Project Title:

Development of a comprehensive physiologically based pharmacokinetic (PBPK) model for drug absorption – inclusion of gut tissue distribution processes

Project description:

Prediction of drug absorption following oral administration of drugs is a very important aspects in the development of new drugs. Several (commercial) softwares on drug absorption are available, and some of these are used in pharmaceutical industries, but there is in some cases substantial room for improvement on their predictive power. Recently we have developed a comprehensive physiologically-based pharmacokinetic model for human central nervous system drug distribution, which is extensive in its physiological compartments and many processes that are explicitly addressed, which has good predictive power on drugs for which human data were available (1).

In this project a current draft version of a gut absorption model will be used as a start, and data from Janssen Pharmaceutica on multiple drugs with distinct physico-chemical properties are available for further in-depth model development of the PBPK gut drug distribution model.

1. Yamamoto Y, et al. Prediction of human CNS pharmacokinetics using a physiologically-based pharmacokinetic modeling approach. Eur J Pharm Sci. 2018 Jan 15;112:168-179.

Supervisor: Prof dr Elizabeth de Lange

Selection criteria:

- Profound understanding of pharmacokinetics
- Experience with pharmacokinetic and pharmacodynamic modelling software (NONMEN, R, Matlab, WinNonlin, or other)
- Scientific enthusiasm and persistence

Applications:
To apply for this vacancy, please send an email to ecmdelange@lacdr.leidenuniv.nl. Please ensure that you upload the following additional documents quoting the project title:

- Curriculum vitae;
- Bachelor's and master's transcripts;
- (Draft of) MSc thesis.

Deadline:

Project Title: Development of a 3-dimensional brain to predict spatial distribution of drugs in the brain

Project description:

CNS drugs development is very challenging. Drug distribution to desired locations in the CNS has many questions still unanswered and a quantitative understanding is needed to understand the complex processes that govern the pharmacokinetic profile of a drug in the brain at its target site. Recently, a comprehensive physiologically-based pharmacokinetic CNS distribution model has been developed. This model adequately predicts the pharmacokinetics of any small molecule drug in multiple CNS locations in rat and human CNS, based on drug properties (1). However, this model does not include spatial aspects of the brain. To that end, we first developed a small network of brain tissue units and capillaries (2).

In this project the 3D brain tissue units will be used to really build a 3D brain. In the 3D brain, local differences in brain tissue parameters can be incorporated in individual units to reflect local spatial differences in drug distribution, for example as a result of disease conditions. This will improve our understanding of factors that influence spatial CNS drug distribution.

1. Yamamoto Y, et al. Prediction of human CNS pharmacokinetics using a physiologically-based pharmacokinetic modeling approach. Eur J Pharm Sci. 2018 Jan 15;112:168-179.
2. Esmée Vendel, Vivi Rottschäfer, Elizabeth C M de Lange. The 3D Brain Unit Network Model to Study Spatial Brain Drug Exposure under Healthy and Pathological Conditions. Pharm Res. 2020 Jul 9;37(7):137. doi: 10.1007/s11095-020-2760-y.

Supervisor: Prof dr Elizabeth de Lange

Selection criteria:

- Profound understanding of pharmacokinetics
- Experience with pharmacokinetic and pharmacodynamic modelling software (NONMEN, R, Matlab, WinNonlin, or other)
- Scientific enthusiasm and persistence

Applications:
To apply for this vacancy, please send an email to ecmdelange@lacdr.leidenuniv.nl. Please ensure that you upload the following additional documents quoting the project title:

- Curriculum vitae;
- Bachelor's and master's transcripts;
- (Draft of) MSc thesis.

Deadline:

Project Title: Development of a CNS distribution model for large molecules

Project description:

Drug development targeting the central nervous system (CNS) has been challenging due to poor predictability of drug concentrations in various compartments within the CNS. Today, for small molecules, transport across the blood-brain barrier (BBB) and intra-brain distribution are relatively well understood, although much progress now should be made to understand the impact of diseases on these processes, as well as the link between target site distribution, target occupancy, and subsequent signal transduction processes that ultimately lead to the effects.

The large(r) molecules (typically biologics) bind to specific cell receptors that are associated with disease processes. For example, monoclonal antibodies are specialized in recognizing a very specific target. This makes such molecules of high interest to be added to investigation on the CNS drug treatment spectrum. For large(r) molecules, however, BBB transport , intra-brain diffusion and elimination, may differ substantially from that of small molecules, indicating the need for additional information to be included in the development of a CNS model for this category of drugs.

