BIONANOTECHNOLOGY: NEXT-GENERATION THERAPEUTIC TOOLS

Editors:
Alaa A. Aljabali
Kaushik Pal

Bentham Books

Bionanotechnology: Next-Generation Therapeutic Tools

Edited by

Alaa A. Aljabali
Department of Pharmaceutics and Pharmaceutical Technology, Yarmouk University
Irbid 21163, Jordan

&

Kaushik Pal
Department of Physics University Centre for Research and Development (UCRD)
Mohali, Gharuan, Punjab 140413
India

Bionanotechnology: Next-Generation Therapeutic Tool

Editors: Alaa A. Aljabali, Kaushik Pal

ISBN (Online): 978-981-5051-27-8

ISBN (Print): 978-981-5051-28-5

ISBN (Paperback): 978-981-5051-29-2

need for a court order if at any point you breach any terms of this License Agreement. In no event will any delay or failure by Bentham Science Publishers in enforcing your compliance with this License Agreement constitute a waiver of any of its rights.

3. You acknowledge that you have read this License Agreement, and agree to be bound by its terms and conditions. To the extent that any other terms and conditions presented on any website of Bentham Science Publishers conflict with, or are inconsistent with, the terms and conditions set out in this License Agreement, you acknowledge that the terms and conditions set out in this License Agreement shall prevail.

Bentham Science Publishers Pte. Ltd.
80 Robinson Road #02-00
Singapore 068898
Singapore
Email: subscriptions@benthamscience.net

CONTENTS

PREFACE

This book describes the design and characterization of bionanomaterials, which exhibit distinctive physical, chemical, and biological properties, and discusses how these functional nanomaterials enable the precise manipulation of the architectural, physical, and biochemical cellular environment *in vitro* and *in vivo*. Besides, it covers how they can act as carriers of diagnostic or therapeutic agents, thus providing new pathways or strategies for disease diagnosis and treatment. Specific chapters discuss protein delivery, drug delivery, tissue regeneration, bioimaging, bio-detection, molecular imaging, nucleic acid therapeutics, and DNA-based nanomaterials.

Furthermore, the book focuses on a unique subset of nanomaterials originating from biological entities and explores their potential as nanomedicine tools for selective drug delivery and molecular imaging. Bionanomaterials hold great potential as naturally occurring nanomaterials with enhanced properties, such as biodegradable, biocompatible, safety, and amenability for chemical and genetic manipulation to impart new surface functionalities for the selective targeting. Subsequently, such nanomaterials will enhance the therapeutics payload delivered selectively to the diseased cells. Besides, nanomaterials should have a higher signal-to-noise ratio, making them ideal as molecular imaging tools. Bionanomaterials can be produced in larger quantities at low cost, and most importantly, they are highly monodisperse, making them ideal candidates as tools in nanomedicine. Their composition in terms of chemical and structural point of view is unmatched to their synthetic counterparts, and as they comprise natural amino acids or natural monomers, they are safe and hold no side effects for the development as tools in nanomedicine and drug delivery.

The book series will be an international collaboration to present a comprehensive overview of bionanomaterials from natural sources and explore their benefits, advantages, and disadvantages compared to their synthetic counterparts. It will mainly help in practical academic research innovations in the areas of bionanomaterials. Furthermore, this book will explore the clinical demand for a subset material comprised of natural sources for advanced applications. The book is directed toward researchers, academics, and higher education students working on bionanomaterials in medical, pharmaceutical, environmental applications.

Alaa A. A. Aljabali
Department of Pharmaceutics and Pharmaceutical Technology
Yarmouk University, Faculty of Pharmacy
Irbid
Jordan

&

Kaushik Pal
Department of Physics
University Centre for Research and Development (UCRD)
Mohali, Gharuan, Punjab 140413
India

List of Contributors

Alaa A A Aljabali	Faculty of Pharmacy, Department of Pharmaceutics and Pharmaceutical Technology, Yarmouk University, Shafiq Irshidat Street, Irbid 21163 - P. O. BOX-566, Jordan
Amal Ali Elkordy	School of Pharmacy and Pharmaceutical Sciences, Faculty of Health Sciences and Wellbeing, University of Sunderland, Sunderland SR1 3SD, UK
Basma Milad Aloud	Department of Physiology and Pathophysiology, University of Manitoba, Winnipeg, Canada
Donald W. Miller	Kleysen Institute for Advanced Medicine, University of Manitoba, Winnipeg, Canada
Ejlal Abu-El-Rub	Department of Basic Medical Sciences, Faculty of Medicine, Yarmouk University, Irbid, Jordan Department of Physiology and Pathophysiology, University of Manitoba, Winnipeg, Canada
Ezaldeen Esawi	Faculty of Medicine, The University of Jordan, Amman 11942, Jordan
Hana M. Zegallai	Department of Pharmacology & Therapeutics, University of Manitoba, Winnipeg, Canada DREAM, Children's Hospital Research Institute of Manitoba, Winnipeg, MB, Canada
Hanin Alyamani	Strathclyde Institute of Pharmacy and Biomedical Sciences, University of Strathclyde, 161 Cathedral Street, G4 0RE Glasgow, United Kingdom
Hamdi Nsairat	Pharmacological and Diagnostic Research Center, Faculty of Pharmacy, Al-Ahliyya Amman University, Amman 19328, Jordan
Hassan Elsana	School of Pharmacy and Pharmaceutical Sciences, Faculty of Health Sciences and Wellbeing, University of Sunderland, Sunderland SR1 3SD, UK
Ismail Sami Mahmoud	Department of Medical Laboratory Sciences, The Hashemite University, Zarqa, 13133, Jordan
Kaushik Pal	Federal University of Rio de Janeiro, Cidade Universitaria, Rio de Janeiro, 21941-901, Brazil
Manal Alsaadi	Department of Industrial Pharmacy, Faculty of Pharmacy, University of Tripoli, Tripoli, Libya
Murtaza M. Tambuwala	SAAD Centre for Pharmacy and Diabetes, School of Pharmacy and Pharmaceutical Science Ulster University, Coleraine, UK
Marta Ruano	Strathclyde Institute of Pharmacy and Biomedical Sciences, University of Strathclyde, 161 Cathedral Street, G4 0RE Glasgow, United Kingdom
Mohammad A Ismail	Faculty of Medicine, The University of Jordan, Amman 11942, Jordan
Mohammad A. Obeid	Department of Pharmaceutics and Pharmaceutical Technology, Faculty of Pharmacy, Yarmouk University, Irbid, Jordan

Mohammed Al Qaraghuli	Department of Chemical and Process Engineering, University of Strathclyde, 75 Montrose Street, Glasgow, G1 1XJ Glasgow, United Kingdom Strathclyde Institute of Pharmacy and Biomedical Sciences, University of Strathclyde, 161 Cathedral Street, G4 0RE Glasgow, United Kingdom Basra University College of Science and Technology, Al-Wofod street, Basra, Iraq
Neha Sharma	School of Pharmaceutical Sciences, Lovely Professional University, Phagwara (Punjab), India Rayat Institute of Pharmacy, Railmajra, Shaheed Bhagat Singh Nagar, (Punjab), India
Pooja Saxena	Medicago R&D Inc., 1020 Route de l'Eglise, Quebec City, Quebec, G1V 3V9, Canada
Rajarshi Roychoudhury	enGene Inc, 7171 Frederick Banting, Saint-Laurent, QC H4S 1Z9, Canada
Rasha M. Bashatwah	Faculty of Pharmacy, Department of Pharmaceutics and Pharmaceutical Technology, Yarmouk University, Shafiq Irshidat Street, Irbid 21163 - P. O. BOX-566, Jordan
Said I. Ismail	Faculty of Medicine, The University of Jordan, Amman 11942, Jordan Qatar Genome Project, Qatar Foundation, Doha, Qatar
Saravanan Sekaran	Department of Biotechnology, School of Chemical and Biotechnology, SASTRA Deemed to be University, Thanjavur- 613401, Tamil Nadu, India Department of Pharmacology, Saveetha Dental college and Hospital, Saveetha Institute of Medical and Technical sciences (SIMATS), Chennai 600 007, Tamil Nadu, India
Shrouq Alsotari	Cell Therapy Center, The University of Jordan, Amman 11942, Jordan
Shubham Bisht	School of Pharmaceutical Sciences, Lovely Professional University, Phagwara (Punjab), India
Sirikwan Sangboonruang	Biotechnology section, Graduate School, Chiang Mai University, Chiang Mai, Thailand, 50200
Srijana Sharma	School of Pharmaceutical Sciences, Lovely Professional University, Phagwara (Punjab), India
Valerie A. Ferro	Strathclyde Institute of Pharmacy and Biomedical Sciences, University of Strathclyde, 161 Cathedral Street, G4 0RE Glasgow, United Kingdom
Vijay Mishra	School of Pharmaceutical Sciences, Lovely Professional University, Phagwara (Punjab), India
Walhan Alshaer	Cell Therapy Center, The University of Jordan, Amman 11942, Jordan
Yachana Mishra	Department of Zoology, Shri Shakti Degree College, Sankhahari, Ghatampur, Kanpur Nagar (Uttar Pradesh), India
Yingmanee Tragoolpua	Division of Microbiology, Department of Biology, Faculty of Sciences, Chiang Mai University, Chiang Mai, Thailand, 50200

