# Polymers for Drugs, Drug–Protein Conjugates, and Gene Delivery

by Ruth Duncan, Helmut Ringsdorf, and Ronit Satchi-Fainaro

Use of polymers in biomedical materials applications — e.g., as prostheses, medical devices, contact lenses, dental materials and pharmaceutical excipients — is long established, but polymer-based medicines have only recently entered routine clinical practice (**1–4**). Many 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. These demand both a cost-effective and profitable medicine or diagnostic and a safe and efficacious profile that justifies administration to patients.

The first clinical proof of concept with polymer therapeutics coincided with the explosion of interest in the fashionable area of nanotechnology, leading to exponential growth in the field. An increasing number of polymer chemists are turning their attention to the "bio–nano" arena. Application of nanotechnology to medicine to construct nanometer-sized assemblies (**5, 6**) offers a unique opportunity to design improved diagnostics, preventative medicines, and more efficacious treatments of life-threatening and debilitating diseases.

The term *polymer therapeutics* (**2, 3**) has been adopted to encompass several families of construct (Figure 1), all using water-soluble polymers as components for design: polymeric drugs (**1, 7**), polymer–drug conjugates (**2, 3, 8**), polymer–protein conjugates (**4, 9**),
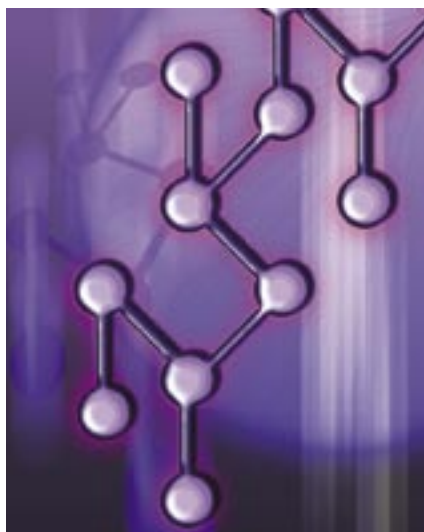
polymeric micelles to which drugs are covalently bound (**10**), and multicomponent polyplexes being developed as nonviral gene vectors (**11**). Nanosized medicines are more like new chemical entities than conventional drug delivery systems or formulations, which simply entrap, solubilize, or control drug release without resorting to chemical conjugation.

HISTORICAL PERSPECTIVE

Efforts in the 1970s and 1980s allowed rational design of the first polymer therapeutic candidates. Translation to the clinic solved for the first time many important challenges relating to specific product development of polymer therapeutics: industrial-scale manufacture; development of "validated" analytical techniques required to confirm identity and batch-to-batch reproducibility of these

often heterogeneous, hybrid macromolecular constructs; the development of pharmaceutical formulations able to ensure shelf-life stability; and rapid solubilization of particle-free solutions for safe injection. Definition of preclinical toxicological protocols that could ensure a necessary degree of safety was also required to justify clinical trials, and optimization of clinical protocols 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. At the same time in Japan, a stryene-co-maleic anhydride conjugate of the anticancer protein neocarzinstatin was approved as a treatment for patients with primary liver cancer (a difficult disease to treat). In that case, the aim of polymer conjugation was to hydrophobize the protein, thus allowing dispersion in a phase-contrast agent that is used for patient imaging. The formulation is administered locally through the hepatic artery. During related research, a passive tumor targeting phenomenon called the enhanced permeability and retention (EPR) effect was discovered. It is now well established that long-circulating macromolecules including polymer conjugates and even polymer-coated liposomes accumulate passively in solid tumor tissue by the EPR effect after intravenous administration.

