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Polymer Therapeutics I

Polymers as Drugs, Conjugates and Gene Delivery Systems

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Volume Editors: Ronit Satchi-Fainaro · Ruth Duncan

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Polymer Therapeutics: Polymers as Drugs, Drug and Protein Conjugates and Gene Delivery Systems: Past, Present and Future Opportunities

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Abstract As the 21st century begins we are witnessing a paradigm shift in medical practice. Whereas the use of polymers in biomedical materials applications – for example, as prostheses, medical devices, contact lenses, dental materials and pharmaceutical excipients – is long established, polymer-based medicines have only recently entered routine clinical practice [1–4]. Importantly, many of the innovative polymer-based therapeutics once dismissed as interesting but impractical scientific curiosities have now shown that they can satisfy the stringent requirements of industrial development and regulatory authority approval. The latter demand on one hand a cost-effective and profitable medicine or diagnostic, and on the other hand, a safe and efficacious profile that justifies administration to patients.

The first clinical proof of concept with polymer therapeutics has coincided with the explosion of interest in the fashionable area called "nanotechnology". This has resulted in exponential growth in the field, and an increasing number of polymer chemists are turning their attention to the "bio-nano" arena. An attempt to define "nanotechnology" is beyond the scope of this review, but suffice it to say there is widespread agreement that application of nanotechnology to medicine, either via miniaturisation or synthetic polymer and supramolecular chemistry to construct nano-sized assemblies [5, 6], offers a unique opportunity to design improved diagnostics, preventative medicines, and more efficacious treatments of life-threatening and debilitating diseases. It is thus timely for this volume of Advances in Polymer Science to review the field that has been named "polymer therapeutics" (Fig. 1).

The term "polymer therapeutics" [1] has been adopted to encompass several families of constructs all using water-soluble polymers as components for design; polymeric

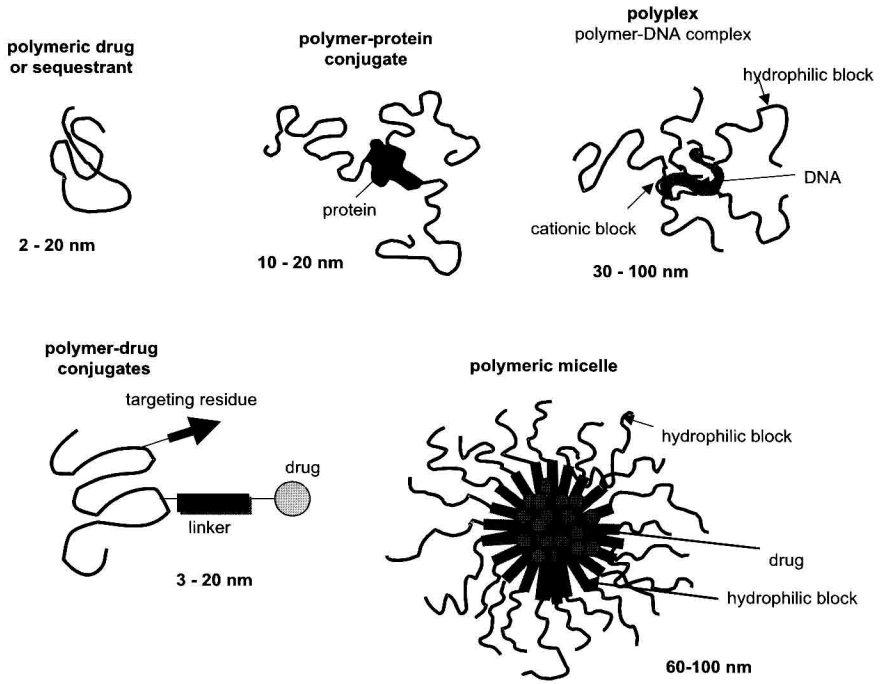

Fig. 1 Schematic showing the families of polymer constructs called"polymer therapeutics"

drugs [3, 7], polymer-drug conjugates [1, 8], polymer-protein conjugates [2, 9], polymeric micelles to which a drug is covalently bound [10], and those multi-component polyplexes being developed as non-viral vectors [11]. From an industrial standpoint, these nanosized medicines are more like new chemical entities than conventional "drug-delivery systems or formulations" which simply entrap, solubilise or control drug release without resorting to chemical conjugation. In this issue of Advances in Polymer Science, the current status of those technologies in preclinical and clinical development is reviewed, together with presentation of an emerging area of novel synthetic chemistry – the new field of polymer genomics – and also a description of some of the sophisticated analytical methods being developed to characterise complex polymer constructs.

