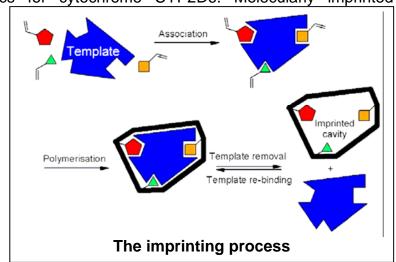
Chemical and Computational Modeling of Substrate Recognition in Cytochrome P_{450} CYP2D6

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Most drugs are metabolised by the cytochrome P450 family of enzymes and as a result the half-life of a drug within the body is linked with its rate of cytochrome P450 mediated biotransformation. To complicate matters some P450s, such as CYP2D6, are subject to population-based polymorphisms. Thus it is crucial that potential CYP2D6 activity is identified amongst libraries of drug candidates.

This project will build on our success to date¹ in using molecular imprinting to prepare fluorescent polymeric binding mimics for cytochrome CYP2D6. Molecularly imprinted

polymers (MIPs) are crosslinked polymers containing bespoke functionalised cavities arising from the temporary inclusion of template molecules. Binding sites are created which have a memory for the templates both in terms of shape and functionality. With matching appropriate selection of template the imprinted cavity resembles the active site of the enzyme. Fluorescent MIPs have the benefit of a fluorophore in their cavities that respond to the presence of bound test compound by



a change in their fluorescence output, which is the heart of the assay.

The project will involve the design, synthesis and evaluation of the next generation of fluorescent MIPs with a view to optimization of CYP2D6 binding prediction. Much of the effort will go into the design and synthesis of an appropriate template that can represent the internal shape and functionality of the enzyme's active site. To this end a recently published crystal structure of the enzyme² will be used as a starting point for developing a series of *in silico* models that will complement and assist in the design of the MIP-based physical models.

References

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- 2. Rowland et al, Crystal Structure of Human Cytochrome P450 2D6, *Journal of Biological Chemistry*, 2006, 281, 7614–7622.