2018 NIH/NCATS-Lilly Fellowship Program Project Proposal

Title: Mechanistic modeling of effects of drug candidates on QTc prolongation

Functional areas: Pharmacokinetics/Pharmacodynamics (PK/PD), Toxicology

Background:

Cardiac safety risk assessment is a critical part of drug candidate screening in the discovery and early translational phases of drug development. Due to the potentially fatal effects of the arrhythmia Torsades de Pointes (TdP), regulatory guidances require that all compounds without intended effects on cardiac electrophysiology undergo ventricular repolarization safety assessment through measurement of the QT interval of the electrocardiogram. Prediction of clinical effects from *in vitro* data has been a key component of compound decision-making. Systems pharmacology models of cardiac repolarization offer the possibility of using a computational model to facilitate this prediction for man [1]. Additionally, having an early evaluation of drug-induced effects on cardiac repolarization can help to prioritize potential drug candidates within a development program and reduce late phase drug attrition due to clinical QTc increases at therapeutic doses. Current modeling efforts have been focused on inhibition of the human ether-a-go-go (hERG) channel, the primary mechanism of action contributing to QTc prolongation. However, a multitude of other factors also plays important roles [2], including hypokalemia (low serum potassium level), hypocalcemia (low serum calcium level), hypo and hyperglycemia (low/high blood glucose), hypothermia, and gender. Understanding and combining these additional factors in the model predictions will allow for evaluation of QTc liability with improved specificity and accuracy, increasing the probability of selecting the right drug candidate.

Project plan:

The qualified Fellow will work closely with several experienced scientists in PK/PD and Toxicology (covering both nonclinical and clinical development) to gain a broad understanding of drug discovery and development. The intended project will allow the Fellow to have hands-on experience with the quantitative aspects of translational medicine, including the role that computational modeling plays in providing dosing recommendations, evaluating drug efficacy and safety, and translating *in vitro* data to preclinical (animal studies) and ultimately clinical (human studies) predictions. The project involves understanding and incorporating drug effects into a mechanistic model of cardiac repolarization. The first step of the work involves familiarization with modeling biological mechanisms and the components of the O'Hara-Rudy human ventricular action potential model [3]. The Fellow will complete a series of focused literature surveys to better understand the relationship between certain drugs and their effects on potassium and calcium concentrations, the relationship of hypokalemia to hypoglycemia [4] and hyperglycemia, and the direct effects of plasma glucose levels on QTc beyond those mediated through potassium. Finally, the Fellow will work with a member of the modeling and simulation group to incorporate a model of drug effects on these factors into the cardiac model and predict the effects of hypokalemia-, hypocalcemia-, hypoglycemia- and hyperglycemia-induced QTc prolongation. Important in this step is an evaluation of how well *in vitro* data translates to preclinical (animal studies) and ultimately clinical (human studies) predictions. If appropriate, the Fellow will present their findings at key Lilly scientific forums and publish in a suitable journal.

References:

[1] Leishman D. (2014) Predicting QTc Prolongation in Man From Only *In Vitro* Data. *CPT:PSP*. 3 e131.
[2] Heemskerk CPM et al. (2018) Risk factors for QTc interval prolongation. *Eur J Clin Pharm.* 74.
[3] O'Hara T et al. (2011) Simulation of the Undiseased Human Cardiac Ventricular Action Potential: Model Formulation and Experimental Validation. *PLoS Comput Biol.* 7(5) e1002061.
[4] Heller SR et al. (2000) Hypoglycaemia and associated hypokalaemia in diabetes: mechanisms, clinical implications and prevention. *Diabetes, Obesity and Metabolism* 2, 75-82.