Smart External Stimulus-Responsive Nanocarriers for Drug and Gene Delivery

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Dedicated to our beloved parents, and wives
for their sacrifice through the years.

Contents

Preface

In recent decades, innovative breakthroughs have emerged in the broad and flourishing field of nanobiotechnology. This arena of technology and its particular branch, nanomedicine, have made a significant impact on numerous fields of science and technology including materials science, biotechnology, and biomedicine. On the other hand, design of smart systems possessing controllable behavior with accurate feedbacks to different stimulations has focused the concentration of various researches in nanbiotechnology, nanomedicine, and the associated field of drug delivery systems (DDSs). Hence, innovative smart stimulus-responsive drug delivery systems have recently attracted the interest of multifarious research and studies.

This matching pair of E-books weaves together many of the strands that make up the emerging field of modern nanomedicine. Drug-delivery, controlled-release, gene therapy, nanocarriers and smart intelligent nanosystems are highly relevant to the design of stimulus-responsive drug and gene delivery systems.

Much of the motivation for the development of this field has come from an appreciation of the drawbacks of traditional cancer chemotherapy. Many of the approved drugs, which are actually quite good at killing cancer cells, are also highly toxic to normal cells. This unfortunate truth explains the high (almost universal) incidence of side-effects in cancer chemotherapy, which can rapidly become intolerable to patients and even life-threatening. Moreover, many of the drugs used in cancer chemotherapy are highly insoluble in biological media and have sub-optimal pharmacokinetics and biodistribution. A range of nanocarriers and nanovehicles has been designed to solubilize these drugs, and allow them to be transported intact in the bloodstream (after intravenous injection) until they reach their intended tumor target. But how are these nanocarriers meant to know when their target has been reached? The pressing need to find an answer to this question has been the driving force for the creation of an impressive range of smart or stimulus-responsive nanocarriers, which have been engineered at the molecular level to respond to a physical, chemical, or biological stimulus that is present at, is overexpressed at, or can be externally applied at the tumor site. It is noteworthy that considering the high potential of smart stimulus-responsive drug/gene delivery systems, they are increasingly being applied in diagnosis and therapy of other formidable disorders, infections, inflammations and diseases such as Alzheimer's, cardiovascular diseases, diabetes, etc, and are prompting newfound and efficient concepts.

As the reader may well imagine, this effort started out as a single E-book covering the field of smart drug-delivery nanovehicles. However, as the work progressed, it became clear that this was a highly active field with new publications coming out in the scientific literature almost every day. Faced with the E-book becoming greatly extended in length, we decided to prepare the subject in two distinct parts. Fortunately, this was not too difficult as there is a natural divide between those stimuli, which can be classified as 'internal' in nature (E-book 1), and those which would be considered 'external' in nature (E-book 2). The internal stimuli comprise

those factors which are naturally characteristic of tumors, other disease states, or particular organs or tissues. These stimuli include pH, specific enzymes, redox potential (oxidizing or reducing), and specific biomolecules such as glucose or ATP etc. The external stimuli include those physical energies and forces, which can be applied from outside the body either to guide a nanovehicle to its destination, or to activate it at a specific location once it has arrived. These stimuli include light, temperature (which can be either internal or external), magnetic fields, ultrasound, and electrical and mechanical forces. Dual stimulus and multi-stimuli-responsive systems, and the global market for DDSs are covered in E-book 1, while the important subject of nanotoxicology is covered in E-book 2; subsequently, comprehensive discussions are provided under scrutiny in both E-books.

Acknowledgments

The authors would like to express their gratitude to all who helped them. Special thanks should be given to Professor Michael R Hamblin, for his permanent advice and encouragement of our research into smart nanosystems in nanomedicine and drug/gene delivery systems, and his guidance through the process of writing this book. Second, the authors would like to express their heartfelt gratitude to their beloved families for all their love and encouragement through the years and also while completing this book, to their parents who raised them with a love for science and a conscience, and also to their wives.

The authors deeply extend their appreciation to Seyed Masoud Moosavi Basri and Mahnaz Bozorgomid for composing some of the schematic figures used in this book. Finally, it is our pleasure to acknowledge the guidance and contribution of the Production team at Morgan & Claypool and IOP Publishing, for their expert help.

Author biography

Mahdi Karimi

Mahdi Karimi received his BSc degree in *Medical Laboratory Science* from the Iran University of Medical Science (IUMS), in 2005. In 2008, he achieved the MSc degree in Medical Biotechnology from Tabriz University of Medical Science and joined the Tarbiat Modares University as a PhD student in the nanobiotechnology field and completed his research in 2013.

