Design of new fluorescent sensors for measuring heme in cells

Supervisory team:
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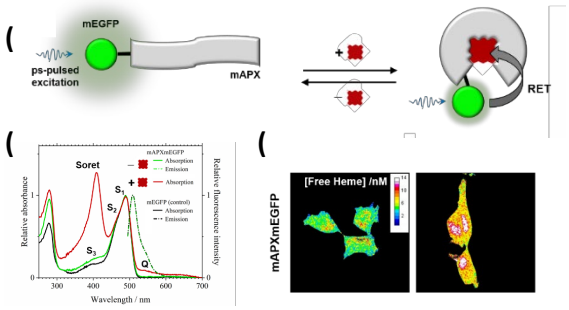

(A) Design of fluorescent heme-binding sensors. (B) Characterisation of sensor.

Project description:
Heme is a small organic molecule which contains iron at the centre. Heme is essential for the survival of virtually all living systems - from bacteria, fungi and yeast, through plants to animals. No eukaryote has been identified that can survive without heme. It is involved in the control of many fundamental biological processes - such as oxygen transfer, redox control, respiration, photosynthesis, and drug metabolism. The role of heme in biology appeared to be well understood up until the most recent years, but we have now demonstrated that heme can also act as a regulatory molecule in the cell, regulating complex signalling events. The role of heme in biology is, therefore, much more com-plicated than previously imagined. To act in these new roles, heme concentrations need to adapt to different cellular demands, and heme needs to move around the cell from its place of synthesis to other locations. This presents logistical problems for the cell. Heme is insoluble in water, so it cannot be moved around on its own. Heme is also toxic in high concentrations so cells cannot simply hoard supplies of heme or let it loose in uncontrolled concentrations. How does biology solve this problem? Where is heme located? What are the concentrations and do they vary under different cellular conditions? When and how is heme moved, and which proteins are involved in moving it? We intend to provide the first answers to these questions.

We will build new fluorescently-tagged heme sensors that can be targetted to different parts of the cell (using signal pepties in recombinant proteins); these sensors will report on heme concentrations and will reveal heme locations under different cellular conditions. The project is a collaboration between the Schools of Chemistry and Biochemistry, and will be wide-ranging in its approach; you will collaborate extensively with scientists from different disciplines. You can expect to become exposed to a wide range of methodologies, including molecular biology, imaging techniques (FRET, FLIM), protein expression and cell culture, protein crystallography, computational approaches to protein design and reactivity, enzyme kinetics (steady state and pre-steady state) and various spectroscopies (e.g. EPR, uv-visible). The overall aim is to use all of these methods to build the first detailed picture of cellular-heme dynamics and mobilisation.

See for example some of our other work in this area:
Proc. Natl. Acad. Sci, USA. 2021, 118, e2104008118;
Proc. Natl. Acad. Sci, USA. 2020, 117, 6484-6490;
Proc. Natl. Acad. Sci. 2019, 116, 19911-19916;
Nature. Comm. 2018, 9, 907.
Nature Comm. 2016, 7, 13445;
Proc. Natl. Acad. Sci. 2016, 113, E5144-5152;
Proc. Natl. Acad. Sci. 2016, 113, 3785-3790;
Science, 2014, 345, 193-197.

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.