Chapter 1
Nanomaterials for Its Use in Biomedicine: An Overview

Caitlin Lazurko, Erik Jacques, Manuel Ahumada and Emilio I. Alarcon

Abstract The rapid incorporation of nanostructures in regenerative medicine can be considered one of the biggest leaps in the production of novel materials for repair and regeneration of damaged tissues. However, despite a large number of articles published, clinical use of these materials is still in its infancy. The complexity and interdisciplinary nature of research aimed to repair damaged tissue and failing organs are the main limiting factors that have halted the progression for developing novel structures for tissue repair. In the present chapter, we revise fundamental concepts to be considered when designing technologies that will have to undergo scrutiny by regulatory agencies prior to being used in humans.

1.1 Introduction

Modern medicine relies on functional materials to provide tools which allow the partial, or even more desirable, the complete restoration of the functionality of damaged organs and tissues. Paradoxically, the increase in life expectancy and improved surgical outcomes presents a new challenge for developing novel materials for organ repair. Thus, what was considered a significant achievement in tissue engineering in the past, such as the first human donor cornea transplant, has become a routine procedure. However, cornea transplantation is limited by donor shortage and graft rejection in chronically inflamed eyes (see Chap. 8). Thus, novel therapeutics in the field of corneal tissue repair needs to circumvent the worldwide shortage while

C. Lazurko · E. Jacques · E. I. Alarcon (✉)
Division of Cardiac Surgery, University of Ottawa Heart Institute,
40 Ruskin Street, Ottawa, ON K1Y 4W7, Canada
e-mail: Ealarcon@ottawaheart.ca

C. Lazurko · E. I. Alarcon
Department of Biochemistry, Microbiology, and Immunology, Faculty of Medicine,
University of Ottawa, Ottawa, ON K1H 8M5, Canada

M. Ahumada
Facultad de Ciencias, Centro de Nanotecnología Aplicada, Universidad Mayor,
Huechuraba, RM, Chile

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providing implants capable of modulating chronic inflammation. The level of complexity for engineering tissues become more challenging in highly perfused and contractile organs, as is the case of the heart muscle, where materials must also incorporate electroconductive moieties (see Chap. 9). Synchronic conductivity and alignment are also of prime importance in regenerating nerves (Chap. 7). Considering soft tissues, for example, the skin which is the largest organ in the human body and the primary target of external insults; nowadays developing functional biomaterials for skin repair requires pushing the boundaries of materials chemistry for producing novel biologically compatible templates that allow functional skin regeneration with minimal scarring (see Chap. 6). This push in materials with improved biological properties becomes even more challenging for tissues that will be exposed to high shear forces such as articular cartilage (Chap. 5). Alongside the exponential growth in knowledge surrounding the underlying mechanisms involved in wound healing and tissue regeneration during the last two decades, there has been an evident need for novel strategies and therapeutics for tissue repair. This new body of literature, however, is not enough for us to fine tune the biophysical properties of the biomaterials to make them better "at healing". Thus, incorporating nanoscale components as structural building blocks for modulating the biophysical properties of the materials, which will ultimately allow the manipulation of cell-matrix interactions (Fig. 1.1).

