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Chapter

Nanotechnology-Based Stem Cell Therapy: Current Status and Perspectives

Ponpandian Samuel, Shenbagamoorthy Sundarraj and D.N.P. Sudarmani

Abstract

The nanoparticles or nanobots are equivalent to the size of biological molecules of the human body and this is claimed to be the massive advantage of nanotechnology. Currently, top-down and bottom-up fabrication methods are being adopted to synthesize nanomaterials. Hence, the products developed from nanotechnology can be used for assessment of several biological parameters under *in vitro* and *in vivo* conditions. Effective production of nanoparticles, accompanied by the advent of novel characterization studies, enables us to manipulate the arrangement of atoms distributed on the surface of the nanomaterials to make it functionally more effective than before. In addition to the support imparted by nanotechnology, it also plays a primary role in the field of diagnostics. Another important outcome of nanotechnology is nanomedicine, which deals with the site-specific delivery of drugs with the aid of fabricated nanosystems. The advent of technology in recent years has enabled researchers to build novel forms of drug delivery systems like liposomes, dendrimers, nanoparticles and nanocrystals, which in turn ensure the précised delivery of drugs to suitable targets. Several need-based and value-added applications of nanotechnology are enlisted in the chapter.

Keywords: nanoparticles, nanobots, liposomes, nanosystems, nanocrystals, dendrimers

1. Introduction

Nanotechnology and stem cell therapies are two diverse fields and recent prominent areas of research in the direction of improvement to solve challenges during the treatment. Stem cell therapy, also known as regenerative medicine, promotes the repair mechanism of dysfunctional, incapacitated or wounded tissue by stem cells or their derivatives. Stem cell therapy is a treatment that has been done with stem cells. Stem cell therapy holds promise for treating a broad spectrum of diseases, such as cancer, heart disease, diabetes and neurodegenerative diseases. Researchers are still studying various sources for stem cells, which are applied for stem-cell treatment [1]. It is fascinating that the integration of two disciplines, nanotechnology and stem cell sciences, divulges new ways to identify the role of molecular apparatus in the

mechanism of the differentiation of stem cells regulation and elucidate more about the stem cell-based treatment strategies for insight into the human disease, prevention and theranostics.

Nanotechnology-based approaches in stem cell research have been established by utilizing biocompatible, biodegradable, solubility, stability, specificity, multimodality and efficacy for undergoing attachment to cognate receptors. Researchers have already shown that the following nanoparticle has been developed for the applications in stem cells differentiation and regeneration therapy, such as superparamagnetic iron oxide nanoparticles (SPIONs)-(ferucarbotran) NPs [2, 3], auto-assembled peptide [4], magnetic NPs [5], polyelectrolyte NPs [6], cerium oxide NPs [7], graphene oxide NPs [8], poly-ε-caprolactone [9], ZnO NPs [10, 11], SiO_2-NPs [12], iron oxide NP [13], collagen nanofiber [14], retinoic acid loaded with polymeric nanoparticles [15], tri-$CaPSO_4$ (tricalcium phosphate) [16], carbon nanofiber [17, 18], graphene-oxide nanoparticles (GO-NPs) [19], AuNPs [20, 21], PANPs [22], Au@BSA@PLL [23], USPIO [24], PFCE-NPs [25] and tri-Ca-silicate [26].

In the latest time, the application of nanotechnology in stem cell research has engaged better advances, which is attractive to an emerging interdisciplinary field. Stem cell nanotechnology is developing towards stem cell isolation, lineage and differentiation, stem cell imaging, active tracking, regenerative medicine and tissue engineering of stem cells (**Figure 1**). Nevertheless, stem cell nanotechnology also faces many challenges similar to any emerging interdisciplinary field. The mechanism of interaction between nanomaterials and stem cells still needs to be elucidated well as nanomaterials and nanostructures are modified to enhance the function of stem cells, and the action of metabolizing nanomaterials inside stem cells is arduous. The fabrication of multifunctional or homogenous nanostructures developed by existing knowledge and principles has been a great challenge in synthesizing, modifying and characterizing the quality and stability of nanomaterials and the mechanism of interacting with the stem. However, stem cell nanotechnology shows great fascinating

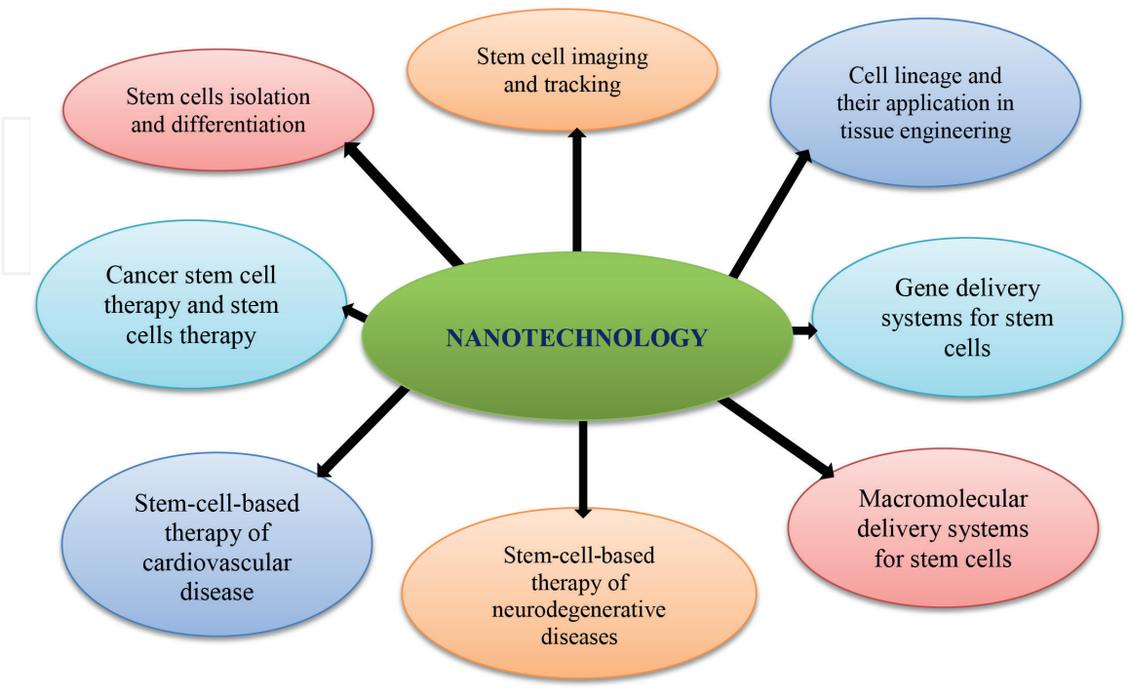

Figure 1.
Applications of nanotechnology in stem cell.

scenarios, stem cells are emerging for the application of the drug and macromolecular delivery for degenerative diseases [27].

