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Project title: Synthesis and evaluation of sequence-defined branched polymers
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The research in my lab is focused on the development of novel scalable synthetic methodologies for the assembly of sequence-defined macromolecules and the use of primary sequence-control to probe the relationship between structure and material properties. Precise control over primary sequence via synthetic monomers has many scientific and technological implications. However, only few examples of synthetic primary sequence control have been reported due to numerous practical challenges. Motivated by the need for synthetic sequence-control, my research group invented a process for the rapid and efficient assembly of precise sequence-defined linear oligothioetheramides (oligoTEAs) with a tunable and flexible thioether backbone(1,2). Our unique methodology utilizes reaction orthogonality (instead of protecting and deprotecting groups) and a soluble fluorous support to achieve precise sequence-control in the liquid-phase. With precise sequence-control in hand, my research focus turned to investigating the relationships between sequence, structure/macromolecular properties and biological function. To probe structural effects, my research group recently demonstrated the pre-programmed assembly of macrocyclic oligoTEAs (3). The precise and modular synthesis of both folded and linear oligoTEAs places my group one step closer towards creating a body of knowledge that seeks to explore the link between molecular composition, sequence and ultimately chemical and biological properties. My group is particularly interested developing oligoTEAs for new materials discovery, drug discovery and drug delivery applications. Our current focus is on applications that leverage the advantages of oligoTEAs such as backbone control, increased serum stability, rapid assembly with precise sequence-control and a large scope of chemically diverse monomers.

Novelty: A New Process for the Assembly of Sequence-Defined Polymers

Ideally, any approach to produce sequence-defined polymers/oligomers should enable rapid and efficient production with substantial structural diversity. Our approach for achieving sequence-control deviates from the standard solid-phase reaction scheme via two innovative concepts. The first involves the design of a unique *N*-allylacrylamide monomer with two orthogonal reactive sites to the same nucleophile (a thiol group). The monomer framework includes a reactive acrylamide for phosphine-catalyzed Michael additions with thiols, the desired pendant functional group, and a reactive allyl group for photoinitiated thiol-ene "click" reactions. Both reactions have rapid solution-phase kinetics. The second innovative concept involves decoupling solid-phase reaction and purification via the use of soluble fluorous tags and a fluorous solid-phase extraction (FSPE) technology (Figure 1). Fluorous tags are soluble in common organic solvents, yet selectively partition onto a fluorous solid phase. Building sequence-defined polymers on soluble fluorous tags, unlike solid phase resins, allows us to perform monomer addition in solution with fast reaction kinetics, while simultaneously benefitting from rapid FSPE for step-wise purification. Fast solution-phase kinetics of both reactions coupled with the FSPE technology makes this platform a unique and efficient approach for the synthesis of sequence-defined oligoTEAs.

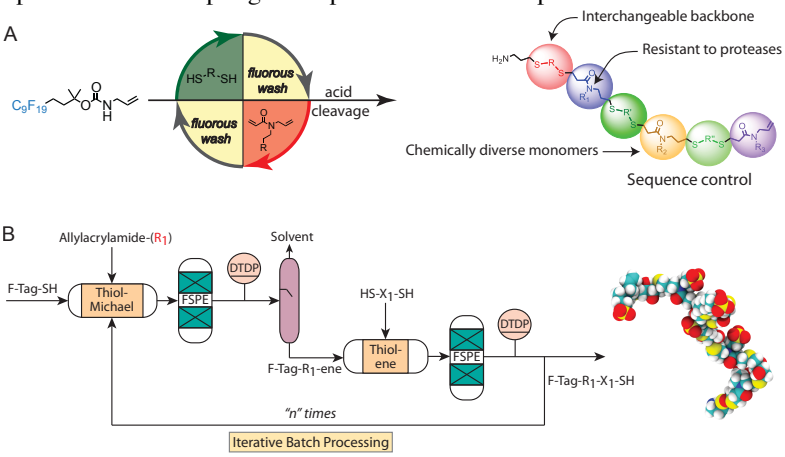

Figure 1. A) OligoTEA assembly (*J. Am. Chem. Soc.*, 2014, 136, 13162) B) Process flow diagram for oligoTEA assembly

