Overview and Abstract.

Amyloid formation plays a central role in more than 40 different human diseases and a much larger subset of proteins can be induced to form amyloid *in vitro*. Amyloids are partially structured assemblies of proteins that are rich in β-sheet secondary structure and form long unbranched fibrils. Protein deposition diseases that involve amyloids include Alzheimer's disease, Parkinson's disease, and type-2 diabetes (T2D). Conversely, there are a number of examples of "functional amyloids" which serve desirable functions in biology. In these cases, the self-assembly process to form amyloid is likely to be highly regulated to avoid toxicity. The amyloid cross-β structure has also served as a guide for bio-inspired materials.

It is difficult to overstate the importance of gaining a molecular level understanding of the features that control amyloid deposition and fibril stability. Despite their importance, the factors that control the stability of amyloid fibrils and control the tendency of proteins to aggregate are not understood. Amyloid fibrils exhibit structural plasticity and a range of polymorphs structures are typically observed. Determining the structure of multiple polymorphic forms is critical for a full understanding of amyloid formation, but is prohibitively costly in terms of effort using conventional approaches.

This OVPR Seed Grant Program proposal seeks funds to develop and validate novel approaches to address these critical problems. The co-PI's bring synergistic expertise to the application; Professor Raleigh is a leader in experimental studies of the biophysics of amyloid formation and of mechanisms of cell death in amyloid diseases, with particular emphasis on islet amyloid formation in T2D. Professor Simmerling is well known for his contributions to computational biology and molecular dynamics simulations of proteins and protein complexes. Professor Dill is a world leader in the modeling and theory of protein folding, aggregation and homeostasis. Professors Simmerling and Raleigh have a successful track record of collaborations on a range of topics and a long history of jointly mentoring PhD students. Professor Dill and Simmerling also have a long history of successful collaboration.

We will use new computational methodologies developed in the Dill and Simmerling and Raleigh groups in combination with new experimental approaches developed by Professor Raleigh and Simmerling to define the stability of amyloid fibrils, deduce correlations between fibril stability and toxicity, deconvolve the relative contribution of sidechain and backbone interactions in fibrils and model polymorphic structures. These are long standing goals in the field, but have not been possible due to limitations in computational methods and experimental approaches.

The proposed studies build upon our exciting recent advances: The co-investigators have developed an approach for accurately, precisely and rapidly calculating the energetics of protein-protein interactions and the effect of mutations on protein stability and the energetics of protein drug interactions. The methodology is applicable to amyloid fibrils. A novel simulation methodology developed by Professor Dill's lab allows a rigorous interface between experiment and simulation and is ideally suited to simulations of protein aggregation and modeling of polymorphs. Professor Raleigh's team has developed high resolution experimental methods for quantitatively monitoring specific backbone and specific sidechain interactions in amyloid fibrils and has optimized protocols for producing amyloid formatting proteins.