2. Application of nanotechnology in stem cells isolation and differentiation

A crucial point in stem cell-based therapy is the segregation of appropriate cell types. The magnetic cell isolation technique was used to isolate specific types of cells. Magnetic nanoparticles can be used to label the stem cells for identification from a pool of different cell types by magnetic-activated cell sorting (MACS) [28]. This process involves combining MNPs with monoclonal antibodies (MAB) directed against unusual cell surface antigens, which causes the magnetic field of the cells expressing these antigens to be retained. It has been demonstrated that MNPs and anti-CD34 antibodies work together to efficiently label and distinguish peripheral blood progenitor cells from the blood. An uninterrupted quadruple magnetic flow sorter consisting of a flowing carrier and a quadrupole magnet with 1.42 T maximum field loudness and optimal field strength was able to separate these cells from mononuclear cells suspension of whole blood when MNP-conjugated anti-CD34 proteins were used to label CD34-cells. The CD34 cells collected had a purity of 60–96%, a retrieval rate of 18–60%, an improvement rate of 12–169 and a throughput of (1.7–9.3) 104 cells/s [29]. The optimized cells could be employed for cell transplantation-based regenerative medicine.

For SC proliferation and differentiation, scaffold-dependent nanomaterials and associated polymers have been used. Different scaffolds have been investigated with a focus on nanotubes, nanoparticles and nanofibers to control the differentiation of SC. Carbon nanotubes (CNTs) and titanium dioxide (TiO_2) are viable possibilities for scaffold creation, such as bone replacement therapy, due to their outstanding mechanical properties [30]. The impact of biological molecules and intricate interactions with scaffold substances improves SC development. Due to their exceptional electrical, mechanical and refractive indices and extensive surface topographical features, many nanomaterial-based scaffolds have been used in tissue engineering applications; nevertheless, this sector is focused on graphene and graphene oxide (GO) as non-toxic scaffolds [31, 32].

The researchers identified several peptide sequences that can firmly attach to NSCs. The new peptide (HGEVPRFHAVHL, HGE) was combined with quantum dots, Zhao et al. [30] discovered that the 48/34 kDa proteins on the membranes of NSCs produced from monkey ESCs but not human ESCs were particularly identified by this HE-quantum dot combination. According to this work, ESC-conjugated particular peptides may be used to examine the lineages they have committed to, and they may also be a mechanism for separating differentiated cells from ESC-differentiated cell populations. iPSCs often need to be cultivated on the feeder layer cells to preserve their pluripotency. Graphene (G) and graphene oxide (GO) have lately been established as cell culture substrates due to their biocompatibility at low concentrations and 2D structure with a large surface area. G and GO can support the culture of mouse iPSCs by allowing stem cells to differentiate. The cell proliferation and differentiation properties are induced by graphene materials (**Figure 2**). While iPSCs cultured on GO surfaces exhibit faster rates of adherence and proliferation than those on glass surfaces, iPSCs cultured on G surfaces show a similar effect on cell adhesion and proliferation [34]. Another benefit of GO is that it keeps the iPSCs in the undifferentiated stage while speeding up the differentiation [33].

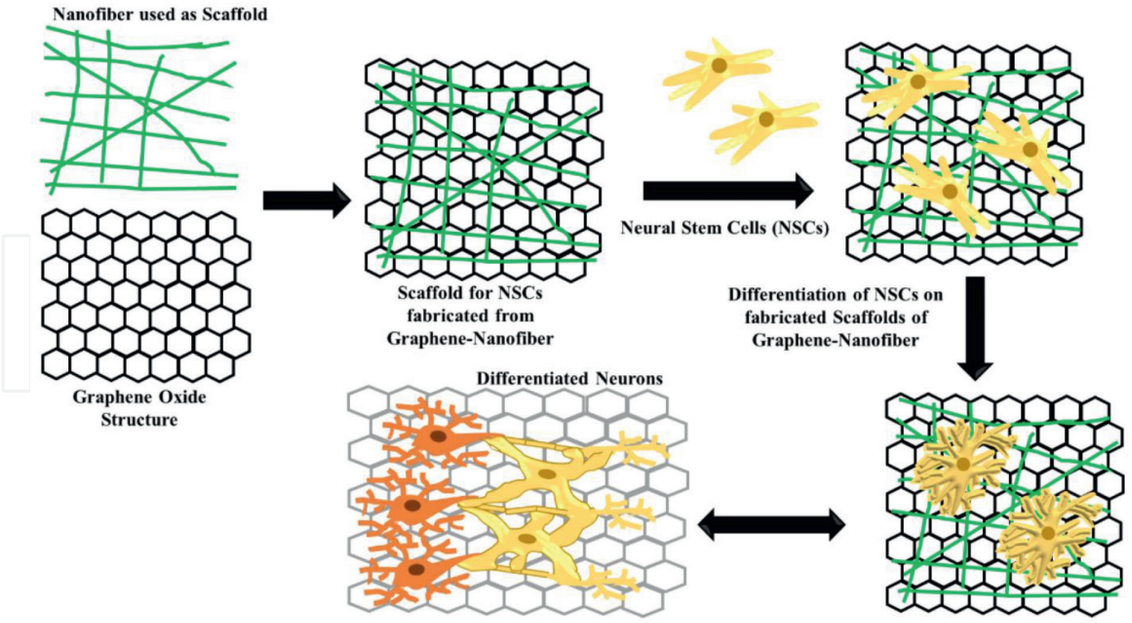

Figure 2.
Schematic representative of scaffold structure fabricated from graphene–nanofiber for differentiation of neural stem cells. The illustration was created by Asil et al. [33], and published in Appl. Sci. 2020, 10(14), 4852; https://doi.org/10.3390/app10144852. Licensed under CC by 4.0.

