between the AAA+ motif and DNA imposes a unique polarity of Orc on the initiator binding site. These multiple protein-DNA contacts distort and bend DNA 20° to 35° and untwist their respective DNA sites without actually breaking hydrogen bonds between the nucleotide bases. *S. solfataricus* Orc proteins are noted for their sparse sequence-specific contacts, which is quite interesting given that higher eukaryotes lack defined replication origin sequences. Gaudier *et al.* suggest that the eukaryotic ORC may recognize specific DNA structures that can be deformed to fit into the ORC. This method of DNA recognition is used by another class of AAA+ proteins—the replication clamp loaders—which recognize DNA structure rather than sequence.

An important future goal in the study of initiator proteins is to understand the architecture of an initiator oligomer bound to a complete replication origin and how the nucleoprotein complex couples ATP hydrolysis to the unwinding of DNA. Oligomers in the other replicative AAA+ classes—clamp loaders and certain helicases—have been solved and may provide insight into the arrangement of initiator subunits within this complex. For example, both the eukaryotic RFC clamp loader (*13*) and the papillomavirus E1 helicase (*14*) form circular structures (see the second figure), and their AAA+ domains are arranged in a spiral that contacts DNA. The findings of Gaudier *et al*. and Dueber *et al.* that the AAA+ domains of archaean Orc bind directly to DNA suggest a close functional relationship of initiators to other replicative AAA+ proteins and imply that archaean initiator oligomers may also encircle DNA. Indeed, circular and helical arrangements have been observed in previous structural studies of initiator oligomers in the absence of DNA [bacterial DnaA (*15*) and eukaryotic ORC (*16*, *17*)]. The present findings bring us closer to resolving how the replication of DNA gets started and how conserved or divergent the strategies are across species.


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MATERIALS SCIENCE

# Polymer Therapeutics

Polymers are finding increasing use as drugs, both in development and in clinical practice.

**Kristi L. Kiick**

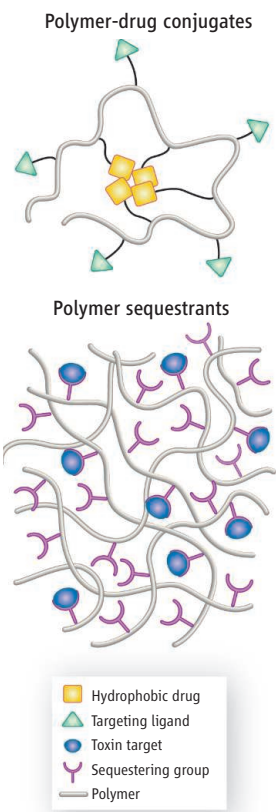
Polymers have been used for decades as drug-delivery vehicles and implants owing to their useful mechanical properties (*1*–*3*), but were long thought too heterogeneous for use as bioactive pharmaceuticals in their own right. However, the physical properties of polymers can offer distinct advantages critical for treating human disease, including improved drug targeting and circulation, and polymer drugs have thus entered into routine clinical practice (*4*).

Various strategies have advanced the biomedical application of polymeric drugs, including the chemical attachment of drugs to a polymer scaffold, the production of polymers directly from a polymerizable drug, and the use of polymers to sequester and eliminate toxic compounds. Polymer drugs of these categories are in or near clinical application. New approaches, mainly at the research stage, exploit improved understanding and control of polymer structure in the design of polymeric drugs with biological activities controlled by polymer architecture.

The author is in the Department of Materials Science and Engineering, University of Delaware, Newark, DE 19716, USA. E-mail: kiick@udel.edu

In some of the most developed and clinically applied approaches, the drug of interest is chemically attached to the polymer scaffold (see the first figure, top panel); these polymer-drug conjugates lead to improved drug targeting, circulation, and solubility. Attachment of targeting ligands to the polymer offers further enhancement in targeting, and judicious choice of the linker between the drug and polymer enables targeted liberation of drugs in response to pH, enzymatic, or redox-responsive mechanisms (*4*, *5*). In a different approach, certain drugs (such as nonsteroidal anti-inflammatory drugs and antiseptics) can be polymerized directly to yield drug-based polymeric drugs that can be easily processed and that degrade to directly release the bioactive drug (*6*).

Polymer sequestrants (see the first figure, bottom panel) have also been widely used clinically in the form of crosslinked hydrogels or resins, taking advantage of their ability to remain intact in the gastrointestinal tract and to not be absorbed through the intestinal wall. Control of their electrostatic charge and hydrophobicity has permitted their use for removal of ions, bile acids, fats, and other toxins (*7*). For example, Renagel—a crosslinked hydrogel with controlled densities of select amine groups—has been used clinically to sequester phosphate ions in patients with chronic renal failure. Additional sequestrants containing hydroxamic acid groups can arrest the intestinal absorption of dietary




**Polymer-drug conjugates and polymer sequestrants.**

iron and may find future use in the treatment of iron-overload conditions.