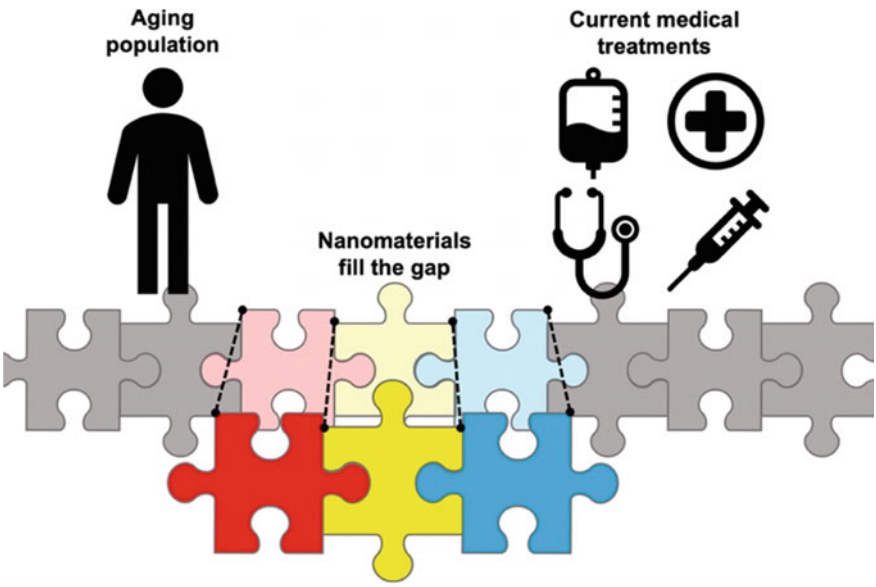

Fig. 1.1 The role of nanomaterials is to fill the unmet needs in the field of medicine. These materials can be used to modify the biophysical properties of biomaterials, control cell-matrix interactions, and revolutionize the field of tissue engineering and regenerative medicine, especially with the aging population and increased medical demands

In the following sections of this chapter, we will briefly revise the history of biomaterials alongside with fundamental principles of nanotechnology and regenerative medicine.

1.2 Brief History of Materials Used in Medicine

The term nanotechnology was first introduced in 1974 by Taniguchi to describe the engineering of nanoscale materials [1, 2]. However, nanomaterials have been present in human history since ancient times, when colloidal solutions of gold nanoparticles were used to dye glass [3, 4]. The Lycurgus Cup, an example from the fourth century A.D., used nanoparticulated metal dispersed in glass to give color to the cup, and the color changed depending on the light incidence angle [3–5]. Nanotechnology advances in the last decades have provided scientists with tools to investigate, engineer, and control assemblies of atoms and molecules less than 100 nm in size [6, 7]. As nanotechnology has progressed, its nature has exponentially diversified, becoming an intrinsically interdisciplinary field, where understanding the nanoscale interactions are essential for developing new technologies and therapies [1, 4]. In the 1990s, the term nanomedicine started to be used to refer to nanomaterials with potential medical applications [4, 6–9]. Today, nanomedicine is often subdivided into either the development of tools for medical diagnosis and therapies or fundamental research on understanding interactions and interface between chemical, biological, and physical sciences [1, 9].

Early applications of nanomaterials in medicine were often completed without a deep understanding of the interactions at the nanoscale level. Nanomaterials were used without the devices and technologies available today, such as electron microscopy, to be able to identify the importance of the nanoscale size of the materials and the nanoscale interactions that were occurring. For example, in the nineteenth century, nanoporous ceramic filters were used to separate viruses [4]. Advancements in microscopy led to a better understanding of cell structures and interactions, and further microscopy development including the development of atomic force microscopy and the scanning tunnel microscope resulted in the ability to visualize objects at the nanometer scale [4]. It was these advancements in technology that allowed the field of nanotechnology and nanomedicine to boom [4]. During the 1990s, tissue engineering had a boost when it merged with stem cell transplantation to become a much more influential field also known as regenerative medicine (William Haseltine would later coin the term in 1999) [10–12]. As products began to be successfully commercialized, the interest of the private sector also increased, which catalyzed the development and testing of a large variety of biomaterials [13]. However, the excitement was rather short-lived, as scientists tried to copy tissue formation rather than seek to understand the underlying mechanisms for tissue repair [11, 13, 14]. As a result, products that showed great promise in the lab failed, and coupled with the Y2K crash, meant that by 2002 the value of the industry was down by 90% [13, 15]. Out of the 20 FDA-approved products during that time, none remain on the market today [15].

Presently, the field has recovered from that crash and is now much more diversified [16–18]. There has been a switch in focus to simpler acellular products such as biomaterials, and a continued search for other avenues of inquiry, such as nanotechnology, which are actively being introduced into the field of medicine for a range of applications including drug delivery, tissue engineering, diagnostics, therapies, and imaging [1, 7, 9, 19–21]. There has also been an increase in nanomaterial funding worldwide, with over $7 billion per year is being allocated to nanotechnology. The United States is leading the way in nanotechnology funding, which has increased since the signing of the twenty-first century Nanotechnology Research and Development Act (NRDA) in 2003. Many other countries, including the EU, Japan, and South Korea, are following suit and prioritizing research and development of nanotechnologies for various applications [1, 22].

