Chapter 3

Trends in Tissue Regeneration: Bio-Nanomaterials

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Abstract

Tissue engineering requires functional platforms or scaffolds with specific properties concerning the morphology, chemistry of the surface and interconnectivity to promote cell adhesion and proliferation. These requisites are not only important for cellular migration but also to supply nutrients and expulsion of waste molecules. Cell type must be considered when designing a specific cellular grown system as a scaffold; for instance, if they are autologous, allogeneic or xenogeneic. The challenge in tissue engineering is to develop an organized three-dimensional architecture with functional characteristics that mimic the extracellular matrix. In this regard, with the advent of nanotechnology scaffolds are now being developed that meet most of the aforementioned requisites. In the present chapter, the use of biopolymers based nanostructures is addressed, including biomaterials and stem cells, bio-nanocomposites, and specific clinical cases where these systems were employed. We emphasize the future challenges and perspectives in the design of biocompatible and nontoxic nanocomposites with high efficiency as a promoter for tissue regeneration and many other biomedical applications.

Keywords: antimicrobial, nanomaterials, nanoparticles, regenerative medicine, tissue engineering

1. Introduction

As part of the novel scientific challenges, the use and design of biocompatible and functional materials based on nanostructured systems have gained industrial and scientific interest due

to the surface of the material shows an exponential increase in their contact area, which can enhance significantly the physicochemical properties. In this regard, nano-sized particles (ranging from 1 to 100 nm) have been considered as an effective strategy for pharmaceutical carriers, antibacterial and skin regenerator systems [1, 2].

Nanotechnology research has been intensively developed over the last decades; it is rapidly expanding and providing significant contributions to materials science. The main reasons for its success are the interesting properties of nanostructures that have led to greater efficacy systems, based on their physical dimension, shape, and composition [3]. Nowadays, these materials represent a broad potential for market growth, and recently these are commercialized as nanotechnology-enhanced products [4]. In the majority of these products, the presence of nanoparticles (NPs) is related to the addition of reinforcing agents such as additives, to improve physical/chemical or antibacterial characteristics.

The overall standings of NPs as additives involve organic systems, such as polymers [5], lipids [6], dendrimers [7], nano gels [8], nano emulsions [9], supramolecular structures [10] and others [11, 12]. In particular, inorganic NPs used for tissue regeneration such as carbon nanostructures (graphene, carbon nanotubes, fullerenes) [13], metallic nanoparticles, (such as silver, copper gold, titanium dioxide), quantum dots [14], and magnetic nanoparticles [15] have also been described.

Recent advances in the use of nano-sized particles in pharmaceutics involves the design of controlled drug delivery systems [16], biomarkers as diseases detection [2], pathogen/protein identification [17], molecule separation/purification [18] and regenerative medicine approaches [17, 19, 20]. Recent studies have been focused in biomedicine in order to execute multidisciplinary research, combining topics such as chemistry, biology, physics, engineering and materials science; associated with the design of functional systems, addressed to the tissue regeneration responses in organisms. The development of tissue engineered systems from health sciences is aimed to promote specific cell growth to replace tissue damage, associated with diseases such as cancer, trauma, hepatitis or congenital malformations [21].

In this chapter, the recent trends in the use of nanostructured systems combined with biopolymers will be discussed, divided into three parts: biomaterials and STEM cells, bio-nanocomposites and the current clinical cases where these systems were employed; aiming to emphasize the future challenge and perspectives in the design of biocompatible and nontoxic nanocomposites with high efficiency as promoter for tissue regeneration and many other biomedical applications.

2. Biomaterials and stem cells

Tissues in the human organism are generated, maintained and repopulated by stem cells. These are specialized cells capable of cell renewal and are able to differentiate into the different cell types in the human body. Stem cells have several differentiation programs, therefore, they possess information to allow them to become any cell in the body or a restricted cell type with a specialized function. These abilities make stem cells extremely useful for biomedical applications and regenerative medicine and have become the main molecular tool for these purposes [22].