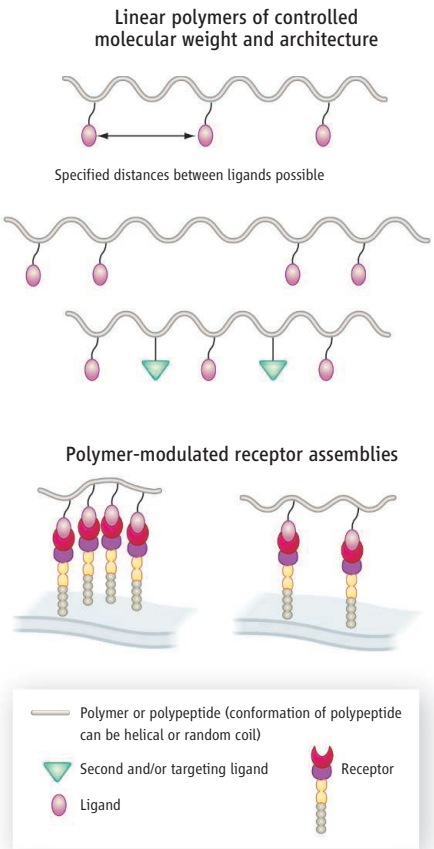
Polymeric drugs can also show therapeutic action by binding directly to biological targets. Approaches in development include co-polypeptide-based polymers that can slow the progression of multiple sclerosis by competing with autoantigens and preventing sensitization of T cells (*8*), and ligand-decorated polymers that bind efficiently to toxins (*9*).

New and exciting approaches in the design of future polymeric drugs use ligand-modified scaffolds with activities derived distinctly from controlled scaffold structure and consequent controlled presentation of ligands (see the second figure, top panel). Detailed knowledge of the biological target, informed macromolecular design, and high levels of synthetic control are all necessary to produce such polymers.

With appropriate design and synthesis, these well-defined polymers can be used to study and manipulate cell-surface–receptor assemblies (see the second figure, bottom panel). The organization of cell-surface receptors into arrays serves as a key signaling mechanism in processes such as cell adhesion, immune responses, and bacterial chemotaxis. In some cases, receptor dimerization activates maximum signaling, but often, the recruitment of a greater number of receptors to the array amplifies or otherwise alters the resulting signal. These receptor arrays occur on length scales of 1 to 100 nm. Macromolecular ligands are thus uniquely suited for manipulation of the arrays and offer enormous promise in characterizing cell surfaces, targeting specific cell types, and regulating cell activities. They may serve not only as mechanistic probes, but also as therapeutics that control cellular responses.

A variety of controlled polymerization methods have been used to produce well-defined polymers for receptor binding, with ring-opening metathesis polymerizations (ROMP) (*10*) showing much recent promise. Gestwicki and Kiessling have shown that ROMP-derived polymers of different molecular weights have different propensities for initiating chemotaxis in bacteria (*11*). Baessler *et al.* have used ROMP-derived polymers (see the second figure, top panel) to study organization of egg cell-surface receptors during fertilization. Fertilization can be inhibited by receptor dimerization by end-functionalized, ROMP-derived polymers; inhibition potency is not improved by using higher-valency or longer polymers (*12*).

Signaling functions of immune cells can also be studied and controlled with macromolecular ligands. Leukocyte surfaces contain a carbohydrate-binding protein, L-selectin, that regulates leukocyte rolling and adhesion at sites of injury, initiating the inflammatory response. Molecules that modulate L-selectin adhesion may thus be useful in regulating the inflammatory process. L-Selectin binding on the surfaces of leukocytes can be engaged via ROMP-derived multivalent ligands, and ligand potency has been shown to increase with multivalency (*13*).




**Macromolecular ligands for manipulation of receptor arrays.**

Multivalent ligands have also been used to manipulate B cell signaling. B cells produce antibodies in response to antigen binding. Puffer *et al.* have shown that modulating the organization of the B cell receptors alters antibody production to favor either tolerance or immunity (*14*). Binding of low-valency ligands promotes tolerance, whereas binding of high-valency ligands activates gene-expression changes necessary to stimulate antibody production. These differences are thought to result from controlled differences in receptor aggregation by the well-defined polymeric ligands, and are not observed with traditional antibody-based approaches to receptor aggregation. Such polymer approaches may therefore be useful in the treatment of autoimmune diseases and in adjuvant therapy and vaccine development.

There are many further opportunities in the development of polymers for these applications. Increasingly precise ligand placement will permit independent manipulation of ligand and number and spacing, offering opportunities to tune receptor organization and cell activity. Biosynthetic methods afford unique synthetic capability in this regard, allowing production of perfectly defined polypeptide-based polymers with specific backbone conformations and with one or more different ligands in specific positions (see the second figure, top panel). Such polypeptide-based macromolecular ligands bind bacterial toxins (*15*), and offer substantial potential for manipulating cell signaling and mapping unknown receptor topologies.

Many challenges remain. Controlled trafficking of a given polymer drug, and minimization of its inflammatory and immunological properties, continue to be challenges in the design of therapeutic macromolecules. Improved molecular-level characterization of the interactions of these macromolecular drugs with their targets—for example, with advanced imaging techniques and single-molecule characterization methods—will facilitate their design. The continued development of systems biology approaches will also aid in the prediction of cellular outcomes upon drug administration. With convergence of advances in these areas, the prospects continue to be bright for the use of polymer therapeutics in the treatment of human disease.

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