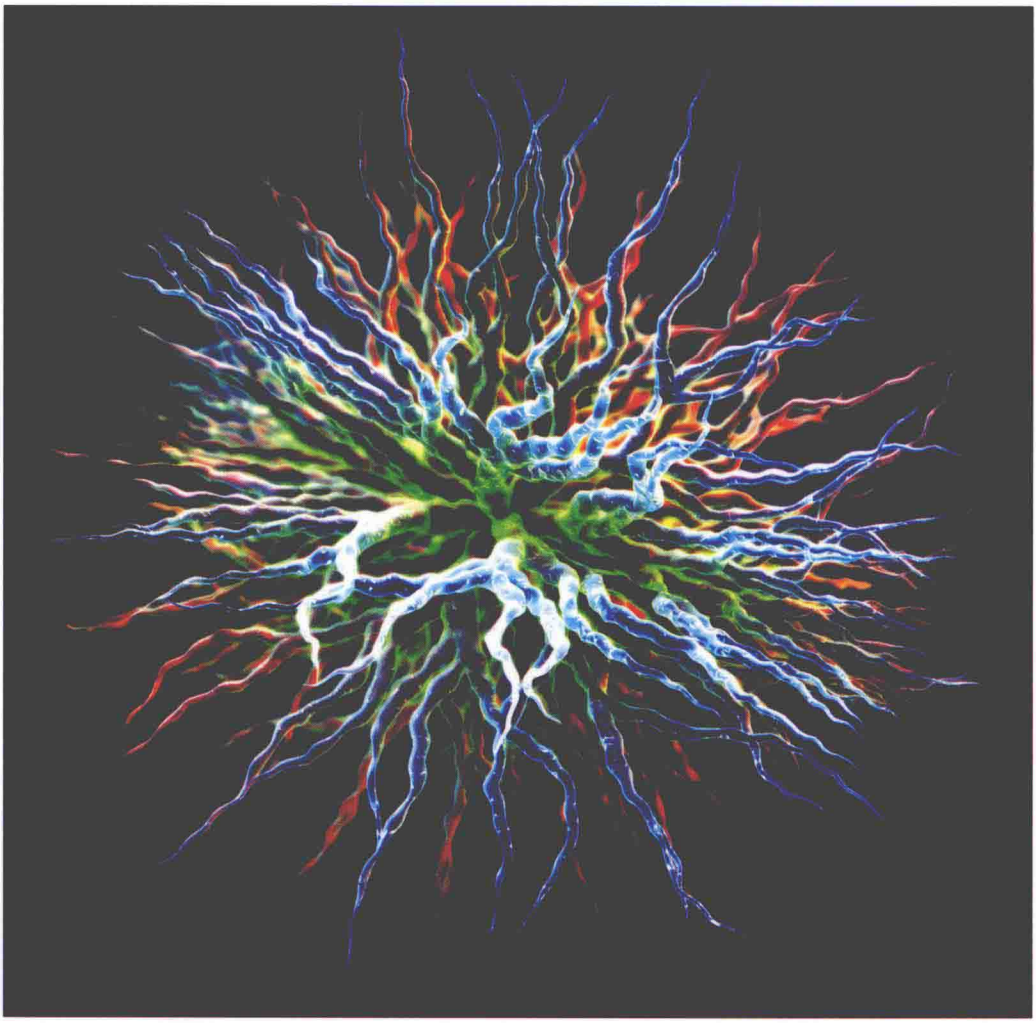
RSC Polymer Chemistry Series

Edited by Youqing Shen

Functional Polymers for Nanomedicine



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Functional Polymers for Nanomedicine

Edited by

Youqing Shen
Zhejiang University, Hangzhou, China
Email: shenyq@zju.edu.cn

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Preface

It has been already more than a decade since nanotechnology was introduced to the field of controlled drug delivery. The nanotechnology push by various funding agencies throughout the world has resulted in significant advances in the drug delivery field, as evidenced by the explosive increase in the number of publications on the subject during the last several years. The term "nanotechnology" has permeated into every aspect of drug delivery research. The thrust of nanotechnology, at least in the drug delivery field, has been the use of nanosized drug delivery systems, which are collectively called "nanoparticles" or "nanovehicles". The goal of utilizing nanovehicles is to develop drug delivery systems that can enhance the efficacy of various drugs by making them more bioavailable through targeted delivery, and thus reducing side effects. The question we have to ask now is whether the nanovehicles have fulfilled their intended function of producing more clinically useful drug delivery systems. The answer is unfortunately "not quite".