3. Application of nanotechnology in stem cell-based regeneration

One of the main concerns in cell therapy is whether SCs can be guided to specific areas to repair damaged brain regions [35]. In earlier studies, cells could only be observed after the animals were sacrificed. The mechanism of stem cell homing to specific tissues was identified using novel labelling techniques or materials without compromising SC proliferation, differentiation or migration, which is vital for tissue engineering and regenerative medicine. Proper labelling enables the practical detection of transplanted cells and the tracking of cells at the defect site to ascertain their role in tissue regeneration. For example, hMSCs were labeled with different nanoparticles, including quantum dots, fluorescence-labeled silica nanoparticles, gold nanoparticles and super-paramagnetic iron oxide nanoparticles, to follow these cells during live imaging and ascertain whether SCs are taking part in repair processes. Magnetic nanoparticles (dMNPs) coated with polyamidoamine dendrimer are used to incorporate the pluripotent transcription factors Oct4, Sox2, Lin 28 and Nanog to manufacture lentiviruses that generate iPSCs [36]. The generated lentivirus was ten times more potent than viruses produced by the liposome method. After generating iPSCs, these cells were labeled with fluorescent magnetic nanoparticles. The fluorescence signals were observed using fluorescence microscopy, and the magnetic nanoparticles were located using magnetic resonance imaging. Successful cellular uptake and long-term retention of these nanoparticles in cells are advantageous for monitoring and labelling these cells after implantation. Even though these different nanoparticles can penetrate and mark cells effectively and efficiently, cytotoxicity has been raised as a concern about nanoparticle application. The cytotoxic effect of a substance is influenced by its size, shape, content, surface charge and hydrophobicity. These NP characteristics result in a rise in cytosolic reactive oxygen species, chromosomal aberrations and cell death. Therefore, it is crucial to focus on enhancing this nanoparticle's cellular absorption for monitoring and labelling while reducing their cytotoxicity and interference with cellular differentiation in the context

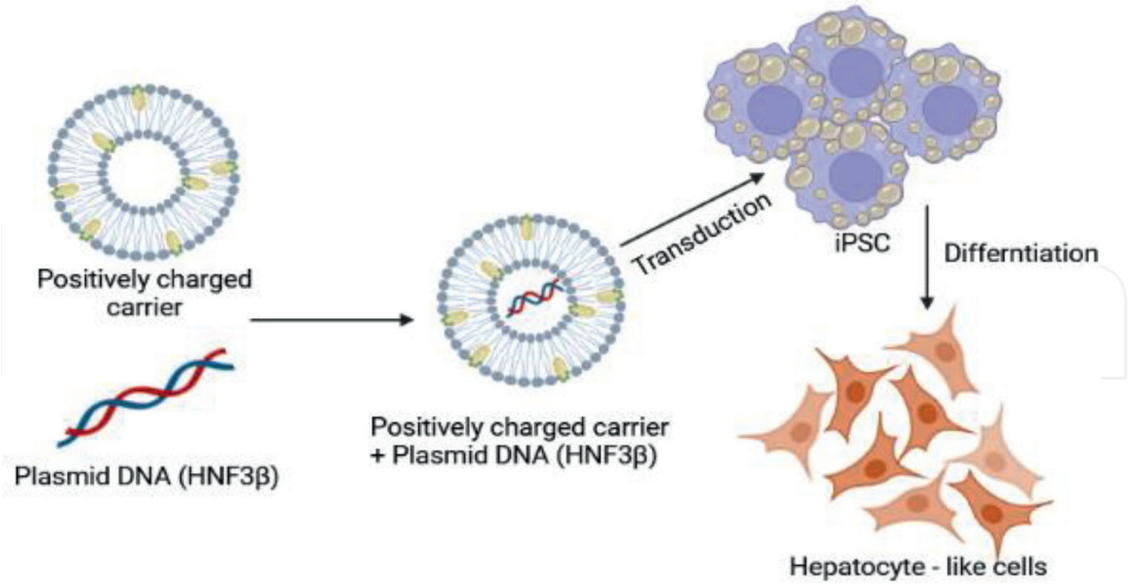

Figure 3.
Nanoparticle mediated transduction of induced pluripotent stem cells differentiate into specialized cells.

of biocompatibility. Future research on NP applications should concentrate on advancements in tissue-specific cell labelling, imaging and tracking (**Figure 3**).

Metallic NP-induced processes stimulate the proliferation and differentiation of stem cells through several mechanisms, including the alteration of signaling pathways, the production of reactive oxygen species and the tinkering of numerous transcription factors. Metallic nanoparticles have a potential impact on stem cell differentiation and proliferation both *in vivo* and *in vitro*. The superparamagnetic properties of the IONPs (iron oxide nanoparticles), often referred to as superparamagnetic iron oxide (SPIO) NPs, enable them to travel to the injured region, making them a potentially valuable tool for the treatment of degenerative illnesses. Human MSCs (hMSCs) can multiply when treated with SPIO- (Ferucarbotran) nanoparticles, which work by reducing intracellular H_2O_2. They can also speed up the cell cycle by upregulating proteins like cyclin D1, cyclin B, and cyclin-dependent kinase 4. Consequently, SPIO-NPs can be exploited as a secure supply of nanomaterials to promote the proliferation of stem cells [37].