CHAPTER 1

An Overview of Biomaterial Toxicity and Excretion

Srijana Sharma[1], Yachana Mishra[2], Shubham Bisht[1], Neha Sharma[1,3] and **Vijay Mishra[1,*]**

[1] *School of Pharmaceutical Sciences, Lovely Professional University, Phagwara (Punjab), India*

[2] *Department of Zoology, Shri Shakti Degree College, Sankhahari, Ghatampur, Kanpur Nagar (Uttar Pradesh), India*

[3] *Rayat Institute of Pharmacy, Railmajra, Shaheed Bhagat Singh Nagar, (Punjab), India*

Abstract: Biomaterial is a growing family of materials with specific physicochemical properties. Significant studies have been made to characterize the potential *in vivo* and *in vitro* toxicity of biomaterials. The cytotoxicity may be attributed to variations in the physicochemical properties, target cell types, particle dispersion methods, *etc*. The reported cytotoxicity effects mainly include the impact on the biological system and organ-specific toxicity such as CNS toxicity, lung toxicity, cardiac toxicity, dermal toxicity, gastrointestinal toxicity, *etc*. Despite cellular toxicity, the immunological effects of biomaterials, such as the activation of pulmonary macrophages and associated inflammation, have been extensively studied. In this chapter, the latest research results on the toxicological profiles of nanomaterials, highlighting both the cellular toxicities and the immunological effects, have been incorporated. This analysis also offers details on the overall status, patterns, and research needs for dealing with the toxicological behavior of biomaterials.

Keywords: Biomaterials, Cytotoxicity, Nanocarriers, Toxicity.

INTRODUCTION

With the development of human civilization, biomaterials evolved by incorporating various materials on various lengths from nano- to micro- to macro level with a simple focus on extending human life and improving quality of life. More than 1000 years ago, silver, in various ways, was used as an antimicrobial agent to prevent infection. Different surgical procedures can be found at the very beginning of civilization. However, perhaps the most significant development took place in biomaterials in 1901-2000. Over the past 60 years, the quality of life

* **Corresponding author Vijay Mishra:** School of Pharmaceutical Sciences, Lovely Professional University, Phagwara (Punjab), 144411, India E-mail: vijaymishra2@gmail.com

Alaa A. Aljabali and Kaushik Pal (Eds.)

for millions of people has been improved through artificial limbs. Regenerative sutures have simplified surgical procedures, and various cardiac devices have saved lives. The advent of tissue engineering and organ rehabilitation pushes science limits today to make 2001-2100 the most exciting years in the biological field.

The term biomaterial describes something derived from biological sources, and it also describes substances that can be used in the human body as a machine. Polymer science took birth with medicinal polymers in the past, and research continues to expand the performance and stability of these components *in vivo*. Biomaterials are needed in clinical practice as a vital part of permanent implants like large blood vessels, waist implants, catheters, *etc*. In surgery, the early use of polymers has mainly focused on the evolution of connective tissue. Many new systems are emerging due to significant advances in the development and molecular cell biology. The drugs based on lots of unique nucleic acid and protein, which are not administered in the form of pills, provide the impetus for new polymers that can be incorporated to control the delivery of drug and genetic treatment. Tissue engineering has new applications that are integrated with physical requirements where the biomaterials assist the regeneration of body limbs and tissues [1].

Various polymers are utilized in several environmental programs, including polyethylene etherketone (PEK), polysulfone (PS), Silicone (SR), polyethylene terephthalate (PET), polymethylmethacrylate (PMMA), polyacetal (PA), polytetrafluoroethylene (PTFE), polyurethane (PU), polyethylene (PE). The most common composite polymer biomaterials are CF, carbon fiber/ultra-high molecular weight polyethylene (CF/UHMWPE), carbon fiber/epoxy (CF/epoxy), silica/SR, and HA/PE. Polymer materials are used for medicinal applications. Application in various disciplines has been received by polymers, such as tissue engineering, orthopedics, implants, dentistry, ophthalmology, and many other medical fields. Delivery programs designed for polymer enable the slow release of the drug from the body.

An investigation on the use of polymer in genetic therapy has been done. They show safer genetic predisposition as compared to viruses and vectors. Synthetic polymeric materials are widely used for biosensors, experienced devices, and biocontrols. Polymeric essentials should be made biocompatible for biomedical applications. Many of the polymeric systems utilized in the body for medical devices are termed biocompatible, whereas collagen encapsulation after implantation separates them from the body tissues. Polymeric implants may be considered biocompatible if they do not cause adverse responses. When polymers interact with blood cells, a thrombus is generated rapidly. Therefore, items with

blood adhesions that are non-thrombogenic should be utilized for bloodstream contact. Properly balanced polymers employed in treatments should detect and interact harmoniously with living cell components without unspecified interactions. Non-toxic biomaterials are used in various medical and surgical applications. During the growing phase, NDB'S are meant to degrade the body.

Polymers that can be natural or manufactured can be decomposed. The benefits offered by the latter are more significant than the first since they may be flexibly adapted to produce the required property portfolio. Synthetic polymers provide a dependable and immunogenic supply of materials. The standard method includes mechanical characteristics (friction, density, and cutting) and the breakdown time necessary for a given system as a common technique for selecting a polymer to be used as a biomaterial. After completing its goal, it should be lowered to the planting area, leaving non-toxic products. Important issues to consider here are additional biomaterial properties, such as land charge, polarity, distribution of active chemical groups, hydrophobicity, and hydrophilicity (or wettability). It is important to blend polymers with hydrolytically unstable reinforcement for biological control. Esters, anhydrides, orthoesters, and amides are the most active chemical groups [2].

Any synthetic or natural compound except drug, which treats, enhances, or alters muscle or organ function, is called a biomaterial. The most challenging issue to deal with is biomaterial selection due to its biological compatibility and needs. In recent years, material designers have shown much interest. The discovery of different polymers has significantly influenced the growth and control technologies in the tissue engineering industry. However, operators must guarantee that polymer-based biomaterials have long-term strength and dependability to be effective. Utilizing biomedical composite polymer materials gives numerous new choices and design options. Composites composed of polymers can gain several mechanical and biological characteristics that significantly enhance numerous biological applications.

Nevertheless, the manufacturing and marketing of partial or complete medical instruments built from compounds have begun in relatively few situations. Biocompatibility is an essential condition that all living things must meet. The medical study investigates new scientific obstacles to cell/genetic diagnosis, treatment, and prevention. Destroyed biomaterials change over time as the biomaterials undergo mass and surface degradation, leading to changes in the material's surrounding area. Non-corrosive materials also experience changes in chemical and structural properties. However, these changes are not so significant, and the time involved in the physical and chemical changes is much longer than in organic matter [3].

CHAPTER 2

Nano-Biomaterials for Immunotherapy Applications

Pooja Saxena[1,*]

[1] *Medicago R&D Inc., Canada 1020 Route de l'Eglise, Quebec City, Quebec G1V 3V9, Canada*

Abstract: Because of their nano-size, biological compatibility, and ability to precisely engineer antigens displayed, payloads packaged, and destinations targeted, nano-biomaterials are gaining traction as next-generation therapeutic tools. Oncolytic viruses were the first to be exploited in cancer immunotherapy because these are natural cell killers and, in some cases, highly selective for cancerous cells. Further, oncolytic viruses can be engineered to encode immune-stimulators and therapeutic genes. However, for oncolytic viruses to work, it is essential to develop these as viable viruses with the ability to infect. This raises safety concerns and poses hurdles in regulatory approval. To circumvent this limitation, non-replicating viruses and virus-like particles have been explored for immunotherapeutic applications. The advantage of these is their inability to infect mammals, thereby eliminating bio-safety concerns. Nonetheless, concerns related to toxicity need to be addressed in each case. Several virus-like particle candidates are currently in preclinical development stages and show promise for clinical use *via* intertumoral administration, also referred to as vaccination *in situ*. In cases where *in situ* administration is not possible due to the absence of solid tumours or inaccessibility of the tumour, nano-biomaterials for systemic administration are desired, and extracellular vesicles fit this bill. Exosomes, in particular, can provide controlled abscopal effects – a property desirable for the treatment of metastatic cancer. This chapter discusses the state-of-the-art in the development of nano-biomaterials for immunotherapy. With a plethora of candidates in development and over two hundred clinical trials ongoing worldwide, nanobiomaterials hold great promise as effective cancer immunotherapies with minimal side effects.

