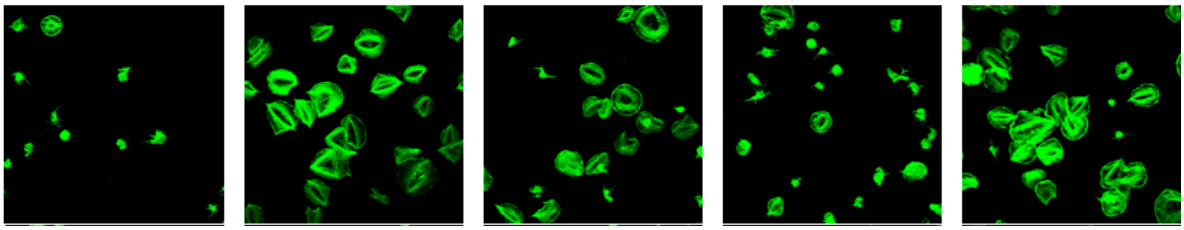

PhD studentship available in the Hers lab!

Start date: 1st of October 2021
Deadline for applications: Friday the 29th of January
Duration: 3 years

https://www.findaphd.com/phds/project/targeted-protein-degradation-as-a-novel-approach-to-study-protein-function-in-human-platelets/?p128506

We are looking for an enthusiastic PhD student with a BSc degree in Chemistry, Pharmacology, Physiology, Biochemistry or related subject for our NC3R funded PhD studentship, starting in 2021. The project involves novel ways to modulate platelet function and will provide the opportunity to be trained in a wide range of techniques. If you are interested in the project (see description below) and have further questions, please do not hesitate to contact Prof Ingeborg Hers (i.hers@bris.ac.uk).

Targeted protein degradation as a novel approach to study protein function in human platelets

Platelets are small cells in the blood that are that play an important role in stopping a bleeding but when inappropriately activated also contribute to thrombosis and cardiovascular disease. One of the complications with studying how platelets maintain normal haemostatic control and/or promote thrombosis is that they lack a nucleus thereby prohibiting genetic approaches to reduce protein levels. Most of our present knowledge therefore derives from genetic mouse models and pharmacological targeting of signaling pathways, each having its own drawbacks associated with species differences and pharmacological non-specificity.

Here we propose to optimise a protein degradation approach in human platelets using rationally designed small molecule degraders to investigate signaling pathways involved in their haemostatic and thrombotic function. We will employ small heterobifunctional molecules called PROTACs (PRoteolysis TArgeted Chimeras) that target proteins for ubiquitination leading to proteasomal degradation. We recently made the discovery by proteomic analysis that a generic tyrosine kinase leads to potent and specific degradation of BTK kinase within hours, demonstrating that human platelets have the complete proteasome required for degradation. These are exciting findings as it is the first time that a human platelet 'knockout' has been generated. In this proposal, we will expand these observations and design, generate and optimize PROTACs against BTK kinase in order to develop a highly efficient technology to study signaling pathways in human platelets. We

anticipate that the use and optimalisation of PROTACs will be transformative to the platelet research community and significantly reduce the use of genetic mouse models.

This PhD studentship is funded by NC3R for the replacement, refinement and reduction of animal use in Research. The PhD student will be part of the Bristol Platelet Group based in the School of Physiology, Pharmacology and Neuroscience and work in close collaboration with the group of Varinder Aggarwal in the School of Chemistry on compound design. We are looking for a PhD student with an interest in medicinal Biochemistry/Biology and has a degree in chemistry, biochemistry, pharmacology or related subject area. The student will be trained in a range of experimental techniques, including chemical design, permeability testing, cell culture, platelet isolation, platelet aggregation, FACS experiments, in vitro thrombosis flow studies, western blotting, confocal microscopy and proteomics.