4. Application of nanotechnology in stem cell imaging

For imaging and stem cell tracing, nanoparticles such as gold nanorods, MNPs and quantum dots have been utilized due to their distinct characteristic features. In cellular imaging, immunoassays, DNA hybridization and optical barcoding, QDs have been employed successfully. A new practical platform introduced for bioanalytical sciences and biomedical engineering is provided by quantum dots. Mesenchymal stem cells (MSCs) can internalize the quantum dots coupled with an antibody against the mortalin protein to produce i-QD composites, which label the MSCs. The normal adipocyte, osteocyte and chondrocyte development that the i-QD tagged MSCs underwent *in vitro* and *in vivo* strongly suggests that i-QDs can be used for *in vivo* imaging diagnostics and tracing of stem cells in the distribution of mouse body [38]. QDs can be created nanoprobes with unique functions that can be utilized for molecular imaging, gene or medication administration or molecule tracing. These biomolecules can be added to QDs, such

as liposomes, PEG, peptides or antibodies. MNPs were used for molecular imaging, and stem cell tracing in addition to quantum dots. Superparamagnetic iron oxide nanoparticles (SPIONs) were found to be multifunctional MRI-based contrast agents and the same can be used for labelling and tracking transplanted stem cells [39, 40]. Dextran-coated iron oxide nanoparticles were covalently bounded to fluorescent molecules to define HSC labelling and the engraftment process. Fluorophores were conjugated to the dextran coat for fluorescence-activated cell sorting and purification, which removed false signals from nanoparticle contaminants that were not sequestered [27].

With no significant toxicity *in vitro* or *in vivo*, a short-term specified incubation technique was devised, effectively labeled both cycling and quiescent HSCs. Immunodeficient mice were given purified primary human cord blood cells that were CD34-positive and lineage-depleted, allowing tagged human HSCs to be found in the recipient mice's bones. The cell populations that had snatched up the nanoparticles were precisely quantified, and their destiny after transplantation was monitored using flow cytometry. The presence of MNPs-labeled human stem cells in the bone marrow was confirmed by flow cytometry analysis. There has been substantial research in stem cell treatment for various central nervous system (CNS) illnesses [41]. The Endorem-labeled GFP MSCs were transplanted to rats intravenously into the femoral vein or intra-cerebrally into the hemisphere oblique to the lesion the cells were grafted. A 4.7-T Bruker spectrometer was used to check on rats with grafted stem cells once per week from three to seven weeks after transplantation. On MR scans, the lesion appeared as a hyper-intense signal. Its intensity matched GFP labelling or Prussian blue staining. One week following a transverse spinal cord lesion, MSCs tagged with Endorem were also delivered intravenously into the femoral vein. The lesion cavity appeared as inhomogeneous tissue with a significant hyper-intensive signal on MR images of longitudinal spinal cord slices from animals without spinal grafts but with a lesion. Dark hypo-intense patches were seen as lesions in transplanted animals.

Histological analysis revealed that transplanted mice had a substantial iron positive while lesioned control animals had only a few iron-containing cells. The lesion in grafted animals was significantly smaller than in control rats, indicating that the grafted MSCs had a beneficial impact on lesion repair. There are numerous successful uses of MR tracking in various organs, including the heart, liver, kidney and pancreatic islets. Fluorescent MNPs (FMNPs) can combine with the BRCAA1 antibody to create BRCAA1 antibody-labeled FMMNP probes, BRCAA1 protein showed signs of overexpression in ES CCE cells [27].

5. Application of nanotechnology in stem cell tracking

Conventional methods to track implanted stem cell fate predicted *in vitro* cell labelling for cell transplantation, subsequent follow-up of cell engraftment and existence concluded by the analysis of histological sections of sacrificed animals or tissue biopsies, by this invasive technique did not permit long-term and continuous experimentation. Recent advances in stem cell therapy need more precise and non-invasive methods for qualitatively and quantitatively tracking transplanted cells inside the host to facilitate the understanding of the prognosis of neurodegenerative treatment and eventually improve patients' health.

The traditional techniques have been developed by the improvement of specific contrast agents, such as endogenous biomolecules with intrinsic fluorescence, exogenous fluorescent proteins or non-fluorescent organic dyes, which have been used

for fundamentally two labelling modalities. Which are direct labelling and indirect labelling. (a) direct labelling is the cell incubated with specific intracellular probes; (b) indirect labelling is the cell tracked through the expression of the indicator by a reporter gene inserted in the genome of the cells. Direct methods are simple to apply and less expensive, although potential limitations include fast signal decay due to cell proliferation and subsequent insufficient marker distribution between daughter cells. Alternatively, an indirect technique is much more stable but needs genetic manipulation of cells and has not been suitable for clinical applications. Generally, the active contrast agents frequently present disadvantages like photo-bleaching over time, interference derived from tissue auto-fluorescence, chemical and metabolic degradation *in vivo* and even low transfection efficiency in primary cells and thus are not considered suitable for *in vivo* imaging. Several engineered nanoparticles with unique magnetic and optical properties have been established and employed in biomedicine due to their capability to offer real-time monitoring of tracking intracellular processes at a biomolecular level [42]. The transplanted stem cells labeled by these nanoparticles can be detected by multiple imaging methods, such as magnetic resonance imaging (MRI), nuclear imaging, single-photon emission computed tomography imaging (SPECT), positron emission tomography-computed tomography (PETCT) and photoacoustic imaging [43–46].

Stem cells are tracked by the functional modification of nanoparticles such as Gd-based nanoparticles are the most extensively used T1-contrast agent for labelling and tracking stem cells [47]. The GD-based nanoparticles composed of spherical europium-doped gadolinium oxysulfide (Gd_2O_2S: Eu^{3+}) have been fabricated and observed by MRI, X-ray imaging and photoluminescence imaging. The number of MSCs labeled by Gd_2O_2S: Eu^{3+} have feasible cell tracking in animal models [48].

Au-based nanoparticles are potential contrast agents of photoacoustic imaging developing as a modern method for tracking cells *in vivo*. More significantly, MSCs can be directly labeled by Au-based nanoparticles, so their differentiation after transplantation *in vivo* has been noticed using photoacoustic imaging *in vivo* [49, 50]. Huang et al. [51] synthesized Au-based nanoparticles (AA@ICG@PLL) with dual-modal imaging (CT and near-infrared fluorescence) for labelling and tracking MSCs of mice. AA@ICG@PLL exhibited excellent cellular uptake by MSCs and biocompatibility due to the modification of indocyanine green (ICG) and poly-L-lysine (PLL).