Keywords: Adenovirus, AAV, Cancer vaccines, Checkpoint inhibitors, CPMV, Exosomes, Gene therapy, Immune suppression, Immunotherapy, *In-situ* vaccine, Nanoparticle, Oncolytic virus, Tumour micro-environment, Tumour remission, T-VEC, VLP, Virus-like particle.

[*] **Corresponding author Pooja Saxena:** Medicago R&D Inc., Canada 1020 Route de l'Eglise, Quebec City, Quebec G1V 3V9, Canada; Tell:001 418-658-9393; E-mail: pooja.jic@gmail.com

Alaa A. Aljabali and Kaushik Pal (Eds.)

INTRODUCTION

Immunotherapy warrants the use of tools that stimulate or boost the natural defenses of a patient's immune system to treat or prevent disease. Traditionally, the term was coined to represent treatments for cancer that relied on boosting cellular immune responses, as with T-cell therapy, or manipulating immune regulation, as with checkpoint inhibitors [1]. However, with the world grappling with a pandemic in 2020 and with the realization that is boosting one's immune responses is an effective way to fight a coronavirus infection [2, 3], immunotherapy is now used in the broadest sense for all immune-boosting treatments for infectious diseases and oncology. A significant advantage of cancer immunotherapy for the treatment of cancer over traditional methods is that it treats primary tumour as well as prevents metastasis and recurrence of tumours with few side effects. However, immunotherapy does not work for all patients and all cancers. Therefore, the success of an immunotherapeutic drug in a clinical trial depends immensely on patient selection. Even so, immunotherapy is most effective when supplemented with chemotherapeutic drugs or radiation [4].

Although a new and upcoming field, recent successes in immunotherapy have been catapulted by the application of nanobiomaterials for the administration of immunotherapy. Nanobiomaterials are often the immunotherapeutic agent themselves or a carrier of one. Nanobiomaterials can also lead to activation of immune responses in the tumour micro-environment in case of solid tumours allowing the destruction of cancer cells and cancer remission [5, 6]. Apart from the obvious advantages of nano-size and biocompatibility, what makes nanobiomaterials ideal for immunotherapy applications is their amenability [7 - 10]. Using the knowledge available on structure at the atomic level, as in the case of viruses, engineering is possible to precisely display antigens on the nanoparticle exterior [11, 12]. In parallel, using molecular biology tools for genome engineering, it is possible to introduce functional genes within the nanoparticles to orchestrate immune responses. Moreover, space available within the nanoparticle can be exploited for packaging therapeutics [13, 14] such as drugs or genes or siRNA for delivery either by *in situ* administration at the tumour site or targeted systemic administration [8]. In both cases, side effects are limited. This is a significant advantage over conventional chemotherapy, where side-effects to healthy dividing cells, such as hair follicles, digestive tract, and blood-forming cells, are common [15].

Since the advent of the field of nanotechnology in 1959 by Richard Feynman [16], nanomaterials have been extensively used in material sciences and biotechnology. This chapter focuses on different classes of nanomaterials with applications in immunotherapy. The term nanobiomaterial is used for any nano-

scale product of biological origin, *i.e*., mother nature's own nanoparticle toolkit. Several non-biological nanomaterials are also being developed as immunotherapies with significant promise. These include synthetic polymeric nanoparticles [17], liposomes [18], antigens [19] and peptides [20]. However, these will not be discussed in this chapter. A pictorial depiction of all the nanoparticles discussed in this chapter is presented in Fig. (**1**).

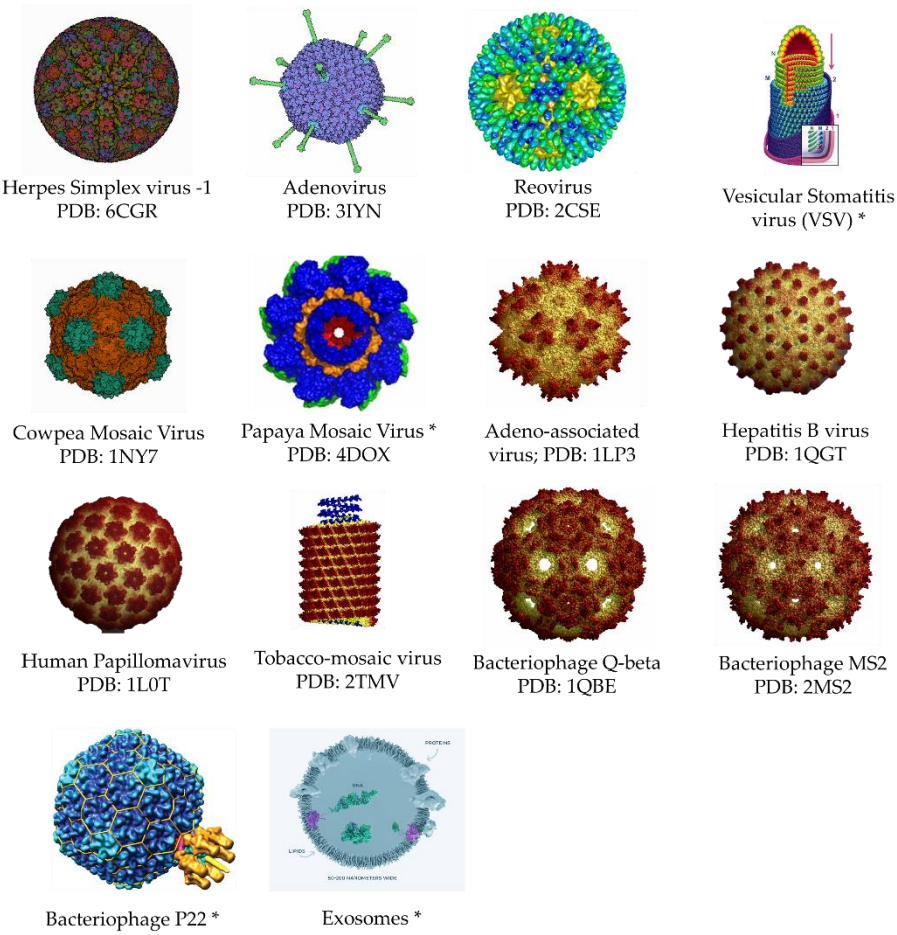

Fig. (1). A pictorial representation of all the nanoparticles discussed in this chapter, in order of their mention. Images are not to scale. Images were acquired from the Protein Data Bank [21] where available and the PDB identification number for each is mentioned in parentheses. Images not obtained from PDB have been marked with an asterisk and duly cited [22 - 25].

IMMUNOTHERAPY & CANCER

This section is intended for those who are not familiar with immunotherapy as it is imperative that immunotherapy concepts are understood to be able to grasp the

CHAPTER 3

Lipid-Based Nanomaterials in Cancer Treatment and Diagnosis

Mohammad A. Obeid[1,*], Mohammed Al Qaraghuli[2,3,4], Marta Ruano[3], Sirikwan Sangboonruang[5], Manal Alsaadi[6], Hanin Alyamani[3], Yingmanee Tragoolpua[7] and **Valerie A. Ferro[3]**

[1] *Department of Pharmaceutics and Pharmaceutical Technology, Faculty of Pharmacy, Yarmouk University, Irbid, Jordan.*

[2] *Department of Chemical and Process Engineering, University of Strathclyde, 75 Montrose Street, Glasgow, G1 1XJ Glasgow, United Kingdom.*

[3] *Strathclyde Institute of Pharmacy and Biomedical Sciences, University of Strathclyde, 161 Cathedral Street, G4 0RE Glasgow, United Kingdom.*

[4] *Basra University College of Science and Technology, Al-Wofod street, Basra, Iraq.*

[5] *Biotechnology section, Graduate School, Chiang Mai University, Chiang Mai, Thailand, 50200.*

[6] *Department of Industrial Pharmacy, Faculty of Pharmacy, University of Tripoli, Tripoli-Libya*

[7] *Division of Microbiology, Department of Biology, Faculty of Sciences, Chiang Mai University, Chiang Mai, Thailand, 50200*

Abstract: Cancer consists of a wide range of diseases that are mainly driven by the continuous unregulated proliferation of cancer cells. Current treatment options include the use of chemotherapies, radiotherapy, and surgery. Recently, there was an increased interest in applying nanoparticles (NPs) in cancer diagnosis and treatment. NPs are materials in the size range 1 to 100 nm and can be classified based on their properties, shape, or size. They have attracted wide attention because of their versatile physicochemical properties, nanoscale sizes, high surface-to-volume ratios, favourable drug release profiles, and targeting modifications. Nanotechnology can be used to improve the personalisation of cancer diagnosis and treatment by enhancing the detection of cancer-specific biomarkers, imaging of tumours and their metastases, specific drug delivery to target cells, and real-time observation of treatment progression. This chapter will highlight the main types of lipid NPs with their preparation methods. The clinical applications of these lipid NPs in cancer diagnosis and treatment will be presented along with the currently approved drugs based on these NPs.

