4l From Synthetic to Natural Colloidal Biomaterials

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The development of novel biomaterials is driving new methods for defining structure at the nanometer length scale. A natural, or "bottom-up," way of addressing this challenge is via self-assembly and supramolecular chemistry. Recognizing that self-assembly and supramolecular chemistry are parts of the larger field of colloidal science motivates fundamental questions in the context of potential applications (such as nano-reactors, intracellular probes or drug delivery vehicles). Integrating control over physical properties, stimulus-responsiveness, and specificity into materials design opens possibilities to circumvent current limitations. Several projects below serve to illustrate each of these aspects.

While understanding the details of the kinetic and energetic factors governing soft assemblies remain open challenges, some general features are now recognized. In my doctoral work, using model amphiphiles based on polyethylene glycol (PEG), we have shown that the interplay between interfacial and bulk properties is characteristic of these systems. Not surprisingly, at the nanometer length scale interfaces can dominate behavior, such as elasticity. Specifically, it is strictly determined by the chemical composition while independent of molecular mass. Interfaces can also dictate bounds on mechanical stability arising from the nature of the self-assembly (i.e., a bilayer structure). By contrast, bending rigidity scales strongly with the molecular weight of the building block. The emergence of nonlinear effects and a transition to macroscopic behavior is eventually reached upon progressively increasing the size of building blocks, thus delineating regimes for future applications. Extending response and stability are possible either by simple variations in chemistry or by mixing.

Other self-assembling systems allow additional flexibility with their ability to respond to stimuli. During my postdoctoral work, we have examined one such class of amphiphilic molecules sensitive to oxidative degradation (PEG-polypropylene sulfide). As a drug delivery carrier, PEG-PPS has the novel property that release can be triggered due to environmental cues such as inflammation. Understanding the physical and chemical mechanisms of degradation, which in turn determine release rate, is essential. By exposing bilayers (vesicles) and monolayers to oxidative species such as hydrogen peroxide, a two-step mechanism is revealed, where initial solubilization is followed by a transition to aggregates of higher curvature (micelles). The effect of molecular architecture is manifested in the kinetic behavior, with slower responses for more entangled systems. For applications, stimuli-responsiveness and its control are essential yet equally important is specific localization so a vehicle can receive necessary signals. One general strategy is to employ immobilized small molecules or short peptide motifs which specifically recognize the desired receptor.

Combinatorial chemistry approaches (i.e., peptide-on-phage display) offer a versatile method for identifying tissue-specific homing peptides. The strength of peptide-on-phage stems from the large diversity of the random library, and the direct linkage between genotype and phenotype, greatly simplifying the screening process. In the context of in vivo targeting, avoiding the reticuloendothelial system, and thus prolonging circulation time, is key. Our basic approach towards this goal is to attach PEG to the surface of bacteriophage. Two main strategies have been employed: (i) non-specific attachment to primary amines using PEG vinyl sulfone and (ii) specific modification to cysteines using PEG acrylates. Non-specific surface attachment of PEG to phage leads to improved in vivo performance over wild-type and thus holds promise for extending this combinatorial technique. By engineering mutants with solvent-accessible cysteines, we intend to specifically attach PEG and thereby preserve the library display for peptide discovery.

Several key aspects of soft assemblies are highlighted by imposing and measuring forces on both individual aggregates and their ensembles. Furthermore, probing cell-biomaterial interactions identifies

specific features necessary for additional functionality. Together, these tools and concepts provide a rational basis for novel biomaterial design.