Stem cells are derived from three primary sources, the embryonic origin, the mesenchymal origin and the so-called induced pluripotent stem cells. Cells from the embryonic origin are obtained from the inner cell mass of the blastocyst. They are considered a very important cell source for cell replacement therapies and have been used in regenerative medicine approaches by virtue of their ability to differentiate into any adult cell type [18]. Ethical considerations have restricted their use in many countries.

Cells from the mesenchymal origin, as opposed to embryonic stem cells, come from adult organisms, and these cells can differentiate into cell lineages organ-specific, the use of these cells in regenerative medicine makes them very appropriated because the lack of ethical concerns of obtaining cells from embryos. As in other tissues, cartilage self-renewal potential is limited due to the absence of a dense population of progenitor cells, multipotent mesenchymal stem cells, have been used therapeutically for the purposes of cartilage repair. Arthrosis of the carpometacarpal joint is common in postmenopausal women and requires surgical treatment; mesenchymal stem cells have been therapeutically used as connective tissue progenitor donors isolated from the anterior and posterior iliac crest. Treatment with mesenchymal stem cells is a very effective therapeutic alternative, the patient avoids surgery and greatly improves articular function and diminishes pain [23].

The so-called induced pluripotent stem cells are adult cells with a modified genetic program, which have gained potency due to transcription factor transfection. According to Mall and Wernig [24], cell reprogramming makes now possible to change cell fate and transform adult skin cells into neurons, hepatocytes or cardiac cells. This approach is useful for many biomedical applications from studying disease progression as well as the efficacy and safety of newly developed drugs even before animal testing on clinical trials [24].

Stem cells have been successfully used to develop organoids. Organoids are stem cell 3D cultures resembling real organs. Cells in this array have interactions with each other, as well as with the extracellular matrix, which are not seen in petri dish monolayer culture [25]. An example in the advance of organoids came from the idea to perform functional studies in human brains, which is not that easy to address due to difficulties to perform studies in whole human brains or the inaccuracies of using postmortem tissue, therefore, researchers were in need of an *in vitro* model system that would mimic the characteristics of the brain during development. Three-dimensional *in vitro* brain models are arising, and more importantly, how they are now used to study the evolution of the brain and the associated neural disorders [26].

Stem cells have clinical potential for injury treatments and degenerative diseases. The challenge of the use of nanomaterials in these systems is related to the optimal control of microenvironment conditions to transplant cells [27]. The combined use of stem cells and nanoparticles has improved cell proliferation and differentiation, used in different diseases, such as ischemic stroke, spinal cord, multiple sclerosis, Parkinson, Alzheimer, and others [28].

In order to recapitulate the function and structure of the native extracellular matrix (ECM) to generate functional tissue, researchers have developed new biodegradable and biocompatible synthetic of natural polymer structures called scaffolds [29]. The supporting scaffold temporarily replaces the function of the ECM, supporting the 3D geometry and providing the appropriated structural conformation, enabling cell adherence, and facilitating the conformation of

a tissue with its functional properties [30]. The microscopic structure must allow nutrient diffusion as well as the efflux of metabolites no longer needed to the cell through the scaffold. Finally, the scaffold must have good mechanical properties, enabling handling during culture in bioreactors and transplantation into the host [30].

One of the biggest health issues worldwide is organ failure derived from disease or a traumatic event; this has been resolved by transplantation of organs from living or deceased patient donors. The list of donors and recipients has increased in the last years and there are many patients on waiting lists for organ donation [31]. According to Gilpin and Yang [31], tissue engineering consists of three important aspects: the participating cells, the signaling molecules used and the scaffold. Scaffolds can be natural or synthetic. Natural scaffolds are derived from decellularization processes using chemical, enzymatic or physical methods. The resulting decellularized scaffold has to be recellularized either with one or different type of cells, in other cases induced pluripotent stem cells are used to recapitulate organ functionality [31–33].