With the increased interest in nanomaterial research, one big question that remains is the potential impact on human health. There are concerns that the unique properties of nanomaterials, which are discussed below, may have a negative impact on human health and the environment [1]. There is a lack of information regarding how nanomaterials interact with the world and their impact on the food chain. Moreover, as nanoparticles vary significantly in size, shape, and composition, their toxicity varies as well, with certain particles being known to be biocompatible and non-toxic, while others showing cell toxicity [23–25]. A collaborative approach should be taken by researchers when designing and testing nanoparticles to ensure they are designed to be effective for their application while remaining biocompatible [1]. There are also ethical questions concerning nanomaterials, including who benefits from and who controls the use of these technologies. Due to the novelty and diversity of nanomaterials and their applications in medicine, it is important to get a complete understanding of the benefits and risks associated with these materials before testing in vivo to ensure the safety of these technologies.

1.3 Fundamental Concepts on Nanomaterials

Some of the fundamental concepts surrounding nanomaterials that must be considered when designing nanomaterials, especially those for medical applications, are discussed here. Nanostructures are typically prepared by either a “top-down” or “bottom-up” method. The top-down method starts with the bulk material and follows a synthetic route to obtain the nanostructure. On the other hand, the bottom-up method starts with atoms and makes them coalescent to form nanostructures. Nonetheless, independent of the chosen route, the final product will have the same nanostructure properties, which will have different physical-chemical properties from those found in the original bulk material. Moreover, the material(s) that form a nanostructure can come from a variety of sources, being either biological or chemical in nature. For instance, metal nanostructures are famous among biomedical applications due to their tunable physical-chemistry, antibacterial, and biocompatibility properties. Popular choices are gold, silver, titanium, and copper [26–30]. Synthetic polymers are also a

source of material for nanostructures, where they can be used to form nanoparticles, mesh-like composites, foams, among others [31]. Common synthetic polymers are poly-ethylene glycol and its derivates, poly-caprolactone and poly-vinyl alcohol, to name a few [32]. Similarly, natural polymers such as polypeptide chains, proteins, and carbohydrates and their derivates have also being used for nanostructure development [33]. Usually mentioned are collagen, fibrin, alginate, chitosan, and gelatin [34]. Nonetheless, proteins by themselves are nanostructures with potential biomedical applications [35]. While they are ubiquitous, their potential as drug nanocarriers has been widely explored, with remarkable cases, such as the use of serum albumin (either from human or bovine sources) [36].

The keystone for the explosion in nanomaterial applications, particularly for those of synthetic nature, lies in the fact that these nanostructures have properties that vary from those of the bulk material [1, 6]. Most of the properties of macroscopic materials are described, unequivocally, by classical physics, which is based on empirical science at the macro-scale. However, nanomaterials, as aforementioned, respond to a different size scale, which dramatically changes the way the physics works. In the early 1900s, the term quantum physics started being introduced from the theoretical field, where later experimental physicists probed the existence of this new branch, that differs entirely from its classical counterpart. Particularly in the case of nanomaterials for biomedical applications, the high surface area along with quantum effects results in unique optical, magnetic, and electronic properties [1, 5, 6, 20, 21].

First, the available surface area is one of the most relevant properties of nanomaterials, independent of their origin or shape [37]. This allows nanomaterials to adsorb different particles, especially proteins and drugs, onto their surface. These molecules bound to the surface can then impact nanoparticle stability, solubility, biocompatibility, and its interactions with other molecules in their environment [20, 21]. Their surface and composition can also be modified to match the environment of the tissue they are interacting with, in a process called surface nano-engineering.

The second relevant feature of nanostructures corresponds to the shape, where virtually any shape can be considered a nanostructure, as long as the structure fulfills the conditions, vide supra. Thus, a wide range of shapes can be found in the literature, including spheres, rods, cubes, tubes, flower, cage, foam, flake, ring, mesh, amorphic [38]. Despite the number of shapes mentioned, the access to those is limited by several factors such as synthesis method, components, and experimental conditions. Furthermore, the target application for nanostructure use also plays a fundamental role in the shape selection; for example, when considering nanoparticles for their use in the near-infrared section of the spectrum, usually, spherical nanoparticles would not present a plasmon response (no absorption), however, the elongation into a rod-like shape for the same nanostructure will increase the longitudinal plasmon promoting the generation of a signal in the near-infrared region. Therefore, it is important to consider the application of the nanomaterial when choosing the structure.