Controlled drug delivery began in the early 1950s, and now we are literally entering the third generation (3G) of the discipline. The first generation (1G) during 1950-1980 has been most fruitful in producing clinically useful sustained release formulations, which are mainly in the areas of oral and transdermal formulations. The second generation (2G) drug delivery systems have not been as successful, however. This is mainly due to the difficulty in overcoming the biological barriers when drug delivery systems, such as pulmonary and injectable systems, are introduced into the body. One of the expectations of the nanovehicles is to overcome the biological barriers. The nanovehicle revolution, which began near the end of the 2G, is currently continuing into the 3G systems. It is time to review the progress made by the nanotechnology-based drug delivery systems in the last decade to prepare for the next decade or two.

Developing better drug delivery systems for the future requires understanding the reasons for successful formulations and the causes for the lack of expected outcomes. The book "Functional Polymers for Nanomedicine", edited by Professor Youqing Shen, is designed for this purpose. In retrospect, it appears that the field of controlled drug delivery has given blind trust to the nanotechnology-based formulations without any critical assessments. The book tries to rectify this by examining the current bottlenecks in the development of

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various nanovehicles. One of the most important goals of nanomedicine is to achieve targeted drug delivery, which is essential in treatment of tumors as well as gene therapy. The goal is to deliver a drug to the target site in large enough quantity lethal to cancer cells with minimized side effects. To do this, we need to be able to control drug release kinetics, and this in turn requires good formulation stability in the blood followed by desired tissue distribution. The nanovehicles also need to deliver a wide range of drugs including small, hydrophobic drugs (both poorly soluble and water soluble drugs) to large hydrophilic drugs (peptides, proteins, siRNA, and DNA). The book describes unique advantages and limitations of a variety of drug delivery vehicles, such as liposomes, polymer micelles, dendrimers, polymersomes, polymer-drug conjugates, polymer-drug complexes, and core-shell-corona micelles. The book also deals with the current misunderstanding of targeted drug delivery and provides paradigm-changing new ideas.

One of the reasons we study history is to find out what happened and not to repeat the same mistakes, thereby making the future better. This book is about learning from the failures, as much as the progresses made in the last ten years and finding ways to design better drug delivery systems in the next ten years. Naturally, this book is expected to be a valuable guide for the drug delivery scientists, especially those who are relatively new in the area.

Kinam Park
Purdue University

Contents

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CHAPTER 1

Targeted Drug Delivery in Oncology: Current Paradigm and Challenges

DARREN LARS STIRLAND[a] AND YOU HAN BAE*[b]

[a] Department of Bioengineering, College of Engineering, University of Utah, Salt Lake City, UT 84108, USA; [b] Department of Pharmaceutics and Pharmaceutical Chemistry, College of Pharmacy, University of Utah, Salt Lake City, UT 84108, USA

*E-mail: you.bae@utah.edu

1.1 Targeted Drug Delivery

Targeted drug delivery seeks to improve the therapeutic index, that is, lower the toxicity but increase the efficacy of a drug. Some designs try to minimize side effects to allow a higher dose and increased therapeutic effects. Other designs focus on increasing efficacy to require less drug that could cause side effects. The methods of targeted drug delivery often control both when and where the drug is effective. If the drug could be presented only to the disease in the body, then there would be no side effects and efficacy would be improved with high concentrations in the target area. In this chapter, we focus on the topic of targeted drug delivery in cancer therapy. Research has been ongoing for years to accumulate a significant amount of knowledge into the field and fill the literature with the term "targeted drug delivery." Some have very aggressive claims of succeeding at targeted drug delivery and others, perhaps more accurately, state a goal of improving targeted drug delivery. While clear