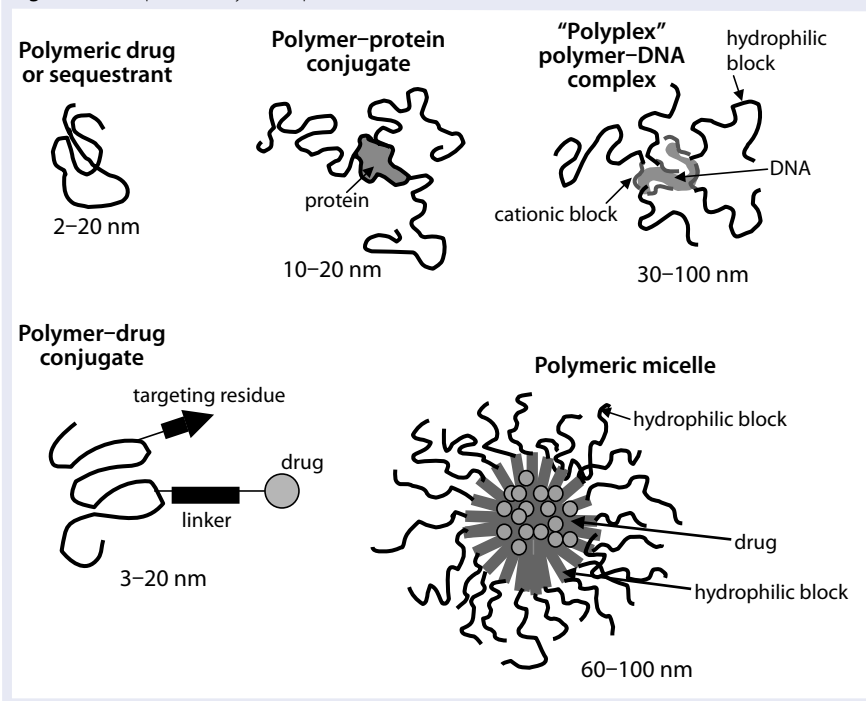Throughout the 1990s, a steady stream of polymeric drugs began to

emerge. And a growing number of compounds have since entered clinical trials. They include the first dendrimer-based drug tested clinically, which is a vaginal virucide against HIV. The first synthetic polymer anticancer drug conjugate entered clinical trials in 1994, an *N*-(2-hydroxypropyl)methacrylamide (HPMA) copolymer conjugate of doxorubicin (**2, 3, 12**). Since then, five more such copolymer conjugates have progressed into the clinic, and the first bearing antiangiogenic therapy is now being tested in vivo (**13**). Anticancer conjugates based on other polymeric carriers are also now in clinical trials. An alternative approach for targeted delivery of anticancer agents uses block copolymer micelles within which an anticancer drug can be simply entrapped or covalently bound. Of this type, there are currently three systems in early clinical trials.

Gene Therapies: With growing appreciation of the molecular basis of disease in the late 1980s, hopes for gene therapy began to gain momentum. Although viral vectors are still preferred for gene delivery, there has been a continuing hope that polymeric nonviral vectors can become a credible alternative: biomimetics delivering DNA safely without the threat of toxicity. Pioneering early research used simple polycationic vectors such as poly(L-lysine) and poly(ethyleneimine). A wide range of complex multicomponent, polymer-based vectors have been designed as gene delivery systems (**14**). But with still some distance to the first polymeric viral vectors as marketed products, there is still much to do.

FUTURE OPPORTUNITIES AND CHALLENGES

At present, the core business of the pharmaceutical industry is still low–molecular-weight drugs (natural product extracts and synthetic molecules) and pro-drugs, particularly those amenable to oral administration, which provides patient convenience. As a rule, macromolecular drugs — such as proteins, polymer therapeutics, and gene therapies — are not orally

Figure 1: Complementary concepts

Polymeric drug or sequestrant
2–20 nm

Polymer–protein conjugate
protein
10–20 nm

"Polyplex" polymer–DNA complex
hydrophilic block
DNA
cationic block
30–100 nm

Polymer–drug conjugate
targeting residue
drug
linker
3–20 nm

Polymeric micelle
hydrophilic block
drug
hydrophilic block
60–100 nm

bioavailable. Coupled with their chemical complexity and perceived technological difficulties, that made them unattractive development candidates for most large pharmaceutical companies up until the end of the 20th century. But the FDA approved more macromolecular drugs and drug delivery systems than small molecules as new medicines in 2002 and 2003, which suggests that the tide has turned.

In the 21st century, the time is ripe to build on lessons learned over the past few decades, and with the increased efforts of polymer chemists working in multidisciplinary teams this 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 driven by a rise in interest toward using dendrimers and nanotubes for applications in drug delivery (**2, 3**) and the need for bioresponsive polymers that can be designed as three-dimensional scaffolds for tissue engineering. Innovative polymer synthesis is leading to many new materials, but although they provide exciting opportunities, they also present challenges for careful

characterization of biological and physicochemical characterization.

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 each 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. Such effects may be relatively weak so that they do not cause major toxicity. Studies are assessing the pharmacogenomic effects of polymers. Development of analytical techniques that can accurately characterize 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. Atomic-force microscopy has already begun to demonstrate an ability to provide structural and physicochemical information for a range of synthetic and biopolymers.

For those new to the field, there are several historical milestone publications, including papers published in *Advances in Polymer Science* (**15, 16**) and elsewhere (**8, 17**). Several fairly recent reviews are essential reading for experts and newcomers alike (**18, 19**).

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