For more than 20 years, scientists started developing nano-bio-materials and it is thought that nano bio-composites will be more important than non-nanometric materials at the physiological level. The advancement in biomedical research due to the incorporation in biomaterials to biological models has had a great impact in health sciences [34].

Decellularized scaffolds have been improved by combining them with biomaterials, not only to provide the extracellular matrix required for the cells to proliferate and differentiate but also to provide structural, biochemical and biomechanical support to the regenerated organ. Cheng et al. [35], developed silk-based scaffolds for bone regeneration, but their therapeutic efficacy was not optimal, therefore they developed a composite material of mesoporous bioactive glass/silk scaffold to improve mesenchymal stem cell regeneration activity in a rodent model for postmenopausal osteoporosis. They proved that the composite material provided the optimal environment for mesenchymal stem cell differentiation, attachment, and proliferation as treatment of osteoporotic defects [35]. Sterling and Guelcher [36] proposed another example of scaffolds to heal fractures derive for osteoporosis. In this research, the authors have argued that bone autografts (bone sample from the same patient), that have been used to improve fractured bone healing, have some pitfalls due to the limited amounts of bone that can be harvested, instead, hybrid scaffolds have been fabricated made with silk and calcium phosphate to stimulate bone formation and to reverse bone loss. The same group has shown that local delivery of recombinant bone morphogenic protein from microspheres made with polylactic glycolic acid has improved the mechanical properties of vertebrae in animal models [36].

We have been addressing some examples of the use of nanomaterials in conjunction with biological models or cells, but we are also going to show how these systems have to be visualized for further biomedical characterization.

Regarding tissue engineering, once the bio-engineered tissue is developed, it has to be evaluated in its structure and function. Histological and histochemical techniques have been used. For example, it is important not only to evaluate the 3D structure of scaffolds and its possible interaction with cells prior deciding on a biological or clinical application, but also the functionality of the cells contained the manufactured tissues. Different imaging techniques can be used to assure the efficiency of the biocomposites, such as ultrasound, microscopy, magnetic resonance imaging (MRI), and other optical imaging techniques [20].

Confocal imaging is a very useful to imaging technique in biomedical research, offering the ability to visualize different cell structures and their interaction with nanomaterials by using fluorescent dyes, as well allowing the creation of Z-stacks to recreate the three-dimensional architecture. Confocal imaging has been used to analyze the safety of dental nanostructured materials made from methacrylate monomers [37]. Another approach of engineered tissues has been the generation of oral soft and non-soft tissue. Recent advances involve the regeneration of whole teeth. Cells dissociated from epithelium and mesenchymal tissue of tooth buds were used to create a bioengineered tooth in vitro: cells were seeded to biodegradable polyglycolic/polylactide scaffolds having the shape of a tooth and implanted to rat hosts for 30 weeks and tooth structures were obtained [38].

The use of cell combined with nanostructured materials has greatly improved translational research making now areas like biomedical research and nanomedicine, important contributors of many peer-reviewed papers, publications and funding in these areas have had an exponential increase since 2011. It is expected even a more dramatic increase in the years to come [39]. In accordance with these new developments, another branch of research has been developed, *nanotoxicology*. This increase in published data now has to be proved innocuous to the biological system or organism where is going to be applied. Eventually, this will lead to more research to discover the advantages or disadvantages of using nanostructured materials with potential biomedical applications. Toxicity of nanomaterials has to be verified at different levels, whereas is about the systemic effects or the inflammatory and immunological response toward them, as well as the intra or extracellular effects [39].

3. Bio-nanocomposites

Biomaterials research has been concerned with the use of nanomaterials to enhance the tissue regeneration process. In this regard, nanomaterials can be classified into organic and inorganic systems. Diversity in organic materials derived mainly from polymers, such as polysaccharides, collagen, and chitosan have been recently used with different morphologies into the biomedical application and stem cell differentiation [19]. In particular, the use of polymer NPs as carriers or drug delivery systems is promising materials used as neuroprotectors to avoid acute ischemic stroke, which is actually considered one of the most common causes of death worldwide [40]. Nanostructured drug delivery systems offer many advantages, such as the avoidance of drug degradation, the possibility to improve the pharmacokinetic profile and the specificity at nano scale.

