Protein Choreography of CRISPR/Cas9: How do genome editing enzymes move in order to function?

Supervisory team: Dr Jonathan Phillips (Primary supervisor, LSI Exeter); Prof. Marc Goodfellow (LSI Exeter); Dr Fabrice Gielen (LSI Exeter); Dr Remy Chait (Biosciences/LSI Exeter); Prof Jonathan West (Institute for Life Sciences Univ. Southampton); Prof. Eamonn Reading (School of Biological Sciences Univ. Southampton).

Essential background: Genome editing enzymes, first characterised as molecular defences in bacteria, now drive transformative advances across biology, biotechnology and medicine. Their ability to make precise, programmable changes to DNA is revolutionary – yet off-target cleavage remains a major barrier to clinical translation. Understanding the catalytic mechanisms behind these errors is essential to unlock the full potential of genome editing and to design safer, more specific next-generation tools.

Aims: This highly interdisciplinary PhD will uncover the structural pathways of CRISPR/Cas9 catalysis – learning how these large proteins move to function and how certain movements lead to off-target effects. You will identify the critical 'molecular joints' required for activity and re-engineer them, aiming to develop enzymes with enhanced specificity and efficiency.

Research activities: You will create a coupled loop between cutting-edge structural proteomics and mathematical modelling. Using non-equilibrium hydrogen/deuterium-exchange mass spectrometry (HDX-MS) with prototype robotics and custom microfluidics, you will observe functioning Cas9 with per-amino-acid, per-millisecond spatiotemporal resolution. Dynamical models trained on this experimental data will simulate atomistic 'molecular movies' of CRISPR/Cas9 in action, identifying dynamic features to target by mutation for functional optimisation.

Training: You will become expert in cutting-edge structural proteomics, microfluidics, dynamical mathematical modelling and generative AI tools (e.g. RFdiffusion). You will also develop highly transferable skills in molecular biology, recombinant protein production and scientific communication, building your independence during and beyond the PhD.

More information: Please contact Dr Jonathan Phillips (jj.phillips@exeter.ac.uk) and see The Protein Choreography Group website (https://lsi.exeter.ac.uk/groups/phillips-group) for more information.