Systems Biology in Drug Safety Assessment: Use of a Recalibrated Hund-Rudy Model to Predict the Effect of Novel Drug Compounds on Action Potential Duration

Mark Davies*, Hitesh Mistry, Leyla Hussein, Najah Abi-Gerges, Chris Pollard and Jonathan Swinton

Advanced Science and Technology Laboratory, AstraZeneca, Macclesfield, United Kingdom

Objective: Drug-induced ion channel modulation in ventricular myocytes can prolong action potential duration (APD), which is seen on the electrocardiogram (ECG) as a prolongation of the QT interval. This is associated with a cardiac arrhythmia and therefore QT interval duration is carefully monitored in animal and man. Therefore, all candidate drugs are screened in an in vivo model of QT duration. This is however a late-stage, low throughput assay and also not entirely predictive for cardiac toxicity. For this reason, and much earlier in the drug discovery path, AstraZeneca screens compounds using IonWorksTM technology for their effects in vitro on several key cardiac ion channels. This information by itself is insufficient to infer APD change however.

Results: We have taken a publicly available model of cardiac action potentials (Hund Rudy) and calibrated it against a series of DMSO-control experiments from a voltage-sensitive dye based assays on isolated canine ventricular myocytes (VM). This calibration allows us to capture the variation in inter- and intra-experimental drift and create an ensemble of parameter sets, differing only in the ion-channel current parameters which are consistent with variations observed in electrophysiology experiments. We have then simulated the anticipated change in APD for a series of compounds with known channel inhibition profiles and compared this to experimentally derived estimates in order to assess the predictivity of the model.

Conclusions: Using a mathematical model of cardiac action potentials, we are able to integrate potency estimates from a range of ion channels and assess the potential cardiac risk that a particular compound may pose. This risk assessment can be performed at a much earlier stage in the drug pipeline and with the intention of improving and speeding up drug decision making.