

Nanotechnology in Tissue Engineering and Regenerative Medicine

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Abstract

Nanotechnology has shown incomparable advancements in case of tissue engineering and regenerative medicine and are now considered as advanced techniques instead of other conventional techniques which are used to treat diseases related to human health. With the prominent advantages of utilizing nanotechnology-based techniques such as nanocarriers, gene therapy and stem cell therapy, scientists have utilized these techniques noticeably. With the advancements in the production of nanoscale, scientists and researchers are now being able to use these in the existing and new innovative techniques. However, this chapter briefly reviews a basic overview related to the various nanotechnological techniques which are being analyzed and utilized in the tissue engineering and regenerative medicines, along with some of the challenges and future aspects associated with these strategies which further confirms that tissue engineering and regenerative medicine would be accepted by the patients to a great extent in near future in the place of other conventional approaches available.

Keywords: Nanotechnology, Nanoparticles, Tissue engineering, Regenerative medicine, Stem cell therapy

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Introduction

Nanotechnology is a discipline of science and engineering which further combines chemistry, physics, colloidal science, biology, and other scientific fields and used to manipulates atoms and molecules at the nanoscale, these can be nanomaterials, nanoparticles and others. According to the facts, the simplest terminology used for nanotechnology is “Technology on the nanoscale”. The term nanoscale is used to focus on the objects with the dimensions on the order of 1-100 nanometers (Satyannarayana, 2022). There are various areas where this nanotechnology is applicable. Some of the major areas of applications are shown in Figure 1.

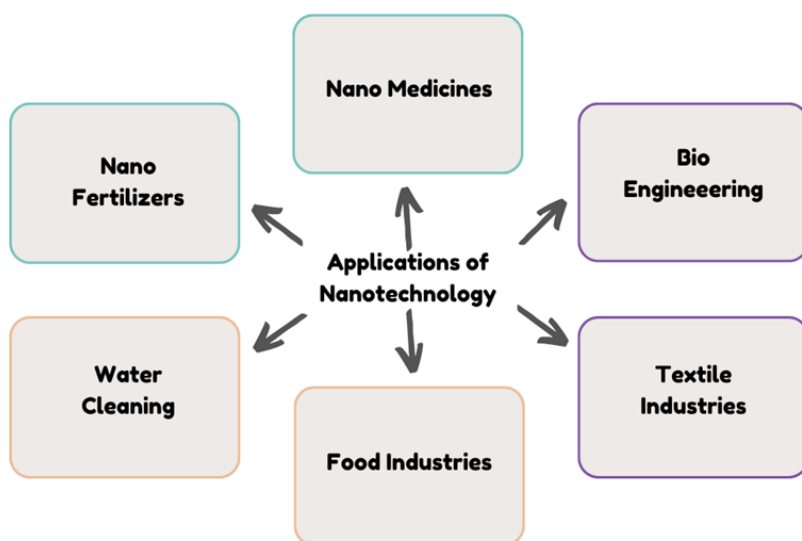


Fig. 1: Utilization of nanotechnology in various fields (Designed by Word)

There are different classifications of nanoparticles (NPs) depending on their size, morphology and chemical properties i.e. carbon based, metal based, ceramics based, polymeric based and lipid based and all these have many applications. There are mainly two methods which are used to prepare nanoparticles i.e. bottom up approach and top down approach (Khan et al., 2019). However, the recent advancements in the

field of nanotechnology have extended many possibilities related to its applications in medicine which includes the enhancement of early diagnosis and its therapy (Malik et al., 2023).

Furthermore, the most recent advances in the field of nanotechnology related to bioengineering are to initiate nano-antimicrobials for the reduction or the prevention of infections along with new nanostructured drug delivery systems and their interaction with cells, tissues, and living systems (Zong et al., 2022).

Nanotechnology in Regenerative Medicine and Tissue Engineering

Nanotechnology has provided a new opportunity for the development of medicines and its constant development has made possible early diagnosis and the precise treatment. However, due to these properties, nanomaterials have been extensively examined and utilized in the medical field. Thus, nanotechnology has now become a powerful tool in regenerative medicine and tissue engineering (Guo et al., 2018).

