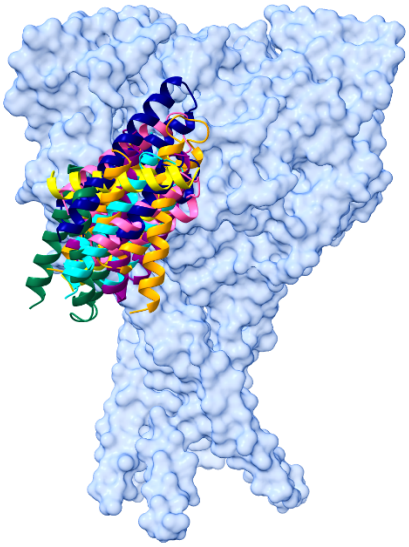
Characterisation of *de novo* designed peptides to target pain & stroke



Background:
Acid-Sensing Ion Channels (ASICs) are proton-gated cation channels crucial for fear and pain processing, and synaptic plasticity, the neurochemical foundation of learning, and memory.[1] However, ASICs remain underexplored as therapeutic targets despite their increased attention in the treatment of disorders such as ischemic stroke and pain.[1] Our objective is to develop novel, highly selective, and easily synthesisable peptides capable of modulating hASICs for potential use as therapeutics. We design *de novo* peptides generated by the machine learning tool RFdiffusion[2] and hundreds of these *de novo* peptides will be expressed, biophysically characterised, screened in automated patch clamp assays to identify ASIC modulating peptides.

Project:
The aim of the Master project is the expression and electrophysiological characterisation of the modulating peptides. The master student will introduce single mutations into the peptides and compare the potency of these mutated peptides to the non-mutated peptides in two-electrode voltage clamp or patch clamp experiments. This approach will pinpoint and confirm the key interaction sites responsible for the binding and modulation, and therefore contribute to the identification of pharmacologically accessible sites of hASICs.

Methods:
Molecular biology, electrophysiology, protein expression, pharmacology

References:

1. Heusser, S.A. & Pless, S.A. Acid-sensing ion channels as potential therapeutic targets. *Trends Pharmacol Sci* **42**, 1035-1050 (2021).
2. Watson, J.L. *et al.* De novo design of protein structure and function with RFdiffusion. *Nature* (2023).