Mechanistic analysis of DNA helicases using nanopore-based single molecule assays

Supervisory team:
Main supervisor: Prof Mark Dillingham (University of Bristol)
Second supervisor: Prof Mark Szczelkun (University of Bristol)
Non-academic (CASE) supervisor: Dr Mark Bruce (Oxford Nanopore Technologies)

Host institution: University of Bristol
CASE partner: Oxford Nanopore Technologies

Project description:
Next generation DNA sequencing methods such as those pioneered by Oxford Nanopore Technologies (ONT) have revolutionised biology by allowing rapid DNA sequencing at the whole organism level and impacting fields as diverse as evolutionary biology, structural and molecular biology, agriculture, diagnostics and personalised medicine. The ONT technology works by utilising an ATP-dependent DNA motor protein and a membrane embedded nanopore. As the motor delivers DNA through the pore, the base composition is determined by changes in the current across the membrane ultimately yielding accurate long read DNA sequencing data. In addition to their core uses for long-read DNA sequencing and rapid diagnostics, nanopore-based assays have also found unexpected applications in basic science. For example, because nanopore DNA sequencing is rate-limited by the activity of the motor, the sequencing traces also contain rich information on the kinetics of DNA translocation providing unique insights into the mechanism(s) of essential enzymes such as helicases.

In this project, you will integrate new DNA helicases into nanopore-based DNA sequence devices with two major goals. Firstly, we aim to improve the speed, accuracy, simplicity and robustness of nanopore DNA sequencing by using DNA helicases with novel and desirable biochemical properties. Secondly, we aim to study the mechanism of action of DNA helicases of medical interest and how they are affected by small molecule drugs or genetic mutation. Importantly, we anticipate that nanopore traces will yield unprecedented detail on the nature of the individual steps that are made along DNA and their chemo-mechanical coupling to ATP hydrolysis. Your project will be based in the laboratory of Prof. Mark Dillingham in the DNA:protein interactions Unit at the University of Bristol but will also involve close collaboration with Oxford Nanopore Technologies (1) including internships spent at their Oxford headquarters. The Dillingham lab (2) is studying helicases involved in the repair of broken DNA, including bacterial enzymes that are considered attractive targets for antibiotics and human enzymes implicated in genetic diseases including cancer. For further details and examples of our recent work see our website or contact the laboratory (2).

(1) https://nanoporetech.com/ (2) https://research-information.bris.ac.uk/en/persons/mark-s-dillingham

Our aim as the SWBio DTP is to support students from a range of backgrounds and circumstances. Where needed, we will work with you to take into consideration reasonable project adaptations (for example to support caring responsibilities, disabilities, other significant personal circumstances) as well as flexible working and part-time study requests, to enable greater access to a PhD. All our supervisors support us with this aim, so please feel comfortable in discussing further with the listed PhD project supervisor to see what is feasible.