NPs from different materials have been functionalized with bioactive molecules in order to describe their effects in cells and tissues. Bio-composites of silica NPs with fluorescent compounds from the tree *Eysenhardtia polystachya* were internalized into MCF-7 breast cancer cells and observed with confocal microscopy to analyze their possible anti-tumor effect [41].

Cells interact with each other through their own synthesized ECM, which provides support and allows proliferation and differentiation processes. In consequence, ECM produces high membrane adherence with specific ligands associated with signaling pathways and possible migration, which can regulate the cell growth [42, 43]. Our body possesses natural ECM, mainly

conformed by fibrous proteins and proteoglycans, ranging in size from 50 to 500 nm [44]. In this regard, collagen is an important source of ECM, present in the majority of connective tissues, such as bone, skin, and tendons. It is confirmed by a three-dimensional protein network by nano-sized fibers, with high resistance and adherence [29, 45], and recently, many studies have been focused to mimic this behavior and replace it with functional materials.

The challenge in the research of materials able to replace the ECM is the recreation of a functional nanostructured network which allows cellular growth and differentiation. In fact, there are a lot of techniques for this task but there is one in particular that has been used more frequently in the recent years by researchers because it actually generates a fibrous structure like the ECM [46]. Electro spinning technique can produce nano-sized fibers from different sources, such as polymers, biocompatible systems, sol-gel, and nanocomposite materials. This technique generates three-dimensional porous fibers with high electrostatic attraction, associated with their high surface area/aspect ratio [47]. In this regard, this technique works from a solution (polymer, nanocomposite, and others) passed through a syringe, ending from a Taylor cone to control the efflux. A voltage source creates a drop and is collected at different distances to create variable morphology fibers. The surface tension produced between the collector and the needle is created by the electrostatic forces of the fibers [47].

Chitosan (CTS) has been defined as one of the most common biopolymers and chemically is a linear polymer derived from the deacetylated process of chitin, which is obtained from crustaceans [48]. The main characteristics of CTS are their biocompatibility and degradability [49], and can be easily processed in many different structures such as films, scaffolds, and fibers. CTS has been studied as antibacterial, biocompatible material, as a carrier for specific drug delivery and wound healing dressings [50, 51]. Some of its chemical properties are its solubility in organic acids [52] and low solubility in water. In order to improve the biological behavior of CTS material, different authors propose the addition of nano-sized structures to increase the physic-chemical and antibacterial properties, such as silver nanoparticles (AgNPs) [53] and gold nanoparticles (AuNPs) [54].

NPs of noble metals are some of the most promising materials, owing to their high surface area and their facility of functionalization or coordination with organic molecules. For example, AuNPs are easily prepared in colloidal solutions. Novel research has been done exploring the potential use of AuNPs as phototherapeutic agents, in the detection and treatment of cancer, in gene therapy and in the transport and selective vectorization of drugs and macromolecules [17, 54]. Otherwise, the AgNPs are widely applied to produce artificial skin, sterilized materials, functional contraceptive devices, antibacterial surgical instruments, bone prostheses, bone coating, surface cleaners, antimicrobial paints, automotive upholstery, food storage, and others [55, 56].

Many synthesis methods have been designed to create blends with metallic NPs and enable the combination and/or synergism of their catalytic, electronic, and optical qualities. Therefore, synthesis of supported gold and silver NPs has attracted lots of attention, in view of their remarkable properties, which depend on the NP size and the amount of each material [57]; they have been used in oxidation reactions, tumor cell targeting and detection, H_2O_2 production and catalytic applications [58–60].