Regenerative medicine may be defined as a field that aims to develop methods to regenerate or replace injured cells, tissues, or organs to restore their normal functions. It a powerful approach in tissue regeneration which creates nanoscale quality of tissues for cellular adhesion, migration and differentiation. The nanomaterials used in nanotechnology have their unique physical, and chemical properties including optical, magnetic and electrical properties and on the basis of their size and functions, nanomaterials can be used for various techniques such as biomolecule delivery, tissue engineering, in vivo cell tracking and stem cell therapy (Yang et al., 2019).

On the other hand, tissue engineering includes combining of cells, scaffolds, and other growth factors to make functional tissues outside the body. Tissue engineering research is a necessary first step in regenerative medicine therapies (Sharma et al., 2019). However, tissue engineering regenerative medicine (TERM) is a multidisciplinary field that combines bioengineering and medicine to develop alternative therapies to repair tissues and organs as shown in the table 1 (Saini et al., 2021).

Table 1: Characteristics of tissue engineering and regenerative medicine

Characteristics	References
Goals	To create new functional organs by creating new cells or tissues to restore body functions. (Saini et al., 2021)
Techniques	Tissue engineering, gene therapy, cell base transplantation, 3D bioprinting and much more. (Xie et al., 2020)
Materials	Cells, biomaterials, scaffolds. (Babbar et al., 2020)
Benefits	Solves the issue of organ shortage and also provides efficient therapies for many clinical disorders. (Parihar et al., 2022)

Nanomaterials for Regenerative Medicines

Nanodevices

Nanodevices are nanotechnological elements and is a powerful strategy for regenerative medicine which allows the recreation of nanoscale tissue features that can be used for many cellular processes. Some of the examples of nanodevices which are used in regenerative medicines are nanoparticles, biosensors, nanofibers, biodegradable nanocarriers (Yang et al., 2019). Advancements in the technology of microfabrication also creates invention in nanodevices. Some of the nanodevices used in regenerative medicines are biocapsules, biosensors, laboratory on a chip and others.

Biocapsules are the form of nanodevices which can be used for the storage and transportation of molecules which are collected in a controlled way. Bioencapsulation is a process which involves the enclosing of tissues or other biological active substances in semi-permeable membranes. This process has been shown to be effective in copying the natural environment of the cell which further improves the efficiency of many metabolites and different therapeutic agents (Aylanc et al., 2023).

Bioreactors can be used to create a suitable environment such as temperature, pH, pressure for cells and tissues to grow fast in vitro methods. Thus different bioreactors which plays important role in regenerative medicine are cell culture, *in-vitro* organ modeling, stem cell therapy and tissue engineering (Ko et al., 2018).

Biosensors are devices which combine biological and electrical components to detect and measure different abnormalities, toxins, to diagnose or predict diseases related to immune system, to monitor the status of tissue culture, to check protein interactions and to evaluate the effects of drug concentration and can even measure harmful chemicals and pH values. They actually change the biological responses into the electrical signals which may be further measured to check abnormalities and interactions. The biological elements, such as enzymes, antibodies or nucleic acids, interact with the samples or specimens which are being tested. They have high specificity and sensitivity thus can analyze samples rapidly (Alma et al., 2022). On the other hand, nanosensors are the sensor which are able to detect different reactions including biological, chemical or electrical reactions in various local environments. Some of the examples of nanosensors used are quantum dots, fluorescent nanoparticles, metallic nanoparticles and molecule release sensor (Solaimuthu et al., 2020; Rong et al., 2019).

However, there is an industrial technique, known as biomanufacturing which can be used to produce biological materials including human tissues by manipulating different biological techniques. One of the examples is DNA biosensing. The figure 2 elaborates DNA biosensing with the application of 3D printing technology on it. The different type of facilities related to biomanufacturing can also be used to modify cells to manufacture different chemical or molecular products. Biomanufacturing can also be used in different types of industries, including healthcare, food production, and agriculture. However, it is important to control the quality and conditions of the biological structures to produce good quality products, and biosensing technologies can help to control these (Alma et al., 2022).