1 Historical Perspective

The use of polymers in medicine is not new. Undoubtedly, natural polymers have been used as components of herbal remedies for several millennia. Modern pharmacognosy is currently more carefully identifying specific natural-product macromolecular drugs and beginning to more rigorously define the molecular basis of their mechanisms of action. The notion of syn-

thetic, water-soluble polymers as macromolecular drugs or components of injectible drug delivery systems has, in contrast, a relatively short history – not surprising given the infancy of polymer science itself. The efforts of Hermann Staudinger and his contemporaries led to the birth of polymer science in the 1920s – less than a hundred years ago [12–14]. Moreover, it wasn't until 1953 that Staudinger was honoured with the first "polymer" Nobel Prize "for his discoveries in the field of macromolecular chemistry". Coincidentally, this is the same year that Watson and Crick published their *Nature* articles on the structure of DNA [15]. Around this time we saw the beginning of water-soluble synthetic polymers as healthcare aids for parenteral administration. During the Second World War synthetic polymeric plasma expanders were widely adopted (e.g. poly(vinylpyrolidone)). Before long the first polymer-drug conjugates appeared (e.g. mescaline-*N*-vinylpyrolidine conjugates with drug attached via non-degradable or enzymatically degradable (gly-leu) side chains [16]). Biologically active polymeric drugs also started to gain popularity [17], and divinylether-maleic anhydride copolymer (pyran copolymer) was tested clinically as an anticancer agent in the 1960s. It failed in early clinical trials due to its severe toxicity, and later it was discovered that deleterious effects were related to subtle changes in polymer molecular weight and administration via the intravenous route [18]. Building on the lessons learnt in these early studies, modified polysaccharides, synthetic polypeptides and synthetic polymers have since all been successfully transferred into the market as polymeric drugs. In fact, it was pioneering work that began to emerge in the 1970s that began to lay the foundations for a clearly defined chemical and biological rationale for the design of polymeric drugs, polymer-protein conjugates [9] and polymer-drug conjugates [8, 19, 20].

2 Current Status

Efforts in the 1970s and 1980s allowed rational design (bearing in mind the proposed use and pathophysiology of the disease target) of the first polymer therapeutic candidates that later entered clinical testing. Translation to the clinic solved for the first time many important challenges relating to specific product development of polymertherapeutics: industrial-scale manufacture; development of "validated" analytical techniques required to confirm identity and batch-to-batch reproducibility of these often heterogeneous, hybrid macromolecular constructs; and the development of pharmaceutical formulations able to ensure shelf-life stability and rapid solubilisation of particle-free solutions for safe injection. Definition of preclinical toxicological protocols able to ensure the degree of safety was also needed to justify clinical trials and the optimisation of clinical protocols (dose and frequency of dosing) is still ongoing for many products.

The first poly(ethyleneglycol) (PEG)ylated proteins were approved by regulatory authorities for routine clinical use in the early 1990s (reviewed in this volume by Pasut and Veronese: "Pegylation of Proteins as Tailored Chemistry for Optimized Bioconjugates"): PEG-adenosine deaminase used to treat acute immunodeficiency syndrome and PEG-L-asparaginase to treat acute lymphoblastic leukaemia. At the same time in Japan, a stryene-co-maleic anhydride conjugate of the anticancer protein neocarzinstatin called SMANCS, developed by Maeda and colleagues, was successfully used as a treatment of patients with primary liver cancer (a very difficult disease to treat) and this led to market approval for the treatment of this disease. In this case the aim of polymer conjugation was to hydrophobise the protein, thus allowing dispersion in a phase contrast agent Lipiodol that is used for patient imaging. The formulation is administered locally via the hepatic artery. During his research, Maeda also discovered the passive tumour-targeting phenomenon called the "enhanced permeability and retention effect" (EPR effect). This phenomenon is attributed to two factors: the disorganised pathology of angiogenic tumour vasculature with its discontinuous endothelium leading to hyperpermeability towards circulating macromolecules, and the lack of effective tumour lymphatic drainage, which leads to subsequent macromolecular accumulation. It is now well established that long circulating macromolecules including polymer conjugates, and even polymer-coated liposomes, accumulate passively in solid tumour tissue by the EPR effect after intravenous administration and can increase tumour concentration manyfold (reviewed in this volume by Maeda et al.: "The EPR Effect and Polymeric Drugs: A Paradigm Shift in Cancer Chemotherapy").

Throughout the 1990s a steady stream of polymeric drugs began to emerge (reviewed in this volume by Dhal et al.: "Polymers as Drugs"). These include a number of products including a synthetic random copolymer of L-alanine, L-lysine, L-glutamic acid and L-tyrosine (M_w = 5000–11 000 g/mol) given subcutaneously to treat multiple sclerosis patients and also those poly(allylamine)s developed clinically as polymeric sequestrants for oral administration. In addition, a growing number of compounds have entered clinical trials. They include dextrin-2-sulfate (M_w = 25 000 g/mol) given intraperitoneally to treat HIV-1 in patients, and most recently, the first dendrimer-based drug tested clinically, which is also a vaginal anti HIV virucide.

