferation capabilities. Additionally, the increased fluorine concentrations inside the hMSCs resulted in tracking these MSCs *in vitro* and *in vivo* [122].

5.2. Magnetic particle imaging (MPI)

MPI is a low-irradiation imaging modality with a high spatiotemporal resolution, no tissue background noise, and high sensitivity, allowing quantification of the tracer from the nanomolar to the picomolar range. MPI is a relatively new technique based on the magnetic properties of SPIONs under an oscillating magnetic field [103,123,124]. Because MPI is an emerging technology, the number of studies in stem cell tracking is limited. In one of these studies, Zheng et al. showed real-time monitoring of SPIONs-labeled hMSCs after *in vivo* administration and compared this trafficking to plain SPIONs (Resovist). The data showed that the injected MSCs were entrapped in the lung tissue and cleared to the liver within 24 h. The plain SPIONs were uptaken directly by the liver and spleen. Monitoring of the labeled MSCs was possible for up to 12 days, whereas the plain SPION clearance from the liver was 4.6 days [125].

SPION size and geometry are important to MRI and MPI since these characteristics affect their properties as contrast agents. Acknowledging the limitations of the current SPION tracers, Wang et al. fabricated a series of different SPIONs and studied their behavior as MPI contrast agents. According to the results, a cubic SPION with an edge length of 22 nm (CION-22) was the best candidate for cellular uptake and sensitivity since even at an extremely low concentration (30 cells/μL) of CIONs-22-labeled BMSCs, their detection by MPI *in vitro* was achieved. Using a hindlimb ischemia mouse model, the authors showed that monitoring a very low number of cells (~2500 cells) was also possible *in vivo* regardless of tissue depth [126]. One more study that showed the high sensitivity and strong potential of MPI, especially compared to ^{19}F MRI, was performed by Sehl and Foster [127]. In this comparative study, the authors could detect 64 times fewer MSCs with MPI than ^{19}F MRI (4000 *vs.* 256,000 MSCs), demonstrating MPI superiority. Nevertheless, these limits were higher *in vivo,* and one of the reasons was the probable dispersion of cells after intravenous administration into mice.

5.3. Photoacoustic imaging (PA)

PA is an imaging modality that detects ultrasonic waves generated by biological tissues due to their thermoelastic expansion after irradiation with non-ionizing laser pulses. This combination of light and ultrasound results in improved imaging depth and high spatiotemporal resolution, especially compared to optical imaging. Additionally, PA can detect light-absorbing biological components like lipids, hemoglobin, and water, rendering it a suitable technique for *in vivo* imaging. Notably, the use of exogenous contrast agents, with strong NIR absorption, like indocyanine green (ICG) [128,129] and Prussian blue [130] or nanostructures like gold [131–134], silica [135], and polymeric [136], enhances the imaging contrast,

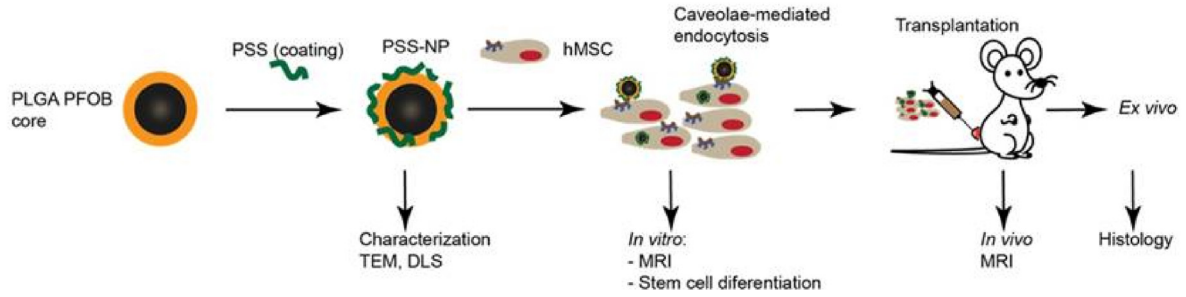

Fig. 3. Experimental workflow showing nanoparticle formulation, uptake, and *in vitro* and *in vivo* studies. PLGA nanoparticles containing PFOB were coated with PSS to form PSS-NPs. The PSS-NPs were internalized by immortalized hMSC *via* caveolae-mediated endocytosis. Cellular proliferation and osteogenic differentiation were tested after the cells were labeled with PSS-NPs. The sensitivity of PSS-NPs in labeled cells was assessed both *in vitro* and *in vivo*. Reproduced with permission by Quang et al. [122], under the terms of the Creative Commons Attribution (CC BY-NC) license.

allowing for advanced applications such as tracking of stem cells. Nevertheless, it should be stressed that each one of the dyes mentioned above or nanostructures presents its advantages and disadvantages.

For example, although ICG is an FDA-approved dye for imaging, its poor aqueous stability and photobleaching limit its use, especially in stem cell tracking. To overcome these limitations, ICG could be encapsulated in a delivery vehicle such as a liposome [129] or silica nanoparticles [137], enhancing its PA imaging abilities like this. Similarly, Prussian blue insolubility in water hinders its use as a PA imaging agent. However, using Prussian blue in nanoformulations like poly-L-lysine nanocomplexes (PB-PLL) or nanocubes [138] overcomes this limitation by increasing the colloidal stability of the formulations and the uptake by MSCs, resulting in better imaging. In fact, Kim et al. showed that the 50 nm PB-PLL nanocomplexes have high sensitivity since the detection limit of the labeled hMSCs *in vivo* was 200 cells/μL. This study also showed that the PA signal is proportional to the cell number, allowing for the quantification of hMSCs after transplantation [130].

Gold nanostructures are one of the contrast agents that have been mostly used in PA. Whether as nanoparticles [132–134] or nanorods [131], these 'biocompatible' nanostructures have proven very efficient for PA imaging, considering their stability and long-term tracking. Gold has been used to label various MSCs in diseases such as glaucoma [133] or the spinal cord [132]. In the former case, Kubelick and his group showed that it is possible for the real-time monitoring of gold-labeled MSCs in the anterior eye, whereas in the latter case, Donelly et al. were able to visualize signals from as few as 1000 cells and quantify the volume of the injected cells (Fig. 4).

Although gold labeling enhances the PA imaging performance, labeling stem cells using gold nanostructures may take up to 24 h, limiting their availability in emergencies. Thus, Laffey et al. decided to study if gold-labeled MSCs can withstand freezing and long-term storage and how these conditions could affect these labeled MSCs [134]. Their study showed that the labeled MSCs were not affected in terms of viability and differentiation ability and that the PA signals and signatures were not lost, suggesting that long-term storage of labeled MSCs is feasible. Another important thing in stem cell therapies, except tracking, is monitoring stem cell health and functions after their *in vivo* administration. Dhada et al. labeled MSCs using gold nanorods coated with a reactive oxygen species (ROS) sensitive near-infrared dye to answer this question [131]. This combination allowed real-time monitoring of the stem cell location through gold PA imaging and viability by comparing the signal between the ROS-sensitive dye and the gold. Except for gold, silica is another inorganic material with strong potential in PA imaging either by itself or in combination with gold [139], ICG [137], or any other contrast agent. In the work of Chen et al. [140] used mesoporous silica nanoparticles to monitor stem cells. They found that the discoidal shape of the nanoparticles can enhance their echogenicity. Additionally, the amine groups on the surface of these nanoparticles increase their affinity for MSCs due to charge-dependent interactions. Even though gold and silica have been proven to be strong contrast agents in PA imaging, they are still limited by tissue accumulation-related toxicity and the narrow

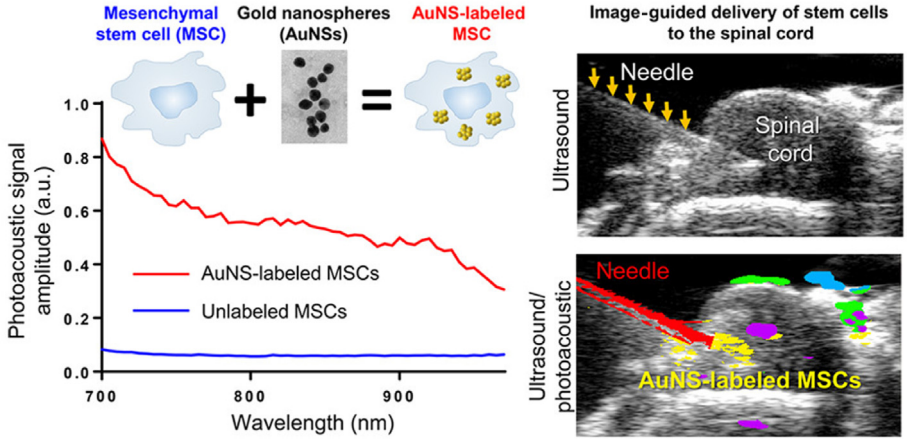

Fig. 4. Photoacoustic imaging of plasmonic gold nanospheres (AuNS)-labeled MSCs (left). Ultrasound images show the advancement of the 33G steel needle into the ventral portion of the spinal cord. Yellow arrows highlight the needle shaft (right). Reproduced with permission by Donelly et al. [132].

range of excitation wavelengths, focused on the first NIR window (NIR-I), which limits their application depth. To overcome these hindrances, Yin et al. [136], used an organic semiconductive polymer (OSP) capable of absorbing in the second NIR window (NIR-II). The OSP demonstrated enhanced cellular uptake that led to highly efficient labeling which consequently resulted in superior performance in deep tissue imaging (40.6- and 21.7-fold enhancement for subcutaneous and brain imaging) compare to unlabeled hMSCs.

5.4. Computed tomography (CT)/single-photon emission computed tomography (SPECT)

CT and SPECT are two more imaging techniques that have been used for tracking stem cells. CT is a robust medical imaging technique that provides anatomical images based on the different contrast deriving from various body tissues after their X-Ray irradiation. However, when it comes to cell tracking, contrast agents like gold nanoparticles [141–143] are used to improve the overall signal [144] (Fig. 5). Although CT has been proven useful for anatomical imaging, its use in cell tracking is inhibited by the high concentration of the contrast agent needed for the *in vivo* tracking, which may lead to toxicity issues. On the other hand, chemical elements that emit radiation, i.e., radionuclides, are used for SPECT. Although a low concentration of these radionuclides is used, there is still the danger of toxic side effects. Moreover, the currently used tracers, such as ^{99m}Tc, has a half-life of 6 h rendering the long-term monitoring of stem cells impractical. A thorough discussion on the use of CT and SPECT in cell tracking can be found in the recent work of Gawne et al. [144].

5.5. Fluorescence imaging

Fluorescence imaging (FLI) is a non-invasive imaging technique widely used in the biomedical field. Its low cost, high spatial resolution, easiness of use, and ability to provide quantifiable data make this technique a necessary tool for imaging biological tissues. However, the limited tissue penetration, especially for fluorescent molecules absorbing in the visible light and NIR-I window (700–900 nm), inhibits its wide use *in vivo*. Several fluorescent agents could be used in FLI, including organic dyes, endogenous biomolecules, and proteins. Nevertheless, the low cellular uptake, the poor chemical stability, and the photobleaching effect limit their use in applications such as stem cell tracking [145]. To address these limitations, innovative fluorescent nanoparticles have been

