

Rationally and computational design of functional protein barrels

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1. Abstract

Peptide and protein design have come of age: it is now possible to generate many stable peptide assemblies and single-chain proteins from scratch using rational and/or computational approaches. A new challenge for the field is to move past structures offered up by nature and to target the so-called ‘dark matter of protein space’; that is, structures that should be possible from chemistry and physics, but which biology seems to have overlooked or not used prolifically. This talk will illustrate what is currently possible in this nascent field using de novo designed coiled-coil-based peptides and proteins.

Coiled coils are bundles of 2 or more α helices that wrap around each other in rope-like structures. They are one of the dominant structures that direct natural protein-protein interactions. Our understanding of coiled coils provides a strong basis for building new peptide assemblies. The first part of my talk will present this understanding, our approaches to and methods for coiled-coil design, and our current “toolkit” of de novo coiled-coil assemblies.

Next, I will describe how the toolkit can be expanded to generate dark-matter structures. For instance, this has led to the rational and computational design of a completely new $\alpha\alpha$ helical barrels with central cavities that can be exploited in a variety of ways. Then I will turn to how the peptide assemblies can be converted quickly and reliably into single-chain $\alpha\alpha$ helical barrel proteins using recently developed AI-based computational design methods. Throughout the talk, I will illustrate the functions that can be accessed by adapting and modifying the central channels of the $\alpha\alpha$ helical barrels. For instance, I will describe how the barrels can be used as a basis for a new type of biosensor that shows promise for detecting disease, including cancers, in blood.