This new PhD project will deal with the characterization and mathematical description of such vesicle-based BBB transport processes would be a very important extension of the currently available comprehensive CNS drug distribution model for small molecule CNS drugs (1,2)

1.Yamamoto Y, et al. Prediction of human CNS pharmacokinetics using a physiologically-based pharmacokinetic modeling approach. Eur J Pharm Sci. 2018 Jan 15;112:168-179.

2.Yamamoto Y, et al. Predicting drug concentration-time profiles in multiple CNS compartments using a comprehensive physiologically-based pharmacokinetic model. CPT PSP. 2017 Sep 11.

Supervisor: Prof dr Elizabeth de Lange

Selection criteria:

- Profound understanding of pharmacokinetics
- Experience with pharmacokinetic and pharmacodynamic modelling software (NONMEN, R, Matlab, WinNonlin, or other)
- Scientific enthusiasm and persistence

Applications:
To apply for this vacancy, please send an email to ecmdelange@lacdr.leidenuniv.nl. Please ensure that you upload the following additional documents quoting the project title:

- Curriculum vitae;
- Bachelor's and master's transcripts;
- (Draft of) MSc thesis.

Deadline:

Project Title: Systematic in vivo approach on the influence of drug properties on drug distribution following intranasal drug delivery

Project description:

Intranasal dug delivery is an important alternative route for drugs that have difficulties reaching their central nervous system (CNS) target sites, as well as to circumvent extensive and variable first pass effect for orally administered drugs. There is, however, still a lack of systematic study approaches to understand the influence of drug properties on nasal absorption into brain and the systemic circulation, as would be needed for ultimate prediction. Recently, we have developed a human CNS drug distribution model that is able to adequately predict CNS drug distribution in human, based on their plasma pharmacokinetic profiles. For this model development we used data that were generated by a series of experiments performed in rats, for 10 paradigm drugs with distinct combinations of physico-chemical and biological properties, with or without blocking active brain barrier transport processes for those drugs that are substrates of active transporters [1]. These drugs were administered intravenously. The rat model was converted to a human model by replacing rat physiology by that of human [2]. This model can now be used for prediction of human CNS drug distribution, using existing and new to be developed drug properties. In this study we will perform experiments in rats, using the abovementioned 10 paradigm drugs, and investigate unbound plasma and CNS drug distribution following intranasally administration. The resulting data will be compared to those obtained after the intravenous administration in a parallel set of experiments [3]. This information will be used to decipher the influence of drug properties on such absorption routes and brain distribution enhancement, in relation to rat nose physiology. Such information will rationalize intranasal drug delivery.

1. Yamamoto Y, et al. Predicting drug concentration-time profiles in multiple CNS compartments using a comprehensive physiologically-based pharmacokinetic model. CPT PSP. 2017 1
2. Yamamoto Y, et al. Prediction of human CNS pharmacokinetics using a physiologically-based pharmacokinetic modeling approach. EJPS. 2018 Jan 15;112:168-179.
3. Stevens J et al. Systemic and Direct Nose-to-Brain Transport Pharmacokinetic Model for Remoxipride after Intravenous and Intranasal Administration. DMD 39:2275–2282, 201

Supervisor: Prof dr Elizabeth de Lange

Selection criteria:

- Profound understanding of pharmacokinetics
- Experience with pharmacokinetic and pharmacodynamic modelling software (NONMEN, R, Matlab, WinNonlin, or other)
- Scientific enthusiasm and persistence

Applications:

To apply for this vacancy, please send an email to ecmdelange@lacdr.leidenuniv.nl. Please ensure that you upload the following additional documents quoting the project title:

- Curriculum vitae;
- Bachelor's and master's transcripts;
- (Draft of) MSc thesis.

Deadline:

Project Title: Biomarker discovery in diagnosis of early stage Alzheimer's disease: the isolation and characterization of CNS derived extracellular vesicles

Project description:

The need in biomarker discovery and strategy development in diagnosis of early stage of Alzheimer's disease (AD) remains the only major cause of mortality without an effective disease-modifying treatment.