Hsieh et al. [52] described a QD-based NP for labelling human MSCs, in which CdSe was used as the core, and the shell was encapsulated by ZnS. Chen et al. [53] stated an AgS_2 QD-based NP for tracking human MSCs transplanted in the mouse by employing fluorescence imaging. Li et al. [54] developed QDs-based nanoparticles (RGD-β-CDQDs) to label and track human MSCs, which were fabricated of QDs, β-cyclodextrin (β-CD) and Cys-Lys-Lys-ArgGly-Asp (CKKRGD) peptide. The QDs altered by b-CD had greater cellular uptake and eased the differentiation of MSCs, due to the small molecule dexamethasone and siRNA carried by b-CD. Further significantly, the labeled MSCs have been identified for one month.

Super-paramagnetic iron oxide nanoparticles (SPIO NPs) are synthesized for labelling MSCs. The labeled MSCs have been tracked in an animal model by MRI [55–58]. Furthermore, these labeled MSCs still upheld differentiation potential. Lee et al. [59] synthesized SPIO NPs with the modification of poly lactic-co-glycolic acid (PLGA) and then utilized fluorescent dye Cy5.5 to functionalize the synthesized nanoparticles for labelling and tracking MSCs to explore the interactions between PLGA-SPIO NPs and MSCs.

Ma et al. [60] stated up-conversion-based nanoparticles, which were fabricated by $NaYF_4$:Yb^{3+}, Er^{3+} NPs, poly (acrylic acid) (PAA) and poly (allylamine hydrochloride)

(PAH), as a fluorescence maker for tracking bone marrow MSCs *in vitro*. Kang et al. [61] developed a UC-based NP with NIR-controllable properties to label MSCs. In a remote-controllable way, stem cell differentiation was regulated. Moreover, Ren et al. [62] produced conversion-based nanoparticles $NaYF_4$:Yb/Erusedligand free labelling and tracking mouse bone MSCs.

Huang et al. [63] synthesized mesoporous silica nanoparticles altered by fluorescein isothiocyanate, and the labeled MSCs have been identified by imaging to track their viability *in vivo*. Due to clathrin-mediated endocytosis, the nanoparticles have been internalized into MSCs and showed greater cellular uptake. Additionally, Chen and Jokerst [64] used silica nanoparticles to label MSCs and then track the MSCs by ultrasound imaging. The results exhibited that silica nanoparticles have expressively increased the ultrasound signal of MSCs *in vivo*. Yao et al. [65] described unique core-shell nanoparticles in which the core is composed of cobalt protoporphyrin IX (CoPP)-loaded mesoporous silica nanoparticles, and the shell is a ^{125}I-conjugated/spermine-modified dextran polymer, to label and guide the transplantation of MSCs by PA imaging and SPCT nuclear imaging. Chen et al. [66] developed three sizes of silicon carbide nanoparticles to label MSCs and showed dual-modality imaging of photoluminescence and photoacoustic imaging. Cyanine dye-doped silica nanoparticles have been used to label hMSC without affecting stemness surface marker expression, proliferation, viability and differentiation capability into osteocytes [67].

Lim et al. [68] fabricated bicyclononyne (BCN)-conjugated glycol chitosan nanoparticles (BCN-NPs) as dual-modal stem cell imaging probes for the cellular imaging system. Yin et al. [69] described an organic semiconducting polymer nanoparticle (OSPNC) as a contrast agent for tracking MSCs. The developed cationic nanoparticles revealed the intensive tissue imaging due to the meaningfully higher signal-to-noise (SNR) and improved the cellular uptake for human MSCs because of their biocompatibility, appropriate size and optimized surface property.

6. Nano patterns drive the fate of stem cells into a specific cell lineage

The instructional and tissue-specific niches of stem cells play a variety of activities, including migration, adhesion and proliferation. Extracellular matrix (ECM) components of nanoscale feature-sized fibrillary collagens, elastin and glycosaminoglycans are particularly prone to affect SCs. The topography and part structure of the ECM can compel stem cells to develop into particular cell lineages.

The crucial step in stem cell-based therapies is to direct SCs with accurate fabrication in a defined direction. Nanotechnologists have created several synthetic nanoplatforms that mimic the topological characteristics of the natural SCs niche to stimulate stem cell activation. The attachment of SCs surface proteins to topography is a fundamental aspect of the mechanism via which stem cells interpret and respond to nanotopographical signals. Focused adhesion, a form of integrin-mediated cell attachment to ECM components, is essential for stem cell regulation. Gene and protein levels will vary with mechanical stimulation and regulating focal adhesions will affect the stem cell differentiation pathway. Integrin-mediated adhesion signaling and other factors that impact the state of the SCs include cytoskeleton (CSK) stress, SC structure and nuclear dynamics. Arginine-glycine-aspartate is a crucial peptide episode in ECM proteins that regulates cell adherence (RGD). Recent studies have concentrated on the effect of RGD-containing nanopatterns on stem cell activity.

Cao et al. [70] planned the synthesis of several charged or neutral oligopeptide motifs connected with RGD using quartz substrates as a model and were employed for surface modification. They showed that, in the presence of RGD, positively charged oligopeptide patterns hinder osteogenic development, but negatively charged and neutral oligopeptide patterns may promote it.

Wang et al. [71] investigated the effects of RGD nanospacings ranging from 37 to 124 nm on the conduct of MSC. RGD nanopatterns were developed on PEG hydrogels. Cells were exposed to these nanopatterns at the highest serum level for eight days. They differentiated SCs into adipogenic and osteogenic lineages with large and small nanospacings. Stem cell activity is influenced by the symmetry, size, and regularity of surface nano-topographic features, which have been shown to have a substantial impact. Park et al. [32] showed that MSC activity, which includes differentiation, development and spreading, is significantly dependent on the diameter (d) of self-assembled layers (SAL) of TiO_2 nanotubes. They showed that osteogenic differentiation of MSC can be significantly reduced by increasing the diameter of the tube to 50 nm or higher after separating SCs into osteogenic cells through a tube having a 15 nm diameter. Researchers have looked into how different-pitch nanogrooves affect the ability of SCs to self-renew, differentiate and proliferate.

