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VIEWPOINT

Self-Assembling Biomolecular Materials in Medicine

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Abstract Materials that mimic or extend the properties of natural molecules are being developed for medical applications. Recent breakthroughs in genetic engineering, polymer synthesis, molecular self-assembly and related areas are greatly expanding the variety of structures available for use in physiological settings.

Key words: abzyme, bacteriostatic agent, bioactive material, biomimetic structure, biosensor, blood coagulation, ceramic, coating, combinatorial synthesis, drug delivery, encapsulation, enzyme, extracorporeal device, genetic engineering, implant, in vitro evolution, LB film, lipid, liposome, molecular imprinting, molecular machine, nanostructure, orthopedics, pore, protein engineering, sensor, silk, S-layer, surface, smart material, synthetic chemistry

Biomolecular materials mimic or extend the properties of molecules found in nature. They are manufactured by using biological processes, such as gene expression in heterologous cells, or by technologies, such as organic synthesis, that are capable of producing biomimetic structures. Sophisticated approaches, e.g., the site-directed chemical modification of genetically engineered proteins, combine biological and chemical synthetic methods. Biomolecular materials will contribute in the search for new materials for improving human health. In a confusing distinction, materials that contact the body are known as biomaterials and need not necessarily incorporate biomolecular materials! Examples of biomaterials that are being sought today include components for artificial organs (including extracorporeal devices) orthopedic materials, resorbable sutures and tissue scaffolding, controlled release and encapsulation systems, and probes for biosensors.

Brief consideration of just one aspect of biomaterials, surface coatings, immediately generates an extensive list of requirements. Such demands are challenging the ingenuity of materials scientists. Coatings are required for implants, sensors and encapsulation. They must have appropriate physical properties including the desired wettability, porosity and elasticity. The exposed surface of a coating may need to be adhesive or not adhesive, depending on the application. Similarly, the coating may be required to be long-lived (70 years or more) or short-lived (resorbable). Often, biologically inert surfaces are needed to prevent blood coagulation, or protein and bacterial adsorption. Alternatively, bioactive surfaces may be necessary including those that release antibacterial agents or guide the movement of cells. Applications of coatings with enzymatic or transport activity, perhaps spatially organized in two-dimensions, can be envisaged. Surfaces that attach to target cells or, more futuristically, actively participate in finding them will also be valuable.

Why might biomolecular materials be suited to these tasks? Certainly, nanofabrication of inorganic materials is now being extended to the atomic level. But, by comparison with even the most finely machined inorganics, biomolecules (natural or engineered) are highly sophisticated. For example, they can recognize other molecules and modify or translocate them. These properties emerge in the size range of a few nanometers and above. Further, many of the traits desired for biomaterials are "biological" (e.g., bacteriostatic surfaces), which is hardly surprising as the materials are to be used in a physiological setting. In several cases biomaterials must form an interface between the physiologic and the synthetic. It is now feasible to generate such interfaces at the molecular level. For example, a combined chemical and genetic synthetic route to polyethylene-protein hybrids can be readily outlined. A much touted asset of biomolecular materials is their ability to self

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assemble into organized arrays, which is, of course, a property of many naturally occuring molecules, e.g., viral coat proteins. Self-assembly is important both for the manufacture of biomolecular materials and in determining their properties (consider for example the uniform size of biological pores). Finally, prospects appear favorable for molecular devices that will allow synthetic structures to respond to their environment (e.g., by expansion and contraction) or even to move around the body. Perhaps, useful man-made self-replicating structures [Tjivikua et al., 1990] are not as far-fetched as some critics would have us think.

Returning to the present, the self assembling materials discussed at this meeting are all simple membrane-based systems. Nevertheless, their potential utility is wide-ranging. For example, their properties impact several of the requirements for coatings outlined earlier. Uwe Sleytr described bacterial S-layers. These membranes are entirely devoid of lipid and contain large pores. Demonstrated applications include ultrafiltration and the immobilization of molecules, especially other proteins, in ordered arrays. By contrast, Alan Rudolph described structures that are entirely lipid-based including liposomes as carriers for proteins, microcylinders for the controlled release of bioactive peptides, and the patterned deposition of lipids for controlling cell adhesion. Between these extremes, this author described a pore-forming protein that can assemble into preformed bilayers. The power of molecular genetics has been used to produce pores with altered properties, including those in which assembly can be controlled by external stimuli. Clearly, aspects of these three systems might be combined to produce yet more intricate materials. For example, as suggested by Sleytr, S-layers might be used as a supports for other membranes, including those containing genetically engineered pores.

Quite different self-assembling systems are being explored by others and it is likely that many of them will ultimately make an impact in biomaterials. Crosslinked enzyme crystals provide extremely robust catalysts with potential as components of implants for correcting genetic enzyme deficiencies [St. Clair and Navia, 1992]. Biomimetic ceramics, such as "organoceramics" [Messersmith and Stupp, 1992], may be useful in bone replacement. Considerable effort is being put into the molecular genetics of silks [Kaplan et al., 1994]. Engineered silks to which bacteria cannot adhere would have surgical applications. A novel detection device for influenza virus is based on a spectral shift in a chromophoric Langmuir-Blodgett film, which extends surface sialic acid residues that bind the virus [Charych et al., 1993]. This ultimately compact detector could be adapted for a variety of ligands and incorporated into "smart" implants.

Recent breakthroughs in biotechnology will soon produce many more biomolecular materials with applications in medicine. Genetic engineering, which is capable of producing virtually any protein, including chimeric molecules, is being extended by combining mutagenesis with chemical modification [Hilvert, 1991]. Furthermore, unnatural amino acids [Noren et al., 1989] and unusual backbone structures [Ellman et al., 1992] can now be introduced during enzymatic protein synthesis, while both nucleic acids [Nielsen et al., 1991] and polypeptides [Borman, 1993] are being mimicked by organic synthesis. Nanostructure synthesis is being extended into three dimensions by using self-organizing building blocks [Whitesides et al., 1991; Philp and Stoddart, 1991], including oligonucleotides [Seeman, 1993] and smectogens [Stupp et al., 1993]. Polymeric surfaces that recognize molecules are being produced by molecular imprinting [Vlatakis et al., 1993], while the use of combinatorial libraries (both genetic and chemical) [Birnbaum and Mosbach, 1992] and in amenable cases in vitro evolution [Szostak, 1993] is revolutionizing the screening and selection of new molecules, which include catalytic antibodies [Lerner et al., 1991] and nucleic acids [Symons, 1992]. Further, control over the activity of materials is now being achieved with built-in triggers and switches [Adams and Tsien, 1993; Higaki et al., 1992]. Add to this the development of molecular machines, ranging from relatively simple elastic materials that respond to the environment [Urry, 1993] to motile structures [Macnab, 1992], and the prospects for biomaterials seem limitless.

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