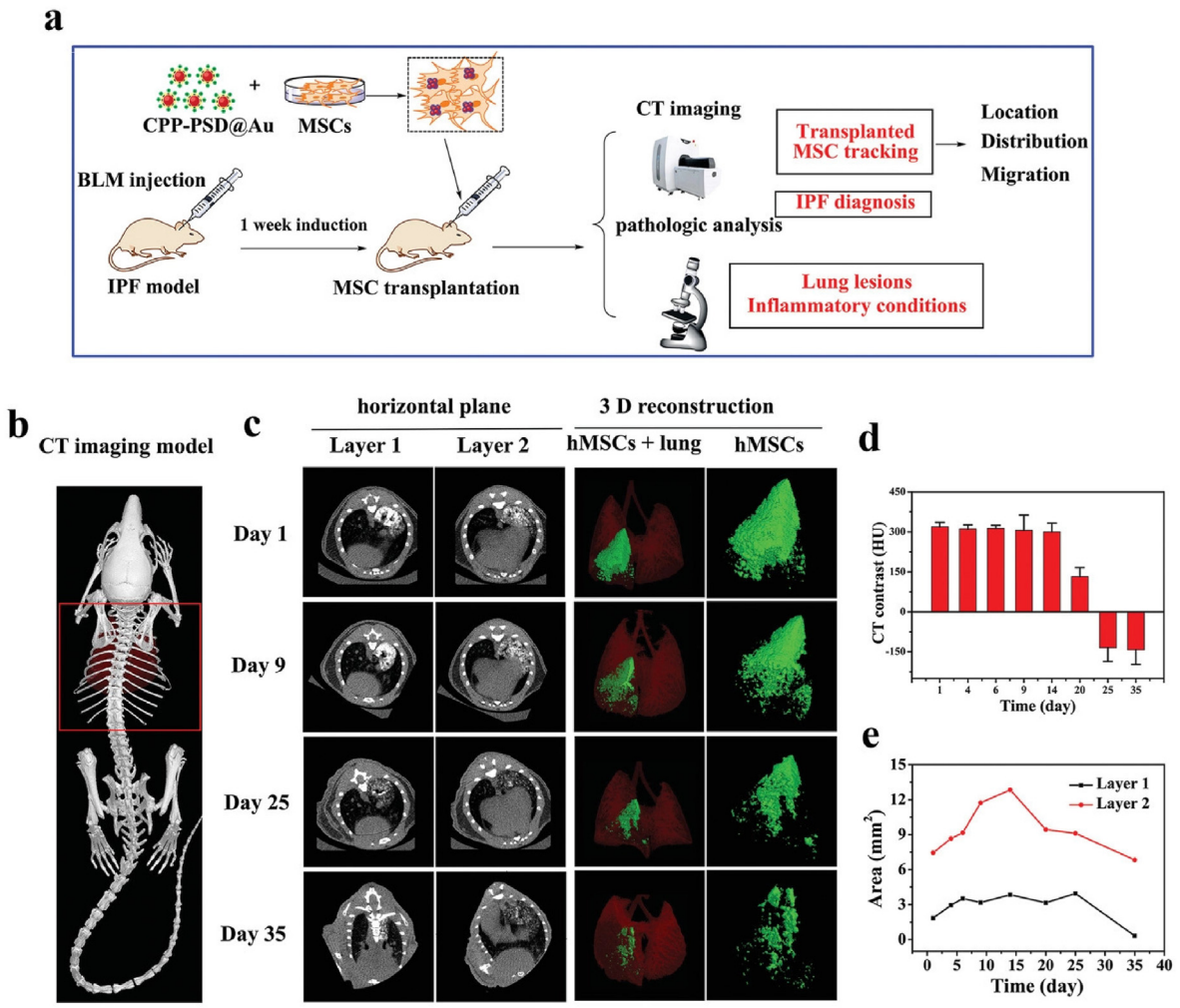

Fig. 5. a) The experimental protocol of MSC tracking in the mouse model of idiopathic pulmonary fibrosis (IPF). b) In vivo CT image of the healthy C57BL/6 mouse and its lung (red rectangle box). c) In vivo CT images of the labeled MSCs in a horizontal plane at 1 day, 9, 25, and 35 days post-transplantation (blue area represents the transplanted MSCs), and their relevant 3D reconstruction images (red: lung, green: the transplanted MSCs). d) CT values of the labeled MSCs after transplantation into the lung at different time points. e) Plot of CT signal distribution area of the labeled MSCs as a function of the transplantation time. Reproduced with permission by Yu et al. [141].

developed. Compared to the aforementioned fluorescent approaches, nanoparticles offer controlled and enhanced cellular uptake, higher stability in the harsh *in vivo* environment, and protection from the photobleaching effect. Additionally, the development of fluorescent probes capable of absorbing in the NIR-II window (1000–1700 nm) allows deeper detection in the tissues while reducing the autofluorescence from neighboring tissues, rendering FLI suitable for stem cell tracking [145,146].

Among the several types of nanoparticles, quantum dots (QDs) [147–151] (Fig. 6) have been extensively used for stem cell tracking due to desirable properties like narrow emission and broad absorption wavelengths, large molar extinction coefficient, size-dependent color ability, and high stability against photobleaching. Nevertheless, QDs are far from perfect as labeling molecules. Their inherent hydrophobicity and toxicity should be carefully considered, especially in biomedical applications. To address the former challenge, various coatings like polyethylene glycol [150,152] or β-cyclodextrin [148] have been applied to enhance the hydrophilic character of these luminescent molecules. Additionally, to reduce the cytotoxicity that derives mostly from the use of heavy metals [149,150], either coatings like those previously mentioned or alternative approaches like the use of carbon [151] and graphene [152] QDs have been proposed. To overcome the QDs limitations mentioned above, organic nanoparticles, either in the form of organic dots [153], fluorescent molecule-loaded nanoparticles [154], or fluorescent conjugates [155], have also been studied. Besides the various QDs and carbon-based fluorescent nanoparticles, upconversion nanoparticles (UCNPs) based on lanthanide-doped nanocrystals have also been used [7,156–158]. Due to their sensitivity in the NIR light, UCNPs can be detected deeper in the tissues compared to other FLI nanoagents such as their organic counterparts. An interesting category of nanoparticles that have also been reported for stem cell tracking is the nanoparticles whose fluorescence depends on their aggregation state. When non-aggregated, these nanoparticles are non-emissive. However, they strongly emit when they are aggregated. Exploiting this property, tracking various cell types such as BM-MSCs [159], and neural progenitor cells [160], but also $D4^{+}$ T cells and macrophages [161] is possible.

5.6. Multimodal imaging

Each one of the single-imaging modalities mentioned above demonstrates various limitations that hinder their clinical use, especially when it comes to stem cell tracking. The limited amount of information acquired using one of these modalities is insufficient for the complex preclinical and clinical scenarios, rendering single imaging insufficient for the current medical needs. To address this challenge, nanoagents with multimodal imaging modalities like the one presented in Fig. 7 have been developed. The multi-imaging modality can derive from various combinations such as CT/bioluminescence [162,163], CT/fluorescence [164], and CT/PET [165], MRI/fluorescence [166], photoacoustic/photoluminescence [167], CT/MRI/Fluorescence [158], MRI/Fluorescence/bioluminescence [168], MRI/Photoluminescence/X-Ray [169], and CT/MRI/Photoluminescence [7], resulting in a more efficient tracking, through enhanced spatiotemporal sensitivity, lower cell detection limit, and more precise quantifiable data.

6. Nanostructured surfaces for manipulating stem cell behavior

The physicochemical interactions of the stem cells with the extracellular environment are crucial for self-renewal, proliferation, and differentiation. The mechanotransductive cues of nanoscale topography are demonstrated to control different cell

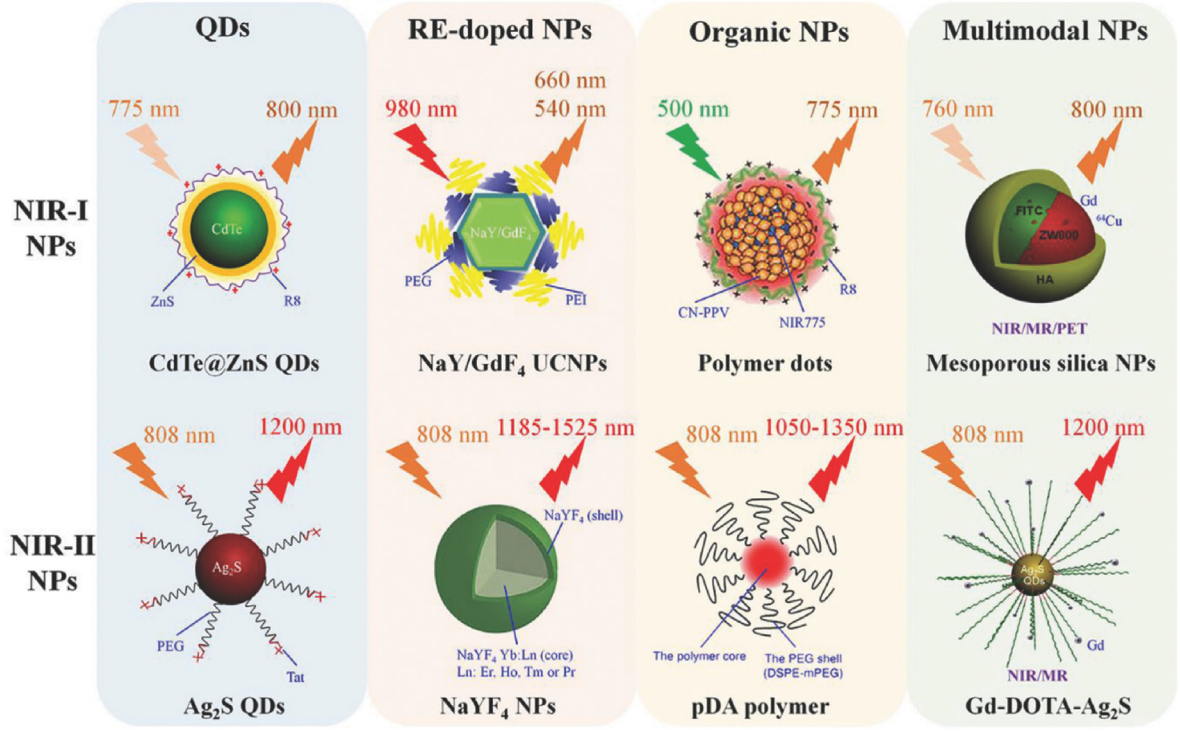

Fig. 6. The structure and excitation/emission properties of representing nanoparticles (NPs) with excitation or emission in the first (NIR-I, 700–900 nm) or second (NIR-II, 1000–1700 nm) near-infrared window. Near-infrared quantum dots (CdTe@ZnS QDs, and Ag_2S QDs), rare-earth (RE)-doped NPs, organic fluorescent NPs, and multimodal NPs can be used for tracking transplanted stem cell research. Reproduced with permission from Chen et al. [146].

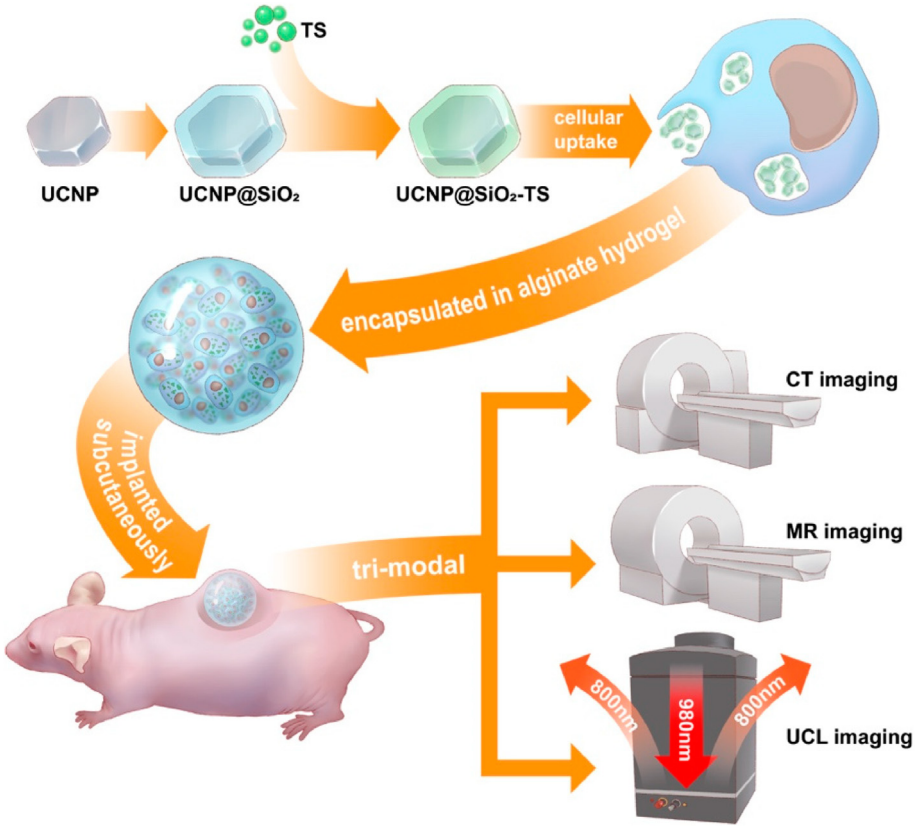

Fig. 7. *In vivo* multimodal imaging of cartilage-derived stem/progenitor cells using upconversion nanoparticles. Reproduced by Chen et al., under the Creative Commons Attribution License.

functions, such as cytoskeleton organization, morphology, migration, polarization, adhesion, proliferation, and differentiation [170]. In this Section, the most interesting and innovative examples of substrates tailored at the nanoscale for the control of stem cell behavior are presented and discussed.

