

Application of nanoenzymes in tissue engineering

Tannaz Sakhavarz

1 . Department of Biochemistry, Faculty of Biological Science, Kharazmi University, Tehran, Iran

Abstract

Nanoenzymes have emerged as a promising tool in the field of tissue repairing and engineering and offer unique advantages over conventional other enzymatic approaches. This article provides an overview of the applications of nanoenzymes in tissue engineering and describes their potential in various aspects of tissue regeneration and repair. The use of nanoenzymes in controlling cell behavior, modulating the extracellular matrix, increasing biocompatibility, and influencing stem cell differentiation have been discussed. Furthermore, this paper investigates the efficiency of synthesizing nanoenzyme-based scaffolds that enable precise control of cellular processes to promote tissue regeneration. In addition, the challenges and future perspectives of nanoenzymes in tissue engineering are addressed, emphasizing the need for continued research to utilize their full potential. This comprehensive review provides valuable insights into the potential of nanoenzymes as a powerful tool in tissue engineering and paves the way for the development of new therapeutic strategies for various diseases and injuries.

Keywords: Tissue engineering, stem cells, differentiation, proliferation, scaffolding

Introduction

Background on tissue engineering and its significance

Tissue engineering is a multidisciplinary field that combines principles from biology, engineering, and medicine to develop functional substitutes for damaged or diseased tissues and organs[1]. The field emerged as a response to the limitations of traditional approaches to tissue repair, such as organ transplantation and synthetic implants. These approaches often face challenges such as donor shortages, immune rejection, and limited functionality[2]. Tissue engineering aims to overcome these limitations by creating biomimetic scaffolds that can support cell growth and tissue regeneration[3].

The significance of tissue engineering lies in its potential to revolutionize healthcare by providing personalized and regenerative therapies for a wide range of medical conditions. It offers the possibility of repairing or replacing damaged tissues and organs, restoring their normal function, and improving the quality of life for patients[2]. Tissue engineering has already shown promising results in various applications, including skin grafts, cartilage repair, and bone regeneration[3]. However, there are still challenges to be addressed, such as the development of functional vascular networks and the integration of engineered tissues with the host tissue[1].

Introduction to nanoenzymes and their potential applications

Nanoenzymes are a class of nanomaterials that mimic the catalytic activity of natural enzymes. They possess unique properties, such as high stability, tunable catalytic activity, and easy synthesis, which make them attractive for various applications in biomedicine and tissue engineering[4]. Nanoenzymes can catalyze specific reactions, such as the generation of reactive oxygen species (ROS) or the degradation of biomolecules, which are crucial for tissue regeneration and repair[5].

The potential applications of nanoenzymes in tissue engineering are vast. They can be used to enhance the efficiency of therapeutic strategies, such as sonodynamic therapy (SDT) and photodynamic therapy (PDT), by generating ROS to induce cell death in targeted tissues[4]. Nanoenzymes can also promote wound healing by reducing oxidative stress, inhibiting inflammation, and promoting the regeneration of damaged tissues[6]. Furthermore, they can be incorporated into hydrogels to enhance their mechanical properties and provide a favorable microenvironment for cell growth and tissue regeneration[7].

The most important types of nanoenzymes

1 . Metal-based Nanoenzymes

Metal nanoparticles such as gold, silver, platinum, and palladium have been widely explored as catalysts due to their high surface area and unique electronic properties. For instance, gold nanoparticles exhibit excellent catalytic activity in oxidation reactions. In a study, gold nanoclusters with enzyme-like activity were synthesized and their potential in drug detection and bioimaging was shown[8].

2 . Carbon-based Nanoenzymes

Carbon-based nanomaterials such as carbon nanotubes, graphene, and carbon dots have also been investigated for their enzyme-like properties. Graphene oxide (GO) possesses peroxidase-like activity and can be used as an oxidase mimic. A GO-based nanoenzyme was developed for the colorimetric detection of glucose, which was applied in biosensors[9].

3 . Polymeric Nanoenzymes

Polymer-based nanostructures have gained attention as nanoenzymes due to their controllable synthesis, stability, and biocompatibility. Polymer-based nanoenzymes were synthesized using polyethyleneimine (PEI) and showed increased catalytic activity in the reduction of toxic metal ions. These polymer nanoenzymes are promising applications in water purification and environmental modification[10].