[*] **Corresponding author Mohammad A. Obeid:** Department of Pharmaceutics and Pharmaceutical Technology, Faculty of Pharmacy, Yarmouk University, Irbid, Jordan; E-mail: m.obeid@yu.edu.jo

Alaa A. Aljabali and Kaushik Pal (Eds.)

Keywords: Cancer diagnosis, Cancer treatment, Lipid nanoparticles, Liposomes, Micelles.

CANCER BACKGROUND

Cancer is considered one of the fatal diseases that has reported high incidence and mortality rates globally [1]. For instance, the Global Cancer Observatory (GLOBOCAN) 2020, an online database of global cancer statistics and estimates of occurrence and death rates in 185 countries for 36 types of cancer, has indicated that 19.3 million new cancer patients were diagnosed and around 10 million deaths caused by cancer in 2020 [1]. Therefore, interest in studying cancer continues to progress at a high rate to investigate the underlying causes of cancer and progression.

On a biological level, cancer consists of a wide range of diseases that are mainly driven by the continuous unregulated proliferation of cancer cells [2]. Over growth of cells may develop a mass of tissues called a tumour. However, tumours can be benign or malignant [3]. Benign tumours are usually non-invasive and can be removed without the risk of reoccurrence. Also, cells of benign tumours do not circulate or spread to other parts of the body [4]. At the same time, malignant tumours can invade nearby tissues and spread to other parts of the body in a process known as metastasis [4].

Cancer types are classified into five main categories according to their origin, for instance, carcinoma usually originating from epithelial cells, sarcoma arising from bone, cartilage, fat, muscle, blood vessels, leukemia from the bone marrow, while lymphoma and myeloma are found to be derived from cells of the immune system, and central nervous system cancers from brain tissues and spinal cord [2, 4]. Therefore, different types of cancer exhibit various behaviors and responses to treatment [2].

Cancer initiation and progression are viewed as a multi-step process at a cellular level, where progressive genetic alterations transform normal human cells into highly malignant ones. These genetic changes are found to affect three gene classes: proto-oncogenes, tumour suppressor genes, which are both involved in normal cell growth and division, and DNA repair genes that are responsible for fixing damaged DNA [2, 5]. For instance, any modifications, amplifications, or deletions in these genes may cause a de-coupling of normal cell growth and differentiation [5, 6]. Moreover, these changes in the cell's genetic material may arise unexpectedly or be induced by a factor or carcinogen that causes cancer [2].

Carcinogens include solar ultraviolet radiation, chemicals in tobacco smoke, and viruses. However, carcinogenesis, the process of cancer development, does not

rely only on single causes in most cancers. It has been found that many factors contribute to both animal models and humans [2].

However, preventive measures can be taken against some carcinogens such as radiation and smoking in order to minimise the incidence rate of cancer, as it has been found that more than half of all cancers are preventable [7]. However, integrating effective therapeutic approaches and developing new ones is limited [8].

In recent years, different forms of cancer have been effectively treated by immunotherapies such as antibodies [9], stem cell therapies [10], and chimeric antigen receptor (CAR)-T cell therapies [11, 12]. The success of these approaches is attributed to the high specificity and efficacy of these molecules in treating both primary and metastasised tumours. Despite the high promise of these approaches, a few undesired side effects can also arise, like autoimmune disease [13]. Furthermore, lymphoma and other non-solid tumours have generally shown better responses to immunotherapies than solid tumours [14, 15] due to the expected difficulty in penetrating solid tumours [16]. The immune-suppressive tumour microenvironment can similarly contribute to this efficacy reduction against solid tumours [17]. These limitations can be surpassed through the utilisation of nanotechnology.

NANOPARTICLE APPLICATIONS

Nanoparticles (NPs) are materials in size range 1 to 100 nm and can be classified based on their properties, shape, or size [18]. They have attracted wide attention because of their versatile physicochemical properties, nanoscale sizes, high surface-to-volume ratios, favourable drug release profiles, and targeting modifications [19, 20]. Nanotechnology can be used to improve personalisation of cancer diagnosis and treatment by enhancing the detection of cancer-specific biomarkers, imaging of tumours and their metastases, specific drug delivery to target cells, and real-time observation of treatment progression [21, 22].

The crucial challenge in treating cancer resides in engineering an effective treatment that targets cancer cells without affecting surrounding healthy cells [23]. The NPs must pass through several physiological and biological barriers to be effective. So their use as delivery systems inflicts necessities to optimise their size, surface chemistry, and biocompatibility to avoid non-specific interactions and enable specific binding to their targets. Attia *et al.* [24], specified different criteria that should be maintained by all therapeutic NPs, including the ability to remain stable in the blood and tumour microenvironment (TME); to evade reticuloendothelial system (RES) clearance, and prevent being seized by the mononuclear phagocyte system (MPS); to accumulate in tumour tissues through

CHAPTER 4

Polymeric Nanomaterials for Cancer Theranostics

Rajarshi Roychoudhury[1,*]

[1] *enGene Inc., Canada 7171 Frederick Banting, Saint-Laurent, QC H4S 1Z9, Canada*

Abstract: Despite global efforts for decades, the number of cancer cases is still on the rise. Although in recent times there has been significant improvement in immunotherapy, chemotherapy remains standard care for cancer patients alongside radiation and surgery. Chemotherapeutic drugs and diagnostic agents (MRI, PET, Ultrasound) lack specificity and often suffer from poor solubility and unwanted biodistribution. This results in unnecessary high dose requirements, systemic toxicity, and compromised quality of life for the patients. Beside therapy, early diagnosis is essential for the successful treatment and cure of cancer patients, just like any other disease. Therefore, a suitable delivery vehicle is always needed for the theranostic agents. Viral vectors are routinely used for the delivery of genetic material. But parallelly, nanoparticles made with biodegradable, non-toxic, and non-immunogenic polymers are often used as a carrier of chemotherapy drugs, diagnostic agents as well as genetic materials. Once decorated with specific ligands, these nanocontainers can deliver cargo molecules to target tissue and organs with high precision.

Keywords: Biodistribution, Cancer, Cargo, Cationic, Chemotherapy, Delivery, Diagnostic, Drug, Encapsulation, Gene, Hydrophobic, Hydrophilic, Immunotherapy, Ligand, Nanoparticle, Polymer, Receptor, Target, Toxicity, Systemic.

INTRODUCTION

Despite significant global efforts into the research and development of cancer therapeutics for decades, the number of cancer cases is expected to increase continuously. It has been estimated that there are currently 18.1 million new cancer cases every year, with 9.6 million deaths per year, accounting for 1 out of 6 deaths globally [1]. Cancer therapies are currently limited to surgery, radiation, and chemotherapy, with very few exceptions of immunotherapy (CAR-T or checkpoint inhibitors). All three methods risk damage to normal tissues or incomplete eradication of cancer. Beside surgery and therapy, a lot of emphasis also needs to be put on the diagnostics of cancer. Just like any other disease, if

[*] **Corresponding author Rajarshi Roychoudhury:** enGene Inc., Canada 7171 Frederick Banting, Saint-Laurent, QC H4S 1Z9, Canada; Tell:+1-514-332-4888; E-mail: rroychoudhury@engene.com

Alaa A. Aljabali and Kaushik Pal (Eds.)

detected early enough, many types of cancer can be cured. Consequently, cancer therapy has become a multidisciplinary challenge requiring close collaboration among clinicians, biological and material scientists, and biomedical engineers.

Though chemotherapy is successful to some extent and remains standard of care for most cancers, the chemotherapy drugs lack specificity. Thus, in the process of killing cancer cells, they also damage healthy tissues leading to systemic toxicity and adverse side effects. It significantly affects the quality of life of the patient. Most chemotherapeutic drugs are administered *via* intravenous or oral route, which leads to rapid clearance and unwanted biodistribution of the drug. Therefore, chemotherapy drugs need to be administered in excess leading to unnecessary side effects [2]. That is why a vehicle with high specificity to cancer cells can circumvent the undesired systemic toxicity of the chemotherapeutic agents and other drugs.

Often that vehicle is a nanoparticle, either polymeric or protein-based. Nanoparticles are submicron-sized particles with diameters ranging from 10 to 1000 nm that can either encapsulate or display a cargo molecule of interest. These nanoparticles can also be decorated with receptor-specific ligands that can deliver the cargo molecule specifically to the desired tissue or organ, curtailing toxicity [3 - 5]. This book chapter discusses the application of polymeric nanoparticles as theragnostic in cancer.