The term stem cell niche was referred for the first time to the microenvironment of hematopoietic stem cells, which undergo asymmetric division and progeny differentiation when transplanted *in vivo* externally to that specific microenvironment [171]. Subsequently, many other niches were found, such as those of germline stem cells (GSCs), NSCs, MSCs, muscle satellite cells, and CSCs. The biochemical and nanotopographical cues of the extracellular matrix (ECM) in the stem cell niche enable the maintenance of the pluri/multi-potency state of the stem cell progeny. For this reason, research was aimed at characterizing and mimicking the ECM of the stem cell niche for preserving the stemness of passaged cells during *in vitro* expansion [172]. In this regard, histologic analysis and scanning electron microscopy (SEM) imaging allowed the characterization of different stem cell niches. As an example, the ECM ultrastructure of the cornea epithelial basement membrane shows porous ultrastructure, with a pore size of about 90 nm [173]. Instead, the basement membranes associated with the aortic cells display a complex nanotopography characterized by bumps, ridges, pits, and grooves [170]. As the last example, ECM generated by bone marrow MSCs is a dense meshwork of filamentous and granular nanomaterial [174]. However, the knowledge in this field is still limited due to the complexity of the behavioral responses of stem cells as well as the technological constraints of the micro/nano-fabrication techniques. In general, the ECM of the stem cell niches has a hierarchical ultrastructure and, therefore, its faithful reproduction *in vitro* represents a technological challenge. Some fabrication approaches based on chemistry-based treatments have been designed to obtain randomly rough self-affine (*i.e.*, fractal) surfaces resembling the hierarchical organization of the ECM [175]. These investigations showed as the fractal dimension represents an optimal descriptor of substrate topography for cell biology studies, modulating adhesion, proliferation, and differentiation. Briefly, substrates with sharp and densely packed peaks induce proliferation whereas more regular ridges promote adhesion [175]. Also, our group exploited advanced photolithography techniques (*i.e.*, two-photon lithography, 2pp) to fabricate highly reproducible surfaces characterized by predetermined fractal dimension and roughness at the nanoscale, with significant differences in MSC adhesion, cytoskeleton conformation, and cellular stiffness (a biomechanic indicator of the MSC differentiation toward osteogenic, adipogenic and chondrogenic fates) [176].

Furthermore, deterministic surface nanotopographies modulate stem cell behavior. An example of spatially organized deterministic topographies typically used for modulating stem cell behavior is represented by the nanopillars. Modulation of their aspect ratio or spatial frequency alters cell adhesion and cell-cell interface, with consequences on self-renewal and differentiation fate. For example, arrays of nanopillars with relatively small diameters (in the range of 120–170 nm) promote the organization of hESCs into more compact colonies compared to those with larger diameters (170–360 nm) and facilitate their expansion in the undifferentiated state without any feeder layer [177]. The mechanotransduction pathway triggered by the small diameter nanopillar substrates involves the formation of numerous focal adhesions and reorganization of the cytoskeleton, with the development of more efficient E-cadherin intercellular adhesions and highly dense cell colonies. The modulation of the nanopillar aspect ratio is used to modify the

stiffness of the substrate. Soft scaffolds are obtained by using tall nanopillars and hard ones with short nanopillars. The substrate rigidity can be tuned for promoting the differentiation of the stem cells toward specific cell types [178,179]. In the case of pluripotent human embryonic stem cells, arrays of tall nanopillars (*i.e.*, soft substrate) induce their differentiation into endoderm cells. However, to further advance the differentiation into pancreatic endoderm, the use of short nanopillars (*i.e.*, hard substrate) is required, therefore demonstrating a change in the mechanical requirements throughout the different differentiation steps [180]. In this regard, the commitment of MSCs to cardiomyocytes can be also enhanced by using arrays of Ti nanopillars [181]. A recent example of deterministic surfaces exploited to improve the differentiation of human iPSCs into neurons was described by Urrutia-Cabrera et al. [182]. The substrates were patterned with densely packed binary colloidal crystals (BCCs) of silica and polystyrene. The surface topography-based mechanotransduction approach was combined with the CRISPR activation (CRISPRa) platform that induces neuronal differentiation within a short period of culture (7 days) through activation of the proneural NEUROD1 transcription factor. In this work, BCC-based surface patterning enhanced the generation of βIII-tubulin$^+$ post-mitotic neurons, neurite outgrowth, and ramification. However, the tuning of the silica and polystyrene particle size induced different effects on neuronal differentiation and neurite outgrowth/branching. Specifically, BCCs characterized by 100 nm polystyrene nanoparticles on 5 μm silica microparticles showed the best performances in terms of neurite outgrowth and arborization sprouting, while BCCs with 2 μm silica and 65 nm polystyrene particles had remarkable effects regarding neuronal enrichment (percentage of βIII-tubulin$^+$ post-mitotic neurons). Despite the molecular mechanisms at the base of mechanotransduction still require further elucidations, the cited literature works highlight the stem cell need for specific mechanical and topographical cues in different stages of molecular differentiation and morphological maturation. A well-known mechanotransduction mechanism inducing stem cell differentiation involves the use of aligned nano-grooves or nano-ridges with consequent effects on cell polarization and alterations in chromatin condensation and gene expression [183]. In the recent work of Liu et al., polycaprolactone substrates with aligned nanogrooves promoted the formation of numerous focal adhesions and activation of the RhoA/ROCK signaling, leading to an increase of the myosin-based intracellular force, a decrease in chromatin condensation, and a promotion of the osteogenic differentiation of MSCs [184]. Specifically, the increase in both mRNA expression of early and late osteogenic markers, alkaline phosphatase (ALP) activity, and calcium deposition was observed in the nanostructured substrates compared to the flat polycaprolactone surfaces. Interestingly, polycaprolactone substrates with micro-grooves were able to induce cell polarization but not the development of focal adhesion and intracellular forces. Eventually, these micropatterned substrates were not able to affect chromatin condensation levels and induce osteogenic differentiation.

Most innovative nanotechnology tools involve dynamic elements for remote modulation of adhesion, mechanotransduction, and differentiation of stem cells. In this regard, a pioneering work by Hong et al. focused on the design of smart nano-assembled magnetic screens with different sizes over RGD peptide-presenting gold nanoparticles to produce nanogaps between the magnetic screens and RGDs [185]. The size of nanogaps could be modulated by using a magnetic field. The presence of a big gap induced integrin clustering, focal adhesion assembly, and stem cell differentiation. In contrast, the small gap reduced both stem cell adhesion and differentiation. Interestingly, the remote control of the nanogaps was effective in regulating stem cell mechanotransduction also *in vivo*. Furthermore, a recent trend in this field contemplates the integration of mechanobiology with other chemical and physical cues, such as electric stimulations, to further improve differentiation efficiency [186]. As an interesting example, titanium dioxide nanocone/bismuth oxide nanodot heterojunctions with an intrinsic electric field at the nanoscale interface and the typical stiffness of bone tissue were used to increase the adhesion and osteodifferentiation of bone marrow MSCs [187]. The authors of this work also demonstrated that bone implants with nanodot heterojunctions on their surface promoted osteogenesis and osseointegration *in vivo*. The mechanism was mediated by yes-associated protein and phosphatidylinositol 3-kinase pathways. Finally, the improvements in substrate nanoengineering, as well as their integration in stimuli-responsive 3D cell culture systems for mimicking *in vivo* conditions, microfluidic devices for the dynamic control of the biochemical microenvironment, and sophisticated genetic platforms for the fine control of gene expression will consent to faithfully recreate *in vitro* the complex physicochemical conditions of the different stem cell niches as well as the stimuli required for their differentiation in mature cells.

7. Summary

Nanotechnology provides unprecedented tools for the control of the biological functions at cellular and sub-cellular level. In this Review, we described how stem cell-based therapies can benefit from nanomedicine, by achieving drug delivery and targeting, tracking capabilities, and modulation of the cellular fate, the latter in particular with the aid of “smart” nanotransducers. While tissue engineering and regenerative medicine represent the main focus of the efforts on nanomaterials/stem cell interaction research, nanotechnology can open important and clinically-relevant perspectives also in other fields of nanomedicine; it is worth mentioning, as an example, applications in cancer therapy and in particular on cancer stem cells, the targeting, and manipulation of which through nanoplatforms could represent a fundamental step in the treatment of cancer recurrence and metastasis.

Credit author statement

Attilio Marino: Writing Abstract, Section 1, 3.5, and 6; Draft Correction; Manuscript Revision. Matteo Battaglini.: Writing Section 2, 3.1, 3.2, 3.3, and 3.4; Manuscript Revision. Christos Tapeinos: Writing Section 5. Aitor Larrañaga: Writing Section 4. Gianni Ciofani: Supervision; Literature Analysis; Writing Summary; Draft Correction.

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.

References

[1] F. Gattazzo, A. Urciuolo, P. Bonaldo, Extracellular matrix: a dynamic microenvironment for stem cell niche, Biochim. Biophys. Acta 1840 (2014) 2506–2519, https://doi.org/10.1016/J.BBAGEN.2014.01.010.
[2] F. Fernandes, P. Kotharkar, A. Chakravorty, M. Kowshik, I. Talukdar, Nanocarrier mediated siRNA delivery targeting stem cell differentiation, Curr. Stem Cell Res. Ther. 15 (2020) 155–172, https://doi.org/10.2174/1574888X14666191202095041.
[3] A. Gupta, S. Singh, Potential role of growth factors controlled release in achieving enhanced neuronal trans-differentiation from mesenchymal stem cells for neural tissue repair and regeneration, Mol. Neurobiol. 59 (2022) 983–1001, https://doi.org/10.1007/S12035-021-02646-W.
[4] J.H. Lee, N. Mandakhbayar, A. El-Fiqi, H.W. Kim, Intracellular co-delivery of Sr ion and phenamil drug through mesoporous bioglass nanocarriers

