PROJECT SYNOPSIS, School of Life Sciences
Director of studies: Dr Mark Odell

Project title: Parasite DNA ligase inhibition

Background and synopsis

In collaboration with the European Screening Port we are seeking to identify inhibitors of *Trichomonas* and *Plasmodium* DNA ligase enzymes, as therapy against these organisms.

Trichomonas vaginalis, a sexually transmitted parasite that leads to infertility and enhanced acquisition of AIDS, infects 180 million people worldwide each year. In the case of *Trichomonas* there is only a single front line therapeutic agent, Metronidazole. Unlike other eukaryotes whose genomes have been studied, parasitic organisms have only a single DNA ligase enzyme, instead of 2 in yeasts, insects, plants and 3 in mammals. The single ligase of the parasite is responsible for sealing all DNA breaks as a result of DNA replication and repair. We have cloned and characterised this DNA ligase from *Trichomonas* and shown that its biochemical properties are very similar to the single DNA ligase of *Plasmodium falciparum*.

Ligase enzymes are essential in all cell types for manipulation of DNA. Whilst having a conserved catalytic core, DNA ligases employ differing mechanisms in interactions with DNA. Three inhibitors, identified in 2008 designed to inhibit human ligase binding to DNA, have been shown to exhibit anti-cancer activity. Peter Moody and I have developed and patented a ligase inhibitor screen that detects modulation of ligase:DNA interaction through use of surface plasmon resonance (SPR). In collaboration with the European Screening Port (ESP) we have developed a high-throughput version of this assay that can identify inhibitors of ligase-DNA interaction. It is our belief that molecules that target the DNA binding step will be capable of selective action against the ligase of parasite origin.

Working with the ESP the student will undertake a preliminary screen with *Trichomonas* DNA ligase. Candidate inhibitor compounds will be evaluated against the *Trichomonas* organism in the laboratory of Pamela Greenwell who is a leading expert in *Trichomonas* biology. In parallel, the student will begin studies with Drs Odell and Moody to determine structure of the *Trichomonas* enzyme and to characterise its mode of DNA binding. Compounds that exhibit good *in vitro* selectivity against *Trichomonas* ligase when assayed in parallel with human ligase enzymes, will then be refined to increase potency using biophysical and structural data combined with studies on the organism.

The student will gain knowledge of expressing and purifying proteins, X-ray crystallographic methods and computational means for solving protein crystal structures. Additional biophysical techniques including SPR and Attana micro-balance technology to study DNA binding, isothermal calorimetry and protein mutagenesis will be employed together with growth and manipulation of *Trichomonas vaginalis*. Screening against purified *Plasmodium* ligase in collaboration with ESP will also be undertaken to identify potential lead compounds that can be employed against malaria. The student will be expected to join key professional societies (British Crystallographic Association and the Biochemical Society) and to present their work at national and international meetings.

Supervisory Team and Research Environment

Supervisor Name	Role (DoS, 2nd Supervisor, 3rd Supervisor)	No. of successful PhD/ MPhil supervisions	Current student load for 2010/11 (FTE)	School (for cross School projects)
Mark Odell	DoS	3	1/2	Life Sciences
Pam Greenwell	2nd	13	2 Part time	Life Sciences
Peter Moody	3rd	5	1	Biochemistry

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