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Editorial

Recombinant Biomaterials for Pharmaceutical and Biomedical Applications

Fundamental advancements in controlled delivery of bioactive agents can be made possible by either the design of novel biomaterials capable of exerting new or better defined functions, or elucidation of new mechanisms of interactions of biomaterials with biological environments. The ideal biomaterial is no longer necessarily one that is considered as "inert" rather one that dynamically interacts with the biological environment in its path of delivery. Examples of motifs included in biomaterials for controlled delivery include those designed to protect the bioactive cargo from release or degradation in the GI tract or blood stream, motifs that specifically interact with cellular receptors (for targeted delivery) or extracellular matrices (for cell delivery and tissue engineering), moieties that are responsible for cell penetration, intra- or extracellular movement and release, and sequences responsible for biodegradation and elimination. By necessity many advanced delivery systems combine several such features into one material design and are therefore complex. The growing complexity of delivery systems necessitates the ability to control the underlying biomaterial structure with a higher degree of precision. In the case of polymeric biomaterials, such control can be exerted at the linear molecular level (e.g., monomer sequence or polymer length), three dimensional level (e.g., order of branches or crosslinks) or at the level of assembly and fabrication (e.g., nano or micro with control over pattern, size, geometry, etc.).

Genetic engineering techniques have allowed the de novo design of protein-based polymers with exquisite control over sequence and length. Methodologies for the biological synthesis of such polymers were established less than two decades ago (1–3). Recently more research is being conducted to explore the use of this technology in drug and gene delivery, regenerative medicine and other biomedical applications. Protein-based polymers (also termed as protein polymers or recombinant polymers) are made of repeating amino acid sequences. Such polymers are distinct from chemically synthesized random poly amino acids (where there is limited control over amino acid sequence or polymer length) and sequential poly peptides (where chemically synthesized amino acid based monomers are polymerized to yield poly disperse polymers). The distinct advantages of recombinant polymers over their chemically synthesized counterparts are that they are monodispers and there is control over amino acid sequence beyond the lengths possible by solid or solution phase peptide synthesis. In such polymers, biorecognizable or stimuli-responsive motifs can be introduced to the polymer backbone at strategic locations to allow material/cell interactions (4,5), or to lead to sharp and precise phase transitions in response to changes in pH, temperature, ionic strengths, etc. (6,7). The mechanical properties of the polymers can be controlled by introduction of motifs responsible for physical or chemical cross-linking. Their spatial and temporal biodegradation can be controlled by introduction of amino acid sequences that are susceptible to degradation in response to specific enzymes. Recombinant block copolymers can be tailor made to design smart protein micellar systems (8) or self-assembled hydrogels with tunable erosion rates (9).

Despite the modest proliferation of research in this area, the field still remains at its embryonic stages. Little information is available about the interactions of these systems with biological environments. For example the prospects of designing artificial protein-based polymeric gene delivery systems where the nucleic acid cargo is delivered to specific target cell types is exciting but a systematic structure–function relationship is yet to be established and issues such as low transfection efficiency and immunogenicity of the systems need to be overcome. Theoretically it is possible to produce three dimensional recombinant polymer matrices where appropriate biochemical, mechanical and topological ques are designed into the scaffold for cell delivery and tissue regeneration. However the task of reproducibly fabricating such three dimensional networks or fibers that make them is daunting. Another exciting area is the design of protein-based polymers that interact with extra- or intra-cellular proteins to trigger (or avoid) specific signaling pathways. It is now clear that drug carriers considered inert a decade ago (e.g. water-soluble polymer-drug conjugates) have biological effects unknown before. Such knowledge can guide in the design of next generation of smart carriers using recombinant DNA technology where desired biological effects (of the carrier) can be programmed at precise sequences. Another area where protein-based polymers can be useful is in micro- and nanofabrication. Advances in fabrication technologies have led to the design of well-defined surfaces or particles with precise geometries and surface functionalities. Control over geometry and surface topology of biomaterials can aid in the understanding of how such parameters influence interactions at the interface of materials and biology. However a challenge in the design of such materials is the underlying heterogeneous chemistry used to functionalized the surfaces. Recombinant DNA technology can potentially lead to the design of homogenous and patterned functionalities on nano or microfabricated surfaces.

The present Theme Section of *Pharmaceutical Research* highlights some of the research being conducted by investigators in the field. Kiick and coworkers describe the synthesis and characterization of multivalent alanine-rich polypeptides and how changes in molecular weight, sequence and distance between glutamic acid residues in these polymers influence their secondary structure and aggregation behavior in solution. Such polymers can provide backbones for multifunctional drug delivery systems. Kopecek and coworkers describe the synthesis and characterization of block copolymers consisting of coiled-coiled and water-soluble polyelectrolyte segments. Hydrogels were formed from these samples. The authors point out that the physicochemical properties of the hydrogels are influenced by factors such as the history of sample, length of the central random coil segment, formation of loops, and intermolecular association of the coiled-coil blocks. Furgeson and coworkers describe their latest work where DNA condensing motifs (repeating units containing lysine residues) are combined with thermally responsive elastin units for potential use in thermoresponsive systemic gene delivery applications. Finally the article by Leong, Ghandehari and coworkers describe the potential use of silk-elastinlike block copolymers in soft tissue engineering applications. In this study the chondrocytic differentiation and cartilage matrix accumulation of human mesenchymal stem cells were investigated after encapsulation in the polymers as an injectable matrix for delivery of cell-based therapeutics. The articles in this issue are intended to introduce the pharmaceutical scientists to samples of work in this burgeoning field. Recent reviews can be found elsewhere (10,11).

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