Currently, an important area of research involves the merger of SC nanotechnology (SC-NTech) and tissue engineering ideas. Nano-engineered 3-D scaffolds are frequently used to make it possible for SCs to differentiate into specific cell lineages. These three-dimensional scaffolds might be biodegradable, allowing cells to produce their own ECM as the synthetic scaffold degrades. For example, using nanofibrous scaffolds in bone tissue engineering intensely increased the differentiation of SCs into osteogenic cells compared to controls.

7. Application of nanotechnology in stem-cell-based tissue engineering

The principle of tissue engineering combined with stem cells enables the development of a stem cell-based therapeutic strategy for human diseases. Stem cell and progenitor cell steering differentiation is presently one hotspot, the differentiation of stem cells that conjugate 3D materials is deliberated as the most perspective tissue engineering. Recently, the developments of several micro/nanofabrication technologies have been used to stimulate stem cells to develop into 3D biodegradable scaffolds. Nanostructured scaffolds are fabricated to initiate stem cells to turn into specific cell types compromising the tissues and organs in the body. Inside these scaffolds, cells secrete their matrix, and as the scaffold degrades, they form a 3D tissue structure that mimics the body's natural tissues. Gelain et al. [72] described that they had established a 3D cell culture system using an exclusive peptide nanofiber scaffold with mouse adult neural stem cells. They prepared 18 different peptides, which directly integrate various functional motifs to stimulate cell adhesion, differentiation and bone marrow homing and engraftment activities. These functionalized peptides are self-assembled into nanofiber scaffolds where cells have been completely entrenched by the scaffold in 3D. Without the addition of neurotrophic factors and soluble growth factors, two of these scaffolds functionalized with bone marrow homing motifs significantly enhanced the survival of the neural stem cells and also encouraged differentiation towards cells expressing neuronal and glial markers.

Carbon nanotube patterns have been used to improve the growth and alignment of MSCs. The MSCs revealed in CNT growth patterns, and the cell culture results

showed that the CNT designs have no harmful consequence on the MSCs [73]. The outcomes demonstrated that CNT patterns have enormous potential as a new platform for basic research and applications expanding stem cells.

Stem cell differentiation is diligently related to their microenvironment. The regulation of stem cells is contingent on their dealings with a highly specialized microenvironment or niche. Secreted factors, stem cell-neighboring cell interactions, extracellular matrix (ECM) and mechanical properties collectively made the stem cell microenvironment. The stem cell niche secretes suitable chemicals to direct the differentiation and development of stem cells. Mineral components are essential to stem cell localization; matrix components are vital to the restraint of stem cells, and bone-forming osteoblasts are also important to the maintenance and proliferation of stem cells, the calcium-sensing receptor located on the surface of HSCs, and other cells are critical to stem cells finding their niche.

Nanotechnology has been employed to create artificial *in vivo* conditions like stem cell microenvironments to discover the fundamental mechanisms of the conversion into differentiated cells. A better solution is presently under exploration: growing the stem cells on a so-called 'lab-on-a-chip'. They synthesize a silicon chip with a thousand nanoreservoir cavities, which surface contains about a thousand reservoir cavities, with each reservoir only about 500 nm across. A reservoir that holds liquid chemicals similar to the stem cells has been exposed to the niche. Each reservoir is covered with a lipid bilayer model resembling a cell membrane. These reservoir bilayers also hold the same voltage-gated channels found in cells. A small charge of electricity has been applied to any individual reservoir to open the channels and allow the chemicals to spill out, delivering them to develop any particular stem cell. The nanoreservoir chip technology also allows the opportunity of growing cells layer by layer, making compound tissues, which are otherwise challenging to produce.

Substrate topography impacts a wide range of stem cell behaviors in a manner discrete from surface chemistry. One physical difference in the topography of divergent basement membranes is the size of pores and ridges. *In vivo* cell never see flat surfaces: on the nanoscale, no basement membrane or extracellular matrix is flat. The great majority of features in the extracellular environment are in the submicron to the nanoscale range, confirming that an individual cell interacts with numerous topographic features. Nanofibrous structures have favorably modulated osteoblast, osteoclast and fibroblast activities towards the implant or scaffold materials. Nanofibrous matrices are presented as scaffolds that have improved structural similarity to target tissues than their bulk counterparts because leading mechanisms in tissues are nanoscale structures, and cells seem to adhere and proliferate enhanced on nanoscale structures than on bulk materials. The synthesis of natural polymer-based nanofibers is advantageous because of their proven biocompatibility and biodegradation. Strategic aspects of natural polymers include less immune reaction, nontoxicity, hydrophilicity, enhanced cell adhesion and proliferation. The electrospinning method was adapted to fabricate natural polymer nanofibers. Chitosan and alginate, abundant natural polymers have been widely used in tissue engineering, but none had been fabricated into nanostructured matrices until recent years. Uzieliene et al. [74] described that they effectively used chitosan and alginate-based nanofibrous matrices to mimic the extracellular matrix of articular cartilage that mainly contains type II collagen and proteoglycans (glycosaminoglycan, GAG). A nanopit template was created with a conglomeration surface less than 100 nm in diameter. The flat culture surface and nutrient medium of nanopit align ordered the stem cell has been not differentiated. The stem cell could grow to the calcified

ossature cell in the nutrient medium concurrent with well-ordered and unordered aligned nanopit. The surface of the transplanted tissue is the nanoengineering surface that has induced the stem cell to propagate into the ossature. Surface character plays a significant role in stem cell proliferation.

8. Nanoparticle-mediated gene delivery systems for stem cells

Recent research has previously revealed the therapeutic uses of embryonic stem cells (ESCs), and the generation of progenitor cells with *in vivo* reconstitution properties has also been described for the treatment of severe hereditary, excruciating and degenerative illnesses [75]. A fundamental barrier to the therapeutic uses of these pluripotent cells is the lack of non-invasive and live cell imaging of grafted cells to manage biodistribution (*in-vivo* tracking). Additionally, reproducible methods for the effective intracellular distribution of biomolecules such as RNA, DNA, peptides and proteins are required to control ES cell development should be developed.