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delineations of what targeted drug delivery is and is not would help, there are challenges with the current state of targeted drug delivery that extend beyond defining the term. These challenges are present in both the carrier and the target. Carrier technology has improved greatly, yet still has trouble delivering drug to the target. The target, cancer in the clinical setting, is still resisting treatment. The challenges associated with this problem need to be addressed in order to move forward. The systems may be targeted by design, but they are not hitting the target fully and exclusively.

1.1.1 Origins of Targeted Drug Delivery

The current paradigm of targeted drug delivery is linked to its origins, which are tied to chemotherapy and immunology. Paul Ehrlich was a pioneer in chemotherapy and is known for the metaphor of a magic bullet. The vision of the magic bullet was inspired from his ability to selectively stain bacteria cultures.[1] He reasoned a toxic molecule could be tied to the stains to selectively kill only that target. Targeted drug delivery has been guided by Ehrlich's vision, particularly in the field of cancer therapy.[2] In the context of cancer and chemotherapy, a magic bullet carrying an anticancer drug is administered to the patient to provide exclusive delivery to the cancer. In contemplating the metaphor of a magic bullet, perhaps the body's immune system fits best. It has both mobility and specificity. Immune cells can follow chemical gradients and have specificity with antibodies and cell receptors. Ehrlich himself stated that cancer would be more prevalent if not for the immune system.[3]

1.1.2 Progress in Targeted Drug Delivery

Advances in immunology and the advent of monoclonal antibodies have become an important part of pursuing the vision of a magic bullet. With immunostaining, the targeting application seems flawless and provides motivation for application in cancer therapy. In targeted drug delivery there is a targeting aspect and a therapeutic aspect. Sometimes these monoclonal antibodies can provide a therapeutic effect on their own. However, monoclonal antibodies and other targeting designs are usually incorporated in a variety of therapeutic carriers, such as microemulsions, inorganic nanoparticles, viruses, and polymers. Liposomes are composed of lipids which assemble into vesicles with a bilayer capable of carrying drug molecules. Gold and iron oxide nanoparticles are among the more popular inorganic molecules used. Viral carriers, made by modifying existing viruses or by using certain aspects from them, have also been used in targeted drug delivery of chemotherapeutics.[4,5] All of these have dimensions on the scale of nanometers and can be described as nanoparticles. While colloidal chemistry and even targeted drug delivery have a long history, nanotechnology and its application in nanomedicine are quickly becoming popular topics. Polymer therapeutics is another major trend in research that seeks after the properties of a magic

bullet. Helmut Ringsdorf suggested a standard model that could be used to improve targeted drug delivery by focusing on different components of the polymer to give abilities for imaging, targeting, and drug loading.[6] The Ringsdorf model has been an inspiration for many polymer designs in drug delivery for cancer therapy.[7] It has led to a trend of polymer therapeutics, with researchers devising various ways to give properties to polymers. The versatility in chemistry and molecular architecture is one of the advantages of polymers in targeted drug delivery. With polymer therapeutics and the newly emerging field of nanomedicine, the possibilities are only limited by one's imagination.

Comparative PubMed searches show an exponential increase in the number of articles related to polymer therapeutics and nanomedicine.[8] Companies are willing to invest large amounts for research and development of these products because of their potential to return large profits. Review articles list various targeted drug delivery approaches that are in clinical trials, which include polymer–drug conjugates, monoclonal therapeutics, some that specialize in multidrug resistance, and those classified as nanoparticle-based therapeutics.[9–12]

1.2 Current Paradigm

The current paradigm associated with targeted drug delivery shapes the design of the drug carriers. Currently, there are certain properties thought to maximize drug delivery to the tumor. First, a stable carrier for the drug can help reduce side effects and increase the therapeutic effect. A stable carrier will mean that the drug is protected from the body and that normal (nontargeted) tissues are protected from the drug. Second, the carrier will accumulate in the tumor *via* the enhanced permeability and retention (EPR) effect. Third, the carrier can target the tumor based on both environmental and cellular components.