Several studies have been directed to design and understanding the composition and structure of new hybrid polymers. These hybrid materials are made of Au and Ag NPs supported on a polymer grill; the matrix prevents NPs aggregation, provides mechanical backing and keeps biocompatibility. In this area, CTS appears as a unique material with polycationic, chelating, and film forming properties. Additionally, through NPs incorporation its antibacterial effect increases and it can either stimulate or inhibit human cells activity [61].

The AgNPs synthesis allows the production of stable metal NPs. When these NPs are incorporated in CTS electrospun fibers, it is possible to obtain high antimicrobial nanomaterials [62]. This behavior is generated due to the polycationic characteristics of CTS matrix and their interaction with the embedded AgNPs, linked by electrostatic attractions [63]. It has been reported that amine/hydroxyl groups presented in CTS matrix can interact with metal ions, in order to form stable complexes, and it is possible to in situ synthesize metal NPs in CTS solution, with high morphology control [64]. Moreover, AuNPs are also used due to their excellent biocompatibility and especially because it was found that CTS-AuNPs nanocomposites enhance the proliferation of human fibroblasts. This significant enhancement of biocompatibility may be due to the altered surface morphology. The size of the nanometric surface domains could have an impact on cellular responses [65].

The mechanical properties of CTS (e.g. swelling), are not good enough for medical applications; to solve this it was inserted into the structure, a natural synthetic polymer CTS-based, grafted with glycidyl methacrylate (CTS-g-GMA) [66]. This arrangement of polymers provided a new material with better biomedical applications.

Ag and Au NPs show a collective oscillation of their electrons from the conduction band when they interact with a specific electromagnetic field; this property is called surface plasmon resonance (SPR). After all the evidence collected from the interaction between noble metals and natural polymers, the results are the evident success in the aggregation of AuNPs and AgNPs. This behavior was confirmed by UV-vis analyses, where the SPR bands were used to identify the metallic elements. As result, characteristic SPR for the AgNPs was located at 427 nm, while the SPR peak of the AuNPs was located around 530 nm [58], as shown in **Figure 1**.

Fibers obtained by electrospinning have been synthesized modifying the film method, the viscosity did not allow the correct stretched from the solutions, then it was necessary to add to the mixture polyethylene oxide and a surfactant to enhance the viscosity in order to obtain nanometric fibers of the polymer with NPs.

These results are promising, the combined UV-vis spectra from the materials show SPR in 432 nm for AgNPs and 532 nm for AuNPs. Transmission electron microscopy (TEM) allows to observe fibers with several particles inserted in the surface, as presented in **Figure 2**. In this case, is not possible to determine if observed NPs are Ag or Au using only TEM imaging (elemental analyses show the presence of both elements), but the presence of them indicates that the NPs synthesis was successful and the electrospinning method is an option to perform materials with the characteristics to be used in biomedical applications.

The major contribution of this research is that normally both metals, Au and Ag, are reduced chemically by separated and joined after these chemical reductions, nevertheless both nanostructured materials shown above as, films and fibers, underwent the chemical reduction *in situ*.

