Applications of Nanomaterials in Medical Procedures and Treatments

Editor:
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(Volume 4)

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PREFACE

Frontiers in Nanomedicine Vol. 4, Applications of Nanomaterials in Medical Procedures and Treatments continues describing relevant topics in nanomaterials for biomedical applications and regulations. Contents of chapters 1 to 7 are organized as follows, molecular imaging and contrast agents; tissue engineering; prosthetics and implants; ophthalmic and cancer therapy; and processing techniques. While last chapter 8 completes the book with a motif of international regulations and standards.

Multidisciplinary research is quickly proliferating in modern times. In this context, nanomedicine intertwines the new wave of high-performance devices with standard methods and pharmaceutics to find final options against deadly diseases.

Once again, I expect you can use this book as a guide to delve into the fundamental issues surrounding nanoscience applied to medicine.

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CHAPTER 1

Molecular Imaging and Contrast Agents

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Abstract: As an emerging technology, molecular imaging combines advanced imaging technology with cellular and molecular biology to highlight physiological or pathological processes in living organisms at the cellular level. The main advantage of *in vivo* molecular imaging is its ability to characterize pathologies of diseased tissues without invasive biopsies or surgical procedures. Such technology provides great hope for personalized medicine and drug development, as it can potentially detect diseases in early stages (screening), identify the extent of a disease/anomaly, help to apply directed therapy, or measure the molecular-specific effects of a given treatment. Molecular imaging requires the combination of high-resolution/sensitive instruments with targeted imaging agents that correlate the signal with a given molecular event. In ongoing preclinical studies, new molecular targets, which are characteristic of given diseases, have been identified, and as a consequence, sophisticated multifunctional probes are in perpetual development. In this context, the discovery of new emerging chemical technologies and nanotechnology has stimulated the discovery of innovative compounds, such as multimodal molecular imaging probes, which are multiplex systems that combine targeting moieties with molecules detectable by different imaging modalities.

Keywords: Contrast agents, Diagnostic, Drug delivery, Imaging, Magnetic resonance imaging, Molecular imaging, MRI, Nanoparticles, Nuclear medicine, Optical imaging, PET, Polymers, SPECT, Targeting, Theragnostic, Therapy, Ultrasounds.

INTRODUCTION

Molecular imaging is a technique that allows the characterization of biochemical processes at the cellular and molecular levels in living organisms. This method

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helps to understand biological phenomena and reactions involved in different physiological and pathological processes at the nanoscopic scale. By allowing the visualization of a characteristic change at the molecular level, a rapid and accurate diagnosis (by assessing the presence or absence of metastases), a follow-up of therapy (by early assessment of response or resistance to a treatment), or detection of disease recurrence are possible. Oncology, neurology, and cardiology are the three principal areas of bioimaging applications [1 - 3]. One of the main advantages of this technique is its ability to characterize diseased tissue noninvasively, allowing for more personalized treatment planning.

The implementation of an active targeting strategy implies the development of a probe resulting from the combination of a specific vector (*i.e.,* a moiety able to specifically recognize the target of interest) and an imaging agent. The use of an imaging probe involves, among other things, the choice of the imaging modality by considering the strengths and limitations of each technique. Many imaging techniques are available for preclinical and clinical studies. Among the most used are X-ray imaging, ultrasound, magnetic resonance imaging, nuclear imaging, and optical imaging [4 - 6]. It is important to choose the appropriate imaging technique based on the desired application. Imaging modalities differ in the equipment used and instrumental properties: sensitivity, precision, spatial and temporal resolutions, tissue penetration, quantification, acquisition time, and cost (Table **1**). Another important parameter is the toxicity induced by certain techniques using ionizing radiation.

Table 1. Characteristics of noninvasive imaging modalities [7].

Imaging Technique	Positron Emission Tomography (PET)	Single Photon Emission Computed Tomography (SPECT)	Magnetic Resonance Imaging (MRI)	Optical Imaging	Ultrasound (US)
Detection	High energy γ rays	Lower energy γ rays	Radio waves (magnetic field)	Visible light and near-infrared	High-frequency sound
Spatial resolution	1-2 mm	1-2 mm	25 -100 μm	2-5 mm	50-500 μm
Depth	No limit	No limit	No limit	1-2 cm	mm to cm
Temporal resolution	10 s to min	min	10 s to min	s to min	s to min
Sensitivity	10^{-11}-10^{-12} M	10^{-10}-10^{-11} M	10^{-3}-10^{-5} M	10^{-9}-10^{-12} M	Not well characterized

(Table 1) cont.....

Imaging Technique	Positron Emission Tomography (PET)	Single Photon Emission Computed Tomography (SPECT)	Magnetic Resonance Imaging (MRI)	Optical Imaging	Ultrasound (US)
Types of probes used common CA	Radiolabeled ^{19}FDG, $^{3}H_2O$, ^{68}Ga-DOTA	Radiolabeled ^{99m}Tc-HMPO, ^{111}In octreotide	Gd-complexes, iron oxide nanoparticles	Fluorophores, quantum dots, rhodamine	Micro-bubbles Sonovue®, Acusphere
Some examples of applications	Cerebral/blood flow, degenerative diseases, brain development	Cerebral infarction, ischemia, dementia, cardiac imaging	Angiography, cell labeling	Gene expression, cell tracking	Echography morphological studies, liver lesions

IMAGING TECHNOLOGIES

Nuclear Imaging

Nuclear medicine, which is based on the disintegration/detection of radioactive atoms injected in the patient, is a functional molecular imaging technique because it allows the visualization and localization of accumulated radiomolecules. In recent decades, the use of radionuclides in medicine has been considerably developed to become a clinical specialty integrating both imaging (diagnosis) and the treatment of pathologies (therapy). Radionuclides exhibit different properties (half-life time, type of emission, energy, scope of action, production, availability, cost, *etc.*). All these parameters influence the choice of radionuclide to be used according to the application envisaged (Table **2**).

Table 2. Main radionuclides used in imaging and therapy and their properties (half-life, mode of disintegration, application).

