iCase Project / AY 2023 -2024

Optimization and characterization of functionally active anti-Cdc42/Ras peptides

Supervisor: Dr Darerca Owen (do202@cam.ac.uk)

Department/Institute: Biochemistry

Industrial Partner: Discovery Science, AstraZeneca

Research area: Biologics development

Project outline:

Ras-driven cancers represent a large percentage of human malignancies. Although some progress has been made recently targeting specific mutations, attacking Ras proteins therapeutically has been extremely challenging. A second small G protein, Cdc42, is involved in Ras signalling and expression of the Cdc42 binding domain from the Cdc42 effector ACK, in cancer cell lines, reverses Ras signalling in those cells. This opens a new avenue for targeting Ras via inhibition of Cdc42-regulated signalling pathways and developing cellular probes to dissect Ras signalling.

We engineered three 16-mer peptides that bind to Cdc42 with mid/low nM affinity and with exquisit specificity over other small G proteins. One representative entered cells when tethered to a cell-penetrating sequence and inhibited both Cdc42/ACK and ERK signalling. This cyclic peptide contains an essential disulphide bridge, which can be rendered permanent by substitution with a thioether bridge, a modification which improves in-cell stability. Introduction of a homocysteine bridge in combination with several selected mutations have resulted in second generation peptides with increased affinity for Cdc42 (Including W14A). We have solved the structures of three second-generation peptides and the Cdc42–W14A complex.

We will now move forward with development of these cyclic peptides as cellular probes to aid understanding of Ras and Cdc42 signalling. Our ultimate goal however is to develop these peptides into potential therapeutic leads.

Expected key outcomes:

- High affinity peptide leads optimized for cellular entry and pharmacokinetic profile.
- Peptides profiled for efficacy in appropriate in vivo mouse models of cancer.
- High quality publication(s), sharing progress with the wider scientific community.

BBSRC DTP main strategic theme: Transformative technologies

BBSRC DTP secondary strategic theme: Bioscience for an integrated understanding of health