synergizes BMP signaling and tissue mineralization, Acta Biomater. 60 (2017) 93–108, https://doi.org/10.1016/J.ACTBIO.2017.07.021.
[5] G.G. Genchi, A. Marino, A. Grillone, I. Pezzini, G. Ciofani, Remote control of cellular functions: the role of smart nanomaterials in the medicine of the future, Adv. Healthc. Mater. 6 (2017), https://doi.org/10.1002/adhm.201700002.
[6] L.C.Y. Lee, N. Gadegaard, M.C. de Andrés, L.A. Turner, K.V. Burgess, S.J. Yarwood, J. Wells, M. Salmeron-Sanchez, D. Meek, R.O.C. Oreffo, M.J. Dalby, Nanotopography controls cell cycle changes involved with skeletal stem cell self-renewal and multipotency, Biomaterials 116 (2017) 10–20, https://doi.org/10.1016/J.BIOMATERIALS.2016.11.032.
[7] C.H. Chen, N. Tang, K. Xue, H.Z. Zhang, Y.H. Chen, P. Xu, K. Sun, K. Tao, K. Liu, Long-term tri-modal in vivo tracking of engrafted cartilage-derived stem/progenitor cells based on upconversion nanoparticles, Biomolecules 11 (2021), https://doi.org/10.3390/BIOM11070958.
[8] X. Cao, W. Deng, R. Qu, Q. Yu, J. Li, Y. Yang, Y. Cao, X. Gao, X. Xu, J. Yu, Non-viral Co-delivery of the four Yamanaka factors for generation of human induced pluripotent stem cells via calcium phosphate nanocomposite particles, Adv. Funct. Mater. 23 (2013) 5403–5411, https://doi.org/10.1002/ADFM.201203646.
[9] M.H. Lee, C.C. Lin, J.L. Thomas, J.A. Li, H.Y. Lin, Cellular reprogramming with multigene activation by the delivery of CRISPR/dCas9 ribonucleoproteins via magnetic peptide-imprinted chitosan nanoparticles, Mater. Today Bio. 9 (2021), 100091, https://doi.org/10.1016/J.MTBIO.2020.100091.
[10] X. Meng, A. Zhou, Y. Huang, Y. Zhang, Y. Xu, K. Shao, X. Ning, N-cadherin nanoantagonist driven mesenchymal-to-epithelial transition in fibroblasts for improving reprogramming efficiency, Nano Lett. 21 (2021) 5540–5546, https://doi.org/10.1021/acs.nanolett.1c00880.
[11] Z.S. Badieyan, T. Evans, Concise review: application of chemically modified mRNA in cell fate conversion and tissue engineering, Stem Cells Transl. Med. 8 (2019) 833–843, https://doi.org/10.1002/SCTM.18-0259.
[12] E.R. Balmayor, J.P. Geiger, M.K. Aneja, T. Berezhanskyy, M. Utzinger, O. Mykhaylyk, C. Rudolph, C. Plank, Chemically modified RNA induces osteogenesis of stem cells and human tissue explants as well as accelerates bone healing in rats, Biomaterials 87 (2016) 131–146, https://doi.org/10.1016/J.BIOMATERIALS.2016.02.018.
[13] J. Li, W.Y.W. Lee, T. Wu, J. Xu, K. Zhang, D.S. Hong Wong, R. Li, G. Li, L. Bian, Near-infrared light-triggered release of small molecules for controlled differentiation and long-term tracking of stem cells in vivo using upconversion nanoparticles, Biomaterials 110 (2016) 1–10, https://doi.org/10.1016/J.BIOMATERIALS.2016.09.011.
[14] B. Yu, B. Dong, J. He, H. Huang, J. Huang, Y. Wang, J. Liang, J. Zhang, Y. Qiu, J. Shen, X. Shuai, J. Tao, W. Xia, Bimodal imaging-visible nanomedicine integrating CXCR4 and VEGFa genes directs synergistic reendothelialization of endothelial progenitor cells, Adv. Sci. 7 (2020), 2001657, https://doi.org/10.1002/ADVS.202001657.
[15] G.G. Genchi, A. Marino, A. Grillone, I. Pezzini, G. Ciofani, Remote control of cellular functions: the role of smart nanomaterials in the medicine of the future, Adv. Healthc. Mater. 6 (2017), https://doi.org/10.1002/adhm.201700002.
[16] M.J. Dalby, N. Gadegaard, R.O.C. Oreffo, Harnessing nanotopography and integrin-matrix interactions to influence stem cell fate, Nat. Mater. 13 (2014) 558–569, https://doi.org/10.1038/NMAT3980.
[17] H. Favreau, L. Pijnenburg, J. Seitlinger, F. Fioretti, L. Keller, D. Scipioni, H. Adriaensen, S. Kuchler-Bopp, M. Ehlinger, D. Mainard, P. Rosset, G. Hua, L. Gentile, N. Benkirane-Jessel, Osteochondral repair combining therapeutics implant with mesenchymal stem cells spheroids, Nanomedicine 29 (2020), https://doi.org/10.1016/J.NANO.2020.102253.
[18] Q. Li, Z. Wang, Involvement of FAK/P38 signaling pathways in mediating the enhanced osteogenesis induced by nano-graphene oxide modification on titanium implant surface, Int. J. Nanomed. 15 (2020) 4659, https://doi.org/10.2147/IJN.S245608.
[19] L. Bacakova, J. Zarubova, M. Travnickova, J. Musilkova, J. Pajorova, P. Slepicka, N.S. Kasalkova, V. Svorcik, Z. Kolska, H. Motarjemi, M. Molitor, Stem cells: their source, potency and use in regenerative therapies with focus on adipose-derived stem cells - a review, Biotechnol. Adv. 36 (2018) 1111–1126, https://doi.org/10.1016/j.biotechadv.2018.03.011.
[20] X. Zhou, L. Yuan, C. Wu, C. chen, G. Luo, J. Deng, Z. Mao, Recent review of the effect of nanomaterials on stem cells, RSC Adv. 8 (2018) 17656–17676, https://doi.org/10.1039/C8RA02424C.
[21] L. Walcher, A.-K. Kistenmacher, H. Suo, R. Kitte, S. Dluczek, A. Strauß, A.-R. Blaudszun, T. Yevsa, S. Fricke, U. Kossatz-Boehlert, Cancer stem cells—origins and biomarkers: perspectives for targeted personalized therapies, Front. Immunol. 11 (2020), https://doi.org/10.3389/fimmu.2020.01280.
[22] V.K. Singh, A. Saini, M. Kalsan, N. Kumar, R. Chandra, Describing the stem cell potency: the various methods of functional assessment and in silico diagnostics, Front. Cell Dev. Biol. 4 (2016), https://doi.org/10.3389/fcell.2016.00134.
[23] Y. Xu, J. Zhao, Y. Ren, X. Wang, Y. Lyu, B. Xie, Y. Sun, X. Yuan, H. Liu, W. Yang, Y. Fu, Y. Yu, Y. Liu, R. Mu, C. Li, J. Xu, H. Deng, Derivation of totipotent-like stem cells with blastocyst-like structure forming potential, Cell Res. 32 (2022) 513–529, https://doi.org/10.1038/s41422-022-00668-0.
[24] A.R. Riveiro, J.M. Brickman, From Pluripotency to Totipotency: an Experimentalist's Guide to Cellular Potency, vol. 147, Development, 2020, https://doi.org/10.1242/DEV.189845/223002.
[25] A. Sobhani, N. Khanlarkhani, M. Baazm, F. Mohammadzadeh, A. Najafi, S. Mehdinejadiani, F. Sargolzaei Aval, Multipotent stem cell and current application, Acta Med. Iran. 55 (2017) 6–23.
[26] N.L. Kennea, H. Mehmet, Neural stem cells, J. Pathol. 197 (2002) 536–550, https://doi.org/10.1002/path.1189.
[27] F. Majo, A. Rochat, M. Nicolas, G.A. Jaoudé, Y. Barrandon, Oligopotent stem cells are distributed throughout the mammalian ocular surface, Nature 456 (2008) 250–254, https://doi.org/10.1038/nature07406.
[28] J. Dulak, K. Szade, A. Szade, W. Nowak, A. Józkowicz, Adult stem cells: hopes and hypes of regenerative medicine, Acta Biochim. Pol. 62 (2015) 329–337, https://doi.org/10.18388/abp.2015_1023.
[29] M. Mimeault, R. Hauke, S.K. Batra, Stem cells: a revolution in therapeutics-recent advances in stem cell biology and their therapeutic applications in regenerative medicine and cancer therapies, Clin. Pharmacol. Ther. 82 (2007) 252–264, https://doi.org/10.1038/sj.clpt.6100301.
[30] D.C. Wu, A.S. Boyd, K.J. Wood, Embryonic stem cell transplantation: potential applicability in cell replacement therapy and regenerative medicine, Front. Biosci. 12 (2007) 4525–4535, https://doi.org/10.2741/2407.
[31] D. Macrin, J.P. Joseph, A.A. Pillai, A. Devi, Eminent sources of adult mesenchymal stem cells and their therapeutic imminence, Stem Cell Rev. Reports. 13 (2017) 741–756, https://doi.org/10.1007/s12015-017-9759-8.
[32] J. Czyz, C. Wiese, A. Rolletschek, P. Blyszczuk, M. Cross, A.M. Wobus, Potential of embryonic and adult stem cells in vitro, Biol. Chem. 384 (2003) 1391–1409, https://doi.org/10.1515/BC.2003.155.
[33] S.C. Bozdağ, M.K. Yüksel, T. Demirer, Adult stem cells and medicine, Adv. Exp. Med. Biol. 1079 (2018) 17–36, https://doi.org/10.1007/5584_2018_184.
[34] S. Oh, R.P. Witek, S. Bae, D. Zheng, Y. Jung, A.C. Piscaglia, B.E. Petersen, Bone marrow–derived hepatic oval cells differentiate into hepatocytes in 2-acetylaminofluorene/partial hepatectomy–induced liver regeneration, Gastroenterology 132 (2007) 1077–1087, https://doi.org/10.1053/j.gastro.2007.01.001.
[35] H. Ilgun, J.W. Kim, L. Luo, Adult stem cells and diabetes therapy, J. Stem Cell Res. Transplant. 2 (2015).
[36] P.K. Nguyen, J.-W. Rhee, J.C. Wu, Adult stem cell therapy and heart failure, 2000 to 2016: a systematic review, JAMA Cardiol 1 (2016) 831–841, https://doi.org/10.1001/jamacardio.2016.2225.
[37] X. Yang, Y. Meng, Z. Han, F. Ye, L. Wei, C. Zong, Mesenchymal stem cell therapy for liver disease: full of chances and challenges, Cell Biosci. 10 (2020) 123, https://doi.org/10.1186/s13578-020-00480-6.
[38] K.A.A. Schilders, E. Eenjes, S. van Riet, A.A. Poot, D. Stamatialis, R. Truckenmüller, P.S. Hiemstra, R.J. Rottier, Regeneration of the lung: lung stem cells and the development of lung mimicking devices, Respir. Res. 17 (2016) 44, https://doi.org/10.1186/s12931-016-0358-z.
[39] A. Ul Hassan, G. Hassan, Z. Rasool, Role of stem cells in treatment of neurological disorder, Int. J. Health Sci. 3 (2009) 227–233.
[40] V.R. Dasari, K.K. Veeravalli, D.H. Dinh, Mesenchymal stem cells in the treatment of spinal cord injuries: a review, World J. Stem Cell. 6 (2014) 120–133, https://doi.org/10.4252/wjsc.v6.i2.120.
[41] M. Wang, Z. Yuan, N. Ma, C. Hao, W. Guo, G. Zou, Y. Zhang, M. Chen, S. Gao, J. Peng, A. Wang, Y. Wang, X. Sui, W. Xu, S. Lu, S. Liu, Q. Guo, Advances and prospects in stem cells for cartilage regeneration, Stem Cell. Int. (2017), 4130607, https://doi.org/10.1155/2017/4130607, 2017.
[42] J. Huang, Y. Kong, C. Xie, L. Zhou, Stem/progenitor cell in kidney: characteristics, homing, coordination, and maintenance, Stem Cell Res. Ther. 121 (2021) 1–18, https://doi.org/10.1186/S13287-021-02266-0, 12 (2021).
[43] K. Okita, T. Ichisaka, S. Yamanaka, Generation of germline-competent induced pluripotent stem cells, Nature 448 (2007) 313–317, https://doi.org/10.1038/nature05934.
[44] J. Bragança, J.A. Lopes, L. Mendes-Silva, J.M. Almeida Santos, Induced pluripotent stem cells, a giant leap for mankind therapeutic applications, World J. Stem Cell. 11 (2019) 421–430, https://doi.org/10.4252/wjsc.v11.i7.421.
[45] J.J. Liu M, W. Yu, F. Zhang, T. Liu, K. Li, M. Lin, Y. Wang, G. Zhao, Fe3O4@Polydopamine-Labeled MSCs targeting the spinal cord to treat neuropathic pain under the guidance of a magnetic field, Int. J. Nanomed. 16 (2021) 3275–3292, https://doi.org/10.2147/IJN.S296398.
[46] P.A. Soto, M. Vence, G.M. Piñero, D.F. Coral, V. Usach, D. Muraca, A. Cueto, A. Roig, M.B.F. van Raap, C.P. Setton-Avruj, Sciatic nerve regeneration after traumatic injury using magnetic targeted adipose-derived mesenchymal stem cells, Acta Biomater. 130 (2021) 234–247, https://doi.org/10.1016/j.actbio.2021.05.050.
[47] Y. Wang, J. Jiang, X. Fu, J. Zhang, J. Song, Y. Wang, L. Duan, P. Shao, X. Xu, L. Zeng, F. Zhang, Fe3O4@polydopamine nanoparticle-loaded human umbilical cord mesenchymal stem cells improve the cognitive function in Alzheimer's disease mice by promoting hippocampal neurogenesis, Nanomed. Nanotechnol. Biol. Med. 40 (2022), 102507, https://doi.org/10.1016/j.nano.2021.102507.
[48] P. García-Belda, H. Prima-García, A. Aliena-Valero, M. Castelló-Ruiz, M.J. Ulloa-Navas, A. Ten-Esteve, L. Martí-Bonmatí, J.B. Salom, J.M. García-Verdugo, S. Gil-Perotín, Intravenous SPION-labeled adipocyte-derived stem cells targeted to the brain by magnetic attraction in a rat stroke model: an ultrastructural insight into cell fate within the brain, Nanomedicine 39 (2022), 102464, https://doi.org/10.1016/j.nano.2021.102464.
[49] S. Simorgh, Z. Bagher, M. Farhadi, S.K. Kamrava, M.E. Boroujeni, Z. Namjoo,