Extracellular vesicles are released by cells and contain genetic material (DNA,RNA), lipid and proteins, and the actual content depends on the cells where they originate from. EV's distribute over the body, including body fluids like plasma and cerebrospinal fluid which can be samples from human. It is hypothesized that CNS derived EV's in such body fluids will provide information that can be used to diagnose early AD.

Though earlier literature indicated that EV isolation was easy, the scientific community now agrees that it is not. In our laboratory we found that the choice of currently used isolation technique has an important impact on the isolated subset of EV's as well as co-isolated materials that may interfere with the outcome and therefore conclusions on potential EV associated biomarkers.

In this project, the EV isolation and characterizations from body fluids will be systematically addressed using molecular biological techniques. First, pooled human body fluid samples will be used. The best methodologies will be miniaturized and used to isolate and characterize EV's in AD and control ageing animal model biobank samples that have been collected in the last years.

Supervisor: Prof dr Elizabeth de Lange

Selection criteria:

- Experience with molecular biology techniques (such as ultracentrifugation, column-based separations, western blotting, immunoprecipitation,
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- Scientific enthusiasm and persistence

Applications:
To apply for this vacancy, please send an email to ecmdelange@lacdr.leidenuniv.nl. Please ensure that you upload the following additional documents quoting the project title:

- Curriculum vitae
- Bachelor's and master's transcripts
- (Draft of) MSc thesis

Deadline:

Project Title: **Cell heterogeneity matters: design of a capillary electrophoresis-mass spectrometry approach for single cell metabolomics**

Project description: It is very important that we obtain more insight into the biochemical mechanisms underlying cancer diseases at the single-cell level, by using strategies like single cell metabolomics analysis. However, endogenous metabolites are very difficult to analyze at a single mammalian cell level because of rapid metabolic turn-over rates, the huge structural diversity of the molecules, the wide dynamic range of analyte amounts per mammalian cell, relatively small size and the inability to amplify endogenous metabolites. As such, there is a strong need for new analytical strategies to develop single cell mammalian metabolomics. Therefore, in this project, the aim is to develop specific analytical approaches for single-cell metabolomics. More specifically, how to isolate targeted cells from its complex environment without perturbing its contents, which approaches should be considered or designed to extract, measure and identify the metabolic content of a single mammalian cell, and how to obtain sufficient detection sensitivity to enable the profiling of a wide range of endogenous metabolite classes in a single mammalian cell. For this innovative sampling, sample preparation and CE-MS metabolomics methods for individual cells need to be developed.

Supervisor: **Dr. Rawi Ramautar**

Selection criteria: Strong background in separation sciences, analytical chemistry principles and mass spectrometry in the field of bioanalysis and/or metabolomics

Applications:

To apply for this vacancy, please send an email to r.ramautar@lacdr.leidenuniv.nl

Please ensure that you upload the following additional documents quoting the project title:

- Curriculum vitae;
- Bachelor's and master's transcripts;
- (Draft of) MSc thesis.

Deadline: -

Project Title: **Enantioselective profiling of amino acids for the screening of novel biomarkers in neurological disorders**

Project description: In present-day metabolomics, advanced analytical separation techniques are used for the global profiling of (endogenous) metabolites in biological samples. A major challenge, in this context, remains the highly sensitive and reliable analysis of metabolites in especially size-limited samples. Moreover, there is a strong need for analytical tools allowing chiral metabolomics studies, as chiral endogenous metabolites, such as for example D-amino acids and some D-organic acids, are more and more recognized as potential new biomarkers for the prediction and/or diagnosis of diseases. Therefore, the aim of this PhD project is to develop microscale analytical technologies for chiral metabolic profiling of especially small-volume biological samples. In this project, capillary electrophoresis-mass spectrometry (CE-MS) will be considered as the main analytical platform for enantioselective profiling of (free) amino acids for the screening of novel biomarkers in material-limited biological samples, such as biofluids from mouse models and neuronal cells from 3D microfluidic organ-on-a-chip systems. CE-MS method development for chiral metabolic profiling including utility assessment for relevant biomedical/clinical applications will be performed in close collaboration with the Leiden University Medical Center.

Supervisor: **Dr. Rawi Ramautar**

Selection criteria: Strong background in separation sciences, analytical chemistry principles and mass spectrometry in the field of bioanalysis and/or metabolomics

Applications:
To apply for this vacancy, please send an email to r.ramautar@lacdr.leidenuniv.nl

Please ensure that you upload the following additional documents quoting the project title:

- Curriculum vitae;
- Bachelor's and master's transcripts;
- (Draft of) MSc thesis.