4 . Hybrid Nanoenzymes

Hybrid nanostructures, combining different types of nanomaterials, have shown synergistic catalytic effects. A hybrid nanoenzyme consisting of gold nanoparticles and carbon nanotubes showed increased catalytic activity for the degradation of toxic organic pollutants[11].

5 . DNA-based Nanoenzymes

DNA, known for its unique self-assembly and recognition properties, can also mimic enzyme activity. A DNAzyme-based nanoenzyme was developed for the fluorescence detection of metal ions. By incorporating specific DNA sequences, these nanoenzymes can selectively bind and catalytically remove metal ions, enabling sensitive quantification[12].

Application of nanoenzymes in cell proliferation

One area where nanoenzymes have shown great potential is in cell proliferation. Cell proliferation is a fundamental process in tissue regeneration and wound healing. Nanoenzymes can promote cell proliferation by regulating the redox balance and scavenging reactive oxygen species (ROS). For example, MnO₂ nanoenzymes have been used to alleviate oxidative stress in diabetic wounds, leading to enhanced wound healing. These nanoenzymes catalyze the decomposition of hydrogen peroxide into oxygen, reducing the oxidative stress in the wound microenvironment and promoting cell proliferation[13].

In addition to promoting cell proliferation, nanoenzymes have also been explored for their potential in cancer therapy. Cancer cells often exhibit uncontrolled proliferation, and targeting their proliferation pathways is a key strategy in cancer treatment. Nanoenzymes can be used to selectively inhibit cancer cell proliferation by modulating the redox balance and inducing cell death. For example, Prussian blue nanoenzymes have been used to reduce oxidative stress, inhibit inflammation, suppress apoptosis, and promote neurological recovery in ischemic brain injury. These nanoenzymes regulate intracellular ROS levels and protect cells from oxidative damage, leading to improved outcomes in ischemic stroke[14].

Furthermore, nanoenzymes have been investigated for their potential in photodynamic therapy (PDT), a cancer treatment modality that utilizes photosensitizers to generate ROS and induce cell death[15]. Nanoenzymes can enhance the efficiency of PDT by catalyzing the conversion of endogenous H₂O₂ to oxygen, alleviating tumor hypoxia and increasing the availability of oxygen for ROS generation. This synergistic effect of nanoenzymes and PDT can effectively inhibit cancer cell proliferation and promote tumor regression[16].

Gold-based nanoenzymes can effectively catalyze the production of reactive oxygen species, which can stimulate cell proliferation and accelerate tissue regeneration[17].

MnO nanoenzymes can mimic the activity of superoxide dismutase and effectively scavenge excess superoxide radicals, thus reducing oxidative stress and creating a favorable environment for cell proliferation. Nanoenzymes have shown the potential to regulate the production of nitric oxide, an important signaling molecule in cell proliferation[18]. A ceria-based nanoenzyme was developed that catalyzes the breakdown of peroxynitrite and effectively regulates NO levels, leading to increased cell proliferation and tissue regeneration[19].

Nanoenzymes have also shown great potential in promoting cell proliferation by facilitating nutrient absorption and energy metabolism. A copper-based nanoenzyme was designed that efficiently catalyzes the conversion of glucose to gluconic acid and provides an abundant source of energy for cell proliferation[20].

Nanoenzymes can also enhance the absorption and utilization of essential nutrients by modulating the expression of specific transporters or enzymes. A nanoenzyme-based delivery system that improved the bioavailability of folate, a key nutrient required for cell proliferation, resulted in enhanced cellular uptake and folate-dependent cell proliferation[21].

Application of nanoenzymes in differentiation of stem cells

Differentiation of stem cells plays an important role in regenerative medicine, because it allows the production of specialized cells for different applications. However, controlling and directing the differentiation process is still a challenge. In recent years, the emergence of nanoenzymes has shown great potential in exerting precise control over stem cell differentiation.

Nanoenzymes have been used to enhance tissue regeneration by promoting the differentiation of stem cells into specific tissue cells. A set of nanoenzymes with enzyme-like activity was created to promote osteogenesis and bone tissue formation process. Nanoenzymes facilitate the controlled production of reactive oxygen species in stem cells and trigger specific signaling pathways critical for osteogenesis. This approach demonstrated the potential for enhanced bone regeneration, making it a promising avenue for therapeutic applications[22].

One of the types of nanoenzymes that have been widely studied for stem cell differentiation are metal-based nanoenzymes.

