Full details of the proposed research project

Waveform analysis of blood pressure and blood flow to improve cardiovascular safety pharmacology.

Host

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Description of the proposed project

The assessment of potential adverse drug reactions is crucial during drug development.1 Cardiovascular (CV) adverse drug effects, comprising direct and indirect toxic effects on the heart and vasculature, are still a major contributing factor to drug attrition.2,3 To minimise the risk of CV toxicity, better preclinical models are needed.4 Currently, the gold standard for preclinical in vivo assessment of haemodynamics is radiotelemetry.5 With this technique, an animal (rodent or non-rodent) is implanted with a radiotelemetric device, recording blood pressure (BP), heart rate, temperature and activity. This enables the monitoring of the CV parameters in conscious, freely-moving rats.5

Another valuable model to assess the haemodynamic effects of a drug, is Doppler flowmetry.6 This technique allows for recording of blood flow (BF) velocity in up to three vascular beds, simultaneously with BP recording, providing more detailed information of how a drug candidate is affecting different organs/vessels.6 Both BP and BF data are recorded as a periodic waveform, a regularly repeating signal over time. In the current analysis of these data, typically, the maximum and minimum values of the waveform (e.g., systolic and diastolic pressure) are evaluated. Although these values provide valuable information, this approach overlooks potential information 'hidden' in changes in waveform shape and variability. In-depth characterisation of recorded waveforms, looking at morphology and variability, may provide more extensive information on the condition of the heart and vasculature when exposed to drugs.7 Several mathematical models intending to utilize all provided data and understand the complexity of physiological waveforms have been explored in recent decades. The Symmetric Projection Attractor Reconstruction (SPAR) is one of those.7 This mathematical model converts a physiological waveform into a 2D image and by analysing different features of this 2D image, such as colour or length of the loops, detailed information on the effects of drugs on the heart and blood vessels can be extracted. More information on SPAR can be found here7. BP and BF recordings obtained from previous studies are currently being analysed using the novel SPAR method and show promising results. The student will help further developing the qualitative and quantitative analysis of blood pressure and blood flow waveforms in this model. This will be done using data from studies assessing drug safety of anticancer drugs that are known to cause CV toxicity, but the mechanisms are not fully understood, and validation compounds with known effects on the CV system. In this way, the student will contribute to answering the question: "Can in-depth characterization of waveform morphology and variability enhance our understanding of CV toxicity and help to predict and prevent such adverse drug effects?"

1. Kenakin TP. A Pharmacology Primer: Techniques for more effective and strategic drug discovery. 4th editio. San Diego: Elsevier Science & Technology, 2014.

2. Cook D, Brown D, Alexander R, et al. Lessons learned from the fate of AstraZeneca's drug pipeline: A five-dimensional framework. Nat Rev Drug Discov 2014; 13: 419–431.

3. Waring MJ, Arrowsmith J, Leach AR, et al. An analysis of the attrition of drug candidates from four major pharmaceutical companies. Nat Rev Drug Discov 2015; 14: 475–486.

4. Weaver RJ, Valentin JP. Today's Challenges to De-Risk and Predict Drug Safety in Human 'mind-The-Gap'. Toxicol Sci 2019; 167: 307–321.

5. Sarazan RD, Mittelstadt S, Guth B, et al. Cardiovascular function in nonclinical drug safety assessment: Current issues and opportunities. Int J Toxicol 2011; 30: 272–286.

6. Woolard J, Bennett T, Dunn WR, et al. Acute Cardiovascular Effects of Sibutramine in Conscious Rats. J Pharmacol Exp Ther 2004; 308: 1102–1110.

7. Nandi M, Aston PJ. Extracting new information from old waveforms: Symmetric projection attractor reconstruction: Where math

This project would suit a full time student or a student working on a part-time basis over a longer period.

What overall scientific training will the student receive during the project?

During the project, the student will have the opportunity to contribute to the development of a novel, promising method to improve preclinical safety testing. The focus will be on the SPAR method and applying the method to various in vivo data. This will include using IdeeQ, a bespoke software for Doppler data analysis, Notocord telemetry software, the novel SPAR application, and data-analysis tools such as GraphPad Prism. However, the student will be part of a multidisciplinary team, working with in vitro, in vivo and ex vivo models; there will also be opportunities to gain experience in our broader research areas, including in vitro cell-based assays. Cell Signalling is a welcoming and supportive research environment, perfect for a student to explore various types of research. The project is part of a collaboration with King's College London, so the student will also benefit from attending joint meetings.

A personal statement from Marieke

"I'm currently in the second year of my PhD. The student will be hosted by my supervisor, Prof. Jeanette Woolard, as well, so they will be supported in an ideal way, and this will also give me the opportunity to gain supervisory experience. I'm sitting on the committee of Team Science (COMPARE) and want to invite students into this supportive environment. During my bachelor and master, I had some opportunities myself to conduct short summer internships in various lab groups. These were great experiences for me to get familiar with academia and helped me in decision making for my career, so I'm excited to host a student in our lab, hope to be able to provide the same experience for them and learn them everything about an interesting research area!"