POLYMERIC NANOMATERIALS IN CANCER THERAPY

Delivery of Chemotherapeutics

Every time any new cell is formed, it goes through a usual process to become a fully functioning (or mature) cell. The process involves a series of phases and is called the cell cycle. Chemotherapeutic drugs target cells at different phases of the cell cycle. Understanding how these drugs work helps doctors predict which drugs are likely to work well together. Doctors can also plan how often doses of each drug should be given based on the timing of the cell phases. Cancer cells tend to form new cells more quickly than normal cells, and this makes them a better target for chemotherapy drugs. However, chemo drugs cannot tell the difference between healthy cells and cancer cells. This means normal cells are damaged along with the cancer cells, and this causes side effects. Each time chemo is given, it means finding a balance between killing the cancer cells (to cure or control the disease) and sparing the normal cells (to lessen side effects). The good news is that most normal cells will recover from the effects of chemo over the time. But cancer cells are mutated (not normal) cells, and they usually do not recover from the effects of chemo. Therefore, chemotherapy is good at killing many types of cancer cells (Table **1**).

Table 1. Different types of chemotherapeutic drugs and their mechanisms of action.

Types of Drugs	Mechanism of Action	Name of Few Drugs
Alkylating agents	Stops cell proliferation by DNA damage	Cisplatin, Busulfan, Oxaliplatin, Trabectedin
Antimetabolites	Interference with DNA and RNA by acting as a substitute for the normal building blocks of RNA and DNA.	5-fluorouracil, Capecitabine, Hydroxyurea, Thioguanine
Antitumor antibiotics	Altering DNA inside cancer cells to keep them from growing and multiplying.	Doxorubicin, Epirubicin Idarubicin, Valrubicin
Topoisomerase inhibitor	Interference with topoisomerases	Irinotecan, Topotecan, Etoposide, Teniposide
Mitotic inhibitors	They work by stopping cells from dividing to form new cells	Paclitaxel, Docitaxel, Vinblastine, Vincristine

We will discuss one specific example of Paclitaxel. It is a microtubule-stabilizing agent that triggers polymerization of tubulin, killing cancer cells by disrupting the dynamics necessary for cell division. It has been found to be effective against a wide range of cancers, including head and neck, ovarian, lung, breast, and colon cancers. However, Paclitaxel is a highly hydrophobic drug with extremely low solubility in water and biological fluid (< 0.5 mg/L) [6, 7]. This drug on its own cannot be administered by intravenous injection as it can aggregate in blood vessels leading to embolization. It often shows local toxicity because of high drug concentrations at the site of deposition. This is why paclitaxel needs to be adequately formulated prior to administration.

The currently available formulation for paclitaxel includes the use of Cremophor EL (polyethoxylated castor oil) and dehydrated ethanol. Unfortunately, Cremophor EL is known to be toxic and can cause serious side effects [5]. Alternatively, surfactants could be used to solubilize the drug, but due to their high critical micellar concentration they cannot maintain the nanoparticle architecture. In this regard, thermodynamically stable polymeric micelles with a hydrophobic core and hydrophilic surface could serve as an effective delivery system for poorly soluble drugs [8 - 10].

The biodistribution of a given drug is a major factor for the success of chemotherapy. To minimize off-target toxicity and rapid clearance from the body, anticancer drugs must show sustained, controlled, and targeted release. In theory, these properties could be obtained by developing formulations that are controlled at the nanometer scale. For example, controlled and sustained drug release may be achieved by precisely adjusting the composition of nanoparticle formulations. Improved drug targeting ability could be obtained by functionalization of the

CHAPTER 5

Magnetic Nanoparticles for Imaging, Diagnosis, and Drug-Delivery Applications

Ejlal Abu-El-Rub[1,2], Hana M. Zegallai[3,4], Basma Milad Aloud[2], Saravanan Sekaran[5,6] and **Donald W. Miller[3,7,*]**

[1] *Department of Basic Medical Sciences, Faculty of Medicine, Yarmouk University, Irbid, Jordan*

[2] *Department of Physiology and Pathophysiology, University of Manitoba, Winnipeg, Canada*

[3] *Department of Pharmacology & Therapeutics, University of Manitoba, Winnipeg, Canada*

[4] *DREAM, Children's Hospital Research Institute of Manitoba, Winnipeg, MB, Canada*

[5] *Department of Biotechnology, School of Chemical and Biotechnology, SASTRA Deemed to be University, Thanjavur-613401, Tamil Nadu, India.*

[6] *Department of Pharmacology, Saveetha Dental college and Hospital, Saveetha Institute of Medical and Technical sciences (SIMATS), Chennai600 007, Tamil Nadu, India.*

[7] *Kleysen Institute for Advanced Medicine, University of Manitoba, Winnipeg, Canada*

Abstract: Magnetic Nanoparticles (MNPs) have gained interest within the research community due to their therapeutic potential in a variety of medical applications. MNPs are generally composed of a metallic core stabilized by the addition of an outer shell that can be further functionalized through the absorbance or conjugation of various targeting ligands. The magnetic properties of these nanoparticles can be utilized for imaging, localized drug delivery, and enhanced diagnostic detection. This chapter highlights the applications of MNPs to enhance magnetic resonance imaging (MRI) capabilities and improve the delivery of therapeutic agents to difficult-to-reach areas in the body. In addition, recent advances in the use of MNPs in stem cell therapy for both the tracking and monitoring of stem cell distribution in the body and improving engraftment and differentiation in stem cell therapy are discussed. Finally, examples of the incorporation of MNPs in diagnostic assays to improve rapid and real-time detection capabilities of many diseases, including cancer, cardiovascular diseases, and pathogen infections, are provided.

Keywords: Diagnostic agents, Drug delivery, Imaging agents, Magnetic Nanoparticles (MNPs), Stem cell therapy.

[*] **Corresponding author Donald W. Miller:** Department of Pharmacology and Therapeutics, University of Manitoba, Winnipeg, MB, Canada and Kleysen Institute for Advanced Medicine, University of Manitoba, Winnipeg, Canada; E-mails: donald.miller@umanitoba.ca

Alaa A. Aljabali and Kaushik Pal (Eds.)

INTRODUCTION

Magnetic nanoparticles (MNPs) are critical components in many biomedical applications. Although concerns regarding long-term safety remain to be addressed, MNPs are currently being explored in a variety of biomedical applications, including MRI imaging [1 - 3], bio-sensing diagnosis [1, 4], stem cell delivery, and tracking [5], gene therapy and drug delivery to treat multiple disorders including cancer, neurodegenerative diseases, HIV/AIDS, ocular diseases, and respiratory diseases [3, 6, 7]. Despite recent advances in nano-medicine using MNPs, there are many challenges to be solved in order to achieve optimal performance of these nanomaterials. The major limitations associated with MNPs include 1) development of synthesis schemes and storage and handling protocols that can be scaled-up for clinical applications while retaining necessary reproducibility in terms of size, charge, and surface properties [8, 9], 2) identification of the long-term toxicity of MNPs [9, 11], and 3) management of unexpected results due to biocompatibility and immunogenicity [9, 12].

While there are a variety of synthetic pathways and a multitude of different compositions, MNPs for medical applications all share the following common components; a magnetic core, a protective outer layer, and a surface that can be functionalized to improve targeting or biodistribution properties (Fig. **1**) [13, 14]. Magnetic nanoparticles can be further classified as either ferromagnetic, paramagnetic, antiferromagnetic, diamagnetic, or ferrimagnetic based on their core material and resulting magnetic properties. Ferromagnetic nanoparticles consist of iron, nickel, or cobalt cores and display strong magnetic moments when placed in an external magnetic field. Ferrimagnetic nanoparticles have maghemite or magnetite iron oxide core material and display similar characteristics as ferromagnetic material in the presence of an external magnetic field. Paramagnetic materials have gadolinium, magnesium, and lithium as core materials. Magnetic nanoparticles formed from paramagnetic material have weaker magnetic moments and do not sustain their magnetic properties following the removal of the magnetic field, as observed with ferromagnetic materials. The MNPs formed from diamagnetic material commonly have copper, gold, or silver cores and have the weakest magnetic moments. The strong magnetic moments of the ferromagnetic and ferrimagnetic nanoparticles make them of interest for diagnostic agents, as well as in hyperthermia-based treatment applications.

General Features of MNPs

While many magnetic core materials are available for MNP synthesis, some, such as cobalt, chromium, and alkaline earth metals, used in ferromagnetic material, are toxic and cannot be used for biomedical applications unless being coated with

a safe, non-toxic protective layer [15, 16]. Thus, despite the strong magnetic moments inherent in these MNPs, the potential toxicity of these ferromagnetic materials has limited their use as imaging agents and therapeutics for animal and human applications. In contrast, the MNPs made with magnetite and maghemite iron-oxide as core material have established safety profiles that make them more suitable for imaging and diagnostic purposes [10, 17, 18].