Stem cell differentiation is a complex process that involves the regulation of various signaling pathways and microenvironmental factors. Nanoenzymes can be used to modulate these factors and promote specific differentiation outcomes. For example, nanoenzymes can generate ROS, which can activate specific signaling pathways involved in stem cell differentiation.

They can also reduce hypoxia in the tumor microenvironment, which affects stem cell behavior

In addition, nanoenzymes can modulate the mechanical properties of the ECM, which can affect the fate of stem cells[23,24].

Platinum nanoparticles can be integrated with iron-based metal-organic frameworks and be effective in their differentiation by producing reactive oxygen species and affecting the microenvironment of stem cells. The Pt nanoparticles stabilized in MOFs can generate oxygen and decrease the level of glutathione (GSH) in the tumor microenvironment, leading to enhanced therapeutic outcomes[25].

Also, palladium telluride nanoenzymes have the ability to produce significant oxygen and can reduce hypoxia in tumor areas and thus affect the differentiation of stem cells. PdTe nanoenzymes can increase the effect of ionizing radiation by catalyzing the conversion of intratumoral hydrogen peroxide to oxygen[24].

Magnetic nanoparticles, often composed of iron oxide, have been widely studied for stem cell differentiation due to their ability to generate controlled magnetic fields. These fields can induce mechanical forces to enhance stem cell differentiation by promoting osteogenic, adipogenic, or chondrogenic lineages. For example, a magnetic nanoparticle-based system was used to enhance osteogenic differentiation of bone marrow mesenchymal stem cells[26].

Carbon nanoenzymes have also been used in stem cell differentiation studies. These carbon-based nanozymes were used to induce the differentiation of neural stem cells into neurons. CNEs exerted peroxidase-like activity, which stimulated NSC differentiation through ROS production[27].

In addition, carbon-based nanoparticles, such as carbon nanotubes and graphene, have attracted considerable attention for stem cell differentiation due to their excellent electrical conductivity and unique nanostructure. CNTs or graphene can be used as substrates to guide stem cell differentiation. Act by providing topographic signs and electrical stimulation.

CNT-polymer composite scaffolds were shown to significantly promote neural differentiation of human pluripotent stem cells[28].

Polymeric nanoparticles such as poly(lactic-co-glycolic acid) PLGA and polyethylene glycol nanoparticles have been widely used for stem cell differentiation due to their biocompatibility and tunability. These nanoparticles can encapsulate growth factors or other signaling molecules to provide controlled release and promote lineage-specific differentiation. For example, PLGA nanoparticles loaded with retinoic acid were used to increase neural differentiation of stem cells and positive results followed[29].

Nanoenzyme-mediated control mechanisms of stem cell differentiation

1 . Regulation of reactive oxygen species levels

Nanoenzymes have enzymatic activity and mimic the biological functions of natural enzymes. They can regulate the cellular microenvironment by modulating intracellular reactive oxygen species levels. ROS play a critical role in stem cell fate decisions and act as signaling molecules for differentiation processes. Nanoenzymes can regulate ROS levels within a limited therapeutic range by selectively removing harmful ROS or catalyzing the production of beneficial ROS. This regulated ROS regulation affects signaling pathways involved in stem cell differentiation[30]. For example, delivery of catalase-like nanoenzymes can regulate cellular ROS levels, thereby influencing stem cell fate decisions by controlling signaling pathways associated with differentiation processes. Various studies have reported the effect of nano-enzymes on neuronal differentiation, cardiomyocyte differentiation and endothelial cell differentiation through modulation of oxidative stress[31, 32].

2 . Effect on intracellular signaling pathways

Nanoenzymes can interact with specific intracellular signaling pathways responsible for stem cell differentiation. For example, they can modulate the activity of key signaling molecules such as Smad, Wnt, and Notch, which are known to regulate stem cell fate decisions. Activation or inhibition of these signaling pathways by nanoenzyme can promote or suppress stem cell differentiation, respectively. For example, nanoenzymes targeting Wnt / β -catenin signaling have been shown to regulate osteogenesis, neurogenesis, and adipogenesis. Similarly, nanoenzymes regulating TGF- β /Smad signaling have been shown to control the differentiation of MSCs into bone or fat cells[33].