Radionuclides	Half-life	Disintegration mode	Applications
^{11}C	20.3 min	β^+	PET
^{18}F	109.8 min	β^+	PET
^{68}Ga	67.8 min	β^+	PET
^{67}Ga	78.3 h	γ	SPECT
^{124}I	99.6 h	β^+	PET
^{123}I	13.2 h	γ	SPECT
^{131}I	8 d	β^-	Therapy
^{64}Cu	12.7 h	β^+	PET/therapy
^{67}Cu	61.9 h	γ	SPECT

CHAPTER 2

Synthetic Biology and Tissue Engineering

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Abstract: Advanced approaches that can mimic the structure and function of natural tissue in tissue engineering applications that use multidisciplinary engineering approaches to repair damaged or dysfunctional tissues are fed forward by current engineering applications. Manipulating cells or cell groups in an integrated manner into the scaffold, similar to the native tissue composition, is the main challenge in these approaches. Synthetic biology approaches, originating from genetic engineering, based on the use of advanced tools in the manipulation of cells at the molecular level, are one of the most current issues in tissue engineering that shed light on the programming of cells. Synthetic biology tools allow the reprogramming of cells whose transcriptional, translational, or post-translational molecular mechanisms have been engineered by stimulating them with intrinsic or extrinsic signals. Combining these advanced and excellent tools from synthetic biology with materials engineering applications of tissue engineering is the latest fashion. This chapter discusses going beyond conventional tissue engineering applications, synthetic biological molecular tools, circuit designs that allow the complex behavior of cells to be manipulated with these tools, and approaches that enable the integration of these tools into the material component of tissue engineering.

Keywords: Biomaterials, Biotechnology, CRISPR, Genetic circuit, Genetic engineering, Genome editing, Hydrogels, Laci, Molecular tools, Reprogramming of cells, Saps, Spytag-spycatcher, Synthetic biology, Talens, Teto, Tetr, Tissue engineering, Transcription factors, Virus-like particles, Zfns.

INTRODUCTION

Tissue engineering is a multidisciplinary science that aims to regenerate and restore the structural and functional properties of biological tissues damaged for any reason [1]. Tissue engineering includes various approaches in which cells are used in combination with biochemical factors and biomaterials to repair damaged tissue and form new tissue [2, 3].

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Cell-material-biochemical factor-based approaches have been investigated for many years to direct cell differentiation and promote tissue formation. Early tissue engineering applications put a lot of effort into promoting cell behaviors by creating many different classes of materials in different scaffold configurations and topographies to mimic the natural microenvironment [4]. Despite the use of a range of physical, chemical, and mechanical cues to support cell proliferation and lineage-specific differentiation in all these studies, it has still not been possible to develop tissue engineering products for clinical applications, except for a few applications [5].

A current limitation of this situation is the inability to maintain the cell phenotype during synthetic new tissue formation, the inability to control the spatial arrangement, and the dynamic interaction of cells and material properties [6]. Tissue development is a very complex process and depends on the appropriate scaffold and a large number of different signaling molecules, as well as precisely tuned cellular responses [7 - 9]. To restore the function of naturally varied tissues more appropriately, high-resolution spatial control over the cell is essential [10]. Biomaterials and bioactive molecules to guide cell behavior indirectly affect the properties of cells, such as survival, proliferation, differentiation and morphogenesis, through the manipulation of cellular events at the molecular level [11, 12]. All these cellular processes are highly related to various receptor-protein interactions, genetic factors, and the expression of genes. For this reason, in recent years, researchers have focused on the development of new tissue engineering strategies that directly involve molecular and genetic processes [13, 14]. In addition to these great advances with the integration of developments in molecular biology and genetic engineering into tissue engineering, the emergence of the concept of synthetic biology in the past decade has paved the way for a new perspective in tissue engineering. Synthetic biology is a new field in which engineering principles are applied to biological components to understand, manipulate, and modify cell function by designing or regulating organisms or devices [15, 16].

Unlike genetic engineering, synthetic biologists bring together various natural biological parts with different functions from an integrated perspective to redesign cells and create new genetic architectures that perform complex functions, using various molecular biology tools for this purpose [17]. Thanks to this bottom-up approach that allows design and manipulation at the molecular level, different biological functional parts have been combined with endogenous pathways in the organism with various synthetic biology tools to create gene circuits for dynamic gene expression [15]. From the point of view of tissue engineering, the creation of genetic circuits and new gene expression patterns that can control gene expression for tissue formation processes in mammalian cells is a remarkable field of

reprogramming of cells. In addition, these techniques can allow the control of cells at the molecular level to better mimic natural cellularity and tissue structure, thereby enabling spatial and temporal manipulation of the artificial tissue formation process with high precision [18]. Moreover, by adapting these modules in synthetic biology to biomaterials, cellular processes can be directly controlled by biomaterials [19].

In this chapter, we aim to discuss synthetic biology techniques and applications within the framework of tissue engineering. In this context, we explain the current synthetic biology tools used in tissue engineering and review studies on how these tools can be applied in cell and biomaterial-targeted tissue engineering strategies.

REPROGRAMMING OF CELLS WITH SYNTHETIC BIOLOGY TOOLS

Transcription Factors

Transcription factors (TFs) are a complex molecular system that directs the expression of various genes by recognizing specific DNA sequences in the genome of living organisms [20]. TFs are key proteins that have important roles in turning genes on and off during the transcription process, which is the first step for gene expression that makes the DNA sequence functional [21]. They function as master regulators for many cellular processes, such as the determination of cell types and developmental patterns, specific cellular mechanisms, and metabolic activities [22, 23]. TFs are distinguished by their sequence specificity, which allows them to activate or inhibit target gene transcription. Recognizing these specific binding sites in the genome and understanding how to control transcription and control gene expression, and determining their specific functional properties of genomes in various species have been very important topics in molecular biology and cell biology [21]. Today, it is thought that many diseases, such as cancers and various metabolic disorders, may be associated with gene expression changes affected by disruptions of TFs and their binding site genes [24 - 26]. TFs are employed as crucial building blocks and regulatory tools in genetic engineering and synthetic biology, in addition to their usual biological and physiological roles in cells [27]. The transfer of transcriptional regulatory parts obtained from different species in mammalian cells is one of the first examples of synthetic biology.

