**iCASE Project / AY 2026 -2027**

# Evolving natural peptide scaffolds for pharmacological tools and therapeutics

**Project Reference:** ICS-PHA-PM26

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**Industrial Partner:** AstraZeneca

**Main BBSRC strategic theme:** Transformative technologies

**Secondary BBSRC strategic theme:** Understanding the rules of life

**Project outline:**

Ion channels and GPCRs are high-value drug discovery targets. However, achieving selectivity between closely related isoforms using small molecules remains challenging. Alternative antibody biologics bind a larger epitope and achieve higher specificity but have limited success in inducing desirable modulatory effects against membrane proteins with small extracellular loops. In contrast, natural toxin peptides can ensure high specificity and strong functional effects, having already proven themselves to be potent and selective modulators of ion channels and GPCRs[1,2]. However, many such peptides possess intricate arrangements of stabilising disulphide bridges which constitute a barrier to production from recombinant cell expression platforms due to disulphide scrambling causing misfolding. Chemical synthesis is used for accurate production but is slow, expensive, and inaccessible. Facile recombinant production would be a considerable advantage for broad accessibility and engineering. We recently developed a robust recombinant expression platform that improved peptide production from low or no yield to high yield for three formats with distinct Cys-bridge patterns[3]. Peptides were stable, functional and selective, but potency was typically reduced 100-fold versus synthetic toxin due to disulphide scrambling reducing the proportion of correctly folded copies.

This project will further advance our platform by generating “easy-fold” scaffolds which will correctly fold with higher efficiency and so improve potency. We will create a yeast surface-display peptide library of millions of variants. Structure-guided mutations will be focused on the peptide scaffold core within and around the Cys bridges. The peptides will be known voltage-gated sodium channel (NaV) modulators that hold promise for the treatment of chronic pain conditions, such as ProTxII, already validated in our expression platform[3]. A Nav channel bait, already developed in the Miller lab, who have proven experience in membrane protein antigen production for generating protein binders[4], will enrich the best binding peptides, i.e. those that fold the most accurately and reliably, by yeast display panning.

Enriched binders will be sequenced and recombinantly expressed for downstream characterisation. The student will test peptides at Astra Zeneca (AZ) for functional effects on NaVs supported by Dr Liz Roberts, Senior Director Mechanistic Biology and Profiling. This represents a considerable advantage because AZ have hard-to-produce stable NaV cell lines combined with advanced automated

electrophysiology robotics such as the Synchropatch 384 and orthogonal platforms such as the SSM Surfer for high throughput functional screening of peptide variants in microlitre volumes, something not possible in Department of Pharmacology.

Overall, this method will identify new “easy-fold” scaffolds for straightforward recombinant production of natural peptides that retain high potency. The project will provide holistic insights through sequence enrichments, functional target engagement, and additionally the solving of cryo-EM structures of peptide-channel complexes to explain the molecular basis for toxin scaffold enhancement, with which the Miller lab has proven expertise[5]. The development of these “easy-fold” scaffolds will represent a major advancement in the future engineering and production of natural peptides for research and therapeutic applications.

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