Introduction

Human impact on the environment presents an ongoing problem; with approximately 85,000 known chemicals being used today, we need to assure the safety of their use is assessed and validated. Various Cytochromes P450 (CYPs) are capable of metabolizing xenobiotic substances, including potential environmental toxins. Selecting and expressing CYPs from model organisms that are orthologous to the major drug metabolizing CYPs found in humans should allow for comparison of their functions and assessment of their capacity in drug detoxification. Environmental bio-indicator species (EBS) e.g. Danio rerio (Zebrafish) or Oncorhynchus mykiss (Rainbow Trout) are of particular interest as they are often used as model species for monitoring the environment and have similar biological pathways to other species. By establishing the relationship between selected environmental toxins and the products formed by action of EBS CYPs orthologous to human drug metabolizing CYPs, we will ascertain the range of substrates, discover if the metabolites are similar to their human counterparts, and establish if metabolites are potentially toxic and/or inhibit or induce orthologue CYP activity.

Cytochromes P450

CYPs are found in eukaryotes, numerous prokaryotes and also in the archaea. CYPs in the human hepatic system have key roles in Phase 1 drug metabolism. They mediate diverse (mostly oxidative) reactions on a large range of substrates. They are responsible for the biotransformation of xenobiotics and ~75% of pharmaceuticals are metabolised by CYPs. During Phase 1 metabolism the biotransformation of the compound occurs, often involving the addition of an oxygen atom (e.g. as a hydroxyl group) by a CYP enzyme, resulting in a more hydrophilic product. However, CYP-dependent oxidative metabolism can also result in other outcomes, including e.g. demethylation/dealkylation, sulfonidation, dehydroxylation and epoxidation, as well as more “exotic” transformations including isomerization, decarboxylation and C-C bond formation. CYPs thus have diverse catalytic activities and have been described as “Nature’s most versatile catalysts”.

Environmetally Sensitive Species and their CYPs

Several species were selected as being of particular interest, since they are often used as model organisms in research projects, and have also been used as bio-indicator species for environment toxicology. These species play an important role in monitoring environmental pollution as they demonstrate sensitivity to changes in aquatic environments. The use of biochemical markers such as cytochromes P450 helps determine the mechanism of toxicity of a pollutant, providing insights into the effects of the pollutant and its potential metabolites on the organism. There is an increasing emphasis on understanding the structure and function of key enzymes that are conserved across species. Selecting key species that demonstrate similarity in relevant biological pathways to other species (e.g. drug metabolism) can expedite the use of these non-traditional species as toxicological models. In this project, we will examine species possessing orthologues of human CYP genes, and establish if these orthologues may have conserved functions in metabolising xenobiotics and/or can make non-human type metabolites that cause toxicity to environmentally sensitive organisms.

Conclusions and Ongoing Work

Cytochrome P450s have an important and evolving role in both pharmaceutical and traditional species as model species in toxicology. The orthologues of key CYPs found in these species would be useful as a tool for understanding the role of cytochrome P450s in drug metabolism and toxicology. This project would also be useful for understanding the role of cytochrome P450s in the metabolism of environmental pollutants and the potential toxicity of these compounds. The results of this project would be useful for understanding the role of cytochrome P450s in drug metabolism and toxicology.