Nanoparticles (NPs)

The nanoparticles which are used for regenerative medicines mainly focus on delivery systems for genetic material, biomolecules and for reinforcing the bioactivity of three dimensional (3D) scaffolds in tissue engineering. The NPs used in delivery systems includes microspheres, microcapsules, liposomes, micelles and dendrimers as shown in table 2. There are different types of magnetic nanomaterials such as iron oxide

NPs which are considered as the most important for the research of stem cell. Iron oxide NPs are emerging tools for Magnetic Resonance Imaging abbreviated as MRI (Dadfar et al., 2019).

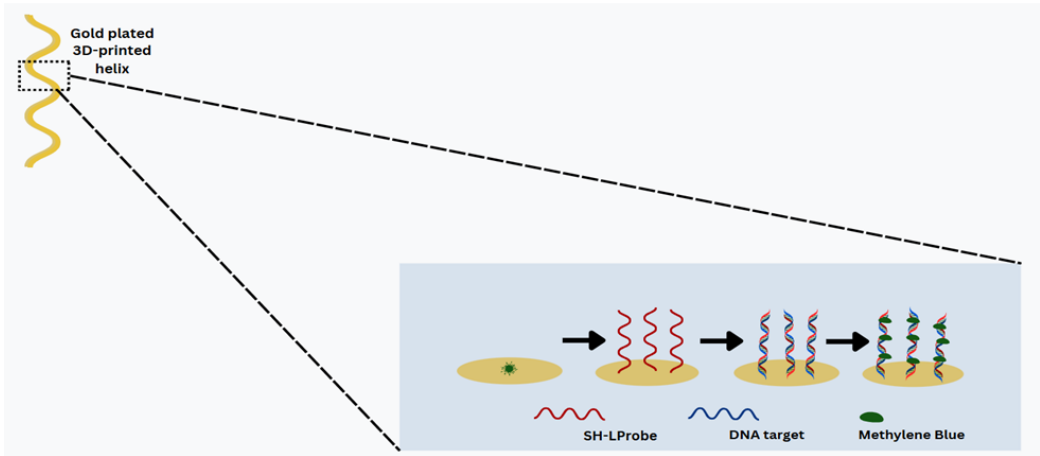


Fig. 2: DNA biosensing by the application of 3D printing technology (Designed by Adobe Photoshop)

Table 2: Types of nanoparticles used in delivery system

Types	Description	References
Microspheres	These are spherical particles made up of biodegradable polymers or proteins which can encapsulate the drugs and release them in a measured way.	(Yusuf et al., 2023)
Microcapsules	These are the carrier systems for pharmaceuticals which can be customized to adhere to the targeted tissue.	(Ladeira et al., 2022)
Liposomes	These are the compact lipid nanostructures which can entrap both hydrophobic and hydrophilic drugs and used to treat diseases like ovarian cancer etc.	(Cheng et al., 2020)
Micelles	These are type of nanocarriers which are formed by the spontaneous arrangement of amphiphilic di-block co-polymers in aqueous solutions.	(Bhardwaj & Jangde, 2023)
Dendrimers	These are the organic nanocarriers which are mostly considered in designing target specific drug delivery systems.	(Ajith et al., 2023)

Nanocarriers

Nanocarriers are used in regenerative medicine to deliver drugs, genetic material, and growth factors, and to monitor cells. They can be used for many purposes in regenerative medicine, for example as drug delivery, cell monitoring, mechanical stimulation, imaging and to overcome multi-drug resistance. They can be generated from a variety of materials, such as ceramics, metals, and polymers, hydrogels, dendrimers, liposomes (Su & P, 2020).