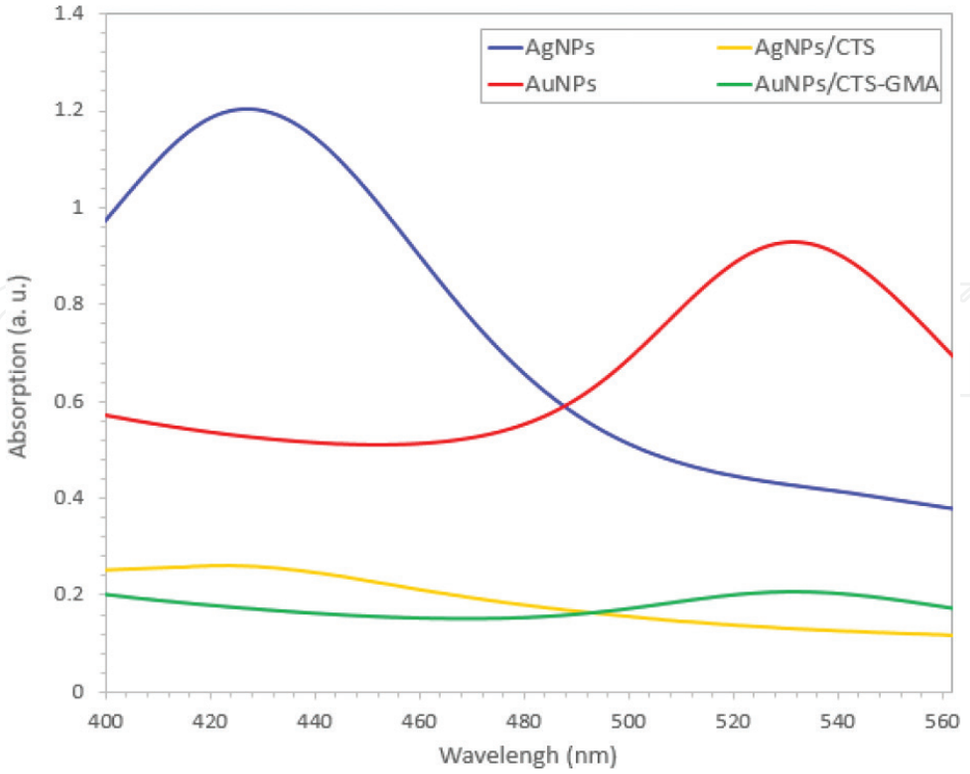

Figure 1. UV-vis absorption spectra of silver nanoparticles (AgNPs), gold nanoparticles (AuNPs), and their corresponding nanomaterials formulated by AgNPs/CTS and AuNPs/CTS-GMA.

Is clear that there are more possibilities for NPs and natural polymers, here we have offered a slight landscape of that, additionally to Au and Ag different metals such as copper (Cu) also could be used in biomedical applications, but the noble metals are a field with an extensive list of contributions elsewhere [67].

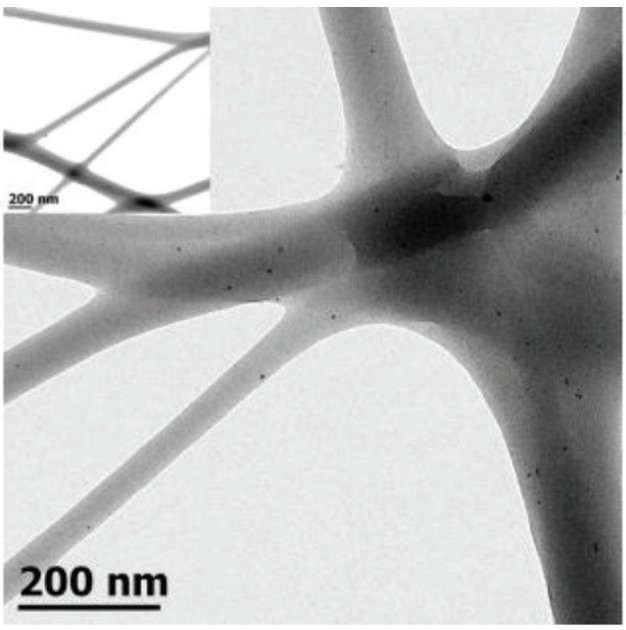

Figure 2. Fibers of CTS with AuNPs and AgNP on the surface of the polymer.

4. Clinical applications

The novel approach to use nanomaterials in regenerative medicine has established the design of functional tools to simulate, diagnose and stimulate cell growth of tissue or organs [16].

Burn wounds are a critical issue due to the widespread deaths due to the constant bacterial resistance to conventional antibiotics. In this regard, novel nanomaterials such as topic antimicrobial systems have been obtained to produce combined antibacterial/tissue regeneration responses in thermal burns. Luna-Hernández et al. [68] report the use of nanocomposites based on CTS/AgNPs synthesized by *in situ* chemical reduction method, obtaining embedded spherical AgNPs around 7 nm, as presented in **Figure 3**.

