COILED-COIL PEPTIDES AS MOLECULAR BUILDING BLOCKS

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April 15th, 2026, 2:30PM
Fintech Room 516
Zoom Link: https://udel.zoom.us/j/97389037588
Passcode: Bundlemer

This thesis explores de novo designed coiled coil peptide assemblies, specifically bundlemers, as a versatile platform for the design of precise materials. Bundlemers are monodisperse, well-defined building blocks with dimensions of approximately 2 nm by 4 nm, making them attractive as programmable units for the construction of complex nanostructured materials. Building on this platform, this work examines three main themes: coiled coil design and modification, covalent stabilization through interhelical linkage, and polymer growth from bundlemers to generate hybrid peptide-based nanomaterials.

Although coiled coil peptides show great promise for materials applications, their broader utility hinges on sufficient conformational stability. While numerous strategies have been developed to stabilize individual alpha helical strands through peptide stapling, comparatively few approaches reinforce the assembled coiled coil through interhelical stapling. To address this challenge, this thesis presents a rapid and facile "assemble-and-click" strategy to stabilize a tetramer coiled coil through covalent interhelical cross-links. Specifically, the thiol-Michael click chemistry between a site-specific vinyl sulfonamide and cysteine residue is used to lock the coiled coil assembly into its native conformation within 10 minutes of pH adjustment. The resulting stapled coiled coil exhibits enhanced thermal stability compared to the unstapled assembly.

A second focus of this thesis is the development of hybrid bundlemer-based nanomaterials through polymer growth from coiled coil assemblies. These materials combine favorable peptide characteristics, such as self-assembly and responsiveness, with desirable polymer properties, such as stability. In this work, coiled coil peptides are modified with bromide initiator handles for subsequent grafting-from polymerization by aqueous photoATRP. This approach builds on a previously developed photoATRP system for polymer growth from coiled coils by improving oxygen tolerance through the addition of sodium pyruvate. Size exclusion chromatography-multi angle light scattering (SEC-MALS) is used to evaluate polymerization kinetics and features, allowing for the precise determination of polymer and peptide molecular weights and providing insight into the structure and behavior of the resulting hybrid materials. A small-molecule initiator containing an amide group is also synthesized to better reflect the peptide-based initiator environment and to establish optimal reaction conditions. These conditions are then translated to synthesize peptide-polymer conjugates from three monomers, hydroxyethyl acrylate (HEA), hydroxyethyl acrylamide (HEAm), and oligoethylene oxide acrylate (OEOA480). Monomer identity is found to influence the polymerization kinetics, aggregation behavior, and dispersity of the subsequent peptide-polymer conjugate.

Finally, this thesis examines dense hybrid polymer-bundlemer nanomaterials prepared by incorporating multiple initiator side chains per alpha helix. The dense grafted materials exhibit low-molar mass tailing within the SEC chromatograms that is not observed for the original sequence. To probe this behavior, initiator handles are installed at different positions along the coiled coil to evaluate the effect of location on polymerization kinetics and control. Variation in initiator placement reveals that polymerization depends strongly on heptad position. In particular, the third position in the heptad polymerizes more rapidly and with better control than the sixth heptad position, despite it being more solvent-exposed. Though the origin of this behavior has not been definitively identified, local charge effects or differences in initiator display are proposed to influence polymer growth from the bundlemer surface. Despite these unanticipated site-dependent effects, this work demonstrates that low-dispersity hybrid bundlemer-polymer materials can be synthesized across different peripheral locations and that multiple polymer arms can be grown from each alpha-helical strand. More broadly, the results show that site selection along the coiled coil can be used to tune polymerization features and should be considered deliberately in the design of future hybrid materials.