Fluorescent multi-walled nanotubes of carbon (dMNTs-C) functionalized with polyamidoamine are very successful at penetrating the CCE embryonic stem cell line in mice [76]. As they are easier to use and can be produced in large quantities than viral vectors, which are riskier for therapeutic use, dendrimers could be a viable non-viral transmission vector. It has been found that dendrimer-modified polyamidoamine (PAMAM) MNPs significantly boost the efficacy of gene delivery [77, 78]. The dMNTs will be a modern method of gene transfer for ESCs and will be used in ES research. Nanoparticles such as MNPs [79] and QDs can penetrate human MSC cells and sustain themselves in ES cells for a long time. Previous studies have shown that SiO_2-coated CdTe nanoparticles can bind to and support inside of induced-differentiated neurons, hematopoietic cells and endothelial cells while exhibiting minimal cytotoxicity at the applied dose. It is simple to show that these transplanted stem cells with MNPs formed teratomas made up of tissues from all three germ layers [41]. Recently, a biological delivery technique that uses nanoneedles and atomic force microscopy (AFM) to transport genes into living cells was created [80].

El-Kharrag et al. [81] examined polymer-based nanoparticles (NPs) for the delivery of mRNA and nucleases to human granulocyte colony-stimulating factor (GCSF)-mobilized CD34+ cells, which might also be employed for *in vivo* administration. The effectiveness of NP-mediated *ex vivo* administration was closely associated with the charge of the nanoparticles and exhibited minimal toxicity. When compared directly to electroporation, NP-mediated gene editing allowed for a 3-fold decrease in reagent usage while maintaining comparable efficiency. Furthermore, employing nanoparticles showed increasing human HSC engraftment capacity in the NSG mice xenograft model. Finally, successfully stored mRNA- and nuclease-loaded nanoparticles were lyophilized, preserving their transfection capacity following rehydration.

9. Nanoparticles as macromolecular delivery systems for stem cells

Stem cells are unique cells found in the body and are rightly called internal repair systems. The unique properties of stem cells are the ability to proliferate extensively and differentiate into specific cells that are used in therapeutic procedures against dreadful diseases. The biggest challenge ahead of using this cell is to find an effective

way to maintain the division and differentiation of stem cells under tightly regulated patterns. It is found that several macromolecules, such as DNA, RNA, proteins and peptides, regulate these pathways effectively. These macromolecules can be introduced into the stem cells at the right time to make it possible. Conventional methods will not work out because of the complexities associated with the cells and macromolecules. Although physical methods such as electroporation and nucleofection could bring out promising results simultaneously, it causes irreversible damage to the cells under some circumstances. Research could also bring in viral vectors concurrently, causing drawbacks, such as toxicity and mutagenesis, and has not been forward to accomplish the transfer. Nanoparticles are found to be very effective after surface modification. They considered several parameters such as size, shape and design of nanoparticles made by Zhu et al. [82] to deliver the plasmid into mouse embryonic fibroblast cells to reprogram it into pluripotent cells. A plasmid carrying OSKM (arginine terminated polyamidoamine) nanoparticle was used to carry out the shipment of macromolecule into the target. In another experiment, Sohn et al. [83] used acid-senitive polyketal-based nanoparticles to activate pluripotency in bone marrow mononuclear cells. The outcome that was fertile in polyketal-based nanoparticles would produce multiple reprogrammed cells. Besides, mesoporous silica nanoparticles were analyzed by Chen et al. [84] for their efficacy against induced pluripotent stem cells. The outcomes of mesoporous silica nanoparticles lead the way by limited cytotoxicity against induced pluripotent stem cells. Positively charged (cationic) nanoparticles were chosen to deliver hepatocyte nuclear 3b factor. It was found that it increased the mRNA concentration in stem cells with liver-specific genes and activated those cells to differentiate into cells resembling hepatocytes with similar functions.

10. Application of nanotechnology in stem-cell-based therapy of neurodegenerative diseases

Neurodegenerative diseases (ND) can be defined as the gradual degeneration of neurons, which are considered the fundamental unit of the nervous system (**Figure 4**). Neural degeneration could affect the patient, their family members and society. Henceforward, there is no prominent treatment procedure to handle the disease even though the symptoms of ND can be slowed down [85]. A team of doctors, neuroscientists and bioengineers are required to standardize procedures to treat the disease effectively [86]. The neurogenesis cascade of complex mechanism leads to the synthesis of neurons, which makes up the CNS. Stems cells derived from different sources can be subjected to a sequence of processes such as proliferation and differentiation. The differentiated stem cells can be used as ideal drug candidates for cell-based therapy [87].

The key objectives of cell-based therapy are to protect the neurons and to enhance the differentiation and regeneration potential. In recent years, applications of stem cells in cell therapy to treat neurodegenerative diseases have gained more attention among researchers [88]. The neuroprotective effect of stem cells has been scientifically proven [89]. Transplantation of stem cells is positive regulation in Parkinson's disease (PD), spinal muscular dystrophy (SMD) and amyotrophic lateral sclerosis (ALS) [90]. Nanomaterials are considered by the biomedical domain, an effective tool to carry value-added drugs and to deliver those chemicals to the specified target. Since nanoparticles are special and unique properties [91], the nanotechnology domain can be coupled with cell therapy to extend better treatment to people

