**BBSRC MIBTP Studentship Project**

**September 2023**

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| **Project Title** | Control mechanisms of IDO1 in cancer cells |
| **Project Summary** | |
| Indoleamine 2,3-dioxygenase 1(IDO1) is a heme-containing enzyme involved in the degradation of tryptophan to kynurenine. Cancer cells upregulate IDO1 to escape normal immune response and, in many cases, a high expression of IDO1 is connected to poor prognosis. This makes IDO1 an attractive drug target, however, this project will be concerned with addressing a fundamental question concerning how the activity of IDO1 could be modulated in both healthy and diseased tissue.    Heme is a versatile small molecule that is pivotal to the functionality of a large number of heme proteins; for example, it is responsible for binding oxygen in the globins, and facilitating charge transfer process in the cytochromes. Heme is also pivotal to the enzymatic activity of IDO1. A number of studies have shown1, 2 that IDO1 is predominantly expressed in an inactive, heme-free, form in cells. Because the catalytic activity of IDO1 depends on the presence of heme, it is important to understand the cellular processes that control the availability of heme for binding to IDO1 and hence the activity of this enzyme for conversion of tryptophan to kynurenine.    This project will seek to understand how heme availability changes in cancer, or adjusts to the increasing demand for heme in disease conditions that resulting in higher expression levels of IDO1. We will also investigate exactly how heme is delivered to IDO1; for example, are specific chaperone proteins necessary for the insertion of heme into the protein? We will attempt to answer these questions in this project using structural (cryoEM and X-ray crystallography), physical (spectroscopy and microscopy) methods and computational analysis. A PhD student will gain a broad range of interdisciplinary skills in structural biology, chemical biology and biophysics in order to address an important question in cancer biology.  Techniques that will be undertaken during the project   * Molecular Biology (cloning & mutagenesis) * Protein expression and purification (bacterial and mammalian) * Enzyme kinetics * Confocal and fluorescent microscopy * Protein crystallisation * Structure determination (X-ray crystallography & cryo-EM)   BBSRC Strategic Research Priority: Understanding the Rules of Life - Structural Biology | |
| **References** | |
| 1. M. T. Nelp *et al.* (2018), *Proceedings of the National Academy of Sciences* **115**, 3249-3254.  2. S. R. Thomas *et al.* (2001), *The Journal of Immunology* **166**, 6332-6340. | |