The first synthetic polymer anticancer drug conjugate entered clinical trials in 1994. This was an *N*-(2-hydroxypropyl)methacrylamide (HPMA) copolymer conjugate of doxorubicin [21, 22]. Since then, five more HPMA copolymer conjugates have progressed into the clinic, and the first conjugate bearing antiangiogenic therapy is now being tested in vivo [23]. Anticancer conjugates based on other polymeric carriers including poly(glutamic acid), PEG and polysaccharides are also now in clinical trials, and it is anticipated that the first product in this class will appear very soon (reviewed here in Satchi-Fainaro et al.: "Polymer Therapeutics as Anticancer Treatments: Current Status and Fu-

ture Challenges"). An alternative approach for targeted delivery of anticancer agents utilises block copolymer micelles within which the anticancer drug can be simply entrapped or covalently bound. Of this type there are currently three systems in early clinical trials (reviewed in Nishiyama and Kataoka, "Nanostructured Devices Based on Block Copolymer Assemblies for Drug Delivery: Structural Design for Enhancing Drug Function").

With growing appreciation of the molecular basis of disease in the late 1980s, the hope of "gene therapy" began to gain momentum. While the viral vectors are still preferred for gene delivery, there has been a continuing hope that polymeric non-viral vectors can become a feasible alternative – i.e. biomimetics delivering DNA safely without the threat of toxicity. Pioneering early research used simple polycationic vectors such as poly(L-lysine) and poly(ethyleneimine). Since then a wide variety of complex multicomponent, polymer-based vectors have been designed as gene delivery systems – see Wagner and Kloeckner, "Gene Delivery Using Polymer Therapeutics" and also elsewhere [24]. With still some distance to the first polymeric viral vectors as marketed products, there is still much to do.

3
Future Opportunities and Challenges

It should not be forgotten that it was only the turn of the last century when Paul Ehrlich proposed the first synthetic small molecules as chemotherapy. Introduction of the first biotechnology and polymer-based products over the last two decades has been greeted with the same suspicion that Ehrlich encountered when introducing modern chemotherapy in his day. Nevertheless, at the present time, the core business of the pharmaceutical industry is obviously low-molecular-weight drugs (both natural product extracts and synthetic drugs) and prodrugs, particularly those that are amenable to oral administration providing convenience for the patient.

The fact that macromolecular drugs, such as proteins, polymer therapeutics and genes, are not orally bioavailable, coupled with their chemical complexity and the perceived difficulties in realising them in practice made them unattractive development candidates for many large pharmaceutical companies until the end of the 20th century. Observation that the FDA approved more macromolecular drugs and drug-delivery systems than small molecules as new medicines in 2002/2003 suggests that the tide has now turned.

Now that we are in the 21st century, the time is ripe to build on the lessons learnt over the last few decades, and the increased efforts of polymer chemists working in multidisciplinary teams will surely lead to the design of improved second-generation polymer therapeutics. The polymer community's interest in synthetic and supramolecular chemistry applied to biomedical applications has never been greater. This has in part been due to the rise in interest

in using dendrimers and nanotubes for applications in drug delivery (reviewed in this volume by Amir and Shabat:"Domino Dendrimers" and [21]) and not least the need for bioresponsive polymers that can be designed as (3-D) scaffolds for tissue engineering. Innovative polymer synthesis is leading to many new materials, but while they provide exciting opportunities, they also present challenges for careful characterisation of biological and physicochemical characterisation. These two important areas are reviewed in this volume.

For clinical use, it is essential to identify biocompatible synthetic polymers that will not be harmful in relation to their route, dose and frequency of administration. For many years, the general cytotoxicity, haematotoxicity and immunogenicity (cellular and humoral) of water-soluble polymers has been widely studied. Before clinical studies, rigorous preclinical toxicity testing of the candidate has also been mandatory. However, it is becoming evident that synthetic polymers can display many subtle and selective effects on cells affecting a diverse range of biochemical processes. These effects may be relatively weak so they do not result in major toxicity. Studies have recently commenced that assess the pharmacogenomic effects of polymers, and this important, emerging field is reviewed here by Kabanov et al. ("Polymer Genomics"). Development of analytical techniques able to accurately characterise polymer therapeutics in terms of identity, strength, stability and structure in real time (to allow correlation with biological properties) has proved a real challenge in itself. However, atomic-force microscopy has already begun to demonstrate the ability to provide structural and physicochemical information for a wide range of synthetic and bio-polymers. The latest developments in the latter area are described here by Davies "Characterisation of polymer constructs by Real Time Molecular AFM investigations".

This volume highlights some of the key areas of research and development relating to synthesis, characterisation and use of polymer therapeutics. For those new to the field, the text should be read in parallel with the historical milestone publications (see the bibliography), including papers published in Advances in Polymer Science (for example [25, 26]) and elsewhere [8, 19]. There are also several recent reviews that are essential reading for the expert and newcomer alike [27, 28].

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