Regardless of the magnetic core material used, the MNPs are typically coated with biocompatible materials to prevent corrosion or the leaching of the core [11, 19]. Silane-based coatings have been particularly useful for MNPs with iron oxide core material as they readily react with the core to form a protective silane shell that can be further modified for the particular application. The ability of silane-based coatings to retain the crystallinity of the metal oxide core preserves the magnetic properties while providing an outer shell that enhances the stability of the MNPs (*i.e.*, prevents aggregation), making them ideal surface components. The utility of the silane coatings as intermediates for further surface modifications is particularly attractive. This is illustrated in the studies of Yathindranath and coworkers [20]. Using aminosilane functionalization of iron oxide nanoparticles as intermediates, Yathindranath and coworkers demonstrated the utility of silane-based surface coatings properties to accommodate changes in surface charge, through variations in amide and carboxylic acid function groups, as well as hydrophobic/hydrophilic balance, through covalent attachment of oleic acid and albumin [20]. Silane-based coatings of iron oxide nanoparticles have shown favorable safety profiles in various models [21, 22] while providing flexibility for a multitude of different surface modifications.

In addition to the silane inorganic surface modifications other coatings have also been considered. Natural coatings consisting of carbohydrates, such as dextran and starch, or proteins such as albumin and various synthetic polymers have been used as surface coatings for MNPs [23, 24]. The natural polymer surface coatings are mostly hydrophilic and require cross-linking to prevent them from disassociating in aqueous environments and to enhance their mechanical strength. In contrast, commercially available synthetic polymers used for coating purposes such as poly (ethyleneglycol) (PEG) and polyvinyl alcohol (PVA) [25, 26] are hydrophobic and display improved mechanical strength over the hydrophilic coatings. Surface modifications of MNPs are important to ensure proper attachment of biomolecules and, in the case of drug delivery applications, to control release of drug at the target site [27]. Organic linkers such as carboxylic acid and aldehyde thiol allow for the attachment of biomolecules to a variety of functional groups on the surface of the MNPs [28, 29].

CHAPTER 6

Aptamers in Theranostic Bionanomaterials

Hamdi Nsairat[1], Walhan Alshaer[2,*], Ismail Sami Mahmoud[3], Mohammad A Ismail[4], Ezaldeen Esawi[4], Shrouq Alsotari[2] and **Said I. Ismail[4,5]**

[1] *Pharmacological and Diagnostic Research Center, Faculty of Pharmacy, Al-Ahliyya Amman University, Amman19328, Jordan*

[2] *Cell Therapy Center, The University of Jordan, Amman11942, Jordan*

[3] *Department of Medical Laboratory Sciences, The Hashemite University, Zarqa, 13133, Jordan*

[4] *Faculty of Medicine, The University of Jordan, Amman11942, Jordan*

[5] *Qatar Genome Project, Qatar Foundation, Doha, Qatar*

Abstract: Theranostic nanomaterials hold the potential to revolutionize future disease management. Recent progress in nanomaterials technology and aptamer-base--targeting molecules have promoted efficient theranostics models. Aptamers are unique three-dimensional structures consisting of oligonucleotide (25-80 nt) polymers. They are comparable to monoclonal antibodies in their receptor-driven binding efficacy toward specific target receptors and binding ability to specific target molecules with high affinity and specificity. Aptamers have several other advantages, including prolonged shelf life, little or no variation from batch to batch, and ease of chemical modifications for enhanced stability and targeting capacity. Owing to the advantages mentioned above, aptamers are attracting great attention in diverse applications ranging from therapy, drug delivery, diagnosis, and functional genomics as well as biosensing. Herein, the aim is to give an overview of aptamers, highlight the opportunities of their application as means of effective therapeutic tools as well as functionalize them as potential diagnostic probes. Furthermore, the diverse modifications of aptamers for theranostic purposes, including therapeutic agents and targeted delivery nanomaterials, are comprehensively summarized.

Keywords: Aptamers, Bionanomaterials, Nanomaterials, Theranostics.

INTRODUCTION

Over the last decade, theranostic bionanomaterials have emerged as an invaluable tool in personalized medicine [1]. The term theranostics refers to the combination of molecular imaging and therapy. Indeed, some bionanomaterials per se have

* **Corresponding author Walhan Alshaer:** Cell Therapy Center The University of Jordan Amman 11942, Jordan; Tel: (+962) 790823678; E-mail: walhan.alshaer@ju.edu.jo

Alaa A. Aljabali and Kaushik Pal (Eds.)

very interesting therapeutic and diagnostic characteristics [2]. Recent progress in nanomaterials technology and aptamer-based targeting molecules have provoked efficient theranostics models.

Aptamers are functional single-stranded DNA or RNA oligonucleotides ranging in size from 5 to 30 KDa that can fold into unique three-dimensional structures, providing an ability to bind their targets with high affinity and selectivity [3, 4]. Aptamers were first described in 1990 by two independent groups. Tuerk and Gold worked on translational regulation of the DNA polymerase gene to find nucleic acid ligands that interact with T4 DNA polymerase and repress its activity in an attempt to get a better understanding of the recognition site. By the end of their experiment, they were able to produce a high-affinity RNA ligand through a novel protocol termed SELEX (Systematic Evolution of Ligands by EXponential enrichment). In the meantime, Ellington and Szostak isolated specific RNA ligands capable of binding organic dyes, and they, in turn, called these ligands as Aptamers [5, 6]. Since the discovery of aptamers, several major advances have been witnessed in the aptamers field. A main progress was achieved by introducing chemical modifications of aptamers, thereby enhancing stability and binding properties [7]. Moreover, aptamers were selected for a wide range of targets, including ions, small chemical molecules, peptides, proteins, infected cells, pathogens, and even cancer cells. In the following years, aptamers found their way into several applications involving diagnostics, therapeutics, regulation of gene expression, high throughput screening, and targeted drug delivery. In 2004, Macugen® (pegaptanib sodium) was announced as the first aptamer FDA approved for the treatment of age macular degeneration disease (AMD).

Theranostics bionanomaterials have been created great growth avenues for the development of precision medicine. Various aptamer-dependent systems were successfully developed for molecular imaging and targeted therapy. The focus of the current chapter is to highlight the utilization of aptamers as targeting molecules for theranostic biomaterials. Aptamers are increasingly proving to be a powerful tool in research and drug development for various conditions, with minimal effect on healthy tissues by assuring more selective drug targeting and delivery and, thus, better therapeutic efficacy and potency.

APTAMERS

The word Aptamer is derived from the Latin “aptus”, which means “fit” and the suffix “- meros” which means “portion”. An Aptamer is a single-stranded DNA or RNA molecule [4] obtained through Systematic Evolution of Ligands by EXponential enrichment (SELEX). An Aptamer’s binding to its target is quite specific. Aptamers are also known as chemical antibodies, like antibodies; they

bind to targets with high affinity, modulate target function, deliver cargo to specific sites, and are used in diagnostic and analytical assays, whether in solution or immobilized forms. However, aptamers surpass their proteinaceous counterparts by their low immunogenicity, physical stability, facile chemical modification, and the relative ease of their large-scale synthesis at affordable costs with little or no batch-to-batch variation. These alluring properties have propelled aptamers to the forefront of therapeutic and diagnostic agent development as well as bio-sensing platform construction [3]. Numerous aptamers have been developed during the past 2 to 3 decades for a variety of medical applications, such as chemical sensors, imaging molecules, diagnostic assays, and active therapeutic molecules [4].

Aptamers can be generated using either DNA or RNA oligonucleotides. Both types act similarly as binding molecules. However, RNA aptamers are widely believed to produce more complex 3D structures, whereas DNA aptamers are more stable and have a lower cost of production [8]. Although several unmodified DNA and RNA aptamers have been successfully selected for different targets, these aptamers are highly susceptible to degradation by nucleases and rapid clearance from the circulation. Therefore, several chemical modifications have been applied and investigated at different parts of the aptamers sequences. These chemical modifications were shown to improve the physio-chemical properties of the aptamers, increasing their stability, bioavailability, diversity, and establishing hydrophobic interactions [3, 9].