During his research, in 2012, he affiliated with the laboratory of Professor Michael Hamblin in the Wellman Center for Photomedicine at Massachusetts General Hospital and Harvard Medical School as a researcher visitor, where he contributed to the design and construction of new smart nanoparticles for drug/gene delivery. On finishing the study, he joined, as Assistant Professor, the Department of Medical Nanotechnology at IUMS. His current research interests include smart nanoparticles' design in drug/gene delivery and microfluidic systems. He has established a scientific collaboration between his lab and Professor Michael Hamblin's lab to design new classes of smart nanovehicles in drug/gene delivery systems.

Parham Sahandi Zangabad

Parham graduated with a BSc from Sahand University of Technology (SUT), Tabriz, Iran, in 2011. He received his MSc in Nanomaterials/Nanotechnology from Sharif University of Technology (SUT), Tehran, Iran. Concurrently, he became the research assistant at the Research Center for Nanostructured and Advanced Materials (RCNAM), SUT, Tehran, Iran. As a BSc and then MSc student he worked on the assessment of the microstructural/mechanical properties of friction stir welded pure copper and friction stir processed hybrid TiO_2–Al_3Ti–MgO/Al nanocomposites. Furthermore, he has done several experiments on synthesis and characterization of sol–gel fabricated ceramic nanocomposite particles.

The advent of innovative nanomaterials and nanotechnology interested him in interfacial sciences/technologies and also nanomedicine, including nanoparticle-based drug delivery systems and nanobiosensors.

He has now joined Professor Karimi's Nanobiotechnology Research lab in the Iran University of Medical Science, Tehran, Iran, in association with Professor Hamblin from Harvard Medical School, Boston, USA; working on smart micro/nanocarriers applied in therapeutic agent delivery systems employed for diagnosis and therapy of various diseases and disorders such as cancers and malignancies, inflammations, infections, etc.

Amir Ghasemi

Amir did his BSc at Sharif University of Technology (SUT), the most prestigious technical university in Iran. He joined polymeric materials research group since 2012, and received his MSc in Materials Engineering from SUT. For the MSc project, he worked on *thermoplastic starch (TPS)/cellulose nanofibers (CNF) biocomposites*, under the supervision of Professor Bagheri. He synthesized a fully biodegradable nanocomposite, and evaluated the effects of CNF on mechanical and biodegradation of TPS.

His research interests lie in the area of mechanical properties of biopolymers and polymer composites, ranging from material design to the performance of the final product. He also works on micro/nano materials, and bio-based polymers as drug carriers under the supervision of Professor Karimi and Professor Hamblin from Harvard Medical School.

Now, he works at Parsa Polymer Sharif, involved in thermoplastics compounding. He would also like to thank Professor Karimi and Professor Hamblin for the opportunity to contribute and most importantly learn about such drug delivery systems.

Michael R Hamblin

Michael R Hamblin PhD is a principal investigator at the Wellman Center for Photomedicine, Massachusetts General Hospital, an associate professor of dermatology, Harvard Medical School and the affiliated faculty of Harvard–MIT Division of Health Science and Technology. He directs a laboratory of around 12 scientists who work in photodynamic therapy and low-level light therapy. He has published 274 peer-reviewed articles, is associate editor for eight journals and serves on NIH study sections. He has edited ten proceedings volumes, together with four other major textbooks on PDT and photomedicine. In 2011 Dr Hamblin was honored by election as a Fellow of SPIE.

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Chapter 1

Introduction

In recent decades, nanotechnology has emerged as a highly innovative field showing great potential in various areas of science and technology. Nanotechnology is influential in pure science (e.g. chemistry, physics, etc), materials science, energy science, biotechnology, biomedicine and pharmaceutics. Due to the widespread and increasing burden of perilous diseases, such as drug-resistant infections, malignancies like cancer, Alzheimer's disease, diabetes, hepatitis, cardiovascular disease, systemic inflammatory disorders and so on, more efficacious therapies are urgently required with a focus on the targeted and individualized treatment of the diseased site. Furthermore, the diagnostic and imaging aspects of therapy have become of interest, especially in the diagnosis and treatment of various cancers. In this respect, important breakthroughs have been accomplished in diagnosis and therapy, particularly in the combination form called theranostics. There is an increasing requirement for clinical trials in nanomedicine, which has resulted in many successes, and more nanoparticles (NP) are receiving approval from the US Food and Drug Administration (FDA) [1–6].