The lactose repressor system (LacI) and tetracycline-controlled transcriptional activation (TetR, TetO) mediated gene regulation, which are bacterial gene expression regulatory systems, are the first examples of synthetic biology and have paved the way for many studies for the controlled expression of endogenous and exogenous genes [28, 29]. In the lac repressor system, lactose and its molecular analog isopropyl β-D-1-thiogalactopyranoside (IPTG) block LacI from

CHAPTER 3

Innovative Approaches to Prosthetics and Implants

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Abstract: The use of prosthesis plays an important role in rehabilitation in the case of congenital absence or loss of an extremity. Apart from lower and upper extremity prostheses, there is a wide variety of prostheses used in different parts of the body. Unlike limb prostheses, these are permanently placed in the body by surgical intervention and are also called implants. New studies emerge every day in the development of innovative prostheses and implants. These innovations include material selection, new material development, control strategies, feedback system development, sensor and actuator development, power supply methods, and power equipment development work. Besides, many studies aim to increase user comfort as well as acceptance rate and the useful life of prostheses. Some researchers are working to develop prostheses exclusively for the use of children. Innovative developments in prostheses and implants are examined in this section. Developments are presented from various aspects, and information is given about the research that has made significant contributions to the field. As an example of technological development in prosthetics, an autonomic tumor prosthesis developed for children with bone cancer is introduced at the end of the section as a case study.

Keywords: Active prosthesis, Implant, Innovation, Material selection, Orthopedic implant, Pediatric prosthetics, Prosthesis classification, Prosthetics, Tumor prosthesis.

INTRODUCTION

In the event of a loss of any limb in the human body, the artificial components produced in order to fulfill the function of this limb partially or completely are called prostheses. The artificial body attachments used in cases that require support, protection, or correction in any limb without loss of the limb are called orthoses. Implant, on the other hand, is the name given to all solid substances that are surgically placed in the body for treatment.

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Prosthetics, orthoses, and implants can be in a very simple structure formed by shaping a raw material with classical methods, or they can be in a structure that includes high technology and active works. For this reason, prostheses, orthoses, and implants can be examined and separated from each other not in terms of their structure or technology but in terms of their functions and methods of placing them on the body. Implant is a more general expression and can be reclassified as prosthesis, orthosis and other (for example, it may be used for some medical measurements), depending on its function, provided that the implants are placed inside the body. In this section, prostheses, including implant prostheses, are examined in detail.

For most amputated, an artificial limb increases mobility and the ability to perform daily activities, reducing the rate of dependency on other people. Limb amputations are one of the oldest surgeries in history that affect patients both psychologically and physically. Today, when the causes of amputation are examined, accident-induced trauma takes the first place due to the developing technologies and the increase in motor vehicles. Apart from this, non-traumatic reasons, such as diabetes, atherosclerosis, hypertension, and peripheral vascular diseases, may also require amputation. There is a wide variety of limb prostheses that are designed to function as a natural arm, leg, hand, or foot and are, in most cases, visible from the outside. Although there are many products available on the market and used clinically, most of them consist of similar parts. For conventional prostheses, these consist of a socket surrounding the residual limb, the suspension holding the prosthesis on top of the residual limb, the shaft, the limb-like body it replaces, and a cosmetic coating. The socket part is usually covered with silicone or similar soft material to protect the contact area and is worn on the residual limb after wearing socks for adaptation. In determining the prosthesis to be used, the body area where the prosthesis will be used, the amputation level, the condition of the residual limb, the activity level and the expectations of the person play significant roles.

Prostheses have been developed since the first ages of history. The first examples of prostheses are simple structures, such as legs made of wood or hooks to replace the forearm and hand limb. The earliest recorded use of a limb prosthesis was reported by Herodotus. According to Herodotus's account, the Persian soldier Hegesistratus cut off one of his feet in 484 BC and fled using a wooden foot instead [1]. The oldest known artificial limb is a leg, unearthed in Capri, Italy, in 1858, made of copper and wood around 300 BC. In the 15th century, artificial hands made of iron were used by knights. The Alt-Ruppin hand, which is exhibited with other hands belonging to the 15th century in the Stibbert Museum in

Florence, Italy, is one of these examples.

Amputation cases have increased in post-war periods as a result of the injuries of many people and diseases of the musculoskeletal system and neuromuscular diseases, calling for an increase in prostheses development. The United States government has started to support research projects on orthoses and prostheses to improve the quality and performance of assistive devices, especially for amputated veterans [2]. Research and education committees have been established and developed several projects in this regard. With advances in modular components and bioengineering, the use of myoelectric prostheses began in 1950. Special attention has been paid to improving the biomechanical design of prostheses during this period.

The development of new materials that could be used in prostheses after the Second World War led to further advances in the field. The newly emerging transparent plastics were then used in prosthesis production. As a result of the expectation of higher performance from prostheses by special groups, such as athletes, many specially designed prosthetics feet were developed. Innovative designs for prostheses have thus been made possible thanks to carbon composite technology.

The development of computer-aided design/computer-aided manufacturing (CAD/CAM) systems for prostheses in the 1970s was a major technological advance. In the late 1980s and early 1990s, as computers became more economical, prosthetic manufacturers began to integrate CAD/CAM systems into their applications [3].

The use of hand and foot prostheses is possible by performing a surgical intervention called amputation. Ligature in surgery was first described by Hippocrates but was lost in the dark ages [4]. The ligature was reintroduced in 1529 by the French military surgeon Ambroise Pare. Thus, the risk of death due to excessive blood loss in amputation surgeries was reduced [5]. Morel introduced the tourniquet in 1674, which showed a similar effect, reducing the risk of death and accelerating amputation surgeries. In 1536, Pare performed the first elbow disarticulation procedure. Sir James Syme reported the ankle amputation procedure in 1843 [6]. The antiseptic technique was introduced by Lord Lister in 1867 [7]. Ever since, the introduction of antiseptic, chloroform and ether has contributed greatly to the overall success of amputation surgery. Kineplasty, the act of shaping the residual limb to allow comfortable use of the prosthesis in amputation and aimed at strengthening upper limb prostheses by direct muscle contraction, was discovered by Vanghetti in 1898 while trying to improve the prosthetic function of Italian soldiers whose hands were amputated [8]. Ceci

CHAPTER 4

Role of Nanomedicine in Ocular Parasitic Infections

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Abstract: Ocular parasites cause serious vision-threatening diseases. An early diagnosis and effective treatment are crucial to avoid side effects, such as blindness or eye removal. The first important step in diagnosing ocular parasite infections is to suspect them. Diagnosis is aided by ophthalmic examination, direct parasite identification in clinical samples and/or pathological lesions, immunoassays, and molecular methods. Despite this, ocular parasite infection diagnosis is fraught with difficulties in terms of sensitivity, specificity, and accuracy. The usage of nanoparticles may improve diagnosis by providing precise procedures for parasitic DNA, antigens, and antibodies detection in a variety of body specimens with fast, sensitive, and specific results. Low tolerability, long therapeutic duration, multiple adverse effects, and the emergence of medication resistance are all problems with existing anti-parasitic medications. Nanoparticles represent a promising way for the successful treatment of parasitic diseases by developing innovative drug carriers to target medications to infected sites while limiting high doses and adverse effects. They can also overcome the limitations of antiparasitic medications' low bioavailability, poor cellular permeability, non-specific distribution, and fast elimination from the body. The aim of the present chapter is to throw light on possible nanotechnology applications in ocular parasitic diseases caused by *Toxoplasma gondii*, *Acanthamoeba* spp. and *Toxocara* spp. with a focus on diagnosis, treatment, and vaccination.