In this research, controlled thermal burns produced in rats were treated with nanocomposites with different NPs concentration deposited at wound areas. These results showed the combined antibacterial responses to *S. aureus* and *P. aeruginosa*, depending on NPs concentration and the mesh formation of hydrated chitosan, which allowed bacterial penetration. As a result, significant tissue regeneration was shown in the thermal burns treated with CTS/AgNPs nanocomposites in comparison with untreated one, as presented in **Figure 4**. Also, histological assays showed important tissue regeneration responses in contact with nanocomposites, suggesting the myofibroblasts regeneration and accelerated healing processes compared to uncovered thermal burns.

Chemotherapy and radiation exert their effects by inhibiting tumor cell growth and by blocking tumor reformation. However, some cancer patients present tumor relapse due to cancer

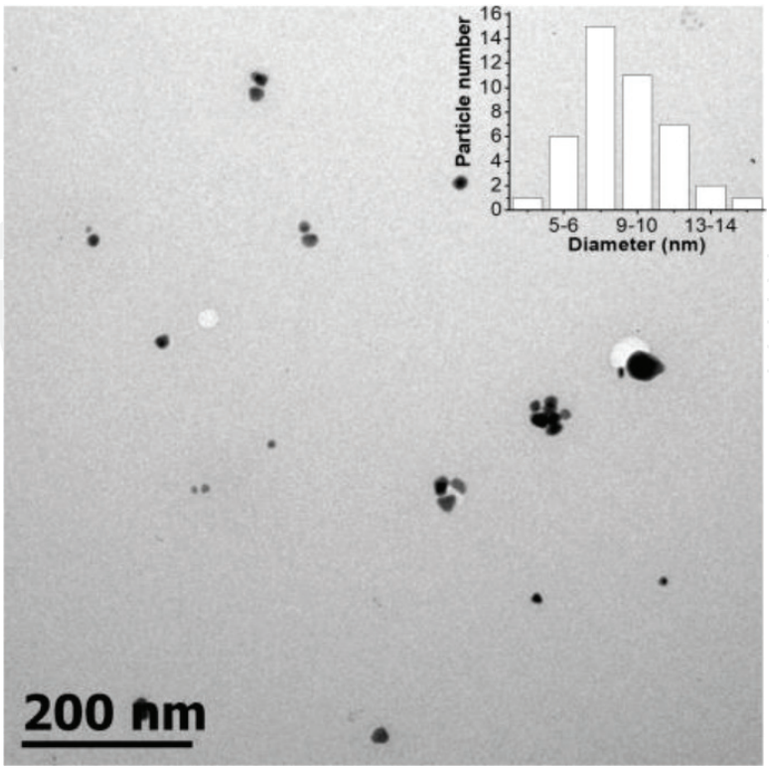

Figure 3. AgNPs synthesized by *in situ* chemical reduction in CTS matrix.

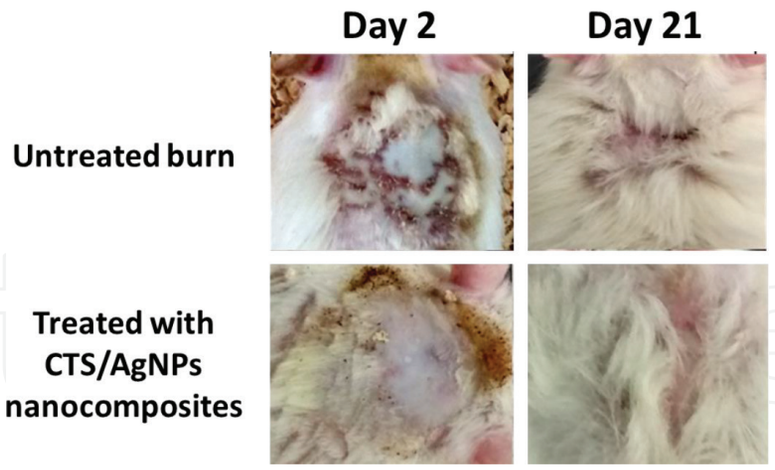

Figure 4. Photographs of controlled thermal burns untreated and treated with CTS/AgNPs nanocomposites.