F.Q. Hour, S. Moradi, R. Alizadeh, Magnetic targeting of human olfactory mucosa stem cells following intranasal administration: a novel approach to Parkinson's disease treatment, Mol. Neurobiol. 58 (2021) 3835–3847, https://doi.org/10.1007/s12035-021-02392-z.
[50] Y.J. Ahn, W.S. Yun, J.S. Choi, W.C. Kim, S.H. Lee, D.J. Park, J.E. Park, J. Key, Y.J. Seo, Biodistribution of poly clustered superparamagnetic iron oxide nanoparticle labeled mesenchymal stem cells in aminoglycoside induced ototoxic mouse model, Biomed. Eng. Lett. 11 (2021) 39–53, https://doi.org/10.1007/s13534-020-00181-6.
[51] D. Li, Y. Hu, H. Wei, W. Chen, Y. Liu, X. Yan, L. Guo, M. Liao, B. Chen, R. Chai, M. Tang, Superparamagnetic iron oxide nanoparticles and static magnetic field regulate neural stem cell proliferation, Front. Cell. Neurosci. 15 (2021), 815280, https://doi.org/10.3389/fncel.2021.815280.
[52] L. Labusca, D.-D. Herea, A. Emanuela Minuti, C. Stavila, C. Danceanu, P. Plamadeala, H. Chiriac, N. Lupu, Magnetic nanoparticles and magnetic field exposure enhances chondrogenesis of human adipose derived mesenchymal stem cells but not of wharton jelly mesenchymal stem cells, Front. Bioeng. Biotechnol. 9 (2021), https://doi.org/10.3389/fbioe.2021.737132.
[53] M. Walker, I. Will, A. Pratt, V. Chechik, P. Genever, D. Ungar, Magnetically triggered release of entrapped bioactive proteins from thermally responsive polymer-coated iron oxide nanoparticles for stem-cell proliferation, ACS Appl. Nano Mater. 3 (2020) 5008–5013, https://doi.org/10.1021/acsanm.0c01167.
[54] W. Li, G. Zhang, L. Liu, Near-infrared inorganic nanomaterials for precise diagnosis and therapy, Front. Bioeng. Biotechnol. 9 (2021), https://doi.org/10.3389/FBIOE.2021.768927.
[55] D. An, J. Fu, B. Zhang, N. Xie, G. Nie, H. Ågren, M. Qiu, H. Zhang, D. An, J. Fu, B. Zhang, N. Xie, G. Nie, H. Zhang, H. Ågren, M. Qiu, NIR-II responsive inorganic 2D nanomaterials for cancer photothermal therapy: recent advances and future challenges, Adv. Funct. Mater. 31 (2021), 2101625, https://doi.org/10.1002/ADFM.202101625.
[56] H. Sun, Q. Zhang, J. Li, S. Peng, X. Wang, R. Cai, Near-infrared photoactivated nanomedicines for photothermal synergistic cancer therapy, Nano Today 37 (2021), 101073, https://doi.org/10.1016/J.NANTOD.2020.101073.
[57] M.E. Hossain, K. Matsuzaki, M. Katakura, N. Sugimoto, A. Al Mamun, R. Islam, M. Hashimoto, O. Shido, Direct exposure to mild heat promotes proliferation and neuronal differentiation of neural stem/progenitor cells in vitro, PLoS One 12 (2017), https://doi.org/10.1371/JOURNAL.PONE.0190356.
[58] D.J. Miller, P.E. Fort, Heat shock proteins regulatory role in neurodevelopment, Front. Neurosci. 12 (2018), https://doi.org/10.3389/FNINS.2018.00821.
[59] R. Chaerkady, C.L. Kerr, A. Marimuthu, D.S. Kelkar, M.K. Kashyap, M. Gucek, J.D. Gearhart, A. Pandey, Temporal analysis of neural differentiation using quantitative proteomics, J. Proteome Res. 8 (2009) 1315–1326, https://doi.org/10.1021/PR8006667.
[60] M.G. Shapiro, K. Homma, S. Villarreal, C.P. Richter, F. Bezanilla, Infrared light excites cells by changing their electrical capacitance, Nat. Commun. 31 (2012) 1–11, https://doi.org/10.1038/NCOMMS1742, 3 (2012.
[61] S. Jung, N. Harris, I.I. Niyonshuti, S.V. Jenkins, A.M. Hayar, F. Watanabe, A. Jamshidi-Parsian, J. Chen, M.J. Borrelli, R.J. Griffin, Photothermal Response Induced by Nanocage-Coated Artificial Extracellular Matrix Promotes Neural Stem Cell Differentiation, vol. 11, Nanomater., Basel, Switzerland, 2021, https://doi.org/10.3390/NANO11051216.
[62] Y. Xiao, J. Peng, Q. Liu, L. Chen, K. Shi, R. Han, Q. Yang, L. Zhong, R. Zha, Y. Qu, Z. Qian, Ultrasmall CuS@BSA nanoparticles with mild photothermal conversion synergistically induce MSCs-differentiated fibroblast and improve skin regeneration, Theranostics 10 (2020) 1500, https://doi.org/10.7150/THNO.39471.
[63] M.Y. Chiang, Y.Z. Lin, S.J. Chang, W.C. Shyu, H.E. Lu, S.Y. Chen, Direct reprogramming of human suspension cells into mesodermal cell lineages via combined magnetic targeting and photothermal stimulation by magnetic graphene oxide complexes, Small 13 (2017), https://doi.org/10.1002/SMLL.201700703.
[64] R. Zhu, Z. Sun, C. Li, S. Ramakrishna, K. Chiu, L. He, Electrical stimulation affects neural stem cell fate and function in vitro, Exp. Neurol. 319 (2019), 112963, https://doi.org/10.1016/j.expneurol.2019.112963.
[65] W. Heng, M. Bhavsar, Z. Han, H.J. Barker, Effects of electrical stimulation on stem cells, Curr. Stem Cell Res. Ther. 15 (2020) 441–448, https://doi.org/10.2174/1574888X15666200129154747.
[66] L. Liu, J. Wu, S. Wang, L. Kun, J. Gao, B. Chen, Y. Ye, F. Wang, F. Tong, J. Jiang, J. Ou, D.A. Wilson, Y. Tu, F. Peng, Control the neural stem cell fate with biohybrid piezoelectrical magnetite micromotors, Nano Lett. 21 (2021) 3518–3526, https://doi.org/10.1021/acs.nanolett.1c00290.
[67] L. Liu, B. Chen, K. Liu, J. Gao, Y. Ye, Z. Wang, N. Qin, D.A. Wilson, Y. Tu, F. Peng, Wireless manipulation of magnetic/piezoelectric micromotors for precise neural stem-like cell stimulation, Adv. Funct. Mater. 30 (2020), 1910108, https://doi.org/10.1002/adfm.201910108.
[68] Y. Li, X. Dai, Y. Bai, Y. Liu, Y. Wang, O. Liu, F. Yan, Z. Tang, X. Zhang, X. Deng, Electroactive BaTiO(3) nanoparticle-functionalized fibrous scaffolds enhance osteogenic differentiation of mesenchymal stem cells, Int. J. Nanomed. 12 (2017) 4007–4018, https://doi.org/10.2147/IJN.S135605.
[69] G. Ciofani, L. Ricotti, C. Canale, D. D'Alessandro, S. Berrettini, B. Mazzolai, V. Mattoli, Effects of barium titanate nanoparticles on proliferation and differentiation of rat mesenchymal stem cells, Colloids Surf. B Biointerfaces 102 (2013) 312–320, https://doi.org/10.1016/j.colsurfb.2012.08.001.
[70] B. Ma, F. Liu, Z. Li, J. Duan, Y. Kong, M. Hao, S. Ge, H. Jiang, H. Liu, Piezoelectric nylon-11 nanoparticles with ultrasound assistance for high-efficiency promotion of stem cell osteogenic differentiation, J. Mater. Chem. B. 7 (2019) 1847–1854, https://doi.org/10.1039/c8tb03321h.
[71] E. Esmaeili, M. Soleimani, M.A. Ghiass, S. Hatamie, S. Vakilian, M.S. Zomorrod, N. Sadeghzadeh, M. Vossoughi, S. Hosseinzadeh, Magnetoelectric nanocomposite scaffold for high yield differentiation of mesenchymal stem cells to neural-like cells, J. Cell. Physiol. 234 (2019) 13617–13628, https://doi.org/10.1002/jcp.28040.
[72] H.L.A. Vieira, P.M. Alves, A. Vercelli, Modulation of neuronal stem cell differentiation by hypoxia and reactive oxygen species, Prog. Neurobiol. 93 (2011) 444–455, https://doi.org/10.1016/j.pneurobio.2011.01.007.
[73] S. Fatima, R. Alfrayh, M. Alrashed, S. Alsobaie, R. Ahmad, A. Mahmood, Selenium nanoparticles by moderating oxidative stress promote differentiation of mesenchymal stem cells to osteoblasts, Int. J. Nanomed. 16 (2021) 331–343, https://doi.org/10.2147/IJN.S285233.
[74] M.S.M. Ardawi, M.H. Badawoud, S.M. Hassan, A.M.S. Ardawi, A.A. Rouzi, M.H. Qari, S.A. Mousa, Lycopene nanoparticles promotes osteoblastogenesis and inhibits adipogenesis of rat bone marrow mesenchymal stem cells, Eur. Rev. Med. Pharmacol. Sci. 25 (2021) 6894–6907, https://doi.org/10.26355/eurrev_202111_27238.
[75] J. Li, J. Zhang, Y. Chen, N. Kawazoe, G. Chen, TEMPO-conjugated gold nanoparticles for reactive oxygen species scavenging and regulation of stem cell differentiation, ACS Appl. Mater. Interfaces 9 (2017) 35683–35692, https://doi.org/10.1021/acsami.7b12486.
[76] J. Zhang, C.-A. Peng, Enhanced proliferation and differentiation of mesenchymal stem cells by astaxanthin-encapsulated polymeric micelles, PLoS One 14 (2019), e0216755, https://doi.org/10.1371/journal.pone.0216755.
[77] A. Rocca, V. Mattoli, B. Mazzolai, G. Ciofani, Cerium oxide nanoparticles inhibit adipogenesis in rat mesenchymal stem cells: potential therapeutic implications, Pharm. Res. 31 (2014) 2952–2962, https://doi.org/10.1007/s11095-014-1390-7.
[78] A.R. Gliga, K. Edoff, F. Caputo, T. Källman, H. Blom, H.L. Karlsson, L. Ghibelli, E. Traversa, S. Ceccatelli, B. Fadeel, Cerium oxide nanoparticles inhibit differentiation of neural stem cells, Sci. Rep. 7 (2017) 9284, https://doi.org/10.1038/s41598-017-09430-8.
[79] D. Wu, Y. Zhang, X. Xu, T. Guo, D. Xie, R. Zhu, S. Chen, S. Ramakrishna, L. He, RGD/TAT-functionalized chitosan-graft-PEI-PEG gene nanovector for sustained delivery of NT-3 for potential application in neural regeneration, Acta Biomater. 72 (2018) 266–277, https://doi.org/10.1016/j.actbio.2018.03.030.
[80] G. Tiram, E. Segal, A. Krivitsky, R. Shreberk-Hassidim, S. Ferber, P. Ofek, T. Udagawa, L. Edry, N. Shomron, M. Roniger, B. Kerem, Y. Shaked, S. Aviel-Ronen, I. Barshack, M. Calderón, R. Haag, R. Satchi-Fainaro, Identification of dormancy-associated MicroRNAs for the design of osteosarcoma-targeted dendritic polyglycerol nanopolyplexes, ACS Nano 10 (2016) 2028–2045, https://doi.org/10.1021/acsnano.5b06189.
[81] J.J. Green, B.Y. Zhou, M.M. Mitalipova, C. Beard, R. Langer, R. Jaenisch, D.G. Anderson, Nanoparticles for gene transfer to human embryonic stem cell colonies, Nano Lett. 8 (2008) 3126–3130, https://doi.org/10.1021/nl8012665.
[82] N. Rouatbi, T. McGlynn, K.T. Al-Jamal, Pre-clinical non-viral vectors exploited for in vivo CRISPR/Cas9 gene editing: an overview, Biomater. Sci. (2022) 3410–3432, https://doi.org/10.1039/d1bm01452h.
[83] A. Tschiche, A.M. Staedtler, S. Malhotra, H. Bauer, C. Böttcher, S. Sharbati, M. Calderón, M. Koch, T.M. Zollner, A. Barnard, D.K. Smith, R. Einspanier, N. Schmidt, R. Haag, Polyglycerol-based amphiphilic dendrons as potential siRNA carriers for in vivo applications, J. Mater. Chem. B. 2 (2014) 2153–2167, https://doi.org/10.1039/c3tb21364a.
[84] X. Zhao, Z. Glass, J. Chen, L. Yang, D.L. Kaplan, Q. Xu, mRNA delivery using bioreducible lipidoid nanoparticles facilitates neural differentiation of human mesenchymal stem cells, Adv. Healthc. Mater. 10 (2021) 1–7, https://doi.org/10.1002/adhm.202000938.
[85] F. He, J. Cao, J. Qi, Z. Liu, G. Liu, W. Deng, Regulation of stem cell differentiation by inorganic nanomaterials: recent advances in regenerative medicine, Front. Bioeng. Biotechnol. 9 (2021) 1–10, https://doi.org/10.3389/fbioe.2021.721581.
[86] A.A. Dayem, H.Y. Choi, G.M. Yang, K. Kim, S.K. Saha, J.H. Kim, S.G. Cho, The potential of nanoparticles in stem cell differentiation and further therapeutic applications, Biotechnol. J. 11 (2016) 1550–1560, https://doi.org/10.1002/biot.201600453.
[87] W. Chen, P.H. Tsai, Y. Hung, S.H. Chiou, C.Y. Mou, Nonviral cell labeling and differentiation agent for induced pluripotent stem cells based on mesoporous silica nanoparticles, ACS Nano 7 (2013) 8423–8440, https://doi.org/10.1021/nn401418n.
[88] J. Wei, T. Cheang, B. Tang, H. Xia, Z. Xing, Z. Chen, Y. Fang, W. Chen, A. Xu, S. Wang, J. Luo, The inhibition of human bladder cancer growth by calcium carbonate/CaIP6 nanocomposite particles delivering AIB1 siRNA, Biomaterials 34 (2013) 1246–1254, https://doi.org/10.1016/j.biomaterials.2012.09.068.
[89] D.B. Trushina, T.N. Borodina, S. Belyakov, M.N. Antipina, Calcium carbonate vaterite particles for drug delivery: advances and challenges, Mater. Today Adv. 14 (2022), 100214, https://doi.org/10.1016/j.mtadv.2022.100214.
[90] H. Moradian, H. Fasehee, H. Keshvari, S. Faghihi, Poly(ethyleneimine) functionalized carbon nanotubes as efficient nano-vector for transfecting mesenchymal stem cells, Colloids Surf. B Biointerfaces 122 (2014) 115–125,