The delivery of biomolecules in a controlled manner is the main thing to consider in the support and enhancement of tissue growths during regeneration processes. Bone regeneration and osteoblast adhesion are found to be enhanced with hydroxyapatite nanoparticles. The multi-functional property of nanocarriers make them ideal for treating MDR cancer. The nanocarriers basically reduces the effects of ABC transporter mediated drug efflux, which is the main mechanism of MDR and further they overcomes the drug resistance as a conclusion (Gao et al., 2024).

Nanotechnology Based Stem Cell Therapy

Nanotechnology and stem cell therapy are two disciplines which show prominent areas of research during the treatment and contributes towards the improvement in human health. The stem cell therapy is also known as regenerative medicine and is a treatment which is done with stem cells. This therapy as shown promising results while treating number of diseases such as cancer, cardiac disorders, diabetes and neurodegenerative diseases. Although, it is very interesting and useful as it integrates two disciplines i.e. nanotechnology and stem cell which further contributes towards human health. The nanotechnology based strategies in the research related to stem cell have now been established by using various techniques and different mechanisms (Ponpandian et al., 2023). This figure 3 shows the process of stem cell briefly as stem cell is isolated from donor (human), then the propagation of stem cells are done by culture methods in laboratories and then nanoparticles associated stem cells are prepared by the combination of nanoparticles with stem cells and then these new stem cells are applied to treat various diseases including cardiac, neurodegenerative diseases, cancer and others. Additionally, there are different factors which involves during the production of nanomaterials based stem cells (Dong et al., 2021).

However, when the conventional therapy does not work then cell based therapies can be an excellent alternative to treat a number of diseases and different types of infections in humans. For this purpose, it is important to understand different processes such as cell cycle and cell differentiation, which will further help to design cell-based therapies in proper way and imaging techniques to check cell imaging. Some of the imaging methods which are used for cell imaging involves MRI, fluorescent imaging, and radioactive cell imaging (Dong et al., 2021).

According to the recent studies, the utilization of nanotechnology in stem cell research has showed better advancements, which are important for this interdisciplinary field. Some of the applications of stem cell nanotechnology includes isolation and identification of stem

cells, lineage and differentiation of stem cell, imaging and tracking of stem cells, gene and macromolecule delivery system of stem cells which further involves the stem cell based therapies for neurodegenerative diseases, cardiac diseases and cancer (Ponpandian et al., 2023). This figure 4 shows the important applications of nanotechnology in stem cell therapy.

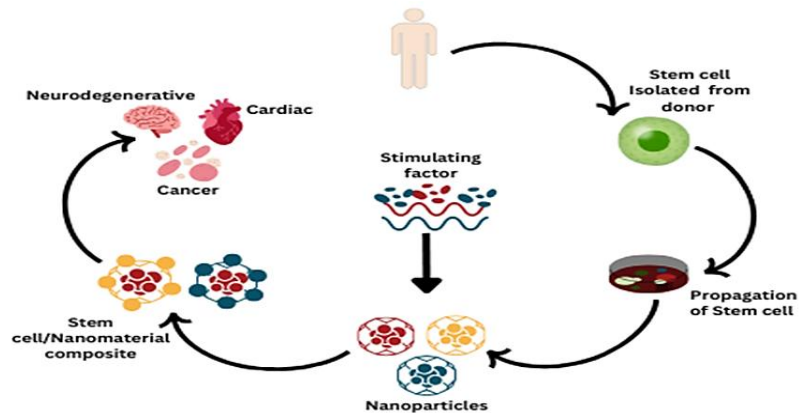


Fig. 3: The process of stem cell therapy (Designed by Adobe Photoshop)

