A FULLY-FUNDED 3 YEAR PHD SCHOLARSHIP IS AVAILABLE FROM OCTOBER 2018

Developing artificial hemoglobin-based blood substitutes: Understanding the mechanisms and effects of targeting damaging oxidative reactions and nitric oxide scavenging.

Background:
The use of cell-free synthetic Hemoglobin (Hb) is an ideal starting material for blood substitutes or oxygen therapeutics. However, these Hemoglobin Based Oxygen Carriers (HBOCs) display an inherent capacity to induce oxidative reactions, causing cell and tissue damage. They also scavenge nitric oxide (NO) leading to hypertension. At Essex we have engineered HBOCs that are designed to decrease the intrinsic damaging oxidative reactivity of Hb through enhanced ferryl and ferric reductase activities. In addition, we have also developed HBOCs with decreased NO scavenging without associated loss of heme from the protein.

Aims:
With the recent development of novel HBOCs at Essex, we have a much firmer understanding of the ability of HBOCs to induce oxidative damage and the key technologies to prevent such damaging reactions. Nevertheless, there are still unresolved fundamental questions. For example, engineered electron pathways using model globins can exhibit much higher ferryl reduction rates compared to engineered HBOCs based on human adult or foetal Hb (1,2). Furthermore, the addition of mutations designed to decrease NO scavenging significantly alters the stability (and hence reactivity) of the high oxidation states of the HBOCs. Therefore, further understanding the biochemical mechanisms of electron pathways in globins and the effects of multiple mutations on the redox chemistry of Hb would underpin the continuing development of HBOCs. The studentship will support the future development and steering of the blood substitute project towards commercialisation and clinical studies.

Objectives:
- Examine the effects of NO scavenging mutations on the redox activity of HBOCs, specifically why these mutations lead to a destabilisation of the higher oxidation states of the heme iron and what effect this has on the capacity of these proteins to induce oxidative damage.
- Investigate why globins such as myoglobin from *Aplysia faciata* can exhibit significantly more enhanced ferryl reductase activities compared to our HBOCs and whether high rates of ferryl reduction and enhanced ferric reductase activities correlate with changes in the redox potentials of the heme iron.
- Examine intermolecular and intramolecular electron/radical migration through the generation and study of hemoglobin redox hybrids.
- Explore the dynamics of heme loss in various mutations to better understand what influences rapid reduction of the heme iron and heme binding.
- Determine the consequence of mutations in lead HBOCs on the Bohr effect. The Bohr effect can be an important mechanism of releasing oxygen under conditions of acidosis associated with ischemia, an effect often overlooked in the development of HBOCs.

References:

1. Reeder B.J., Svistunenko D.A. Cooper, C.E. and Wilson M.T. “Engineering tyrosine-based electron flow pathways in proteins: the case of Aplysia myoglobin” J. Am. Chem Soc. (2012) 134, 7741-7749.
2. Silkstone, G., Silkstone, R.S., Wilson, M.T., Simons, M., Bulow, L., Kallberg, K., Ratanaspo, K., Ronda, L., Mozzarelli, A., Reeder, B.J., Cooper, C.E. “Engineering tyrosine electron transfer pathways decreases oxidative toxicity in hemoglobin: implications for blood substitute design” Biochem J. (2016) 473, 3371-3383

Entry requirements and application procedures
Informal queries may be addressed in the first instance to Dr Brandon Reeder reedb@essex.ac.uk Applications should be submitted electronically by **28th February 2018**. See https://www.essex.ac.uk/pgapply/enter.aspx for details. The intended start date for this 3-year, fully-funded PhD studentship is 4th October 2018. This scholarship will be to the value of £14,553 per annum plus UK/EU tuition fees.

Please note: International students need to have additional funding to cover the difference in tuition fees which is £11,815.00, evidence will be requested that you have these additional funds.

Applicants should write 500 words explaining why they are interested in this project and submit this with their CV.

This scholarship is generously supported by a bequest from the estate of Professor Peter Nicholls (https://www.theguardian.com/theguardian/2014/dec/30/peter-nicholls-obituary**)**

The University of Essex
In the recent Research Excellence Framework 77% of research at the University of Essex research is 'world leading' or 'internationally excellent' (REF 2014).We offer world-class supervision and training opportunities and our research students work at the heart of an internationally-acknowledged and well-connected research community. In the 2013 Postgraduate Research Experience Survey, 84% of respondents said that they were satisfied with the quality of their research degree. At Essex we win awards for our pioneering student support schemes. We are the most recent winners of the prestigious *Times Higher Education* award for Outstanding Support for Students. Essex is a genuine global community. With more than 130 countries represented within our student body, and 40% of our students from overseas, we are one of the most internationally-diverse universities in the UK.