The backbone (phosphate/ribose) of the aptamer sequence is a common site for chemical modification. A common modification is the introduction of the phosphorothiolated linkage instead of the normal phosphodiester linkage. However, thiolated aptamers may induce toxicity and nonspecific interactions. When it comes to RNA aptamers, ribose sugar is the preferred site for modifications. The ribonuclease A (RNase A) targets 2′-hydroxyl group of ribopyrimidines and breaks the phosphodiester bond in the sugar-phosphate backbone of RNA strands. Thus, substituting the 2′-hydroxyl group of ribopyrimidines by 2′-amino, 2′-fluoro, or 2′-O-methoxy groups lead to a significant increase in the stability of RNA. Several reports showed that the 2′-amino modification increases the RNA half-life in serum to 170 hours compared to 10 seconds of the unmodified RNA aptamers. However, the 2′- amino modification affect thermodynamic stability of the aptamer, thus hindering binding affinity [10]. On the other hand, 2′-fluoro modifications also increase stability with half-life around 90 hours in serum. This type of modification was used in Macugen® development [11]. Moreover, 2′-fluoro modifications showed better base pair stability and binding affinity of the aptamers [11]. Another interesting approach to develop nuclease-resistant and stable aptamers is through

CHAPTER 7

Viral and Non-viral Nanoparticles for Gene Therapeutics

Hassan Elsana[1] and **Amal Ali Elkordy**[*, 1]

[1] *School of Pharmacy and Pharmaceutical Sciences, Faculty of Health Sciences and Wellbeing, University of Sunderland, Sunderland SR1 3SD, UK*

Abstract: The recent accomplishment of the human genome and DNA discovery has led to the diagnosis of many diseases caused by imperfections in genes. These diseases involve gross disturbances in the number or arrangement of a person's chromosomes. Hence, gene therapy has become a promising new therapy for the treatment of somatic diseases, for example, malignant tumours [1], severe infectious diseases, such as AIDS [2], and many genetic disorders, including haemophilia and cystic fibrosis [3]. Gene therapy introduces a gene into human cells to replace, delete, or correct gene function to produce a therapeutic protein with the desired action. This adjustable gene can be used to cure any disease. In 1990, a gene therapy clinic was initiated to find treatment for severe combined immunodeficiency (SCID). However, the first success of gene therapy was not observed until 2000 when Cavazzana calvo *et al.* [4] reported a success using gene therapy for the treatment of SCID [4]. While it has been 30 years since the first gene therapy trial, gene therapy is still a high-risk treatment, and only a few drugs have been approved, such as Glybera®, Gendicine®, and Strimvelis®.

Keywords: Dendrimers, Gene therapy, Liposomes, Non-viral vectors, Viral vectors.

INTERNAL AND EXTERNAL BARRIERS TO GENE THERAPY

The delivery of genes into eukaryotic cells faces many barriers. It is estimated that the half-life of naked DNA is ten minutes following intravenous injection [5]. Many nucleases present in the extracellular matrix will rapidly degrade unprotected nucleic acid following systemic administration. Phagocytes, such as Kupffer cells in the liver, and resident macrophages in the spleen, are responsible for the clearance of DNA-loaded colloidal particles administered through blood circulation. In addition, poor penetration due to high hydrophilicity, hepatic first-

[*] **Corresponding author Amal Ali Elkordy:** School of Pharmacy and Pharmaceutical Sciences, Faculty of Health Sciences and Wellbeing, University of Sunderland, Sunderland SR1 3SD, UK; E-mail: amal.elkordy@sunderland.ac.uk

Alaa A. Aljabali and Kaushik Pal (Eds.)

pass metabolism, and a highly negatively charged phosphate backbone of DNA prevent its passage across negatively charged cellular membranes.

For this reason, the encapsulation of plasmid DNA in order to protect it and increase circulation time is a crucial step in developing gene therapy. In addition, the mechanism of gene therapy release from endosomes and lysosomes can significantly impact gene degradation in lysosomes; Fig. (**1**) shows a chart for the gene delivery pathway, an illustration of the gene pathway, and barriers to its delivery [6]. Macromolecules captured within the endosomes usually transform into digestive lysosomes unless some escape mechanisms are used to intercept this maturation process.

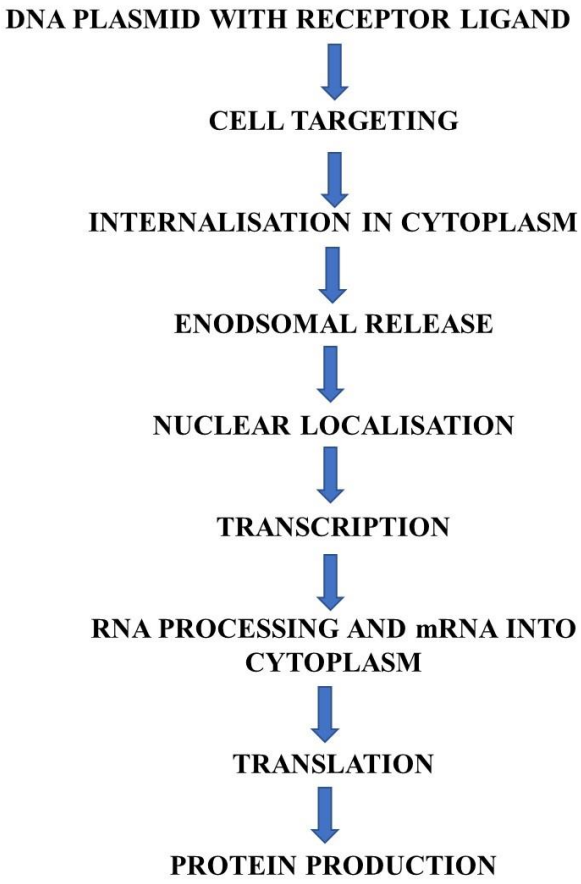

Fig. (1). A chart for the gene delivery pathway.

GENE DELIVERY METHODS

The gene delivery system is an initial phase in the achievement of gene therapy. Polynucleotide molecules (*e.g.*, plasmid DNA, RNA, and antisense oligonucleotides) are sensitive and hydrophilic, with a negatively charged phosphate backbone at physiological pH. Such physicochemical properties restrict their binding to and passive diffusion across lipophilic cell membranes. Moreover, they are rapidly degraded in biological fluids and do not accumulate in target tissues following systemic administration. In order to successfully transfect DNA into cells, DNA must be condensed and protected against nuclease degradation.

Additionally, the negative charge of DNA must be masked in order to allow entry through the negatively charged cell surface. After loading the genetic material to the vector, the vector must be delivered to the blood vessels and must be stable enough to avoid clearance by albumin due to their high surface charge. Next, the vector must pass through the epithelial tissues of the blood vessels and enter the target cell through the endocytosis process [7, 8]. Fig. (**2**) shows the most commonly used non-viral vectors in gene therapy.

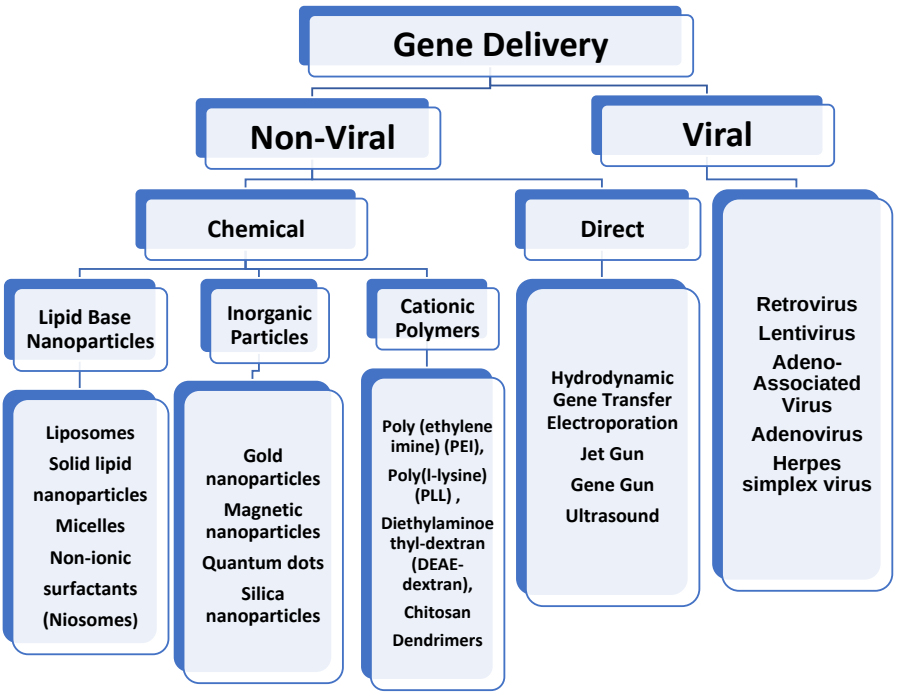

Fig. (2). The most commonly used non-viral vectors in gene therapy.

