Catch me if you can: Better characterizing slow-onset compounds' liability using the "Extended hERG" automated patch-clamp assay

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The human voltage-sensitive K^+ channel hERG plays a crucial role in cardiac action potential repolarization and controls the QT interval of the ECG effectively. Loss- or gain-of-function mutations in hERG can result in dangerous "long" (LQTS) or "short" QT syndromes (SQTS), respectively, and the susceptibility of hERG blocked by a diverse range of drugs underlies an acquired LQTS, which leads to a potential risk of a life-threatening polymorphic ventricular tachycardia – torsades de pointes (TdP). Therefore, *in vitro* investigations for blockade of hERG have become a standard in most early drug discovery projects to reduce this risk.

A triage of automated patch-clamp (APC) assays have been established in AstraZeneca using different platforms to investigate the hERG liabilities for compounds across the drug discovery portfolio. Frontline hERG Syncropatch assay is high-throughput but with a short compound exposure time whilst an Augmented hERG Qpatch assay, with a longer exposure time provides higher quality data with the caveat it is lower-throughput. 21% of all compounds tested in AstraZeneca have a slow-onset flag which underestimated hERG liabilities in the Frontline hERG assay, and while the Augmented hERG assay was able to flag these liabilities, the throughput restricts its wider use.

We have developed an APC assay using the Syncropatch platform to enable faster identification of hERG liabilities for slow-onset compounds by extending the compound exposure time and keeping good cell viability and ion channel signal recording quality. 30% of tested compounds from the Extended hERG assay showed more potent IC50 values compared to the Frontline hERG assay including activity shifted from inactive/weakly active to active providing a more accurate potency value earlier in the drug discovery cascade than previously possible ultimately reducing the risk of compound termination in late-stage drug discovery.