stem cells, which cannot be killed by these therapies. These cancer stem cells are able to form new colonies and regenerate tumors. It is of great importance to develop new therapeutic approaches to selectively target stem cells. There are novel therapies using NPs to target stem cell-specific markers or signaling pathways [69]. In other hand, glioblastoma multiforme tumors show resistance to radiotherapy and chemotherapy and this is believed to happen due to tumor stem cells. NPs carrying antitumor drugs have to be able to reach the tumor cell, by crossing a series of membranes slide across the blood-brain barrier. For NPs to reach the tumor in a specific way, some strategies have been incorporated like the use of antibodies or peptide molecules which recognize tumor cells antigens to improve the therapeutic efficacy by means of increasing tumor cell uptake and accumulation into the cytoplasm [70].

In other hand, Gilbert and Osterhout suggested the use of NPs from the delivery of chondroitinase ABC in rats, a therapeutic enzyme to treat spinal cord injury in order to cause axon regenerative responses. In this case, the released enzyme from NPs produced digestion of chondroitin sulfate proteoglycans, which are the lesion markers [71]. For spinal cord injuries, it has been reported the use of biocompatible polymer NPs based on poly(lactic-co-glycolic) encapsulated methylprednisolone, which can reduce the possible neurological deficits after spinal cord procedures, considering ultralow drug doses at local delivery [72]. Another route to treat spinal cord disease is by using cerium oxide NPs. In this regard, Das et al. report the anti-oxidant, photocatalytic and biocompatibility behavior of nanomolar concentration of NPs, acting as neuroprotectors without cytotoxic effects [73].

Cancer therapy is a major challenge in order to design alternatives for detection and treatment. In particular, the use of aptasensors is emerging as a novel strategy for cancer detection. Aptasensors described as recognition elements derived from artificial fragments of DNA or RNA, easily synthesized and modified to target as biomarkers, with low immunogenicity and high affinity. In this regard, graphene nanocomposites decorated with metallic NPs obtained from Layer by Layer deposition have been considered a novel tool for specific polypeptides detection [74].

For drug delivery systems, Sahu et al. [75] proposed the use of graphene nanosheets integrated into liposomes as drug delivery vehicles, monitored by NIR light. Some advantages of using NIR light to liposomes detection are their non-toxicity, specificity, and high tissue

penetration. Authors claimed that graphene oxide could act as a light activable switch to trigger drug release from liposomes upon NIR irradiation.

5. Conclusions

In the present chapter, the use of biopolymers-based nanostructures is addressed, including biomaterials and stem cells, bio-nanocomposites, and specific clinical cases where these systems were employed. We addressed the current challenges in the formulation of functional materials based on biopolymers/metal NPs to mimic the cellular behavior of living organisms. It is important to note that material functionality must be improved to synergistic properties, for example, combined antibacterial/tissue regeneration responses, aiming to contribute the specific cell regeneration and avoiding the bacterial colonization. In this sense, the recent trend in nanomaterials development must be focused in the design of functional systems which combine their physic-chemical and biological characteristics, aiming to produce efficient cellular growth and contribute to tissue engineering approaches. We emphasize the future challenges and perspectives in the design of biocompatible and nontoxic nanocomposites with high efficiency as a promoter for tissue regeneration and many other biomedical applications.

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Conflict of interest

The authors declare no conflict of interest, financial or otherwise.

Abbreviations

Ag	Silver
AgNPs	Silver nanoparticles
Au	Gold
CTS	Chitosan

Cu	Copper
DNA	Deoxyribonucleic acid
GMA	Glycidyl methacrylate
H_2O_2	Hydrogen peroxide
MCF7	Epithelial cancer cell line
NIR	Near infrared
NPs	Nanoparticles
RNA	Ribonucleic acid
SPR	Surface plasmon resonance

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