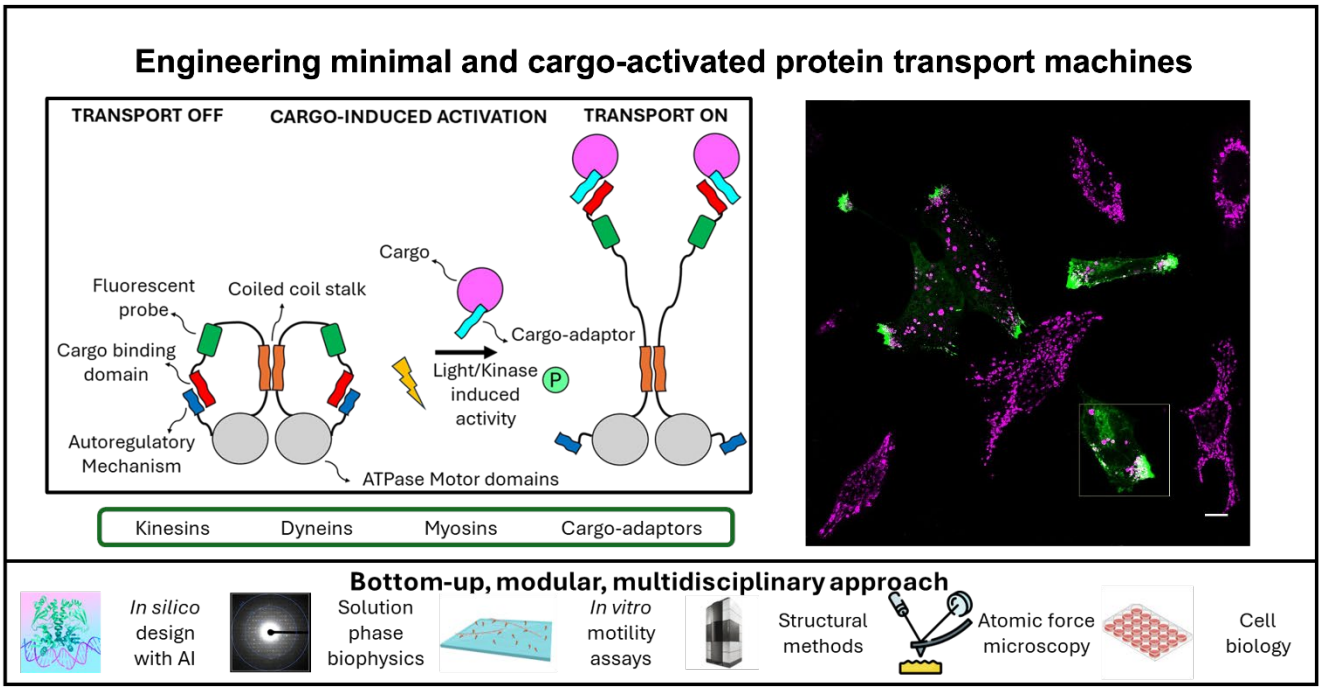
Engineering minimal and cargo-activated protein transport machines

Supervisory team:
Main supervisor: Dr Jessica Cross (University of Bristol)
Second supervisor: Prof Dek Woolfson (University of Bristol)

Collaborators: Prof Mark Dodding (University of Bristol)

Host institution: University of Bristol

Project description:
Molecular motors are essential for life and efficiently transduce chemical energy to mechanical work. This project aims to elucidate the requirements for motility and energy transduction in motor proteins. You will apply a modular approach to engineer a synthetic motor from the bottom up, understanding the minimal components needed for regulation and motility and generating new engineered machines for applications in drug-delivery and building synthetic cells.



This project builds on a proven collaboration across the labs (Relevant publications DOIs: 10.1016/j.ceb.2019.02.010, 10.1016/j.chembiol.2021.03.010, 10.1101/gad.348691.121, 10.1126/sciadv.abg6636, 10.1038/s41589-022-01076-6, 10.1126/sciadv.abp9660, 10.1038/s41589-024-01640-2), with a PhD student who has established a minimal motor system with engineered autoregulation. Building on the scaffold of an ATPase motor domain from a natural kinesin protein, we have engineered de novo designed autoregulatory elements to supress enzyme activity, leaving it poised for ligand-induced activation. Here, you will extend this work by probing natural ATPase motors to optimise the activity. You will seek to develop motors with different processivities, directionalities and that travel on different tracks (e.g. based on natural kinesin, dynein and myosin motor domains), ultimately aiming to deliver a bi-directional and regulated transport machine.

To tackle this, you will introduce well-characterised de novo designed coiled-coil protein modules from the Woolfson lab to replace the complex coiled-coil scaffold of natural motor proteins with minimal components for assembly, autoregulation and cargo-binding. The potential to fine-tune the stability, length and oligomeric state and to

introduce heteromeric systems will allow you to optimise and expand the functionality of your designs. In addition, you will seek to include switches for light and phosphorylation dependent activation. To couple these well-characterised individual components, you will optimise linkers to allow binding and required dynamic flexibility whilst still imposing sufficient steric constraints on the motors to inhibit processive motility. During this project, you will develop skills in computational protein design, molecular biology, cell biology, and advanced cell imaging techniques. This research will deliver self-regulated, cargo-activated, protein machines that are responsive to activation by both soluble proteins and membrane-bound organelle cargoes and can perform transport functions within the complex cellular milieu. Engineered autoregulation and cargo-activation will be an important component of bioengineered cells with de novo designed enzymes, and so principles learned in this research will have applications throughout engineering biology. In addition, this project will address a key unmet protein design challenge in how best to couple domains to achieve cooperative functionality in a single machine.

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.