In order to arrive at the tumor, the drug needs a stable carrier. The majority of anticancer drugs are hydrophobic and do not dissolve in aqueous solutions. The first requirement of a stable carrier is simply the ability to carry the drug. As the carriers transport the drug, they need to form a stable barrier between the drug and the body. Protecting the body from the drug requires that the drug not interact with nontargeted cells, tissues, or organs. Protecting the drug from the body provides long circulation in the bloodstream. Increasing the blood circulation half-life of the carrier can increase chances of interactions with the target. To achieve long blood circulation, it needs to avoid interaction with the reticuloendothelial system (RES), also known as the mononuclear phagocyte system (MPS). Cell uptake by the MPS will decrease the efficacy of the treatment. There should also be protection against blood-borne proteins that would lead to inactivation, destabilization, or opsonization. The carrier should also be designed to limit accumulation in the kidney, liver, spleen, and other non-targeted organs. Administration of the chemotherapeutic agent

Taxol® is a good example of the need for good carriers. Taxol® consists of paclitaxel solubilized in Cremephor EL®, which is a highly toxic mixture of castor oil and ethanol. This excipient can cause hypersensitivity reactions in patients undergoing chemotherapy and can be a treatment limiting problem.[13] Furthermore, the active pharmaceutical ingredient, paclitaxel, is known to cause dose limiting neurotoxicity at high doses.[14] If stability and long circulation are achieved, it will be able to travel through the body and eventually reach the site of the tumor. Here, carrier technology can encourage treatment preferentially to the tumor by using environmental characteristics or cellular components, such as surface proteins, as targets.

The carrier can target environmental characteristics of the tumor. Some of the environmental characteristics provide a means for passive accumulation *via* the EPR effect. The EPR effect is possible because of two hallmarks of cancer: unchecked growth and continued angiogenesis.[15] Continuous growth of the tumor leads to a chaotic tumor environment, with cells in hypoxic regions producing angiogenic factors which stimulate the production of new blood vessels. These new blood vessels are poorly formed and have gaps or fenestrations in the endothelium that allow passage of macromolecules into the tumor from the blood.[16] Increased mass transport from the blood vessels is beneficial for a tumor that is starved of nutrients. Therapies can take advantage of this hyperpermeability that allows nanoparticles to accumulate in the tumor where this leakiness occurs. Furthermore, retention in the tumor is aided by the lack of functional lymphatics that would normally drain the tissue.[17]

Once in the tumor environment, molecular targeting is a method used to provide treatment preferentially to tumors. Some cancer cell types overexpress certain surface markers. These markers are present in other cells, but can be much more abundant in some tumors. Overexpression of folate receptor and human epidermal growth factor receptor 2 (HER2) have been shown to be a predictor of poor prognosis of breast cancers.[18,19] These and other overexpressed proteins have become a target implemented into the designs of drug carrier technologies.[20–22] Alternatively, some carriers use a membrane penetration mechanism, such as the TAT peptide, to increase cell internalization in a nonspecific way.[23] While techniques not relying on protein expression can increase efficacy, methods must be used to block activity outside the tumor environment. To achieve this, the carrier's actions can designed to be triggered by environmental characteristics of the tumor. Some drug carriers use pH-sensitive groups to provide a triggered action in the acidic environment.[24] The low pH is a result of metabolism in hypoxic conditions that exist in the core of most solid tumors.[25] As not all tumors possess a markedly low pH, it has been shown that a glucose infusion in nondiabetic patients can lower the pH in tumors.[26] It also might be possible to use the high concentration of matrix metalloproteinases (MMPs) in the extracellular matrix (ECM) of tumors for triggering an active form of the carrier.[27]

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