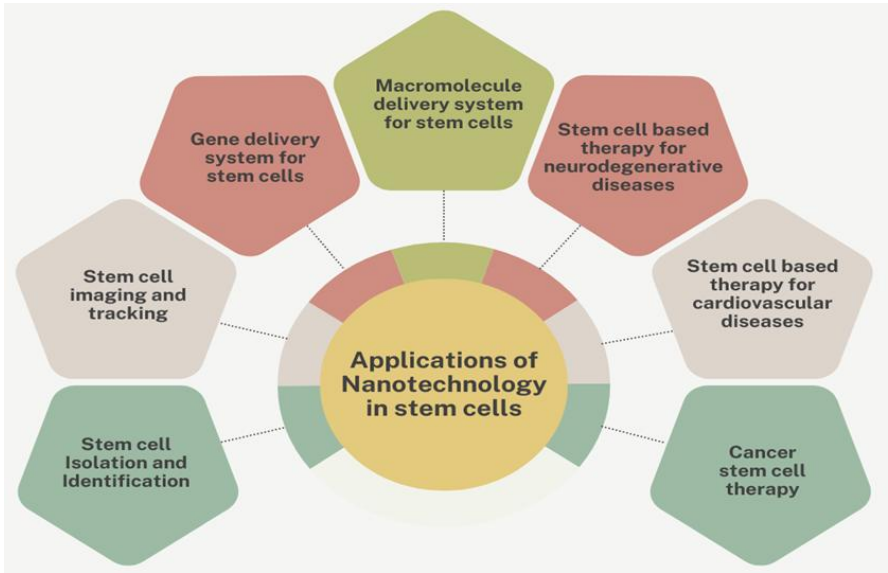


Fig. 4: Utilization of nanotechnology in stem cell therapy (Designed By Word)

Why Carbon Nanoparticles are Suitable for Tissue Engineering

The properties of nanostructures depend on the nanomaterials used. Carbon nanomaterials are mostly used in tissue engineering research along with drug delivery process because as compared to some traditional strategies because the carbon nanomaterials have the capability of large surface areas, have excellent mechanical, electrical and thermal features, strong enough and are suitable to use in drug delivery and tissue engineering after modifications. Additionally, some of the properties of carbon nanoparticles such as their high drug and tissue loading property, their good biocompatibility and long duration of action, make them good and suitable to use in tissue engineering. However, cells which attach directly onto carbon nanotube containing structures which further produces good cell growth (Zheng et al., 2022).

Types of Carbon Nanotubes used in Tissue Engineering

Some of the types and properties of carbon nanotubes are shown in table 3, as they as suitable and considered best for tissue engineering.

Table 3: Types of carbon nanotubes used in tissue engineering

	Single-walled carbon nanotubes	Multi-walled carbon nanotubes	References
Diameter	Their diameter is between 0.5 to 2.5 nm	Their diameter is between 7 and 100 nm	(Omrani et al., 2019)
Aspect ratio	Their aspect ratio is typically greater and goes up to 10,000.	Their aspect ratio is between 50 and 4,000	(Aminul Islam et al., 2024)
Description	These types of nanotubes consist of a single layer of graphene rolled into a hollow cylinder	These types of nanotubes consist of multiple layers of graphene sheets rolled up into a tube shape	(Anzar et al., 2020)
Applications	<ul style="list-style-type: none"> Cancer treatment Bio-imaging Drug delivery 	<ul style="list-style-type: none"> Bone regeneration Drug delivery Drug delivery 	(Krishnaveni et al., 2022)

Carbon Nanotubes in Bone Tissue Engineering

Carbon nanotubes are considered more suitable biomaterial for bone tissue engineering because of some unique features such as mechanical strength, electrical conductivity, and chemical stability. Their electrical conductivity can be controlled by changing their length or diameter accordingly, which can make them as electron cell biosensor. According to their characteristics, they support bone tissue regeneration in many ways and can be used to deliver drugs and biomolecules and can also be used to bind with other molecules including antibodies and radioisotopes. They can also be used to regulate the morphology of the cell (Chen & Li, 2022).

Carbon Nanotubes for Neural Tissue Engineering

As previously discussed, that carbon nanotubes are considered suitable bone tissue engineering, they are also suitable for neural tissue engineering as they have some unique properties and has potential to promote neural development. As they have excellent electrical conductivity, good strength, which makes them good for neural development, as they interact with neurons and thus promotes neural development which is important in the engineering of neural tissues. However, the aim of this technique is to develop future strategies to repair tissues which further promotes the functional recovery after any kind of damage related to the brain (Redondo-Gómez et al., 2020).