https://doi.org/10.1016/j.colsurfb.2014.06.056.
[91] H.Y. Choi, T.J. Lee, G.M. Yang, J. Oh, J. Won, J. Han, G.J. Jeong, J. Kim, J.H. Kim, B.S. Kim, S.G. Cho, Efficient mRNA delivery with graphene oxide-polyethylenimine for generation of footprint-free human induced pluripotent stem cells, J. Contr. Release 235 (2016) 222–235, https://doi.org/10.1016/j.jconrel.2016.06.007.
[92] J. Chen, Q. Wang, J. Zhou, W. Deng, Q. Yu, X. Cao, J. Wang, F. Shao, Y. Li, P. Ma, M. Spector, J. Yu, X. Xu, Porphyra polysaccharide-derived carbon dots for non-viral co-delivery of different gene combinations and neuronal differentiation of ectodermal mesenchymal stem cells, Nanoscale 9 (2017) 10820–10831, https://doi.org/10.1039/c7nr03327c.
[93] F. Yang, S.W. Cho, S.M. Son, S.R. Bogatyrev, D. Singh, J.J. Green, Y. Mei, S. Park, S.H. Bhang, B.S. Kim, R. Langer, D.G. Anderson, Genetic engineering of human stem cells for enhanced angiogenesis using biodegradable polymeric nanoparticles, Proc. Natl. Acad. Sci. U.S.A. 107 (2010) 3317–3322, https://doi.org/10.1073/pnas.0905432106.
[94] J.M. Oliveira, N. Kotobuki, A.P. Marques, R.P. Pirraco, J. Benesch, M. Hirose, S.A. Costa, J.F. Mano, H. Ohgushi, R.L. Reis, Surface engineered carboxymethylchitosan/poly(amidoamine) dendrimer nanoparticles for intracellular targeting, Adv. Funct. Mater. 18 (2008) 1840–1853, https://doi.org/10.1002/adfm.200800165.
[95] J.M. Oliveira, R.A. Sousa, P.B. Malafaya, S.S. Silva, N. Kotobuki, M. Hirose, H. Ohgushi, J.F. Mano, R.L. Reis, In vivo study of dendronlike nanoparticles for stem cells "tune-up": from nano to tissues, Nanomed. Nanotechnol. Biol. Med. 7 (2011) 914–924, https://doi.org/10.1016/j.nano.2011.03.002.
[96] E. Marin, C. Tapeinos, J.R. Sarasua, A. Larrañaga, Exploiting the layer-by-layer nanoarchitectonics for the fabrication of polymer capsules: a toolbox to provide multifunctional properties to target complex pathologies, Adv. Colloid Interface Sci. 304 (2022), https://doi.org/10.1016/j.cis.2022.102680.
[97] K.Y. Choi, S. Correa, J. Min, J. Li, S. Roy, K.H. Laccetti, E. Dreaden, S. Kong, R. Heo, Y.H. Roh, E.C. Lawson, P.A. Palmer, P.T. Hammond, Binary targeting of siRNA to hematologic cancer cells in vivo using layer-by-layer nanoparticles, Adv. Funct. Mater. 29 (2019), https://doi.org/10.1002/adfm.201900018, 0–31.
[98] U. Reibetanz, D. Hübner, M. Jung, U.G. Liebert, C. Claus, Influence of growth characteristics of induced pluripotent stem cells on their uptake efficiency for layer-by-layer microcarriers, ACS Nano 10 (2016) 6563–6573, https://doi.org/10.1021/acsnano.6b00999.
[99] S. Facca, C. Cortez, C. Mendoza-Palomares, N. Messadeq, A. Dierich, A.P.R. Johnston, D. Mainard, J.C. Voegel, F. Caruso, N. Benkirane-Jessel, Active multilayered capsules for in vivo bone formation, Proc. Natl. Acad. Sci. U.S.A. 107 (2010) 3406–3411, https://doi.org/10.1073/pnas.0908531107.
[100] F. Wang, J. Gao, J. Xiao, J. Du, Dually gated polymersomes for gene delivery, Nano Lett. 18 (2018) 5562–5568, https://doi.org/10.1021/acs.nanolett.8b01985.
[101] H.F. Moffett, M.E. Coon, S. Radtke, S.B. Stephan, L. McKnight, A. Lambert, B.L. Stoddard, H.P. Kiem, M.T. Stephan, Hit-and-run programming of therapeutic cytoreagents using mRNA nanocarriers, Nat. Commun. 8 (2017), https://doi.org/10.1038/s41467-017-00505-8.
[102] J. Estelrich, M.J. Sanchez-Martin, M.A. Busquets, Nanoparticles in magnetic resonance imaging: from simple to dual contrast agents, Int. J. Nanomed. 10 (2015) 1727–1741, https://doi.org/10.2147/IJN.S76501.
[103] C. Tapeinos, M. Battaglini, A. Marino, G. Ciofani, Smart diagnostic nanoagents for cerebral ischemia, J. Mater. Chem. B 8 (2020) 6233–6251, https://doi.org/10.1039/d0tb00260g.
[104] S.C. Baetke, T. Lammers, F. Kiessling, Applications of nanoparticles for diagnosis and therapy of cancer, Br. J. Radiol. 88 (2015), https://doi.org/10.1259/BJR.20150207.
[105] M. Ma, Y. Shu, Y. Tang, H. Chen, Multifaceted application of nanoparticle-based labeling strategies for stem cell therapy, Nano Today 34 (2020), https://doi.org/10.1016/j.nantod.2020.100897.
[106] H. Huang, X. Du, Z. He, Z. Yan, W. Han, Nanoparticles for stem cell tracking and the potential treatment of cardiovascular diseases, Front. Cell Dev. Biol. 9 (2021), 662406, https://doi.org/10.3389/fcell.2021.662406.
[107] N. Liao, M. Wu, F. Pan, J. Lin, Z. Li, D. Zhang, Y. Wang, Y. Zheng, J. Peng, X. Liu, J. Liu, Poly (dopamine) coated superparamagnetic iron oxide nanocluster for noninvasive labeling, tracking, and targeted delivery of adipose tissue-derived stem cells, Sci. Rep. 6 (2016), 18746, https://doi.org/10.1038/srep18746.
[108] R. Jiang, Y. Liao, F. Yang, Y. Cheng, X. Dai, J. Chao, SPIO nanoparticle-labeled bone marrow mesenchymal stem cells inhibit pulmonary EndoMT induced by SiO2, Exp. Cell Res. 383 (2019), 111492, https://doi.org/10.1016/j.yexcr.2019.07.005.
[109] L. Gu, X. Li, J. Jiang, G. Guo, H. Wu, M. Wu, H. Zhu, Stem cell tracking using effective self-assembled peptide-modified superparamagnetic nanoparticles, Nanoscale 10 (2018) 15967–15979, https://doi.org/10.1039/c7nr07618e.
[110] C.L. Tseng, I.L. Shih, L. Stobinski, F.H. Lin, Gadolinium hexanedione nanoparticles for stem cell labeling and tracking via magnetic resonance imaging, Biomaterials 31 (2010) 5427–5435, https://doi.org/10.1016/j.biomaterials.2010.03.049.
[111] K. Luo, G. Liu, W. She, Q. Wang, G. Wang, B. He, H. Ai, Q. Gong, B. Song, Z. Gu, Gadolinium-labeled peptide dendrimers with controlled structures as potential magnetic resonance imaging contrast agents, Biomaterials 32 (2011) 7951–7960, https://doi.org/10.1016/j.biomaterials.2011.07.006.
[112] K. Luo, J. Tian, G. Liu, J. Sun, C. Xia, H. Tang, L. Lin, T. Miao, X. Zhao, F. Gao, Q. Gong, B. Song, X. Shuai, H. Ai, Z. Gu, Self-assembly of SiO2/Gd-DTPA-polyethylenimine nanocomposites as magnetic resonance imaging probes, J. Nanosci. Nanotechnol. 10 (2010) 540–548, https://doi.org/10.1166/jnn.2010.1742.
[113] R. Lu, Y. Zhang, H. Tao, L. Zhou, H. Li, T. Chen, P. Zhang, Y. Lu, S. Chen, Gadolinium-hyaluronic acid nanoparticles as an efficient and safe magnetic resonance imaging contrast agent for articular cartilage injury detection, Bioact. Mater. 5 (2020) 758–767, https://doi.org/10.1016/j.bioactmat.2020.05.009.
[114] J. Wang, H. Wang, I.A. Ramsay, D.J. Erstad, B.C. Fuchs, K.K. Tanabe, P. Caravan, E.M. Gale, Manganese-based contrast agents for magnetic resonance imaging of liver tumors: structure-activity relationships and lead candidate evaluation, J. Med. Chem. 61 (2018) 8811–8824, https://doi.org/10.1021/acs.jmedchem.8b00964.
[115] L. Garcia-Hevia, M. Banobre-Lopez, J. Gallo, Recent progress on manganese-based nanostructures as responsive MRI contrast agents, Chemistry (Easton). 25 (2019) 431–441, https://doi.org/10.1002/chem.201802851.
[116] A. Venter, D.A. Szulc, S. Loai, T. Ganesh, I.E. Haedicke, H.L. Cheng, A manganese porphyrin-based T1 contrast agent for cellular MR imaging of human embryonic stem cells, Sci. Rep. 8 (2018), 12129, https://doi.org/10.1038/s41598-018-30661-w.
[117] P.C. van Zijl, N.N. Yadav, Chemical exchange saturation transfer (CEST): what is in a name and what isn't? Magn. Reson. Med. 65 (2011) 927–948, https://doi.org/10.1002/mrm.22761.
[118] B. Wu, G. Warnock, M. Zaiss, C. Lin, M. Chen, Z. Zhou, L. Mu, D. Nanz, R. Tuura, G. Delso, An overview of CEST MRI for non-MR physicists, EJNMMI Phys 3 (2016) 19, https://doi.org/10.1186/s40658-016-0155-2.
[119] G. Ferrauto, E. Di Gregorio, D. Delli Castelli, S. Aime, CEST-MRI studies of cells loaded with lanthanide shift reagents, Magn. Reson. Med. 80 (2018) 1626–1637, https://doi.org/10.1002/mrm.27157.
[120] Y. Yuan, C. Wang, S. Kuddannaya, J. Zhang, D.R. Arifin, Z. Han, P. Walczak, G. Liu, J.W.M. Bulte, In vivo tracking of unlabelled mesenchymal stromal cells by mannose-weighted chemical exchange saturation transfer MRI, Nat. Biomed. Eng. 6 (2022) 658–666, https://doi.org/10.1038/s41551-021-00822-w.
[121] J. Wahsner, E.M. Gale, A. Rodriguez-Rodriguez, P. Caravan, Chemistry of MRI contrast agents: current challenges and new frontiers, Chem. Rev. 119 (2019) 957–1057, https://doi.org/10.1021/acs.chemrev.8b00363.
[122] H. V Quang, C.C. Chang, P. Song, E.M. Hauge, J. Kjems, Caveolae-mediated mesenchymal stem cell labelling by PSS-coated PLGA PFOB nano-contrast agent for MRI, Theranostics 8 (2018) 2657–2671, https://doi.org/10.7150/thno.23206.
[123] J.W.M. Bulte, M.M.J. Modo, Design and applications of nanoparticles in biomedical imaging, Des. Appl. Nanoparticles Biomed. Imaging (2016) 1–469, https://doi.org/10.1007/978-3-319-42169-8/COVER.
[124] M. Graeser, F. Thieben, P. Szwargulski, F. Werner, N. Gdaniec, M. Boberg, F. Griese, M. Moddel, P. Ludewig, D. van de Ven, O.M. Weber, O. Woywode, B. Gleich, T. Knopp, Human-sized magnetic particle imaging for brain applications, Nat. Commun. 10 (2019) 1936, https://doi.org/10.1038/s41467-019-09704-x.
[125] B. Zheng, M.P. von See, E. Yu, B. Gunel, K. Lu, T. Vazin, D. V Schaffer, P.W. Goodwill, S.M. Conolly, Quantitative magnetic particle imaging monitors the transplantation, biodistribution, and clearance of stem cells in vivo, Theranostics 6 (2016) 291–301, https://doi.org/10.7150/thno.13728.
[126] Q. Wang, X. Ma, H. Liao, Z. Liang, F. Li, J. Tian, D. Ling, Artificially engineered cubic iron oxide nanoparticle as a high-performance magnetic particle imaging tracer for stem cell tracking, ACS Nano 14 (2020) 2053–2062, https://doi.org/10.1021/acsnano.9b08660.
[127] O.C. Sehl, P.J. Foster, The sensitivity of magnetic particle imaging and fluorine-19 magnetic resonance imaging for cell tracking, Sci. Rep. 11 (2021), 22198, https://doi.org/10.1038/s41598-021-01642-3.
[128] M. Filippi, F. Garello, C. Pasquino, F. Arena, P. Giustetto, F. Antico, E. Terreno, Indocyanine green labeling for optical and photoacoustic imaging of mesenchymal stem cells after in vivo transplantation, J. Biophot. 12 (2019), e201800035, https://doi.org/10.1002/jbio.201800035.
[129] M. Mazza, N. Lozano, D.B. Vieira, M. Buggio, C. Kielty, K. Kostarelos, Liposome-indocyanine green nanoprobes for optical labeling and tracking of human mesenchymal stem cells post-transplantation in vivo, Adv. Heal. Mater. 6 (2017), https://doi.org/10.1002/adhm.201700374.
[130] T. Kim, J.E. Lemaster, F. Chen, J. Li, J. V Jokerst, Photoacoustic imaging of human mesenchymal stem cells labeled with prussian blue-poly(l-lysine) nanocomplexes, ACS Nano 11 (2017) 9022–9032, https://doi.org/10.1021/acsnano.7b03519.
[131] K.S. Dhada, D.S. Hernandez, L.J. Suggs, In vivo photoacoustic tracking of mesenchymal stem cell viability, ACS Nano 13 (2019) 7791–7799, https://doi.org/10.1021/acsnano.9b01802.
[132] E.M. Donnelly, K.P. Kubelick, D.S. Dumani, S.Y. Emelianov, Photoacoustic image-guided delivery of plasmonic-nanoparticle-labeled mesenchymal stem cells to the spinal cord, Nano Lett. 18 (2018) 6625–6632, https://doi.org/10.1021/acs.nanolett.8b03305.
[133] K.P. Kubelick, E.J. Snider, C.R. Ethier, S. Emelianov, Development of a stem cell tracking platform for ophthalmic applications using ultrasound and photoacoustic imaging, Theranostics 9 (2019) 3812–3824, https://doi.org/10.7150/thno.32546.
[134] M.K. Laffey, K.P. Kubelick, E.M. Donnelly, S.Y. Emelianov, Effects of freezing