Deadline: -

Project Title: Computational modeling of regulation of the T cell immune response

Project description: In this project data-driven mathematical and computational models will be developed to describe the population dynamics of T cells during an immune response, including both activation and the contraction phase of the response. The models take into account various signals received by T cells, including the role of location in space, and for both aspects experimental data are available which will be integrated into the models. Subsequently, the models will be used to predict how manipulations affect the immune response.

Supervisor: Dr. Joost Beltman

Selection criteria:

- The candidate has an MSc degree in a relevant mathematical or computational discipline, preferably in computational biology or pharmacokinetic modeling.
- The candidate has experience with differential equation or spatial modeling approaches or the ability to quickly learn this based on prior computational experience.
- The candidate has a strong interest in biological/immunological questions.
- The candidate is proficient in spoken and written English.
- The candidate has the ability to work independently yet also as part of a team, consisting of both experimental and computational scientists.

Applications:

To apply for this vacancy, please send an email to j.b.beltman@lacdr.leidenuniv.nl. Please ensure that you upload the following additional documents quoting the project title:

- A motivation letter
- Curriculum vitae;
- Bachelor's and master's transcripts;
- (Draft of) MSc thesis.

Deadline:

Project Title: Novel receptor concepts to target G protein-coupled receptors

Project description: The most significant drug targets today are G protein-coupled receptors (GPCRs), as at least 30% of the current drugs target these proteins either directly or indirectly.[1] However, despite the efforts (and successes) in finding high-affinity and selective ligands, attrition rates of candidate drugs in clinical trials are disappointingly high. Hence, it is thought that a better understanding of the drug-target interaction is needed, with the prospect of novel concepts for drug action and, hopefully, better chances in later phases of the drug discovery process. Currently, most efforts in early drug discovery focus on optimization of drug-receptor interactions, i.e. receptor affinity and selectivity, whilst minimizing potential adverse ADME/Tox effects. However, several novel concepts are arising that are seen as increasingly important for *in vivo* efficacy and safety of drug candidates. Examples of these are '**target binding kinetics'**,[2] '**allosteric modulation**,[3] and '**biased signaling**'.[4] Taken together, in this project novel concepts will be studied for a selected class of GPCRs. We aim to get an improved understanding of the underlying mechanisms, which may provide a framework for more effective drug discovery and improved *in vivo* clinical outcomes for GPCR ligands.

Techniques: Cell culture, radioligand binding assays (both equilibrium and kinetic), mutagenesis, in vitro functional assays (e.g. G protein-activation, β-Arrestin recruitment, 'label-free' cell morphology)

References

(1)Overington, J. P.; Al-Lazikani, B.; Hopkins, A. L., How many drug targets are there? *Nat Rev Drug Discov* **2006,** 5, (12), 993-6.

(2)Zhang, R.; Monsma, F., The importance of drug-target residence time. *Curr Opin Drug Discov Devel* **2009,** 12, (4), 488-96.

(3)De Amici, M.; Dallanoce, C.; Holzgrabe, U.; Trankle, C.; Mohr, K., Allosteric ligands for G protein-coupled receptors: A novel strategy with attractive therapeutic opportunities. *Med Res Rev* **2009**.

(4)Whalen, E. J.; Rajagopal, S.; Lefkowitz, R. J., Therapeutic potential of b-arrestin- and G protein-biased agonists. *Trends Mol Med* **2011,** 17, (3), 126-139.

Supervisor: Laura Heitman

Selection criteria: Background in molecular biology or molecular pharmacology, Proficient English in speaking, writing and understanding.

Applications:
To apply for this vacancy, please send an email to l.e.hinne@lacdr.leidenuniv.nl . Please ensure that you upload the following additional documents quoting the project title:

- Curriculum vitae;
- Bachelor's and master's transcripts;
- (Draft of) MSc thesis.