Keywords: *Acanthamoeba* spp., Diagnosis, Eye infection, Nanotechnology, *Toxocara* Spp., *Toxoplasma gondii*, Treatment, Vaccination.

INTRODUCTION

Direct exposure to the environment makes the human eye susceptible to infections from a variety of microorganisms that are known to be major causes of

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ophthalmic diseases all over the world. Several parasitic infections have been associated with ocular lesions in either anterior or posterior segments of the eye. *Toxoplasma gondii*, *Toxocara* species, and *Onchorcerca volvulus* are the most common parasites that infect the ocular tissue(s) in the posterior segment of the eye. There are also case reports on ocular leishmaniasis, malaria, giardiasis, cysticercosis, hydatid cysts, and coenurosis [1]. *Acanthamoeba* spp. and *Loa Loa*, on the other hand, are the most prevalent parasites that impact the ocular tissue(s) in the anterior part of the eye. Moreover, *Microsporidia*, *Mansonella ozzardi*, *Thelazia*, *Gnanthostoma* spp., and *Angiostrongylus cantonensis* have all been documented in published case reports [2]. Infection with ocular parasites has been documented in a variety of geographic areas, largely based on the parasite's endemicity. The parasite's geographic spread, environmental pollution, and the patient's immune status all play a role in the prevalence of these infections.

These parasites may infect the eye directly through trauma or surgery, or indirectly through hematogenous transmission or dissemination from infected nearby tissues [2]. The resulting ophthalmic manifestations are linked to the causative agents and affected ocular tissues. Pathological lesions may result from direct damage caused by the presence of larvae or adult stages, parasite-released toxic products, or the host's immune response [1, 2]. Choroiditis, retinal vasculitis and hemorrhage, retinochoroiditis, detachment of retina, papilledema, orbital cysts, or optic nerve atrophy all affect the posterior segment, resulting in permanent retinal impairment and vision loss.

Clinical diagnosis frequently matches other viral and bacterial infections that induce visual morbidity. Suspecting ocular parasite infections is the most crucial step in diagnosing those [3]. A preliminary diagnosis is also aided by an ophthalmic examination, as well as the associated risk factors and the history of travel to endemic areas. The most common method for confirming the diagnosis is to use direct parasite detection in biological specimens. In ocular toxoplasmosis and toxocariasis, the detection of antigens/antibodies in aqueous humor, vitreous humor and sera samples frequently confirms the diagnosis. The use of molecular approaches, such as polymerase chain reaction (PCR), for the detection of parasite DNA, has improved diagnosis and species identification [1, 4]. Despite that, diagnosis of ocular parasitic infection faces many challenges regarding sensitivity, specificity, and accuracy.

Medical or surgical treatment is available for ocular parasitic infections. The severity of symptomatology, ocular inflammatory responses, affection of vision, macula affection, and presence of eye injuries are all factors that influence treatment. It is worth noting that the clinical response is the most important determinant of cure [5]. However, treating ocular parasitic infections exacerbates

the challenge of limiting the effectiveness of current antiparasitic drugs, as well as their adverse effects and the possibility of the emergence of resistant strains. As a result, it is necessary to search for treatments that are both safer and more effective [6].

Medical nanotechnology can offer a new approach to diagnose and treat ocular parasitic diseases and to develop vaccinations against them. Use of nanoparticles (NPs) may provide precise procedures for parasitic DNA, antigen and antibody detection in a variety of body specimens with fast, sensitive, and specific results. Novel NP-related methods permitted the discovery of new target molecules avoiding cross-reactivity between parasites' antigens that are shared in antigenic epitopes. Moreover, NPs have promise for effective parasite disease therapy because they enable the development of innovative drug carriers or the delivery of new medications while overcoming high doses, low bioavailability, poor cellular permeability, non-specific distribution, and side effects that antiparasitic drugs have. In terms of the role of NPs in vaccine development, they can be used to carry whole or purified antigens, DNA, RNA, or act as adjuvants, enhancing uptake via antigen-presenting cells, producing specific antibodies (Abs), and eliciting the most effective T helper 1 (Th1) cells' immune response [7].

However, due to a lack of systematic studies in this field, nanotechnology has not been widely used in ocular parasitology. Therefore, this chapter clarified the expected role of nanomedicine in ocular parasitic infections caused by *Toxoplasma gondii*, *Acanthamoeba* spp. and *Toxocara* spp. with a focus on diagnosis, treatment, and vaccination.

ROLE OF NANOMEDICINE IN OCULAR PARASITES

Nanotechnology is the science dealing with tiny materials (10-100 nm) that can connect to certain molecules on the surface of cells or intracellularly modify a variety of physical, chemical, and biological characteristics [8]. Chemical and photochemical reactions being microwave-assisted, reverse micelles, thermal breakdown, as well as electrochemical, sonochemical [9], and biological techniques can all be used to create nanomaterials. Also, plant-mediated biological NP production is attracting attention owing to its simplicity and low cost [10].

Different nanomaterials have been used in applied parasitology. Antiparasitic effects of gold and silver NPs have been extensively researched. The conjugation of antiparasitic drugs with NPs has enhanced anti-amoebic [11], antitoxoplasmic [7], and anti-*Toxocara* [12] activities. The antiparasitic potential of metallic NPs is linked to several factors, including NPs interaction with microbial cell walls,

CHAPTER 5

Anticancer Delivery: Nanocarriers and Nanodrugs

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Abstract: Cancer is a disease in which cells grow uncontrollably and spread to different tissues. Existing treatment methods developed for cancer do not allow this disease to be completely cured, and these methods have various side effects. The search for effective cancer treatment has encouraged scientists to produce new ideas with nanotechnological methods. With the help of nanotechnological methods, which are becoming more popular day by day, the material is reduced to nano size, where it shows quantum effect, and gains unique physicochemical, mechanical, and biological properties. Thanks to the large surface area of the nanocarriers, more drug loading can be achieved on the unit surface, and their easy modification procedures enable these materials to be conjugated with biological molecules to become more specific structures. Due to the several advantages of nanocarriers, such as different synthesis methods, being open to modification, and relatively easy production, these materials can provide effective delivery of cancer drugs and even increase their efficacy. Moreover, there are also many nanodrugs approved for different routes of administration. Thanks to all these features, nanocarriers are promising ways to develop new drug formulations for cancer treatment. In this chapter, the anticancer activity of nanocarriers synthesized by different methods is clarified. Besides, the effects of the nanocarriers on different types of cancer, the targeting strategies of nanocarriers, and the effects of their size, surface charge, and shape, on their anticancer activity are summarized.