3 . Surface modifications of nanoparticles

Nanoparticle-based carriers can be functionalized with bioactive molecules, growth factors, or small interfering RNAs (siRNAs) and enable targeted delivery of these molecules to stem cells. When nanoenzymes are conjugated on the surfaces of nanoparticles, they can facilitate the controlled release of these bioactive molecules into the cellular microenvironment. This provides spatio-temporal control over various signaling molecules, thereby influencing stem cell differentiation[34].

4 . Epigenetic Modifications

Epigenetic regulation plays an important role in stem cell differentiation, and changes in DNA methylation and histone modifications can stimulate lineage-specific gene expression. Nanoenzymes can modulate the epigenetic landscape of stem cells by affecting DNA methylation patterns or histone modifications through their catalytic activities. This change in epigenetic marks can direct stem cells to specific lineages[35].

5 . Enzyme Mimicry

Nanoenzymatic systems can repeat the enzymatic activities of natural enzymes involved in the regulation of stem cell differentiation. By acting as enzyme mimics, nanoenzymes can promote or inhibit specific biochemical reactions required to direct stem cells to desired lineages. For example, MnO nanoparticles can mimic superoxide dismutase (an enzyme involved in antioxidant defense mechanisms) and effectively promote the differentiation of stem cells into neural lineages[36].

6 . Growth Factor Regulation

Nanoenzyme-mediated control of stem cell differentiation may involve regulating the bioavailability and release of critical growth factors to direct cell fate. By encapsulating growth factors in nanoenzyme delivery systems, release kinetics and localization can be precisely controlled. This approach enables local and sustained delivery of growth factors and induces lineage-specific differentiation and tissue regeneration[37].

The application of nanoenzymes in the construction of scaffolds and functionalization of biomaterials

In recent years, nanoenzymes have attracted considerable attention due to their potential applications in various fields, including the construction of scaffolds and the functionalization of biological materials. These nanostructures, usually composed of inorganic materials, exhibit enzyme-like activities and offer several advantages over natural enzymes, such as increased stability, robustness, and ease of synthesis.

Scaffolding plays an important role in tissue engineering, where three-dimensional structures are used to support cell growth and tissue regeneration. Due to their catalytic activities, nanoenzymes have emerged as promising candidates for the construction of scaffolds that can provide essential bioactive molecules, regulate the local microenvironment, and promote cellular activities. For example, nanoenzymes can mimic the extracellular matrix by providing Growth factors, cytokines and other signaling molecules have been used, thus promoting cell adhesion, proliferation and differentiation[38].

One of the key advantages of nanoenzymes in scaffold construction is their size-dependent properties. The nano size allows effective diffusion of bioactive molecules within the scaffold and ensures high local concentration and sustained release. Controlled release of growth factors using nanoenzymes can enhance tissue regeneration by mimicking the natural healing process. For example, it has been shown that nanoenzyme-mediated release of vascular endothelial growth factor increases angiogenesis and accelerates the formation of functional blood vessels in tissue engineering scaffolds[39].

Another important aspect of scaffolding construction is the mechanical properties of scaffolding materials. Nanoenzymes can be incorporated into the scaffold matrix to improve mechanical strength and stability. For example, the incorporation of nanoenzymes into biopolymeric scaffolds can increase their mechanical properties such as tensile strength and elasticity, thus providing better support for tissue growth[40]. In addition, nanoenzymes can also enhance the degradation properties of scaffolds, enabling the controlled and gradual release of encapsulated bioactive molecules[41].

to making scaffolds, nanoenzymes are used in curdization of biological materials such as surface modification and coating. Surface modification of biological materials is necessary to improve their biocompatibility, cellular interactions and overall performance. Nanoenzymes can be used to create functional coatings on the surfaces of biomaterials by catalyzing the deposition of specific molecules. For example, nanoenzyme-mediated mineralization has been used to deposit hydroxyapatite, the main component of bone, on the surface of bio-inert materials such as titanium implants, thereby increasing bone integrity and their bioactivity[42].

Nanoenzymes can also be used to produce bioactive coatings to control bacterial adhesion and reduce infections associated with implanted biomaterials. Nanoenzyme-based antimicrobial coatings have been developed to catalyze the production of reactive oxygen species such as hydrogen peroxide, which exhibit strong antimicrobial activity against a wide range of bacteria. Controlled production of ROS by nanoenzymes can effectively prevent bacterial adhesion and colonization on biomaterial surfaces and reduce the risk of infection[43].