Deadline: January 15th 2021

Project Title: **A live metabolic imaging platform to understand clinical kidney Ischemia Reperfusion Injury**

Project description:

Ischemia Reperfusion injury (IRI) may develop upon reperfusion of previously ischemic tissue. IRI is largely responsible for the organ damage following organ transplantation such as the kidney. Despite ample claims for successful interventions in experimental models of IRI, there is still no effective intervention for clinical IRI. This appears to reflect fundamental physiologic contrasts between the preclinical small rodent models and man. The proposed project will innovate by integrating cellular imaging with advanced kidney in vitro cell systems and provide single cell metabolic dynamic level data that are relevant to cellular processes during IRI. Within the timeline set by the program we will (1) expand our fluorescent reporter cell lines toolbox and validate the 2D/3D model for clinical IR; (2) test 3D metabolic imaging with either proximal tubule cells cultured in matrices or kidney organoids and (3) establish iPSC cell lines that express specific cell type markers together with metabolic biosensors for cell type specific metabolic imaging. This live imaging platform will enable multidimensional interrogation of kidney injury in a manner that combines the spatial-temporal strength of imaging metabolites with advanced pre-clinical cell models.

Supervisor: Jan Lindeman (LUMC)/ Sylvia Le Dévédec (LACDR) (promotor prof Bob van de Water, LACDR)

Selection criteria: You have a Msc degree in Biomedical Sciences, Bioengineering or similar. You have experience with advanced cell systems such as organoid culture and/or (stem) cell culture, microscopy techniques, and microfluidics. Experience with microbiology and/or systems biology is a plus. Fluent English communication skills, both in speaking and writing, are essential.

Applications:

To apply for this vacancy, please send an email to s.e.ledevedec@lacdr.leidenuniv.nl.

Please ensure that you upload the following additional documents quoting the project title:

- Curriculum vitae;
- Bachelor's and master's transcripts;
- (Draft of) MSc thesis.

Deadline:

Project Title: Machine learning based de novo generation with rational polypharmacology

Project description: Drug discovery traditionally has a large "serendipity" component. A vast chemical space, which has been estimated to be comprised of 10^{33}~10^{60} feasible drug-like molecules,[1] needs to be searched to identify a single molecule with desired physicochemical and biological properties. Experimentally enumerating this space is infeasible due to cost and time restrains.[2] Moreover, small molecules have a certain promiscuity,[3] *i.e.* each drug-like molecule has on average six protein targets to which a significant affinity is present. This can lead to unexpected toxicity and withdrawal of FDA approved drugs from the market. [3,4]

Machine learning and the availability of public (bioactivity) databases have changed the landscape of academic drug research in multiple ways. Firstly, by the increased scale at which predictive bioactivity models can routinely be trained (with the needed precision of predictions).[5,6] This allows the integration of these models as scoring functions within other workflows. Secondly, machine learning (and more specifically deep learning) can be used for de novo design of molecules. Using these methods machine learning based models can generate simplified molecular-input line-entry specification (SMILES) based molecules that are novel and have not been previously made.[7] Using both machine learning applications in parallel, generation of novel molecules and bioactivity prediction, can semi-automatically produce novel molecules with a desired biological activity. In this proposal we aim to take the next steps to further explore the possibilities and limitations of this technique and aim to apply it to G Protein-Coupled Receptors (GPCRs).

Supervisor: Prof. GJP van Westen and Prof. M vd Stelt

Selection criteria: The candidate has an MSc degree in a relevant chemical or computational discipline, preferably in computational chemistry or machine learning. Experience with python is required, experience with GPU computing is an advantage. The candidate is further expected to have a strong interest in drug discovery, to be proficient in spoken and written English, and has the ability to work independently yet also as part of a team.

Applications:
To apply for this vacancy, please send an email to Lia Hinne (l.e.hinne@lacdr.leidenuniv.nl). Please ensure that you upload the following additional documents quoting the project title:

- Curriculum vitae;
- Bachelor's and master's transcripts;
- (Draft of) MSc thesis.

Deadline:

References:

1.Polishchuk, P.G., et al. J Comput Aided Mol Des, 2013. 27(8): p. 675-9.

2.Macarron, R., et al., Nat Rev Drug Discov, 2011. 10(3): p. 188-195.

3.Giacomini, K.M., et al., Nature, 2007. 446(7139): p. 975-7.

4.Lounkine, E., et al., Nature, 2012. 486(7403): p. 361-7.

5.Cherkasov, A., et al., J Med Chem, 2013.

6.Cortes-Ciriano, I., et al., MedChemComm, 2015. 6: p. 24-50.

7. X. Liu, et al., J Cheminf, 2019. 11(1): p. 35.