Keywords: Active targeting, Anticancer effect, Antitumor effect, Cancer, Cancer cells, Cancer treatment, Carbon nanotubes, Chemotherapy, Drug delivery, Graphene, Lipid nanocarriers, Magnetic nanoparticles, Metallic nanoparticles, Nanocarriers, Nanodrugs, Nanoparticles, Nanotechnology, Passive targeting, Polymeric nanocarriers, Targeted delivery.

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INTRODUCTION

Cancer, a disease characterized by uncontrolled cell proliferation, replicative immortality, and cell death resistance, is the second cause of death worldwide [1]. According to the estimates of the GLOBOCAN 2020 represented by the International Agency for Research on Cancer (IARC), in 2020, there were 19,3 million new diagnosed cases and 10 million cancer-related deaths worldwide [2].

Surgical operations, radiation therapy, and chemotherapy are conventionally used to treat cancer, but these methods have side effects on healthy cells [3, 4]. The action mechanism of radiotherapy is based upon the destruction of cancer cells by DNA damage. It is desirable for healthy tissues to be unharmed or have minimal damage; however, healthy cells can be exposed to radiation doses, albeit at low levels, and this causes damage [4].

Cancer immunotherapy, which is an alternative to these conventional therapy methods, is based on the principle of stimulating the immune system to recognize, target, and destroy cancer cells [5]. Nevertheless, the usage of this therapy is limited due to problems, such as the possibility of immune-related side effects and poor specificity in tumor cell targeting [6].

Another strategy used for cancer treatment is gene therapy. Gene therapy is an approach that enables a gene or gene product to be selectively delivered to a specific cell or tissue with minimum toxicity. Using this therapy, the expression of the defective gene can be blocked, or a normal gene expression can be achieved [7]. Gene therapy depends on gene delivery vectors, and they are classified into two categories according to vectors: viral vectors and non-viral vectors. The drawbacks of viral vectors, such as limited cloning capacity, complicated production, immune response triggering potential, and the risk of insertional mutagenesis, have led researchers to develop non-viral systems [7]. The non-viral delivery systems are less efficient than viral vectors but have advantages, such as flexibility and safety. The recent advancements in non-viral gene therapy are based on nanoparticle technologies [8].

In addition to these treatments, photodynamic therapy (PDT) is an important approach based on the destruction of tumors by the generation of singlet oxygen and reactive oxygen species (ROS) in cancer cells. Although PDT provides many advantages in tumor targeting and minimal toxicity, some challenges limit its utilization [9].

Chemotherapy is one of the most common methods used against cancer. Chemotherapeutic agents, such as etoposide (ETO), docetaxel (DTX),

doxorubicin (DOX), cisplatin, and paclitaxel (PTX), have shown remarkable potential in clinical studies and have enhanced the survival rate of cancer patients. However, cancer cells may develop drug resistance against chemotherapeutic agents, reduce drugs' effectiveness and make treatment less effective or ineffective [10, 11]. Drug resistance causes a reduction in a drug's efficacy and potency to deliver therapeutic benefits, and thus it poses a significant barrier to disease treatment and patient survival [12]. Also, these chemotherapeutic agents can cause some serious side effects. Generally, chemotherapy is not specific to cancer cells, so it can damage healthy tissues. Therefore, it has dose-limiting effects, and as a result, the required critical dose cannot be reached, and the effectiveness of the drug may decrease [13]. Also, low water solubility, lack of stability, rapid metabolism, unfavorable pharmacokinetic properties, and non-selective drug distribution are other disadvantages of many chemotherapeutics [14].

Recently, nano-based drug delivery systems have become one of the most promising strategies to eliminate the side effects of chemotherapeutics and to increase the effectiveness of existing cancer treatment methods [15]. Nanoparticles (NPs) are defined as materials ranging from 1 to 1000 nm in length or 1 to 100 nm in diameter, but particles less than 200 nm in size are preferred for nanomedicine [16, 17]. Since most anticancer drugs are hydrophobic, they have some drawbacks, such as low solubility and weak bioavailability [15]. Nanosizing of drugs overcomes these drawbacks and provides benefits, such as increasing targeting ability, drug stability, and dissolution rate, besides reducing toxicity, drug resistance, and the required dose [18]. They have many advantages compared to free drugs due to their properties, such as continuous and slow release, increased half-life of drugs, and ensuring effective dose at low concentrations [13, 19]. These advantages make nanocarriers promising vehicles for anticancer drug delivery.

In this chapter, the features and targeting strategies of nanocarriers, the properties of the polymer-based, lipid-based, and inorganic NPs and their anticancer research in the literature, and finally, nano-drugs approved by various administrations for cancer treatment will be summarized.

NANOCARRIERS FOR ANTICANCER DRUG DELIVERY

Nanocarrier vehicles, which have an important place for anticancer studies, can effectively reduce the toxic effect of chemotherapeutics by modifying their pharmacokinetic properties, and thus alle*via*te the therapeutic dosage limitation [20]. In order to reduce the disadvantages of free drugs and increase their effectiveness, nano formulations of chemotherapeutic drugs have been developed.

CHAPTER 6

Application of Bioceramics to Cancer Therapy

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Abstract: Despite the great medical developments, cancer remains the main cause of death amongst individuals under 85 years. Novel therapeutic approaches for cancer therapy are constantly being developed, and bioactive ceramics show great promise in this respect. Bioceramics contain inorganic components, which help in the repair, replacement, and regeneration of human cells; for that reason, their use is growing in scope. Bioceramics have a flexible nature and can be modified with biologically active substances for a particular treatment or improvement of tissue or organ functionality. Materials, including glass-ceramics and calcium phosphate, can be loaded with specific drugs, growth factors, peptides, and hormones in a particular fashion. Also, for the elimination of infections and inflammations after surgery, the surface of bioceramics can be modified, and antibiotics can be introduced to prevent bacterial biofilm formation. In the context of bone cancer diagnosis and treatment, mesoporous bioceramics have demonstrated excellent properties not only for being osteoinductive and osteoconductive but also for drug delivery, therefore, being rendered as a remarkable platform for the creation of bone tissue engineering scaffolds for the purpose of bone cancer treatment. Furthermore, the creation of ceramic magnetic nanoparticles as thermoseeds for hyperthermia exhibits promising development for cancer treatment. The conjugation of ceramic nanoparticles with therapeutic agents and heat treatment *via* different magnetic fields improve the efficacy of hyperthermia to the extent that it makes them an alternative to chemotherapy. This chapter discusses the therapeutic value of bioceramics.