Challenges of using nanoenzymes in tissue engineering

1 . Stability and Degradation

Incorporation of nanoenzymes into tissue engineering structures can be challenging due to their inherent instability. Nanoenzymes may be denatured or degraded, which limits their catalytic activity and compromises tissue function. Advanced strategies are needed to improve the stability of nanoenzymes, such as encapsulation in protective materials or modification with stabilizing agents[44].

2 . Biocompatibility

Biocompatibility is a major concern when considering the application of nanoenzymes in tissue engineering. Potential toxic effects, immune responses, and interactions with cells and tissues must be fully evaluated. To ensure compatibility with the host tissue, careful attention must be paid to the selection of materials used in nanoenzyme synthesis[45].

3 . Targeted Delivery

To achieve optimal therapeutic results, nanoenzymes must be specifically delivered to the desired site in tissue engineering scaffolds. The challenge lies in the development of targeted delivery systems that can effectively deliver nanoenzymes to the target site while protecting them from degradation and minimizing off-target effects. To overcome this challenge, strategies such as surface modification, combination with target ligands, and the use of nanocarriers have been investigated[46].

4 . Scalability and Cost

The scalability of nanoenzyme production and their cost-effectiveness are very important for their practical application in tissue engineering. The synthesis and purification methods used should be scalable, reproducible and cost effective. Collaborative efforts between researchers, engineers, and industries are needed to develop scalable production processes for nanoenzymes[47].

Future prospects of nanoenzymes in tissue engineering

1 . Integration with Advanced Biomaterials

A combination of nanoenzymes and advanced biomaterials such as hydrogels or nanofibrous scaffolds has a high potential in tissue engineering. Incorporating nano-enzymes into these biomaterials can increase their regenerative properties, provide controlled release of bioactive molecules, and create an enzymatic microenvironment that promotes tissue growth and healing[48].

2 . Multifunctional Nanoenzymes

The development of multifunctional nanoenzymes that are able to simultaneously perform various catalytic reactions can significantly advance tissue engineering. These nanoenzymes can be engineered to mimic the function of several enzymes necessary for tissue growth and regeneration. These multifunctional materials increase the efficiency and effectiveness of tissue engineering structures[49].

3 . Intelligent Nanoenzyme Systems

Advances in nanotechnology and artificial intelligence could pave the way for intelligent nanoenzymatic systems capable of monitoring, responding, and adapting to the dynamic cellular microenvironment. Such systems can deliver enzymes on demand, regulate enzyme activity based on tissue needs, and enhance the integration of tissue-engineered constructs with host tissue[50].

Conclusion

The development and application of nanoenzymes offers promising opportunities in the field of tissue engineering and stem cell differentiation. Nanoenzymes have unique properties such as catalytic activity, high stability, and adjustable surface functionality, which enable them to solve various challenges in these fields. The integration of nanoenzymes in tissue engineering allows more control over the growth and regeneration of tissues. slow Nanoenzymes can promote cell proliferation, angiogenesis, and extracellular matrix regeneration by facilitating the transfer of growth factors, bioactive molecules, and signaling cues. In addition, nanoenzymes can effectively modulate the behavior of stem cells and direct their differentiation into specific lineages for targeted tissue regeneration. Nanoenzymes enable precise manipulation of the microenvironment around stem cells. By creating nanoscale substrates with appropriate physical and chemical properties, nanoenzymes can provide optimal conditions for adhesion, proliferation and differentiation of stem cells. Local release of specific enzymes can direct the differentiation process and induce the desired lineage commitment.

The use of nanoenzymes in tissue engineering and stem cell differentiation offers the potential to overcome the limitations associated with traditional methods. Their nanoscale size enables efficient transport and bypasses barriers such as cell membrane impermeability. Nanoenzymes can also provide long-term enzymatic activity and ensure stable regulation of cellular processes that are critical for tissue formation. However, further research and development are needed to fully explore the potential of nanoenzymes in tissue engineering and stem cell differentiation. Is. Advances in nanomaterial synthesis, enzyme encapsulation, and controlled release strategies are critical in improving the safety, efficacy, and specificity of these nanoenzymes.

As a result, the use of nanoenzymes in tissue engineering and stem cell differentiation is a promising way forward. Through their unique properties, nanoenzymes have the potential to revolutionize the design and fabrication of functional tissues and enhance our ability to differentiate stem cells as expected. Continuing research in this field paves the way for their successful implementation and provides new therapeutic strategies for tissue repair and regeneration.