Next, the specific optical, magnetic, and electrical properties of the nanostructure stand out, particularly for metal nanostructures, from other materials when designing new biomedical technologies. Two main characteristics describe these phenomena;

first, electrons are distributed differently in the system and second, the nanostructures interact with light in a unique manner. When in a bulk material, electrons can be described as a continuum; however, in the case of nanostructures, electrons have a discontinued behavior, which can likely be controlled. Second, since the nanostructures have smaller sizes, they interact with light, especially wavelengths generally used for biomedicine (UV-A to NIR), in a different manner than the bulk material. The properties mentioned here will be further explored and expanded in the following chapters of this book.

The properties of nanostructures, as mentioned above, can improve the biocompatibility of the materials and alter the interactions of the materials with the host environment [19, 20]. Nanoparticles can also modify the micro-environment in which they are present, which can influence the cell's fate. They can be used to enhance interactions with the host and can be used to engineer biomaterials that more closely mimic native tissue and endogenous conditions [19]. The versatility of nanomaterials extends beyond the materials they are synthesized from and the particles used to coat their surface, as nanomaterials can be applied in a variety of different manners. For example, they can be used as a thin coating on surfaces, such as in electronics or on prosthetic implants, they can be embedded in a material, such as a biomatrix, or free nanoparticles can be used [1].

1.4 Brief Considerations for Regenerative Medicine

Today, tissue loss of function can generally only be solved with organ and tissue transplantation [10, 11]. However, donor availability is scarce, and the demands of the aging population and its chronic diseases are ever-growing [10, 11]. In the 1960s, the limitations of transplantation began to be felt as chronic diseases were on the rise [14, 17, 39, 40]. Concurrently, scientists such as Alex Carrel began culturing cells and thus were beginning to grow and keep tissues alive in vitro [12]. The processes of degeneration and regeneration were now being studied. It was not until the 1980s, in Boston, Massachusetts, where Dr. Joseph Vacanti and Robert Langer decided to use this knowledge to create in vitro grown skin grafts (Epicel® and Apligraf®) [12, 14]. Now everyone was working on trying to create skin or cartilage grafts. This is where regenerative medicine (RM) comes into play (also referred to as tissue engineering and regenerative medicine, or TERM for short).

Surprisingly, the concept of tissue regeneration began in myths, where a common example is the Greek myth of Prometheus, a Titan who received a terrible fate from Zeus after having gifted humanity with fire "*He was bound to a rock where an eagle would feast on his liver every day, and every night said liver would regenerate leading to an endless loop of torture* [41]." The idea of regeneration persisted through the millennia until the twentieth century, where RM came into fruition. Greenwood et al. stated:

> Regenerative medicine is an emerging interdisciplinary field of research and clinical applications focused on the repair, replacement or regeneration of cells, tissues or organs to restore impaired function resulting from any cause, including congenital defects, diseases, trauma and aging. It uses a combination of several technological approaches that moves it beyond traditional transplantation and replacement therapies. These approaches may include, but are not limited to, the use of soluble molecules, gene therapy, stem cell transplantation, tissue engineering and the reprogramming of cell and tissue types. [42]

RM is a branch of biomedical science that uses various strategies to restore function to damaged or diseased human tissue and tries to regenerate lost tissue and/or organs. This has led to immense scientific, private (allied market research estimates that the market for RM will be worth $67.5 billion dollars by 2020), and media interest, which refers to it as "the most promising healthcare technology ever put forward" [12, 40]. The regenerative therapies are leading a paradigm shift from treatment-based to cure-based therapies which will have a profound impact not only on the quality of healthcare but also on its economics as the financial burden of chronic diseases would be significantly lifted [17, 40, 43].

As mentioned in Greenwood's definition, RM's arsenal is vast, and since 2006, it has increased to include bioreactors, bioprinting, and nanotechnology [42]. While RM's focus since the early 2000s has been on the use of human stem cells, this focus has shifted significantly to the use of acellular products either concurrently or without cells for tissue regeneration [10, 12, 17]. In particular, this refers to controlled release matrices and scaffolds; materials where the principles of nanotechnology are being regularly used. These regenerative therapies can currently be divided into three categories: allogeneic, autologous, and scaffolds. Allogenic therapies are cell therapies that use a universal donor cell; autologous therapies utilize donor cells harvested from the patient; and scaffolds include the use of decellularized extracellular matrices (ECMs) or synthesized biomaterials [39, 44, 45]. The authors do recognize that hybrid models exist and that bioprinting could also be considered a category but since they are young strategies, they have yet to be included as such.