Keywords: Bioactive, Bioceramics, Cancer therapy, Clinical trials, Drug release, Glass-ceramic, Hyperthermia, Magnetic nanoparticles.

INTRODUCTION

Cancer is the second most common cause of death in the world. In the United States, around 1.9 million new cases of cancer are estimated, while 608,570 died from cancer in 2020 [1]. The cost of cancer treatment for patients directly was

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about $5.6 billion, which included radiation treatment, surgical procedures, and chemotherapy. In 2015, the United States spent $183 billion on cancer-related health care, which is expected to rise to $246 billion by 2030, amounting to a 34% increase [2]. In the United Kingdom, approximately 250,000 individuals are diagnosed with cancer each year, with over 130,000 resulting in death. The annual cost of cancer care for the NHS is £5 billion, but the total cost for society, including lost productivity, is around £18 billion [3].

Cancer can be divided into five categories, namely carcinomas, sarcomas, leukaemia, lymphoma, and myeloma. Carcinomas are one of the most common types of cancer, which originate in epithelial tissue that covers the surface of internal organs and glands. They mostly occur in skin, breasts, lungs, and pancreas, and usually cause solid tumours. Different types of carcinomas include basal cell carcinoma, melanoma, and Merkle cell carcinoma [4]. Sarcomas are malignant cancers that occur in connective tissues, including muscles, fat, cartilage, tendons, and bone. Chondrosarcoma, Ewing's sarcoma, osteosarcoma, and soft tissue sarcoma are a few examples [5]. Leukaemia is a blood cancer originating in the bone marrow. It prevents the marrow from producing normal white and red blood cells. Consequently, blood cells grow and divide uncontrollably. Acute lymphocytic leukaemia, chronic myeloid leukaemia, chronic lymphocytic leukaemia, and acute myeloid leukaemia are the main types of leukaemia [6]. Lymphoma is a cancer that starts in the lymphatic nodes or glands as well as in organs, like the breast and brain. Therefore, lymphoma is considered a cancer of the immune system [7]. Myeloma is a cancer type that develops in the plasma cells of the bone marrow. Myeloma cells may also congregate in the bone to form a single tumour known as plasmacytoma. In certain cases, myeloma cells accumulate in several bones, resulting in several bone tumours or multiple myeloma [4].

The most common cancer types include breast, lung, and colorectal cancer, which accounted for approximately 50% of all new cancer diagnoses in women in 2020. In men, prostate, lung, and colorectal cancers accounted for an estimated 43% of all cancers diagnosed in 2020. In the history of medicine, cancer treatment has been a long-standing issue. Every year, millions of cases are identified, along with millions of deaths. It is assumed that approximately, 90-95% of cases are caused by environmental factors, while the remaining 5-10% are due to genetic factors [8]. Generally, all cancer-causing factors can be categorised into six groups, namely chemical carcinogens, radiation, viral and bacterial infection, heredity, hormones, and immune system dysfunction [8, 9].

Novel cancer treatment strategies have been introduced thanks to the advancement of new technologies. Amongst these, bioceramics offer great hope and promises.

They are considered an important material class for biomedical engineering applications [10]. During the last few decades, bioceramics have been applied in direct contact with living tissues mainly for the repair and regeneration of tissues affected by trauma or disease. The aim of this chapter is to introduce the current state-of-the-art applications of bioceramics in research and clinic with a focus on cancer therapy.

Extracellular Matrix and Tumour Microenvironment

Healthy cells follow a normal cycle of growth, apoptosis, and cell regeneration. However, cancer cells divide uncontrollably, spread *via* the bloodstream and the lymphatic system, and invade other parts of the body, so-called metastasis [11 - 13]. The extracellular matrix (ECM) plays an important role in the progression and spread of cancer cells in the tumour microenvironment (TME). The ECM provides mechanical and physical support for the cells in the TME, and contains essential chemokines and angiogenic factors, which provide compressive and tensile strength *via* cell surface receptors [14].

Remodelling mechanisms that occur in ECM are categorised into four key processes (Fig. **1**). First, ECM is deposited, which alters the concentration of ECM components. Post-translational modifications (PTM) then occur where the biochemical properties and structural aspects of the ECM are altered (Fig. **1a**). Next, proteolytic degradation occurs, aiding the bioactive ECM fragments and ECM-bound factors (Fig. **1b**). The final step is a force-mediated physical remodelling process (Fig. **1c**), which modifies the ECM arrangement by aligning ECM fibres and open channels for cell migration [15].

Tissue homoeostasis is based on accurate ECM remodelling leading to tissue-specific biochemical and biophysical ECM characteristics. ECM components serve as ligands for diverse cell surface receptors, such as integrins, receptor tyrosine kinases, and syndecans. Hence, changes to the delicate balance in the ECM remodelling process impact complicated cellular signalling networks.

Therefore, it is expected that malignant and tumour-associated stromal cells alter the ECM remodelling processes, resulting in a cancer-supporting matrix, the TEM, that actively supports the tumour's pathogenesis [16]. The TEM consists of malignant cells and a variety of cell types, including immune cells, vascular endothelium cells, adipocytes, lymphocytes, fibroblasts and pericytes. There is also a complex network of cytokines, chemokines, GFs, and multiple subtypes of interleukins that mediate intracellular communication. Table **1** presents different cell lines and their relevant functions in the TME.

CHAPTER 7

Advanced Materials and Processing Techniques

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Abstract: Advanced materials and processing techniques are the backbone of the smart industry. The smart industry could not be run without a furnish of raw materials. Further, the raw materials could become advanced materials by employing good processing technology. Owing to this, new advanced materials exhibit compelling properties and applications in various fields. In the present chapter, we have provided insight into the current development of advanced materials comprising different fabrication methodologies and their incorporation with nanofillers, as well as their advanced processing techniques. Moreover, advanced materials' applications have been emphasized in different fields, like tissue engineering, biomedical, agriculture sector, and pesticides.