on mesenchymal stem cells labeled with gold nanoparticles, Tissue Eng. C Methods 26 (2020) 1–10, https://doi.org/10.1089/ten.TEC.2019.0198.
[135] C.H. Chen, N. Tang, K. Xue, H.Z. Zhang, Y.H. Chen, P. Xu, K. Sun, K. Tao, K. Liu, P. Awasthi, X. An, J. Xiang, N. Kalva, Y. Shen, C. Li, S.C. Baetke, T. Lammers, F. Kiessling, H. Bao, Y. Xia, C. Yu, X. Ning, X. Liu, H. Fu, Z. Chen, J. Huang, Z. Zhang, J.W.M. Bulte, M.M.J. Modo, W.W. Cai, L.J. Wang, S.J. Li, X.P. Zhang, T.T. Li, Y.H. Wang, X. Yang, J. Xie, J.D. Li, S.J. Liu, W. Xu, S. He, Z. Cheng, Q.L. Fan, R.P. Zhang, X. Cai, C.J. Zhang, F. Ting Wei Lim, S.J. Chan, A. Bandla, C.K. Chuan, F. Hu, S. Xu, N. V Thakor, L.D. Liao, B. Liu, Z. Chaudhary, G.M. Khan, M.M. Abeer, N. Pujara, B. Wan-Chi Tse, M.A. McGuckin, A. Popat, T. Kumeria, D. Chen, D. Wan, R. Wang, Y. Liu, K. Sun, X. Tao, Y. Qu, K. Dai, S. Ai, K. Tao, F. Chen, M. Ma, J. Wang, F. Wang, S.X. Chern, E.R. Zhao, A. Jhunjhunwala, S. Darmadi, H. Chen, J. V Jokerst, Efficient photoacoustic imaging using indocyanine green (ICG) loaded functionalized mesoporous silica nanoparticles, Nanoscale 12 (2017), 15877, https://doi.org/10.1259/bjr.20150207.
[136] C. Yin, G. Wen, C. Liu, B. Yang, S. Lin, J. Huang, P. Zhao, S.H.D. Wong, K. Zhang, X. Chen, G. Li, X. Jiang, J. Huang, K. Pu, L. Wang, L. Bian, Organic semiconducting polymer nanoparticles for photoacoustic labeling and tracking of stem cells in the second near-infrared window, ACS Nano 12 (2018) 12201–12211, https://doi.org/10.1021/acsnano.8b05906.
[137] Z. Chaudhary, G.M. Khan, M.M. Abeer, N. Pujara, B. Wan-Chi Tse, M.A. McGuckin, A. Popat, T. Kumeria, Efficient photoacoustic imaging using indocyanine green (ICG) loaded functionalized mesoporous silica nanoparticles, Biomater. Sci. 7 (2019) 5002–5015, https://doi.org/10.1039/C9BM00822E.
[138] K.P. Kubelick, S.Y. Emelianov, Prussian blue nanocubes as a multimodal contrast agent for image-guided stem cell therapy of the spinal cord, Photoacoustics 18 (2020), 100166, https://doi.org/10.1016/j.pacs.2020.100166.
[139] S. James, K. Neuhaus, M. Murphy, M. Leahy, Contrast agents for photoacoustic imaging: a review of stem cell tracking, Stem Cell Res. Ther. 12 (2021) 511, https://doi.org/10.1186/s13287-021-02576-3.
[140] F. Chen, M. Ma, J. Wang, F. Wang, S.X. Chern, E.R. Zhao, A. Jhunjhunwala, S. Darmadi, H. Chen, J.V. Jokerst, Exosome-like silica nanoparticles: a novel ultrasound contrast agent for stem cell imaging, Nanoscale 9 (2016) 402–411, https://doi.org/10.1039/C6NR08177K.
[141] C. Yu, Z. Chen, X. Li, H. Bao, Y. Wang, B. Zhang, J. Huang, Z. Zhang, pH-triggered aggregation of gold nanoparticles for enhanced labeling and long-term CT imaging tracking of stem cells in pulmonary fibrosis treatment, Small 17 (2021), e2101861, https://doi.org/10.1002/smll.202101861.
[142] C. Zong, A. Bronckaers, G. Vande Velde, G. Willems, M. Cadenas de Llano-Perula, In vivo micro-computerized tomography tracking of human periodontal ligament stem cells labeled with gold nanocomplexes, Adv. Heal. Mater. 11 (2022), e2101133, https://doi.org/10.1002/adhm.202101133.
[143] C. Yu, H. Bao, Z. Chen, X. Li, X. Liu, W. Wang, J. Huang, Z. Zhang, Enhanced and long-term CT imaging tracking of transplanted stem cells labeled with temperature-responsive gold nanoparticles, J. Mater. Chem. B 9 (2021) 2854–2865, https://doi.org/10.1039/d0tb02997a.
[144] P.J. Gawne, F. Man, P.J. Blower, T.M. de R R, Direct cell radiolabeling for in vivo cell tracking with PET and SPECT imaging, Chem. Rev. 122 (2022) 10266–10318, https://doi.org/10.1021/acs.chemrev.1c00767.
[145] X. Ni, S. Jia, X. Duan, D. Ding, K. Li, Fluorescent nanoparticles for noninvasive stem cell tracking in regenerative medicine, J. Biomed. Nanotechnol. 14 (2018) 240–256, https://doi.org/10.1166/jbn.2018.2502.
[146] G. Chen, Y. Zhang, C. Li, D. Huang, Q. Wang, Q. Wang, Recent advances in tracking the transplanted stem cells using near-infrared fluorescent nanoprobes: turning from the first to the second near-infrared window, Adv. Heal. Mater 7 (2018), e1800497, https://doi.org/10.1002/adhm.201800497.
[147] Y. Ji, Y.M. Li, J.G. Seo, T. Jang, J.C. Knowles, S.H. Song, J.H. Lee, Biological potential of polyethylene glycol (Peg)-functionalized graphene quantum dots in in vitro neural stem/progenitor cells, Nanomaterials (2021) 11, https://doi.org/10.3390/NANO11061446/S1.
[148] V. Jahed, E. Vasheghani-Farahani, F. Bagheri, A. Zarrabi, H.H. Jensen, K.L. Larsen, Quantum dots-betacyclodextrin-histidine labeled human adipose stem cells-laden chitosan hydrogel for bone tissue engineering, Nanomedicine 27 (2020), 102217, https://doi.org/10.1016/j.nano.2020.102217.
[149] C. Tosat-Bitrian, V. Palomo, CdSe quantum dots evaluation in primary cellular models or tissues derived from patients, Nanomedicine 30 (2020), 102299, https://doi.org/10.1016/j.nano.2020.102299.
[150] P. Awasthi, X. An, J. Xiang, N. Kalva, Y. Shen, C. Li, Facile synthesis of non-cytotoxic PEGylated dendrimer encapsulated silver sulfide quantum dots for NIR-II biological imaging, Nanoscale 12 (2020) 5678–5684, https://doi.org/10.1039/C9NR10918H.
[151] T. Malina, K. Poláková, J. Skopalík, V. Milotová, K. Holá, M. Havrdová, K.B. Tománková, V. Čmiel, L. Šefc, R. Zbořil, Carbon dots for in vivo fluorescence imaging of adipose tissue-derived mesenchymal stromal cells, Carbon N. Y. 152 (2019) 434–443, https://doi.org/10.1016/j.carbon.2019.05.061.
[152] Y. Ji, Y.M. Li, J.G. Seo, T.S. Jang, J.C. Knowles, S.H. Song, J.H. Lee, Biological potential of polyethylene glycol (PEG)-Functionalized graphene quantum dots in in vitro neural stem/progenitor cells, Nanomaterials 11 (2021), https://doi.org/10.3390/nano11061446.
[153] Y. Yuan, Z. Zhang, W. Hou, W. Qin, Z. Meng, C. Wu, In vivo dynamic cell tracking with long-wavelength excitable and near-infrared fluorescent polymer dots, Biomaterials 254 (2020), 120139, https://doi.org/10.1016/j.biomaterials.2020.120139.
[154] B.F. Mogharbel, J.C. Francisco, A.C. Irioda, D.S.M. Dziedzic, P.E. Ferreira, D. de Souza, C. de Souza, N.B. Neto, L.C. Guarita-Souza, C.R.C. Franco, C. V Nakamura, V. Kaplum, L. Mazzarino, E. Lemos-Senna, R. Borsali, P.A. Soto, P. Setton-Avruj, E. Abdelwahid, K.A.T. de Carvalho, Fluorescence properties of curcumin-loaded nanoparticles for cell tracking, Int. J. Nanomed. 13 (2018) 5823–5836, https://doi.org/10.2147/IJN.S171099.
[155] G. Jin, W. Li, F. Song, J. Zhao, M. Wang, Q. Liu, A. Li, G. Huang, F. Xu, Fluorescent conjugated polymer nanovector for in vivo tracking and regulating the fate of stem cells for restoring infarcted myocardium, Acta Biomater. 109 (2020) 195–207, https://doi.org/10.1016/j.actbio.2020.04.010.
[156] Z. Yang, X. Wang, G. Liang, A. Yang, J. Li, Photocontrolled chondrogenic differentiation and long-term tracking of mesenchymal stem cells in vivo by upconversion nanoparticles, J. Mater. Chem. B 10 (2022) 518–536, https://doi.org/10.1039/d1tb02074a.
[157] S. Hua, S. Zhong, H. Arami, J. He, D. Zhong, D. Zhang, X. Chen, J. Qian, X. Hu, M. Zhou, Simultaneous deep tracking of stem cells by surface enhanced Raman imaging combined with single-cell tracking by NIR-II imaging in myocardial infarction, Adv. Funct. Mater. 31 (2021), https://doi.org/10.1002/adfm.202100468.
[158] D. Chen, D. Wan, R. Wang, Y. Liu, K. Sun, X. Tao, Y. Qu, K. Dai, S. Ai, K. Tao, Multimodal nanoprobe based on upconversion nanoparticles for monitoring implanted stem cells in bone defect of big animal, ACS Biomater. Sci. Eng. 4 (2018) 626–634, https://doi.org/10.1021/acsbiomaterials.7b00763.
[159] K. Li, M. Yamamoto, S. Jing Chan, M. Yee Chiam, W. Qin, P. Tsun Hon Wong, E. King Fai Yim, B. Zhong Tang, B. Liu, Organic nanoparticles with aggregation-induced emission for tracking bone marrow stromal cells in the rat ischemic stroke model, Chem. Commun. 50 (2014) 15136–15139, https://doi.org/10.1039/C4CC06921H.
[160] S.E. Jang, L. Qiu, X. Cai, J.W.L. Lee, W. Zhang, E.K. Tan, B. Liu, L. Zeng, Aggregation-induced emission (AIE) nanoparticles labeled human embryonic stem cells (hESCs)-derived neurons for transplantation, Biomaterials 271 (2021) 120747, https://doi.org/10.1016/j.biomaterials.2021.120747.
[161] I.Z. Mukadam, J. Machhi, J. Herskovitz, M. Hasan, M.D. Oleynikov, W.R. Blomberg, D. Svechkarev, A.M. Mohs, Y. Zhou, P. Dash, J. McMillan, S. Gorantla, J. Garrison, H.E. Gendelman, B.D. Kevadiya, Rilpivirine-associated aggregation-induced emission enables cell-based nanoparticle tracking, Biomaterials 231 (2020) 119669, https://doi.org/10.1016/j.biomaterials.2019.119669.
[162] H. Bao, Y. Xia, C. Yu, X. Ning, X. Liu, H. Fu, Z. Chen, J. Huang, Z. Zhang, CT/Bioluminescence dual-modal imaging tracking of mesenchymal stem cells in pulmonary fibrosis, Small 15 (2019), https://doi.org/10.1002/SMLL.201904314.
[163] X. Li, C. Yu, H. Bao, Z. Chen, X. Liu, J. Huang, Z. Zhang, CT/bioluminescence dual-modal imaging tracking of stem cells labeled with Au@PEI@PEG nanotracers and RfLuc in nintedanib-assisted pulmonary fibrosis therapy, Nanomedicine 41 (2022), 102517, https://doi.org/10.1016/j.nano.2022.102517.
[164] J. Huang, J. Huang, X. Ning, W. Luo, M. Chen, Z. Wang, W. Zhang, Z. Zhang, J. Chao, CT/NIRF dual-modal imaging tracking and therapeutic efficacy of transplanted mesenchymal stem cells labeled with Au nanoparticles in silica-induced pulmonary fibrosis, J. Mater. Chem. B 8 (2020) 1713–1727, https://doi.org/10.1039/c9tb02652e.
[165] P.S. Patrick, K.K. Kolluri, M. Zaw Thin, A. Edwards, E.K. Sage, T. Sanderson, B.D. Weil, J.C. Dickson, M.F. Lythgoe, M. Lowdell, S.M. Janes, T.L. Kalber, Lung delivery of MSCs expressing anti-cancer protein TRAIL visualised with (89) Zr-oxine PET-CT, Stem Cell Res. Ther. 11 (2020) 256, https://doi.org/10.1186/s13287-020-01770-z.
[166] B. Das, A. Girigoswami, P. Pal, S. Dhara, Manganese oxide-carbon quantum dots nano-composites for fluorescence/magnetic resonance (T1) dual mode bioimaging, long term cell tracking, and ROS scavenging, Mater. Sci. Eng. C Mater. Biol. Appl. 102 (2019) 427–436, https://doi.org/10.1016/j.msec.2019.04.077.
[167] F. Chen, E.R. Zhao, T. Hu, Y. Shi, D.J. Sirbuly, J. V Jokerst, Silicon carbide nanoparticles as a photoacoustic and photoluminescent dual-imaging contrast agent for long-term cell tracking, Nanoscale Adv. 1 (2019) 3514–3520, https://doi.org/10.1039/c9na00237e.
[168] F.A. Oliveira, M.P. Nucci, J.B. Mamani, A.H. Alves, G.N.A. Rego, A.T. Kondo, N. Hamerschlak, M.S. Junqueira, L.E.B. de Souza, L.F. Gamarra, Multimodal tracking of hematopoietic stem cells from young and old mice labeled with magnetic-fluorescent nanoparticles and their grafting by bioluminescence in a bone marrow transplant model, Biomedicines 9 (2021), https://doi.org/10.3390/biomedicines9070752.
[169] J. Santelli, S. Lechevallier, H. Baaziz, M. Vincent, C. Martinez, R. Mauricot, A. Parini, M. Verelst, D. Cussac, Multimodal gadolinium oxysulfide nanoparticles: a versatile contrast agent for mesenchymal stem cell labeling, Nanoscale 10 (2018) 16775–16786, https://doi.org/10.1039/c8nr03263g.
[170] D.H. Kim, P.P. Provenzano, C.L. Smith, A. Levchenko, Matrix nanotopography as a regulator of cell function, J. Cell Biol. 197 (2012) 351–360, https://doi.org/10.1083/JCB.201108062.
[171] R. Schofield, The relationship between the spleen colony-forming cell and the haemopoietic stem cell, Blood Cell 4 (1978) 7–25.
[172] P.Y. Wang, H. Thissen, P. Kingshott, Modulation of human multipotent and pluripotent stem cells using surface nanotopographies and surface-immobilised bioactive signals: a review, Acta Biomater. 45 (2016) 31–59,