Micro/nanosystems have been applied for drug delivery using various materials and approaches, such as nanostructured particles and surfaces and diffusion-controlled delivery systems, and these are enabling novel therapies. Other new applications in biosensing and implantable devices, such as drug-eluting/bioresorbable stents, can be improved by nanotechnology [7–11]. The administration of different nano/microparticle-based drug/gene delivery systems (DGDS) has been proposed as a way to effect targeted delivery of therapeutic agents towards specific disease locations inside the body, with substantial advantages such as reduced toxicity and lessened damage to normal tissues and cells, enhanced solubility, effective treatment of diseases, minimal/controllable side-effects for drugs or the therapeutic method, etc [12–14]. In this respect, significant improvements in therapeutics and pharmaceutics can be achieved. Furthermore, macromolecules are increasingly used

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as therapeutic agents and their targeted delivery is an important challenge [15]. The delivery of such macromolecules should be both time-controlled and site-specific [16]. For DGDS, smart targeting/delivery approaches are highly desirable and in this area stimuli-responsive systems are important. Therefore, the design of intelligent systems with controllable and accurate feedback to multifarious stimulation has been considered extensively. Newly developed smart nano/microparticles have shown great potential in various fields, particularly for the targeted delivery of drugs/genes [17]. In such smart systems, triggered delivery and the release of therapeutic agents in a targeted and controlled way can be achieved through the application of a wide variety of external or internal stimulations [18]. This is due to the high sensitivity of specific NP to triggering by various stimuli and the resulting far-reaching physicochemical alterations [19, 20].

Different external physical stimuli can take the form of changes in magnetic and electric fields, light irradiation, the application of ultrasound and heating sources, and the use of mechanical force. Figure 1.1 shows a schematic depiction of various external stimulations that can be applied in smart DGDS.

In some cases, using smart DGDS can eliminate the risks and drawbacks of other carrier systems, such as viral vectors in clinical gene therapy [21]. Although NP-based nanocarriers generally show only low cytotoxicity towards normal cells

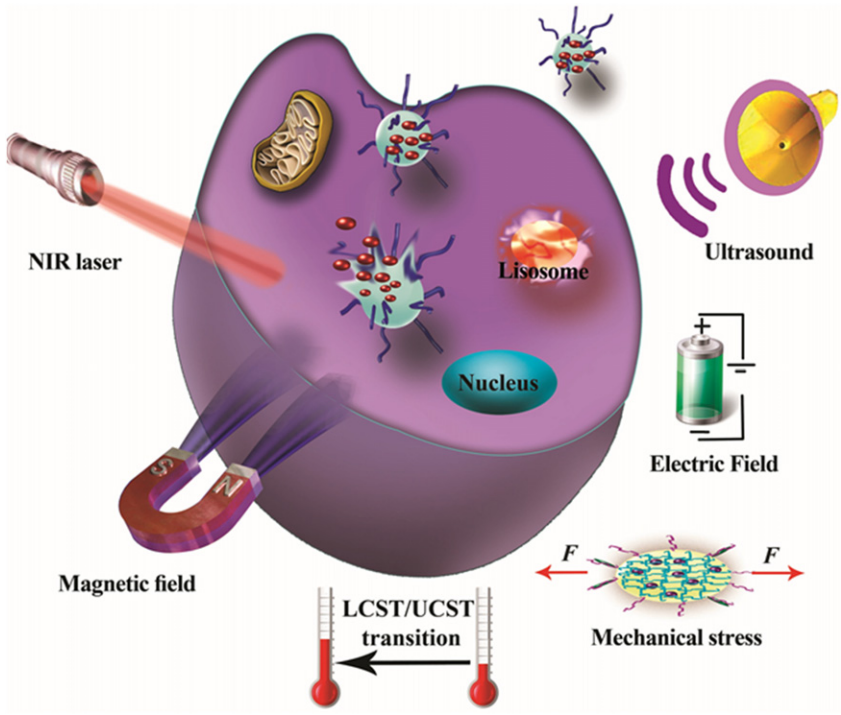

Figure 1.1. Schematic of different classes of stimuli, including the external (e.g. electric and magnetic field, light irradiation and ultrasound), that can act as triggers for the design of smart stimuli-responsive targeted DGDS.

and in biological environments [22], the various effects NP can have on biological environments have led to the establishment of a new field, 'nanotoxicology', and these must be considered in the design of new nanocarriers. These toxicity issues have been one of the main concerns in the recent literature [23] and have worried the general public; efforts have been made to define and, if necessary, reduce this toxicity [24, 25]. In addition, the interactions of NP with biological molecules and materials, and the occurrence of phenomena such as the coating with proteins known as a 'corona' and the cell-type specific effect known as 'cell vision', can significantly affect the biological fate of NP, their targeting ability [26–28] and their cytotoxicity [29]. Smart NP have demonstrated notable therapeutic potential, particularly in cancer therapy where they have been designed to be triggered in tumor sites [30]. Smart NP can respond to a variety of tumor-specific stimuli [31] and dramatically improve the cytotoxicity of anticancer drugs in respect of malignant cells while reducing their toxicity towards normal cells [32]; large-scale molecular simulations and systems biology approaches can be used to model these effects [33].