Keywords: Advanced materials, Agricultural, Biomedical devices, Fertilizers, Pesticides, Processing techniques, Tissue engineering.

INTRODUCTION

The unprecedented and rapid technological development started in the 19th century, especially in the fabrication and processing of advanced materials. Nowadays, advanced materials, particularly nanomaterials (NMs), have become one of the most significant generic materials due to their potential applications in different sectors [1]. The materials considered as advanced materials of 21st century are advanced nanoceramics, smart polymers, graphene-based nanomaterials, and nanocomposites (NCs). The advanced nanomaterials are shown in Fig. (**1**).

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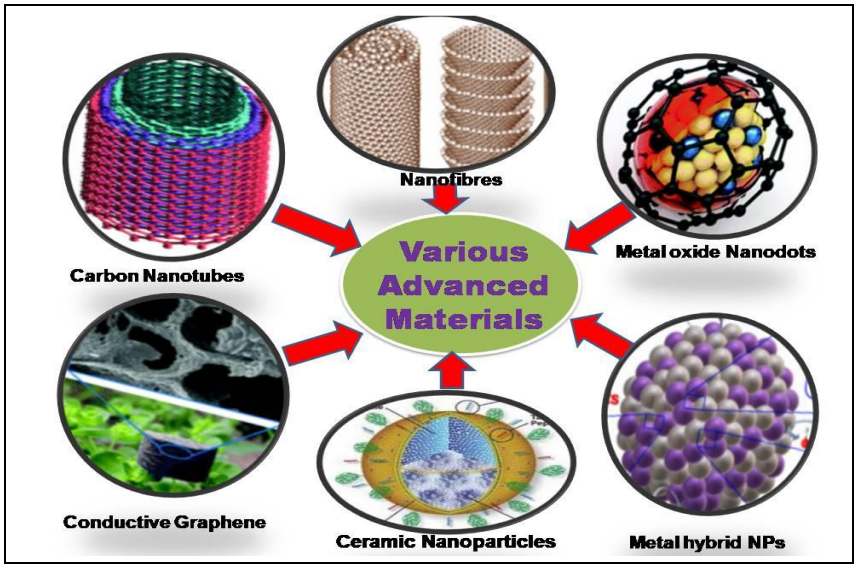

Fig. (1). Advanced nanomaterials.

Basically, advanced materials show higher strength, improved density ratios, better hardness, superior thermal behaviour and electrical, optical, and chemical properties. For instance, the graphene-based NCs are one of the best advanced materials, which have been used for numerous applications. Besides, many researchers have developed different types of advance manufacturing processing techniques to enhance materials' efficiency and productivity [2 - 4]. Material processing is the heart of material science and engineering, which involves fundamental principles responsible for the processing of all types of materials. It is a multi-step process involving chemical, thermal, and physical processes.

Polymer NCs are one of the most the significantly advanced materials as they possess toughness, stiffness, corrosion resistance, and lightness [6 - 8]. These are used in aviation industries because of their advanced features, such as tailor-made mechanical properties, design flexibility, lower weight, anti-corrosion, and better fatigue performance [9]. The material processing technique for graphene-reinforced polymer composites is shown in Fig. (**2**). A well-known aviation industry, Boeing, uses around 80% composites for its single Dremliner-787. Each Dreamliner requires 35 metric tons of carbon fiber reinforced plastic (CFRP) out of twenty-three metric tons of composites made of carbon [10]. Likewise, carbon is the prominent element having new forms of carbon-based materials, such as fullerene [11], carbon nanotubes (CNTs) [12], and graphene [13]. Graphene is popular among carbon-based materials. Graphene has gained significant interest in materials science, and it has been employed in numerous applications, like

sensors, electrodes, energy storage devices, various types of solar cells, *etc*. [14, 15]. Moreover, fibber-reinforced NCs are also important materials and can be manufactured by resin transfer moulding (RTM) and vacuum-assisted resin transfer moulding (VARTM) [16 - 19]. Different types of glasses and their composites with superior properties have been prepared using different techniques [20, 21]. The current trend in materials science is to see beyond conventional and well-known materials, which are new having better properties. It is high time that conventional processing techniques for materials must change. It is of utmost importance that processing techniques must change the properties of advanced materials to a great extent. From the beginning, the processing methods should be integrated into the design and development. There are a number of challenges faced by the industry tycoon to achieve excellence in each process to design, develop, produce, and distribute material products to customers. Excellent functional capabilities must be integrated. Therefore, keeping this perspective, the present chapter highlights a recent development in advanced materials' processing techniques and their important applications in various sectors.

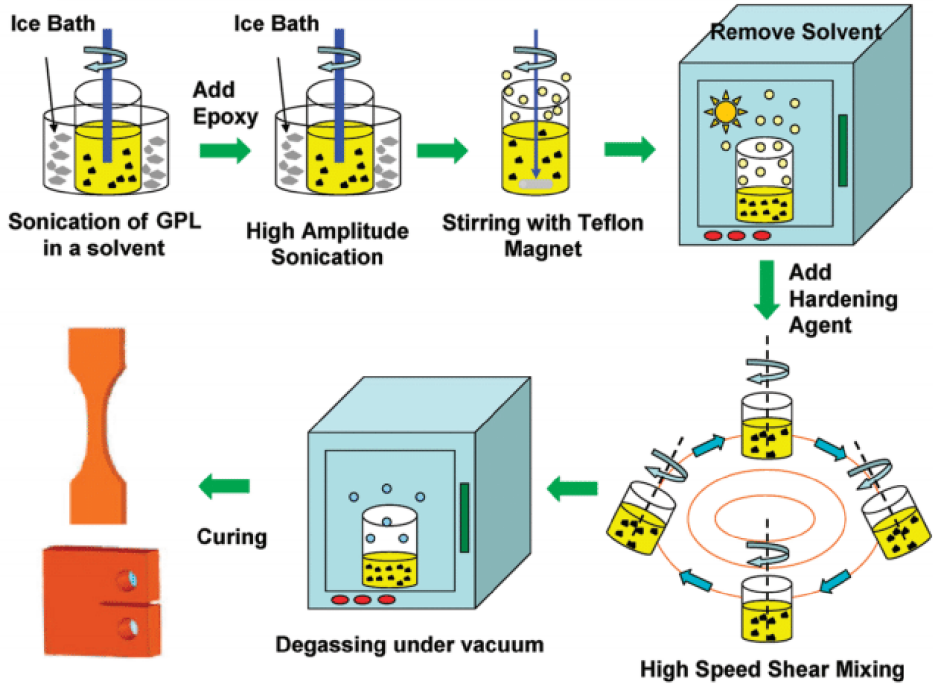

Fig. (2). Solution mixing for the manufacture of graphene-reinforced polymer composites (GRPCs). Reproduced with permission from the American Chemical Society [5].