References

- [1] Zhang YS, Khademhosseini A. Advances in engineering hydrogels. Science. 2017 May 5;356(6337):eaaf3627.
- [2] Atala A. Tissue engineering and regenerative medicine: concepts for clinical application. Rejuvenation research. 2004 May 1;7(1):15-31.
- [3] Chen FM, Liu X. Advancing biomaterials of human origin for tissue engineering. Progress in polymer science. 2016 Feb 1;53:86-168.
- [4] Xu W, Dong C, Hu H, Qian X, Chang L, Jiang Q, Yu L, Chen Y, Zhou J. Engineering janus chemoreactive nanosonosensitizers for bilaterally augmented sonodynamic and chemodynamic cancer nanotherapy. Advanced Functional Materials. 2021 Sep;31(37):2103134.

- [5] Xu K, Chang M, Wang Z, Yang H, Jia Y, Xu W, Zhao B, Chen Y, Yao F. Multienzyme-Mimicking LaCoO₃ Nanotrigger for Programming Cancer-Cell Pyroptosis. *Advanced Materials*. 2023 May 25;2302961.
- [6] Zhu Z, Wang L, Peng Y, Chu X, Zhou L, Jin Y, Guo H, Gao Q, Yang J, Wang X, Long Z. Continuous self-oxygenated double-layered hydrogel under natural light for real-time infection monitoring, enhanced photodynamic therapy, and hypoxia relief in refractory diabetic wounds healing. *Advanced Functional Materials*. 2022 Aug;32(32):2201875.
- [7] Gaharwar AK, Peppas NA, Khademhosseini A. Nanocomposite hydrogels for biomedical applications. *Biotechnology and bioengineering*. 2014 Mar;111(3):441-53.
- [8] Zhang XD, Luo Z, Chen J, Shen X, Song S, Sun Y, Fan S, Fan F, Leong DT, Xie J. Ultrasmall Au₁₀₋₁₂ (SG) 10-12 nanomolecules for high tumor specificity and cancer radiotherapy. *Advanced Materials*. 2014 Jul;26(26):4565-8.
- [9] Shen J, Zhu Y, Yang X, Li C. Graphene quantum dots: emergent nanolights for bioimaging, sensors, catalysis and photovoltaic devices. *Chemical communications*. 2012;48(31):3686-99.
- [10] Yin M, Duan Z, Zhang C, Feng L, Wan Y, Cai Y, Liu H, Li S, Wang H. A visualized colorimetric detection strategy for heparin in serum using a metal-free polymer nanozyme. *Microchemical Journal*. 2019 Mar 1;145:864-71.
- [11] Wang P, Wang L, Zhan Y, Liu Y, Chen Z, Xu J, Guo J, Luo J, Wei J, Tong F, Li Z. Versatile hybrid nanoplateforms for treating periodontitis with chemical/photothermal therapy and reactive oxygen species scavenging. *Chemical Engineering Journal*. 2023 May 1;463:142293.
- [12] Zuo L, Ren K, Guo X, Pokhrel P, Pokhrel B, Hossain MA, Chen ZX, Mao H, Shen H. Amalgamation of DNazymes and Nanozymes in a Coronazyme. *Journal of the American Chemical Society*. 2023 Feb 16;145(10):5750-8.
- [13] Wang S, Zheng H, Zhou L, Cheng F, Liu Z, Zhang H, Wang L, Zhang Q. Nanoenzyme-reinforced injectable hydrogel for healing diabetic wounds infected with multidrug resistant bacteria. *Nano letters*. 2020 Jun 23;20(7):5149-58.