In smart DGDS, various mechanisms can be designed to effect the targeted delivery and release of cargos from nanocarriers, which are strongly dependent on the type of stimulus applied. Detailed understanding of these mechanisms is required for the design and development of smart DGDS in order to study their interactions with biological environments, analyze probable side-effects and obtain the desired delivery and release characteristics, such as drug release rate, controlled delivery and release, sensitivity level of nanocarriers to stimuli, etc.

Various NP and nanotechnology methods have been investigated, not only to provide more reliable micro/nanocarriers triggered by one or more stimuli, but also to deliver facile and economical preparation methods for drug-carrier NP with higher loading efficiency and prolonged and sustained release times [34]. In smart DGDS, much effort has been put into the exploration of novel stimuli-responsive nanocarriers [18]. The most studied classes of nanocarriers are: various types of polymer NP (e.g. hydrogels/nanogels, micelles, etc); liposomes; carbon-based nanomaterials (e.g. graphene, carbon nanotubes (CNT), fullerene); ceramic-based NP (magnetic NP, mesoporous silica NP (MSN), etc); metal NP (gold NP, silver NP, etc); and solid lipid NP (SLN). Several different types of micro/nanoparticles (MNP) employed in the design of smart micro/nanocarriers for DGDS are illustrated in figure 1.2.

In this book and its companion (*Smart Internal Stimulus-Responsive Nanocarriers for Drug and Gene Delivery*), different smart DGDS are discussed according to their stimulus type and have been categorized according to their external or internal stimulation route. The principles and mechanisms of each stimulus type are taken into consideration, and recent progress and the latest achievements in biomedicine and pharmaceutics applications are discussed. The focus is on the use of smart nano/microcarriers to carry out targeted delivery of therapeutic agents to particular cells, tissues or disease states.

In this book, we discuss DGDS triggered via external stimuli (including light irradiation, temperature change, ultrasound irradiation, magnetic and electrical fields, and mechanical stress) in detail. Finally, a conclusion and future perspectives

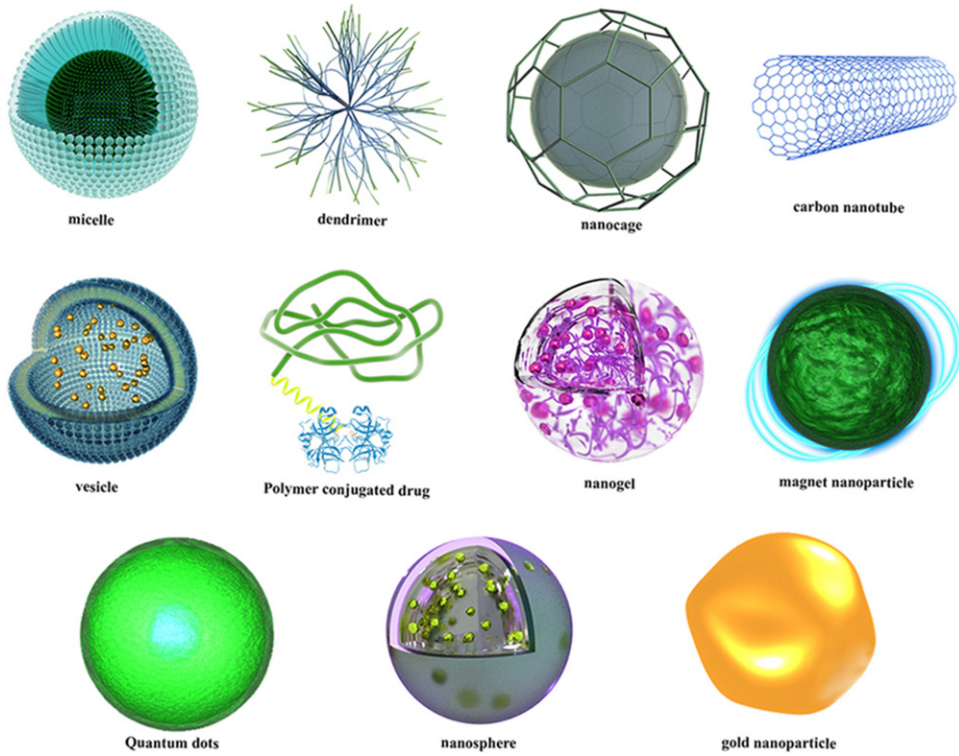

Figure 1.2. Several classes of NP used for the design of smart micro/nanocarriers, including micelles, dendrimers, nanocages, CNT, polymeric conjugates, nanogels, magnetic NP, quantum dots (QD), nanospheres and gold (Au) NP.

section discusses nanotoxicology briefly and addresses innovative future concepts and new challenges in the smart DGDS field.

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