CHAPTER 8

Regulators of Biomedical Devices

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Abstract: Regulators of medical devices in the world regulate global competition in the medical device sector, and on the other hand, they play a decisive role in security, performance, and access issues. Technological development has also increased in the medical device industry, and medical devices have become more important in the diagnosis and treatment of health services. However, it is important that legal regulations must be implemented correctly and effectively in order to prevent public health or unethical behaviors. In this context, the regulations of the United States of America (USA) and the European Union (EU), the leaders in the sector, along with their high markets are discussed. In addition, medical device regulations in Japan, China, and Brazil, which have an important position in technological development and competition and have high potential, are also included. Considering the urgency and possible consequences of healthcare services, it is necessary to consider the fund and the regulations of the medical device sector separately in individual, national and global dimensions, from macro to micro. In addition to the safety, cost, and effectiveness of medical devices, it is important to discuss the conformity assessment, approval system processes, and how long it takes for a medical device to be put on the market. Considering the rapid technology change, regulations should be made to carry out the licensing and approval processes effectively and quickly in medical device regulations.

Keywords: Biomedical devices, Classification, Comparison, Medical devices, Regulations, Regulatory, Safety.

INTRODUCTION

The medical device sector has an important place in the health sector where a lot of effort and the latest technology are used extensively. The reasons, such as the

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increase in the elderly population, the spread of chronic diseases, the development of science day by day, and the high purchasing power have led to the development of the medical device industry. Globalization, countries' development of their own technologies, and countries' desire to export have accelerated the spread of this sector in the world. It seems that global organizations dominate the medical device industry. All over the world, it seems that the end products of medical devices are of high cost. For this reason, medical device production and distribution to the market are mostly carried out by big organizations, and small and medium-sized organizations operating in the medical device sector are usually purchased by big organizations or strategic partnerships are established with them, and activities are carried out at a global level [1].

It is seen that more than 60% of medical device production in the world is foreign trade. This situation reveals that the medical device industry has become global. Therefore, international organizations are included in this sector and they take the competition to a higher level. Of course, some countries do not go into privatization and try to get stronger in their local markets [2].

All processes that medical devices go through until they become available to the market are aimed at ensuring the safety of products and minimizing the risk of error and damage. Therefore, regulations developed for medical devices in the world aim to protect public health and ensure the use of safe products [3].

In this chapter, firstly, medical device regulations are discussed from a general perspective, and then the USA and EU regulations are discussed in detail. Also, medical device regulations in Japan, China, and Brazil, which have an important role and potential in the medical device sector, are briefly discussed, and the subject is evaluated in detail with the results, discussions, and recommendations section.

MEDICAL DEVICE REGULATIONS OVERVIEW

Medical device regulations are made with the participation of all partners. Representatives of the leading countries, scientific committees, universities, medical device manufacturers producing worldwide, notified institutions that check whether the products are at a sufficient level in terms of quality and safety, and international testing and certification institutions and working groups determine the regulations and universal standards in line with the needs [4].

Thanks to international trade agreements, such as the Customs Union and the free-enterprise policy, the circulation of medical devices between countries has become easier, as is the case with many product groups. Within the scope of the agreements made, countries have updated their current legislation and developed

common legislation. As a result of the common laws and rules applied, a product in any country can enter the market and can be exported without any obstacles. For example, a medical device produced and certified in accordance with the requirements of the medical device directives within the borders of the EU can be placed on the market after the necessary customs notifications are made in other Union member countries [5].

The desire of multinational organizations to reduce production and transfer costs, which emerged after the initiation of intercontinental trade, enabled medical device organizations to establish production facilities in different continents. Thanks to the new facilities, although organizations manage to reduce production and transfer costs, the whole world is prevented from turning into a single medical device market due to reasons, such as the absence of a common legislation or audit program covering all countries, including Russia, China, Japan, and America. Today, working groups and boards consisting of representatives of the leading countries of the sector develop projects on this issue [6].

The International Medical Device Regulators Forum (IMDRF) is a voluntary working group that brings together medical device regulators from various countries of the world and aims to accelerate the joint work of international medical device regulators. IMDRF consists of medical device regulatory authorities and representatives of Australia, Brazil, Canada, China, the EU, Japan, Russia, Singapore, and the USA. The World Health Organization (WHO) and the Asia-Pacific Economic Cooperation - Life Sciences Innovation Forum - Regulatory Harmonization Steering Committee (APEC-LSIF-RHSC) are official observers. Among the aims of the organization are to effectively respond to industry challenges, establish a regulatory model for medical devices, protect public health, and maximize safety.

There are different medical device risk groups in the world. These groups are commonly called classification systems. Although there are differences in the classification of medical devices according to countries, in general, products are classified according to the place of use, purpose of use, indication, device components and risks [4]. The first classification system was prepared with a system called “Nomenclature regulation system”. In this system, products are classified as low, medium, and high, according to the increasing risk level. The Nomenclature classification system is still used in the USA and Japan. In these countries, device classes are determined according to the products called generic and with a certain risk class [7]. EU, in 1993, developed a Medical Device Legislation, and Medical Device Directives brought a new perspective to the classification of products. They have established general rules that can be applied to products by identifying potential hazards to the human body. According to the

SUBJECT INDEX

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Dr. Felipe López Saucedo earned his PhD from the National Autonomous University of Mexico (UNAM) at the Institute of Nuclear Sciences in the field of biopolymers and biomedical devices in 2018. He did BSc in chemistry from Faculty of Chemistry UNAM, and submitted thesis in organic synthesis (2011). He did MSc in chemistry from the Institute of Chemistry UNAM, and submitted thesis in homogeneous catalysis in 2014. DGAPA-UNAM has a postdoctoral position in organometallics at the Institute of Chemistry UNAM (2018-2020). CONACyT-UAEMEX postdoctoral position in biotechnology research (2021-2023). He is a coauthor of 21 research articles and 11 book chapters since 2016. He published two books in the book series entitled 'Frontiers in Nanomedicine'.