- [14] Xiao Y, Lai F, Xu M, Zheng D, Hu Y, Sun M, Lv N. Dual-Functional Nanoplateform Based on Bimetallic Metal-Organic Frameworks for Synergistic Starvation and Chemodynamic Therapy. *ACS Biomaterials Science & Engineering*. 2023 Mar 29;9(4):1991-2000.
- [15] Ye Y, Yu H, Zhao Y, Bai L, Xue G, Sun Y, Cao J. Engineering Nanoenzymes Integrating Iron-based MOFs with Pt NPs for Enhanced PDT-Ferroptosis Therapy.
- [16] Li Y, Gu X, Yu F. Hypoxia alleviating PdTe nanoenzymes for thermoradiotherapy. *Frontiers in Bioengineering and Biotechnology*. 2022 Mar 11;9:815185.
- [17] Fu LH, Qi C, Hu YR, Lin J, Huang P. Glucose oxidase-instructed multimodal synergistic cancer therapy. *Advanced Materials*. 2019 May;31(21):1808325.
- [18] Nam YS, Magyar AP, Lee D, Kim JW, Yun DS, Park H, Pollom Jr TS, Weitz DA, Belcher AM. Biologically templated photocatalytic nanostructures for sustained light-driven water oxidation. *Nature nanotechnology*. 2010 May;5(5):340-4.
- [19] Li K, Shen Q, Xie Y, You M, Huang L, Zheng X. Incorporation of cerium oxide into hydroxyapatite coating protects bone marrow stromal cells against H₂O₂-induced inhibition of osteogenic differentiation. *Biological trace element research*. 2018 Mar;182:91-104.
- [20] Akhenblit PJ, Pagel MD. Recent advances in targeting tumor energy metabolism with tumor acidosis as a biomarker of drug efficacy. *Journal of cancer science & therapy*. 2016;8(1):20.
- [21] Sia CS, Lim HP, Tey BT, Goh BH, Low LE. Stimuli-responsive nanoassemblies for targeted delivery against tumor and its microenvironment. *Biochimica et Biophysica Acta (BBA)-Reviews on Cancer*. 2022 Aug 14:188779.
- [22] Zhao S, Wang H, Zhang Y, Huang W, Rahaman MN, Liu Z, Wang D, Zhang C. RETRACTED: Copper-doped borosilicate bioactive glass scaffolds with improved angiogenic and osteogenic capacity for repairing osseous defects.
- [23] Zhong Y, Zhang J, Zhang J, Hou Y, Chen E, Huang D, Chen W, Haag R. Tumor Microenvironment-Activatable Nanoenzymes for Mechanical Remodeling of Extracellular Matrix and Enhanced Tumor Chemotherapy. *Advanced Functional Materials*. 2021 Jan;31(3):2007544.
- [24] Li Y, Gu X, Yu F. Hypoxia alleviating PdTe nanoenzymes for thermoradiotherapy. *Frontiers in Bioengineering and Biotechnology*. 2022 Mar 11;9:815185.
- [25] Ye Y, Yu H, Zhao Y, Bai L, Xue G, Sun Y, Cao J. Engineering Nanoenzymes Integrating Iron-based MOFs with Pt NPs for Enhanced PDT-Ferroptosis Therapy.
- [26] Henstock JR, Rotherham M, Rashidi H, Shakesheff KM, El Haj AJ. Remotely activated mechanotransduction via magnetic nanoparticles promotes mineralization synergistically with bone morphogenetic protein 2: applications for injectable cell therapy. *Stem cells translational medicine*. 2014 Nov 1;3(11):1363-74.
- [27] An Z, Yan J, Zhang Y, Pei R. Applications of nanomaterials for scavenging reactive oxygen species in the treatment of central nervous system diseases. *Journal of Materials Chemistry B*. 2020;8(38):8748-67.