Applications in Materials Synthesis

Achieving sequence-control on a synthetic macromolecular scaffold holds great potential for acquiring predictability over material properties and function. With an eye towards precise modulation of material properties and sustainability, our materials research thrust involves utilizing precise-sequence control on an oligoTEA polymer backbone to tune the bulk properties of a cross-linked polymer network. By controlling sequence, we hope to tune the conformation of the polymer backbone and dynamics of the cross-linking groups, thereby modulating the mechanical response and reprocessability of the resulting polymer network. To do this, we propose the support-free assembly and cross-linking of sequence-defined oligomers with adaptive reversible bonds to yield malleable

polyester vitrimer networks. Unlike traditional cross-linked thermosets whereby applied stress results in permanent deformation, the adaptive cross-links should promote a metathesis reaction and facilitate reprocessing at the appropriate temperature. The synthesis of the oligomer backbone and placement of pendent groups will be based on a support-free approach macromer assembly strategy built off the work accomplished in this ACS PRF grant period.

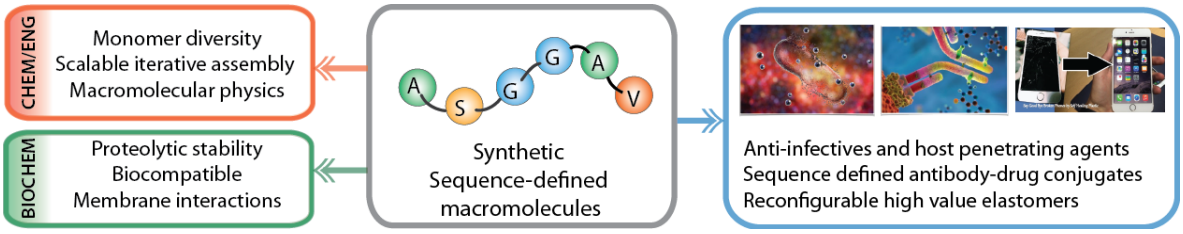

Figure 2. Relationship between the desired properties, analytical/engineering challenges and potential applications of sequence-defined macromolecules.

Applications in Chemical Biology

Our goal in the biomolecular research space is to create macromolecular architectures whose structural and chemical properties can be studied and related to biological activity. By doing this, the relationships between chemical structure and activity can be extrapolated beyond the particular library of compounds under investigation. In other words, we'd like to translate chemical and structural properties into design criteria towards the assembly to functional biomacromolecules. Prior to their use in biological environments, oligoTEAs have been tested and found to be stable (no chemical degradation) in the presence of several proteases (trypsin, chymotrypsin, etc.) under physiological conditions. A unique feature of this synthetic oligoTEA platform is that they can be designed to display chemical moieties analogous to bioactive peptide side chains. Other significant benefits of oligoTEAs include an abiotic backbone that is inherently resistant to proteolysis, relatively inexpensive production costs, straightforward monomer synthesis, and a large scope of chemically diverse monomers(2). Several research projects are currently underway that leverage the afore-mentioned advantages of oligoTEAs towards discovering new drug types (antibacterials(4) and antivirals) and delivering chemotherapeutics via antibody drug conjugates (Figure 2).

Impact to the Field and Society

Our research on sequence-defined oligoTEAs has and will continue to create new fundamental understanding in the general areas of macromolecular assembly and structure-activity relationships. Specific intellectual merits of this research direction are: i) develop the expertise for the assembly of linear, cyclic and branched oligomers for a variety of applications, ii) create a set of governing rules for the assembly of sequence-defined multifaceted architectures, iii) understand the relationship between sequence, structure and chain dynamics towards the use of oligoTEAs for a variety of applications in material science and chemical biology. The discoveries made in this project will be leveraged to improve awareness and basic understanding in the general areas of sequence-controlled assembly. The latter is a rapidly growing field and the requirements for the design of new polymers, as well as development of new characterization techniques especially for flexible polymers, should inform the broad scientific community about the composition, sequence and chain mobility requirements pertinent to the design and assembly of functional macromolecular ligands (Figure 2). This work has and will continue to affect a broad area of research, including studies that involve the use of other well-defined macromolecular ligands such as peptides and peptoids. Finally, the materials that are being designed, particularly the oligoTEA-based antibacterial agents, could yield a new class of potent antibiotics that would be of great benefit to the society at large. In addition to the scientific impact, we also have achieved a number of educational and learning activities that have been integrated throughout the duration of our research. These activities promote peer-to-peer learning and empower young aspiring scientists to take up leadership positions in communicating STEM ideas to the broader public.

References

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