RM seems theoretically promising, however, the results in clinic have not reflected this. Currently, all cell therapies remain experimental, except for hematopoietic stem cell transplants, simultaneously, acellular products have had little success making it to market; it is also a mainstream opinion that cell therapies have shown little efficacy and that, to date, RM has underperformed [12, 45, 46]. The reasons stem from the field's novelty, where it has created many challenges. Pre-clinically, scientists have yet to fully understand the regenerative mechanisms behind their therapies [10]. Clinically, the tumorigenicity, immunogenicity, and risks of the procedure delivery are all unsolved obstacles involved with cell therapies [46]. Additionally, regenerative therapies are meant to be implanted and remain with the patient for a prolonged period. Unfortunately, long-term follow-up studies do not exist for clinical trials which makes it difficult to ensure regulatory agencies and the public of the safety and efficacy of the therapy [40, 43]. Post-clinic, there is difficulty in identifying the proper business model for companies hoping to enter the RM market [12]. The regulatory and reimbursement policies for such novel technologies have been difficult for countries to determine [10]. However, the most significant challenges are the ones related

to manufacturing. The automation and scale-out strategies of the manufacturing process to reduce cost, contamination, and human error do not exist for such complex biological therapies [40, 47]. As well, the industrialization technology simply does not exist [39]. Despite the turnaround, RM and its growing number of clinical trials are reaching a critical mass and becoming a major player into the biomedical field [12, 47]. Whether this will prosper, remains to be seen. Nonetheless, nanotechnology has played a role in the field's progression.

Thus, there is now also a high degree of optimism for regenerative therapies and once again a rush to get them through to clinical trials [45]. Governments now recognize RM as being at the forefront of healthcare and institutions dedicated to its practice have increased over the past decade [39]. As mentioned above, while the discoveries made on the bench-side are ever-increasing (such as the discovery of induced pluripotent stem cells for example), success on the bench-side is still lacking [18, 48]. Therefore, clinical trials have been increasing but are proceeding with caution [45]. Additionally, in accordance with the maturation of the field, various attempts to rectify the challenges already discussed have been made, for example: companies such as Canada's Centre for Commercialization of Regenerative Medicine have been created to help researchers (academic or private) facilitate the translation of their therapies by decreasing risk during the development phase; the Mayo Clinic has created a theoretical blueprint for the "discovery, translation and application of regenerative medicine therapies for accelerated adoption into standard of care"; and legislation in places such as the United States, the EU, and Japan has been passed to allow accelerated conditional approval of RM technologies so as to be more readily available to the public [39, 47, 49–51].

1.5 Outlook and Future Perspectives

Nanotechnology allows for the production of efficient markers and extremely precise diagnostic tools and imaging devices, which allows for early diagnoses, all of which can improve treatments and quality of life for patients and decrease overall morbidity and mortality rates. These devices are also in line with regenerative medicine in that they help improve our understanding of interactions in the human body which allows for the development of new therapies [52]. Understanding the pathophysiological basis of diseases and how nanomaterials interact with cells and tissues in the body are essential to the design, development, and application of nanomaterials in medicine [20, 21]. There is currently a gap in knowledge surrounding nanomaterial interactions in the human body, including, toxicity, pharmacokinetics, and pharmacodynamics, which limits the technologies used and developed today [6]. However, nanomaterials have the potential to improve personalized medicine as well as the targeting of therapeutics, dose-response, and bioavailability, among many other aspects of medicine [6]. They show promise in the development of the multifunctional and next generation of biomedical devices that will further improve healthcare [6, 19]. Moreover, the broad range of nanomedicine to include genetics, molecular

biology, cellular biology, chemistry, biochemistry, material science, proteomics, and bioengineering means that advances in this field will have broad applications in field of science and greatly improve patient care [6]. Overall, nanomaterials hold great promise for medical applications, and many avenues for nanomaterial application have yet to be explored.

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