https://doi.org/10.1016/J.ACTBIO.2016.08.054.
[173] J.A. Last, S.J. Liliensiek, P.F. Nealey, C.J. Murphy, Determining the mechanical properties of human corneal basement membranes with atomic force microscopy, J. Struct. Biol. 167 (2009) 19–24, https://doi.org/10.1016/J.JSB.2009.03.012.
[174] G. Yun, L. Zhenmeiyu, H. Jing, W. Hongkui, G. Xiaosong, G. Jianhui, Application of bone marrow mesenchymal stem cell-derived extracellular matrix in peripheral nerve tissue engineering, Tissue Eng. Regen. Med. 11 (2016) 2250–2260, https://doi.org/10.1002/term.2123.
[175] F. Gentile, R. Medda, L. Cheng, E. Battista, P.E. Scopelliti, P. Milani, E.A. Cavalcanti-Adam, P. Decuzzi, Selective modulation of cell response on engineered fractal silicon substrates, Sci. Rep. 31 (2013) 1–10, https://doi.org/10.1038/SREP01461, 3 (2013).
[176] A. Marino, A. Desii, M. Pellegrino, M. Pellegrini, C. Filippeschi, B. Mazzolai, V. Mattoli, G. Ciofani, Nanostructured Brownian surfaces prepared through two-photon polymerization: investigation of stem cell response, ACS Nano 8 (2014) 11869–11882, https://doi.org/10.1021/nn5052426.
[177] D. Bae, S.H. Moon, B.G. Park, S.J. Park, T. Jung, J.S. Kim, K.B. Lee, H.M. Chung, Nanotopographical control for maintaining undifferentiated human embryonic stem cell colonies in feeder free conditions, Biomaterials 35 (2014) 916–928, https://doi.org/10.1016/J.BIOMATERIALS.2013.10.031.
[178] K. Dey, E. Roca, G. Ramorino, L. Sartore, Progress in the mechanical modulation of cell functions in tissue engineering, Biomater. Sci. 8 (2020) 7033–7081, https://doi.org/10.1039/D0BM01255F.
[179] G. Doron, J.S. Temenoff, Culture substrates for improved manufacture of mesenchymal stromal cell therapies, Adv. Healthc. Mater. 10 (2021), 2100016, https://doi.org/10.1002/ADHM.202100016.
[180] C.H. Rasmussen, P.M. Reynolds, D.R. Petersen, M. Hansson, R.M. McMeeking, M. Dufva, N. Gadegaard, Enhanced differentiation of human embryonic stem cells toward definitive endoderm on ultrahigh aspect ratio nanopillars, Adv. Funct. Mater. 26 (2016) 815–823, https://doi.org/10.1002/ADFM.201504204.
[181] L. Das Ghosh, J. Hasan, A. Jain, N.R. Sundaresan, K. Chatterjee, A nanopillar array on black titanium prepared by reactive ion etching augments cardiomyogenic commitment of stem cells, Nanoscale 11 (2019) 20766–20776, https://doi.org/10.1039/C9NR03424B.
[182] D. Urrutia-Cabrera, R. Hsiang-Chi Liou, J. Lin, Y. Shi, K. Liu, S.S.C. Hung, A.W. Hewitt, P.Y. Wang, R. Ching-Bong Wong, Combinatorial approach of binary colloidal crystals and CRISPR activation to improve induced pluripotent stem cell differentiation into neurons, ACS Appl. Mater. Interfaces 14 (2022) 8669–8679, https://doi.org/10.1021/acsami.1c17975.
[183] M. Versaevel, T. Grevesse, S. Gabriele, Spatial coordination between cell and nuclear shape within micropatterned endothelial cells, Nat. Commun. 31 (2012) 1–11, https://doi.org/10.1038/NCOMMS1668, 3 (2012).
[184] W. Liu, Q. Sun, Z.-L. Zheng, Y.-T. Gao, G.-Y. Zhu, Q. Wei, J.-Z. Xu, Z.-M. Li, C.-S. Zhao, W. Liu, Q. Sun, Z.-L. Zheng, Y.-T. Gao, Q. Wei, J.-Z. Xu, Z.-M. Li, C.-S. Zhao, G.-Y. Zhu, Topographic cues guiding cell polarization via distinct cellular mechanosensing pathways, Small 18 (2022), 2104328, https://doi.org/10.1002/SMLL.202104328.
[185] H. Hong, S. Min, S. Koo, Y. Lee, J. Yoon, W.Y. Jang, N. Kang, R. Thangam, H. Choi, H.J. Jung, S.B. Han, Q. Wei, S.H. Yu, D.H. Kim, R. Paulmurugan, W.K. Jeong, K.B. Lee, T. Hyeon, D. Kim, H. Kang, Dynamic ligand screening by magnetic nanoassembly modulates stem cell differentiation, Adv. Mater. 34 (2022), https://doi.org/10.1002/ADMA.202105460.
[186] I. Jun, N. Li, J. Shin, J. Park, Y.J. Kim, H. Jeon, H. Choi, J.G. Cho, B. Chan Choi, H.S. Han, J.J. Song, Synergistic stimulation of surface topography and biphasic electric current promotes muscle regeneration, Bioact. Mater. 11 (2022) 118–129, https://doi.org/10.1016/J.BIOACTMAT.2021.10.015.
[187] X. Huang, J. Xing, Z. Wang, J. Han, R. Wang, C. Li, C. Xiao, F. Lu, J. Zhai, Z. Zhou, Y. Li, L. Zhou, Z. Song, D. Chen, P. Yu, C. Ning, X. Jiang, 0D/1D heterojunction implant with electro-mechanobiological coupling cues promotes osteogenesis, Adv. Funct. Mater. 31 (2021), 2106249, https://doi.org/10.1002/ADFM.202106249.