In the search of CYP2D6 biomarker: In-vitro metabolism of solanidine and other steroidal alkaloids

Although Cytochrome P450 2D6 constitutes only 2-4% of total hepatic CYP content, it metabolizes approximately 20% of commonly used drugs, comprising of wide range of substrates including analgesics (eg. codeine), antidepressants (eg. paroxetine), antihypertensives (metoprolol) or anti-cancer agents (tamoxifen). The rate of CYP2D6-mediated microsomal metabolism can vary 60-fold between the individuals (poor versus ultra-rapid metabolizers) because of the polymorphic differences within the population, and in some cases may lead to adverse drug reactions (ADR). Additionally, the risk of ADRs increases with the use of multiple drugs (polypharmacy). That is why, finding a biomarker that could predict the actual CYP2D6 phenotype of individual patient is of great importance.

Recently, the amount of diet-derived solanidine (steroidal alkaloid aglycone found in potatoes) together with its metabolites SSDA and 4-OH-solanidine measured in the blood of patients was found to predict the CYP2D6 phenotype.

The proposed master thesis project will use recombinant CYP2D6 (bactosomes) expressing normal function enzyme or decreased function variants (CYP2D6*10 or *17 variant) of the enzyme and look more closely if the solanidine metabolism *in vitro* mimics the clinical observation. In order to simulate the enzyme inhibition, a strong inhibitor of CYP2D6 (fluoxetine or paroxetine) will be added to the reaction mixture.

Additionally, during the project we will check whether metabolism of 2 other plant-derived steroidal alkaloids with a similar structure: tomatidine and solasodine is also driven by CYP2D6.

This project offers the master student to learn how to design the CYP activity assay, the basics of LC-MS/MS and data analysis. What is more the student will have a chance to contribute to the fast growing ADME biomarker field.

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