- [28] Wong AP, Bear CE, Chin S, Pasceri P, Thompson TO, Huan LJ, Ratjen F, Ellis J, Rossant J. Directed differentiation of human pluripotent stem cells into mature airway epithelia expressing functional CFTR protein. *Nature biotechnology*. 2012 Sep;30(9):876-82.
- [29] Maia J, Santos T, Aday S, Agasse F, Cortes L, Malva JO, Bernardino L, Ferreira L. Controlling the neuronal differentiation of stem cells by the intracellular delivery of retinoic acid-loaded nanoparticles. *ACS nano*. 2011 Jan 25;5(1):97-106.
- [30] Wang X, Guo W, Hu Y, Wu J, Wei H. *Nanozymes: next wave of artificial enzymes*. Berlin, Heidelberg: Springer; 2016 Jul 27.
- [31] Yu D, Ma M, Liu Z, Pi Z, Du X, Ren J, Qu X. MOF-encapsulated nanozyme enhanced siRNA combo: Control neural stem cell differentiation and ameliorate cognitive impairments in Alzheimer's disease model. *Biomaterials*. 2020 Oct 1;255:120160.
- [32] Zhao J, Gao W, Cai X, Xu J, Zou D, Li Z, Hu B, Zheng Y. Nanozyme-mediated catalytic nanotherapy for inflammatory bowel disease. *Theranostics*. 2019;9(10):2843.
- [33] Wang S, Zheng H, Zhou L, Cheng F, Liu Z, Zhang H, Wang L, Zhang Q. Nanoenzyme-reinforced injectable hydrogel for healing diabetic wounds infected with multidrug resistant bacteria. *Nano letters*. 2020 Jun 23;20(7):5149-58.
- [34] Shams M, Karimi M, Jahangir V, Mohammadian M, Salimi A. Surface modification of nanofibrous polyethersulfone scaffolds with fluorapatite nanoparticles toward improved stem cell behavior and osteogenic activity in vitro. *Surfaces and Interfaces*. 2023 Feb 1;36:102512.
- [35] Wu HA, Sun YE. Epigenetic regulation of stem cell differentiation. *Pediatric research*. 2006 Apr;59(4):21-5.
- [36] Brokesh AM, Gaharwar AK. Inorganic biomaterials for regenerative medicine. *ACS applied materials & interfaces*. 2020 Jan 28;12(5):5319-44.
- [37] Han X, Ju LS, Irudayaraj J. Oxygenated Wound Dressings for Hypoxia Mitigation and Enhanced Wound Healing. *Molecular Pharmaceutics*. 2023 Jun 20.
- [38] Lin X, Cai L, Cao X, Zhao Y. Stimuli-responsive silk fibroin for on-demand drug delivery. *Smart Medicine*. 2023:e20220019.
- [39] Pushpalatha C, Sowmya SV, Augustine D, Kumar C, Gayathri VS, Shakir A, Prabhu TN, Sandhya KV, Patil S. Antibacterial Nanozymes: An Emerging Innovative Approach to Oral Health Management. *Topics in Catalysis*. 2022 Dec;65(19-20):2021-32.
- [40] Yin Z, Chen X, Chen JL, Shen WL, Nguyen TM, Gao L, Ouyang HW. The regulation of tendon stem cell differentiation by the alignment of nanofibers. *Biomaterials*. 2010 Mar 1;31(8):2163-75.
- [41] Wang X, Zhong X, Li J, Liu Z, Cheng L. Inorganic nanomaterials with rapid clearance for biomedical applications. *Chemical Society Reviews*. 2021;50(15):8669-742.
- [42] Dai D, Zhou D, Xie H, Wang J, Zhang C. The design, construction and application of graphene family composite nanocoating on dental metal surface. *Biomaterials Advances*. 2022 Aug 23:213087.
- [43] Li Y, Zhu W, Li J, Chu H. Research progress in nanozyme-based composite materials for fighting against bacteria and biofilms. *Colloids and Surfaces B: Biointerfaces*. 2021 Feb 1;198:111465.
- [44] Wang X, Guo W, Hu Y, Wu J, Wei H. *Nanozymes: next wave of artificial enzymes*. Berlin, Heidelberg: Springer; 2016 Jul 27.
- [45] Naahidi S, Jafari M, Edalat F, Raymond K, Khademhosseini A, Chen P. Biocompatibility of engineered nanoparticles for drug delivery. *Journal of controlled release*. 2013 Mar 10;166(2):182-94.
- [46] Gao L, Yan X. Nanozymes: an emerging field bridging nanotechnology and biology. *Science China. Life Sciences*. 2016 Apr 1;59(4):400.
- [47] Golchin J, Golchin K, Alidadian N, Ghaderi S, Eslamkhah S, Eslamkhah M, Akbarzadeh A. Nanozyme applications in biology and medicine: an overview. *Artificial cells, nanomedicine, and biotechnology*. 2017 Aug 18;45(6):1069-76.
- [48] Song J, Chen H, Lv Y, Yang W, Zhang F, Wang T, Liu D, Qu Y, Han L, Fu J, Kong X. CuO₂-Assisting-Zn Single Atom Hybrid Nanozymes for Biofilm-Infected Wound Healing. Available at SSRN 4510421.
- [49] Opoku-Damoah Y, Wang R, Zhou J, Ding Y. Versatile nanosystem-based cancer theranostics: design inspiration and predetermined routing. *Theranostics*. 2016;6(7):986.
- [50] Yu Y, Zhao W, Yuan X, Li R. Progress and prospects of nanozymes for enhanced antitumor therapy. *Frontiers in Chemistry*. 2022 Dec 2;10:1090795.