Matt presented this poster at ISSX in October 2011.

Abstract:

Many computational methods have been developed that predict the regioselectivity of metabolism by drug metabolising isoforms of the Cytochrome P450 class of enzymes (P450) [1-5]. Here we describe recent developments to a method for predicting P450 metabolism that combines quantum mechanical (QM) simulations to estimate the reactivity of potential sites of metabolism on a compound with a ligand-based approach to account for the effects of orientation and steric constraints due to the binding pockets of different P450 isoforms.

While valuable, predicting the relative proportion of metabolite formation at different sites on a compound is only a partial solution to designing more stable compounds. The advantage of a quantum mechanical approach is that it provides a quantitative estimate of the reactivity of each site, from which additional information can be derived regarding the vulnerability of each site to metabolism in absolute terms. One such measurement is the site lability, as calculated by StarDrop™ [6], which is a measure of the efficiency of the product formation step. This is an important factor influencing the rate of metabolism and we will illustrate how this provides valuable guidance regarding the potential to redesign compounds to overcome issues due to rapid P450 metabolism.

[1] V.S. Gopaul et. al. (2009) Drug Metab. Rev. 41(s3) pp. 187-196 (abstract 242)
[2] P. Rydberg et. al. (2010) ACS Med. Chem. Lett. 1(3) pp 96–100
[3] M. Hennemann et. al. (2009) ChemMedChem 4(3) p. 657-69
[4] Jones JP et. al. (2002) Drug Metab. Dispos. 30(1) pp.7-12
[5] J. Zaretzki et al. (2011) J. Chem. Inf. Model. 51, pp. 1667–1689
[6] StarDrop
[7] Segall et al. (2010) Drug Metabolism Rev. 42(s1) pp. 324-342 (abstract P279)

A copy of this poster as available as a PDF .

Psychological research has demonstrated that reproducible biases affecting human decision-making, known as cognitive biases, threaten objectivity and balance in individual and team decision-making. Drug discovery leaders receive much conflicting advice on possible ways to improve productivity and restore the rate of successful drug launches; however with help to overcome these psychological barriers, better decision-making can enhance R&D performance [1].

We will discuss four of the common biases that have serious implications for decision-making in drug discovery (summarised below). We will suggest approaches for overcoming these, such as strategies adapted from evidence-based medicine and computational tools that seek to guide the decision-making process, encouraging objective consideration of all of the available information and explicit consideration of the impact of uncertainty in drug discovery.