CHAPTER 8

Conclusion, Outlook, and Prospects: Bionanomaterials in Clinical Utilization

Alaa A A Aljabali[1,*], Kaushik Pal[2], Rasha M. Bashatwah[1] and **Murtaza M. Tambuwala[3,*]**

[1] *Faculty of Pharmacy, Department of Pharmaceutics and Pharmaceutical Technology, Yarmouk University, Shafiq Irshidat Street, Irbid 21163 - P. O. BOX566, Jordan*

[2] *University Centre for Research and Development (UCRD), Department of Physics,Chandigarh University, Mohali, Gharuan, Punjab 140413, India*

[3] *SAAD Centre for Pharmacy and Diabetes, School of Pharmacy and Pharmaceutical Science Ulster University, Coleraine, UK*

Abstract: Nanomaterials have contributed to significant advancements in the realms of biotechnology and medicine. A holistic examination of the different biocompatible nanocomposites is discussed in this chapter. Their compatibility with state-of-the-art engineering techniques, such as additive manufacturing to design practical surgical implants, is also discussed. The importance and potential of nanocomposites and manufacturing processes in implantable medical device industries are also thoroughly considered. Nanomaterials' unique characteristics contrast with their large counterparts, such as high surfaces, reactivity, and reproducibility. Their incorporation in matrices has shown that the resultant composites' mechanical, chemical, and physical properties can be improved.

Consequently, a wide variety of technical technologies, such as energy products, biomedical applications, micro-electrical equipment *etc*., have been intensively researched. Furthermore, the foundation for many new medicines and surgical instruments, including nanorobots, has been built on nanobiotechnology. It has been utilized in almost every medical sector, and its usage in the treatment of different diseases, such as cancer, neurobiology, cardiovascular disorders, joint and bone disorders, eye diseases, and infectious diseases, has been evident through different studies. Nanobiotechnology can promote diagnostics and the advancement of customized medicine, *i.e*., prescribing unique therapeutics that are tailored to an individual's needs. Many advances have already begun, and a definite effect on medicine practice will be felt in a decade.

[*] **Corresponding authors Alaa A A Aljabali and Murtaza M. Tambuwala:** Faculty of Pharmacy, Department of Pharmaceutics and Pharmaceutical Technology, Yarmouk University, Shafiq Irshidat Street, Irbid 21163 - P. O. BOX 566, Jordan and SAAD Centre for Pharmacy and Diabetes, School of Pharmacy and Pharmaceutical Science Ulster University, Coleraine, UK; E-mails: alaaj@yu.edu.jo and m.tambuwala@ulster.ac.uk

Alaa A. Aljabali and Kaushik Pal (Eds.)

Keywords: Naturally occurring nanoparticles, green synthesis, nanomaterials, bacteriophages, biodegradation, biosynthesis.

INTRODUCTION

In recent years, nanotechnology and nanobiology have gained a significant boost. The latest growth in the applications of polymer composites is gathering momentum worldwide. Biotechnology has been revolutionized as an assertive discipline utilizing bionanotechnological research and development. Surface functionalization at nano-levels is a crucial aspect of bionanotechnology, in which several entities have already been exploited. Bio-nano substances can be used for diagnostic and therapeutic purposes by using polymers, bacteria, nucleic acids, antibodies, or other proteins [1]. Bionanotechnological advancement has made early diagnosis and treatment more possible. This makes perfect sense since more lifetimes will be spared if doctors can promptly diagnose lethal disorders and diseases. Bionanotechnology is referred to as an inspirational catalyst in a nanotechnology discipline. Speculation is being made that progress will be made more and more as biotechnology integrates [2, 3].

The extraordinary features and establishment of advanced polymer composites with established environmental analytical techniques contribute to the tremendous success of boosting the environment research era. Over the last few decades, nanotechnology's development has been fueled by the need for new nanomaterials with unmatched properties from their counterpart synthetic nanoparticles. Such properties include biodegradability, biocompatibility, and unmatched uniformity in structure and composition, with the amenability of chemical and biological modification to impart new and novel properties that make biomaterials ideal nanoparticles [4]. Newly developed nanomaterials showed promising medical, pharmaceutical, environmental, and energy applications. This chapter highlights different types of nature-inspired and biosynthesized nanomaterials and their green synthesis methods and some of their emerging applications, especially in nanomedicine, cosmetics, drug delivery, molecular imaging, and catalytic precursors. The chapter covers different types of bionanomaterials (*e.g.*, viruses, protein cages, phages) and highlights their unique properties and potential applications [5, 6].

Treating certain illnesses is a big challenge in delivering treatment compounds to the target site. A typical drug application may be constrained in potency, poor biodistribution, and lack of selectivity. Nanocages have been shown to be preferentially clustered in tumors or inflammatory sites due to antigen sampling due to the improved vasculature permeability and retention (EPR) effect. Present means of treating the bulk of solid tumors are surgery and chemotherapy or

radiation treatment. However, today's therapy destroys healthy tissue and induces unjustified patient toxicity in its general and systematic implementation. Nanoparticular delivery systems in various biomedical applications have been used in recent times. The attributes of these products are biocompatible, well-defined, and readily functional materials. Mainly due to these materials' properties, nanomaterials demonstrate high differentials in the cell or tissue-specific targeting and absorption ability. Besides, before hitting the target, the drug molecule on the nanocarrier is shielded from harsh conditions. Contrary to standard drug delivery, a delayed and regulated release of drugs can be accomplished with nanomaterials. Therefore, nanomedicine represents a revolutionary field of tremendous treatment potential by combining intelligent nanoparticles with a wide variety of functions [7].

ADVANTAGES OF NANOBIOTECHNOLOGY

The pathophysiology and the anatomic modifications of diseased or inflamed tissue have paved various ways for producing targeted nanotechnology products. In the following respects, this growth is advantageous: 1. The pathophysiological properties of diseased tissues may be used to target drugs; 2. Different nanoproducts can accumulate at concentrations above standard medicinal products; 3. Enhanced vascular permeability in tumors and impaired lymph drainage enhance tumors or inflamed tissue effects of nanosystems by improved dissemination and retention. 4. The potential of the nanosystems to locate inflammatory tissues is selective. 5. Nanoparticles may be used to supply/transport medicines to the brain that overcome the blood and brain barrier (meninges). 6. Nanoparticle loading modifies the distribution of cells and tissues and contributes to the targeted delivery of biologically active substances to increase drug production and mitigate drug toxicity [8, 9].

Applications of Nanobiotechnology in the Biomedical Field

Several therapeutic uses of nanobiotechnology are currently being studied on various topics, such as cancer detection, target drug delivery, and molecular imaging. Clinical trials are now underway on several new, exciting drugs. These innovative applications of biological systems will undoubtedly be the basis for future diagnosis, care, and disease prevention. The optimum utilization over alteration and functionalization of certain noncarrier is a significant and critical aspect to be taken into consideration when NPs are used as drug delivery system; two fundamental principles, surface alteration and targeting, are discussed here; these two concepts, nevertheless, can in some cases be used to the same degree. Altering processes are implemented for targeting purposes, including the defense

SUBJECT INDEX

A

B

C

D

E

F

G

H

I

K

L

M

N

O

P

R

S

T

Alaa A A Aljabali

Dr. Aljabali is a nanoscientist by training with extensive experience in polymeric, metallic, lipid-based nanoparticles, and protein-based nanoparticles. Dr. Aljabali holds a Ph.D. from John Innes Centre in nanotechnology in the areas of viral nanoparticles. Dr. Aljabali worked as a Bionanotechnologist at JIC shortly after completing my Ph.D. and further 3 years as a postdoctoral fellow in cardiovascular medicine at Oxford University-UK. Dr. Aljabali has a proven track record in research with over 120 publications in top peer-reviewed journals in the primary research area of nanotechnology and its applications.

My lab's mission is to develop an innovative and novel frontier in biomaterials science and medicine through the design, development, and testing of novel natural bio-inspired materials using plant virus-based scaffolds, polymeric nanoparticles, and lipid-based nanomaterials. Leading a research laboratory interfacing bio-inspired, molecular engineering approaches with medical research, technology development, and materials science.

Kaushik Pal

Kaushik Pal received his Doctorate (PhD) in Physics from the University of Kalyani (India). Most recently awarded Honorís Causà Doctor of Science (D.Sc.) from Higher National Youth Skills Institute (IKTBN) Sepang, Govt. of Malaysia as well as achieved 'Gold Medal' awarded by the Prinminister of Malaysia. Entire academic career Prof. Pal received the prestigious Marie Curie Postdoctoral Fellowship (Greece) offered by European Union Sponsorship, and the Chief-Scientist Faculty Fellow (PDF) nominated by Chinese Academy of Science (CAS) foundation in Wuhan University, China. As a distinguished academician, Prof. Kaushik has contributed innovative discoveries and smart teaching cultivated at the top-tier institutions and currently serving as an Associate Professor in University Centre for Research and Development (UCRD), Chandigarh University, Mohali. A well-known expert supervisor for PhD/Postdoctoral scholars and an experienced group leader to builds Inter- and cross multi-disciplinary Nanoscience excellence, resulted more than 125-significant articles in peer-reviewed (SCI/Scopus) International journals and partially edited or authored 26-renowned books with reputed publishers.