Carbon Nanotubes in Cardiac Tissue Engineering

The unique electrical conducting feature of carbon nanotubes makes them suitable choice to use in cardiac tissue engineering. Their integration along with polymeric scaffold is an ideal approach in cardiac regeneration as their conductivity has an improving effect on cardiac tissues. The research has made success with the production of scaffolds with nanoscale features which aims to regenerate the cardiac tissues to restore cardiac functions. Additionally, regenerating cardiac tissues would be able to improve the chances of recovery of cardiac disorders such as heart failure and other cardiovascular diseases. Overall, they have shown their great prospects to develop new platforms for the repairing of cardiac tissues which further enhanced the function of cardiac tissues (Barrejón et al., 2021).

Current Challenges Associated with Regenerative Medicine

The most challenging aspects of regenerative medicine when they are used to treat diseases are their efficiency and safety issues. For example, during the stem cell therapy, there are many challenges which are faced such as which cell type would be the best choice and which approach would be the suitable one. Additionally, the major challenge in the therapeutic applications of stem cell therapy is the production of a fast, easily operated and low cost techniques to purify the expected cells from the available cell mixture and also to reduce the cell variability in the culture. However, there are also many technical issues which slow down the applications even there are many recent advancements done in this field (Altyar et al., 2023).

Moreover, the use of nanoparticles in diagnostic and therapeutic procedures are somehow restricted due to their safety concerns. On the other hand, the continuous development of gene delivery systems also represents an emerging challenge for regenerative medicine. However, the complications in the wide range of applications are due to lack of knowledge to understand the mechanism of actions between the nanoparticles and the stem cells (Xuan et al., 2023).

Challenges Associated with Tissue Engineering

The major problem of tissue engineering is the neovascularization which is necessary to supply oxygen and nutrients to a cell. It is not possible to expect the neovascularization for a cell scaffold construct in case of *in-vitro* tissue engineering (Brady et al., 2023). Additionally, the four primary issues in tissue engineering involves biomaterials, cell sources, vascularization, and design of drug delivery systems as biomaterials and cell sources should be specific for the engineering of every tissue (Chandra et al., 2020).

Future of Regenerative Medicine and Tissue Engineering

Several research teams have started working to create new treatments techniques to overcome the current strategies due to the limitations of methods currently available for regenerating many vital organs. Consequently, this will allow for significant advancements in regenerative medicines in the near future. Many of the novel regenerative medicine concepts have begun to provide encouraging benefits and outcomes (Altyar et al., 2023). The coming decade is expected to see more advancements which would be considered successful. It is expected that tissue engineering would become recognized medical specialty along with more acceptance of this technique for various treatments among patients instead of other conventional therapy in future (Chandra et al., 2020).

Conclusion

Nanotechnology plays an important role in regenerative medicine as well as in tissue engineering as it creates new functional organs to restore the normal functions of the body. Stem cell therapy is the prominent therapy which is used to treat various diseases including cardiac, neurodegenerative disease and even cancer. Additionally, carbon nanoparticles including single-walled and multi-walled carbon nanotubes are considered good for tissue engineering because of some of the properties of carbon nanoparticles which make them suitable to use in various strategies including bone, cardiac, and neural tissue engineering. Moreover, there are also many challenges associated with tissue engineering and regenerative medicine that's why the use of nanoparticles in diagnostics and therapeutics are somehow restricted in many cases due to their safety issues and due to the lack of knowledge related to the mechanism of actions, creating many complications but many researchers have started working to overcome the current challenges which are associated with the limitations of methods currently available for regenerating many vital organs for significant advancements in regenerative medicines in the near future. Overall, it is expected that tissue engineering regenerative medicine would be accepted more among patients for various treatments in future instead of other conventional therapies.

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