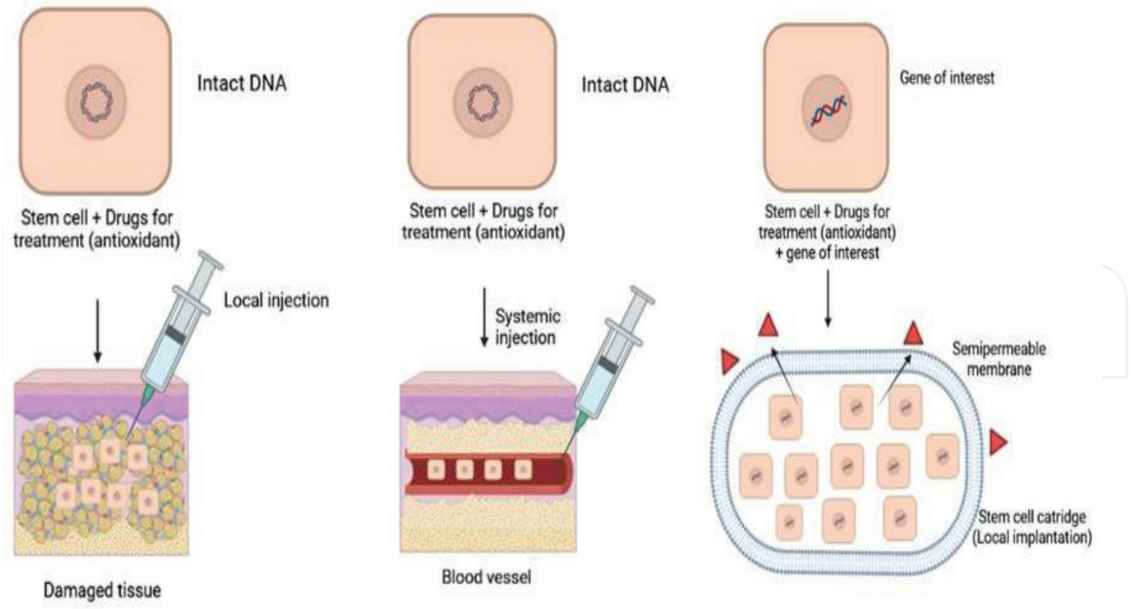

Figure 4.
Current novel methods to utilize stem cells in cell therapy in treatment of neurodegenerative disease.

experiencing severe forms of neurodegenerative diseases. The microenvironment of the CNS is called the stem cell niche. When the stem cell niche is administered with pro-neurogenic factors (proteins), it can kindle the proliferation and differentiation of endogenous and exogenous neural stem cells [92]. After successful internalization of the nanoparticles, it can stimulate neurogenesis, which is a much-expected point in the treatment of neurodegenerative diseases. But still, researchers are needed to find out the mystery behind the relationship between stem cells and nanoparticles. If those mysteries might be identified then it may be easy to use the stem cell—nanoparticle complex to treat the neurodegenerative disease effectively.

A high translational potential exists for neural stem cells (NSCs) in transplantation therapy for neural repair. A vital objective of regenerative neurology is to increase the therapeutic potential of these cells through genetic engineering. Major non-viral vectors for the safe bioengineering of NSCs include magnetic nanoparticles (MNPs), which have imperative advantages over viral vectors in terms of safety, scalability and use.

11. Nanomedicine in cancer stem cell therapy

Conventional therapies such as chemotherapy and radiation therapy remove the tumor but not the cancer stem cell (CSC). Permanent removal of cancer stem cells could result in long-lasting remission of disease, remarkable reduction in metastasis and seems to boost the immune status of the patients. Again, cancer stem cell (CSC) therapies are controlled by nanotechnology and carry them with therapeutic payloads (TPL) [93]. Nanoparticles are engineered in such a way that to attack the cells with over-expressed receptor proteins called CD44. Hyaluronic acid situated on the surface of the B16F10 cells could lead to the bonding with CD44. The study confirms that nanoparticles are remarkably useful for the shipment of CSC suppression antitumour drugs [94].

A novel therapeutic procedure such as nucleus-targeted drug delivery (NTDD) can help researchers to reverse the drug resistance in CSC. Silica nanoparticles are engineered in such a way as to attack the nucleus of the CSC. Surface modulation coupled with thermal sensitive exposure could help to reach the nucleus efficiently. Nucleus-targeted drug delivery facilitates the apoptosis of CSC, which in turn is caused by chemotherapy and thermotherapy [95].

12. Nanoparticles as macromolecular delivery systems for glioblastoma

Macromolecular drug delivery has taken a bounce in the last 20 years [96]. Due to the robust development in the biotechnology domain, enough novel methods have been developed based on macromolecules such as DNA, RNA, siRNA, proteins and peptides. The U.S Food and Drug Administration (FDA) has classified macromolecular drugs into vaccines, blood and blood components and allergen extracts are used for diagnosis and treatment. In the modern drug delivery system (DDS), an important property called "active targeting" is exploited to make the DDS deliver the drugs selectively to the target without affecting the healthy neighboring cells [97]. Glioblastoma is a deadly form of malignant tumor of the central nervous system (CNS). Current treatment relies on giving radiation therapy followed by a chemotherapeutics regime using a DNA alkylating agent. Life expectancy is also less even after undergoing a series of treatment procedures. The cancer progression leads to the impact of GBM (Glioblastoma) after reaching into the deeper areas of the brain. Hence standard and alternative methods are required to extend drug delivery effectively. In this method, one such effective tool is the solid-lipid nanoparticle developed by Kuo et al. [98]. These nanoparticles are conjugated with metallotransferrin antibodies. Further, the transcytosis property of the nanoparticle across human brain-microvascular endothelial cells was examined and found to be very effective, and at the same time, it inhibits the growth of U87MG cells *in vitro*.

13. Conclusion

Stem cell nanotechnology begins new avenues for the manufacture, study and potential application of SCs in regenerative medicine. For imaging and labelling, drug or gene administration, tissue engineering scaffolds and stem cell proliferation monitoring, nanomaterials such as fluorescent CNTs, QDs, fluorescent MNPs and fluorescent CNTs, among others, have been used. Differentiation-engineered nanostructures have been employed, and it is anticipated that they would speed up the detection and monitoring of microenvironmental signals. Despite numerous challenges, stem cell nanotechnology offers new opportunities that will considerably improve the identification and tracking of SC-fate and will develop novel stem cell therapies. As a result, stem cell-based therapies would be furnished as an alternative and effective remedy for genetic disorder.

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Author details

Ponpandian Samuel[1]*, Shenbagamoorthy Sundarraj[2]* and D.N.P. Sudarmani[3]

1 Department of Biotechnology, Ayya Nadar Janaki Ammal College (Autonomous), Sivakasi, Tamil Nadu, India

2 Postgraduate and Research Department of Zoology, V.O.Chidambaram College, Tuticorin, Tamil Nadu, India

3 Department of Zoology, Ayya Nadar Janaki Ammal College (Autonomous), Sivakasi, Tamil Nadu, India

*Address all correspondence to: samuel_sf432@anjaconline.org and shenvsun@gmail.com

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