Internship: Predicting paediatric exposure to pharmaceuticals using *in silico* techniques.

The internship is a collaboration between two research groups within the department of Pharmacology and Toxicology at the Radboudumc. You will be supervised by a team consisting of Hedwig van Hove (PhD student), Joyce van der Heijden (PhD student), dr. Jolien Freriksen and dr. Rick Greupink. Both PhD students will be acting as your daily supervisors. This research group works on the development of computational models to predict drug exposure in special populations, thereby using *in vitro*, *ex vivo* and *in silico* techniques. The internship is an unique opportunity to gain experience with both research focussing on laboratory work, as well as using existing (experimental) data for *in silico* approaches (computer work). The internship is expected to start in September-October and the duration is to be discussed, but takes at least 4 months.

The first part of the project you will be working on will focus on conducting experiments in the laboratory with the ultimate goal to use outcomes of the experiments as input data for the *in silico* technique. Women use medication during their pregnancy, thereby possibly exposing the foetus to these compounds. However, safety data is often lacking, since this special population is mostly excluded (for obvious reasons) in clinical trials. This results in off-label prescription of the drugs. Human placenta cotelydon perfusion experiments can be used to estimate placental transfer of a drug (see also https://radboudumc.bbvms.com/view/research/4121731.html for a demonstration video of the technique). This information can then be incorporated in a physiological based pharmacokinetic model (PBPK model) to estimate maternal and foetal exposure to the drug of interest. Ultimately, these estimations can be used to optimise dosing guidelines. You will be conducting these experiments to investigate placental transfer of thiopurines and/or some tyrosine kinase inhibitors.

The second part of the project focusses on developing a PBPK model for a drug of interest (to be determined) in a paediatric population. PBPK modelling is a bottom-up approach that integrates a large number of drug specific data, parameters on species physiology (system data), and a good understanding of all active processes affecting the pharmacokinetic properties of a drug with the ultimate goal to predict exposure. Outcomes of these predictions can be used to optimize drug dosing for paediatric patients. This is of great importance, because most clinical studies are conducted in an adult population, and dose regimens for children are extrapolated from the adult dosing advise. However, a child is not a tiny adults, since a lot of ADME parameters (absorption, distribution, metabolism, and excretion) differ between this population compared to an adult population. During the internship you will develop a PBPK model yourself using Simcyp, with the goal to predict the optimal dose of the drug of interest in different paediatric subgroups (with respect to age and disease). The outcomes will provide additional information for The Dutch Paediatric Formulary on the correct dosage of this drug, leading to a more accurate prescription of this drug in children and thus to a decreased risk of over- or underdosing.

Are you interested? Please send a short motivation + your CV to Hedwig van Hove, MSc (Hedwig.vanHove@Radboudumc.nl). You can also contact me if you have further questions regarding this internship.