Characterisation and inhibition of snake venom metalloproteinases for next-generation antivenom

Supervisory team:
Main supervisor: Prof Christiane Schaffitzel (University of Bristol)
Second supervisor: Prof Alastair Poole (University of Bristol)

Collaborators: Prof Nicholas R. Casewell (Liverpool School of Tropical Medicine), Prof Loic Quinton (University of Liege, Belgium), Dr George Omondi (Kenya Snakebite Research & Intervention Centre), Prof Andrew Mumford (University of Bristol)

Host institution: University of Bristol

Project description:
Snake venoms are mixtures of toxins, including snake venom metalloproteinases (SVMPs), which cause severe snakebite effects like tissue damage, bleeding, and coagulation disorders, often leading to death or disability. SVMPs and their disintegrin domains target various molecules, such as blood coagulation factors, platelet receptors, and basement membrane components. SVMPs are present in virtually all snake venoms and can represent more than half of the protein content of viper venoms. Snakebite is a major public health concern, affecting millions of people annually, resulting in ~130,000 deaths and ~400,000 disabilities. Our aim is to use modern biotechnology to produce safe and efficient antivenom treatment. Importantly, preclinical studies in mice show that neutralizing SVMP toxins prevents lethal effects and tissue damage induced by different snake venoms, making SVMPs valuable therapeutic targets. Characterisation of the produced proteins will provide valuable insights in their function and potential biomedical application: for instance the SVMPs Ecarin and RVV-X are regularly used as standard components in coagulation tests in the clinics.

You will use state-of-the-art protein engineering and expression technology to produce SVMPs in baculovirus insect cell expression system (Schaffitzel lab). The purified SVMPs and disintegrin domains will be characterised which includes testing their efficiency in platelet aggregation and blood clotting (Poole lab). For instance, identifying new toxins that target blood clotting factors VIII and IX could enable the development of better clinical tests for diagnosis of bleeding disorders like haemophilia and von Willebrand's disease. Subsequently, you will use the SVMPs and disintegrins as targets in ribosome display selections to generate specific nanobodies (small antibody fragments) that efficiently bind and neutralise these toxins (Schaffitzel lab). The neutralisation efficiency and cross-reactivity of the selected nanobody will be subsequently assessed by enzyme-linked immunosorbent assays (ELISA), blood clotting and platelet aggregation assays.

The project offers you training in eukaryotic protein expression and purification, ribosome display selection, and methods for studying platelet aggregation, blood coagulation, and fibrinolysis. You will benefit from our ongoing collaboration with the Liverpool School of Tropical Medicine (LSTM, hosting UK's largest collection of venomous snakes), with University of Liege (venom and Mass spectrometry experts), and our combined expertise in the School of Physiology, Pharmacology & Neuroscience and the School of Biochemistry in Bristol, which offers a dynamic, inclusive and supportive environment.

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.