Targeting subcellular proteins and processes with designed peptides

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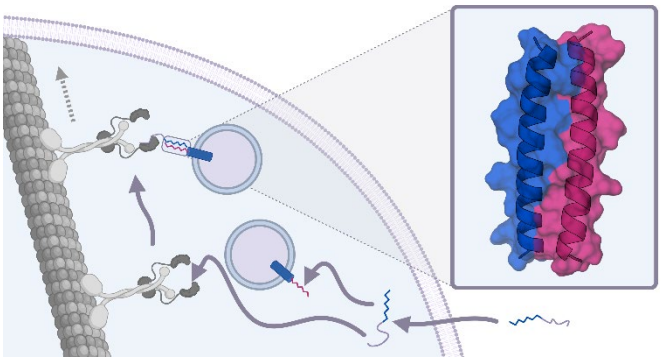

Project description:
Most, if not all, biological processes depend on protein-protein interactions (PPIs). Thus, a general ability to target, disrupt, or augment PPIs would have wide utility both in fundamental cell biology and biomedical applications. A relatively straightforward and widespread PPI is the alpha-helical coiled coil (CC). CCs are assemblies of 2 or more alpha helices that form rope-like structures. Although CCs come in many different forms we understand the sequence-to-structure relationships of CCs sufficiently to design new CCs from scratch (Woolfson J Biol Chem (2023), DOI: 10.1016/j.jbc.2023.104579). A challenge for this field is to apply this understanding to real-life applications. This project proposal will address this by designing synthetic peptides that enter eukaryotic cells and target endogenous CC proteins. In this way, we will develop new reagents for pinpointing proteins of interest in cells for high-resolution in situ structural biology, and for altering the functions of the targeted proteins in specific and predictable ways.

Targeting CCs has several advantages: First, we understand CC assembly sufficiently well to design synthetic or de novo coiled coils with confidence (Woolfson J Biol Chem (2023), DOI: 10.1016/j.jbc.2023.104579). Second, stable and highly specific CCs can be made from short peptides (e.g., natural leucine zippers of ≈30 residues). This is an advantage for design as it renders CC peptides accessible by chemical synthesis. Third, CCs are found widely throughout biology where they direct PPIs ranging from the leucine-zipper transcription factors, through motor-protein assembly, and to large structural assemblies like intermediate filaments (IFs) that contribute to cell shape and dynamics. Thus, with the right tools, there is considerable potential to target the "coiled-coilome" for useful purposes.

This project will leverage this understanding to design synthetic CCs that target natural CCs directly in living cells. It will exploit our recent discovery that synthetic CCs can be designed to penetrate human cells and bind cytoplasmic proteins tagged with a second complementary de novo CC (Rhys et al. Nature Chem Biol (2022), DOI: 10.1038/s41589-022-01076-6). However, this new project will drop the need for de novo tags and target proteins of interest in cells directly. To do this, we will focus on endogenous proteins with predicted CC regions, which we estimate to be of the order ≈2000+ proteins, and design cell-penetrating peptides that bind to them directly. As a proof of concept, we will start with intermediate filament proteins that we have identified have a potential Achilles' heel for us to target.

Our aim as the SWBio DTP is to support students from a range of backgrounds and circumstances. Where needed, we will work with you to take into consideration reasonable project adaptations (for example to support caring responsibilities, disabilities, other significant personal circumstances) as well as flexible working and part-time study requests, to enable greater access to a PhD. All our supervisors support us with this aim, so please feel comfortable in discussing further with the listed PhD project supervisor to see what is feasible.