A new analysis pipeline to improve assessment of cardiac liability in high throughput electrophysiology screens with routine MoA detection for slow onset compounds

Authors: Stephan Steigele, Ana L. Teixeira, Martin Ginkel, Verity A Talbot, Lisa J McWilliams, Matt Bridgland-Taylor, Stephan Heyse

Abstract

Automated patch clamp screens generate highly valuable information for drug research programs. In particular, in safety pharmacology early testing is nowadays seen as a cornerstone for managing risk of later failure and patients' health. Thus, more predictive and affordable screens need to be introduced to gain both specificity and throughput e.g. for cardiovascular liability detection and resolution. At AstraZeneca, we have implemented the Nanion Syncropatch 384PE electrophysiology platform, delivering higher throughput measurements for hERG and other key cardiac ion channels in standard 384 well-based format at dramatically reduced consumable costs and experiment time, whilst capturing full kinetics of channel response. Jointly with Genedata we developed a pipeline for processing and analysing this complex data, reading binary raw data directly from the SyncroPatch instrument into Genedata Screener, then assigning and integrating the sweep recordings from cumulative compound addition series and finally subjecting them to scientists' review using powerful filtering and masking based on quality control measurements. We further developed methods for normalising the cumulative curve recordings compensated for signal variation using time-match control and for automatically detecting "slow onset" compounds using a sigmoidal fit model per concentration step, flagging those compounds which potency against critical cardiac channels has been potentially under-estimated due to their slow onset.

This investment in a next-generation automated electrophysiology platform and an appropriate automated data processing pipeline is resulting in more predictive and affordable safety screens at high scalability and rapid turnover for discovery projects across AstraZeneca.