Screening of hERG Blockers by Automated Patch-clamp System: Qpatch 16

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Introduction

Recent years, one of the major reasons for failing in clinical drug development is the drug-induced sudden cardiac death associated with prolongation of the QT interval in the electrocardiogram. When the QT interval is prolonged, there is an increased risk of ventricular tachyarrhythmias, including the life-threatening form torsades de pointes. Although a direct link between QT interval prolongation and arrhythmogenesis is still unclear, QT prolongation is now the subject of increased regulatory review and is considered as a significant risk factor for predicting human safety of new chemical entities. Even though prolongation of QT can occur through modulation of several types of ion channels, inhibition of the delayed rectifier K+ current (I_kr), which is conducted by hERG (human ether-a-go-go related gene) channel, is the most common mechanism responsible for drug-induced prolongation of QT interval in humans. Therefore, testing the interaction of a compound with the hERG potassium channel in heterologous expression systems is recommended by the International Conference on Harmonisation (ICH) as one of the non-clinical testing methods for assessing the potential of a test compound to prolong QT interval.

Although several alternative technologies have been developed to test hERG channel, conventional (manual) patch clamp remains the gold standard but it becomes the bottle neck of drug safety screening due to its low throughput and high cost. To address this problem, several automated patch clamp platforms were developed. The Qpatch 16 is an automated patch clamp system made by Sophion Bioscience (Denmark). It is based on planar glass-coated silicon chips with micro-etched patch clamp holes. The Qpatch 16 performs 16 independent patch clamp experiments in parallel in a disposable electrode group called Qpatch. It employs the same true gapless seal principle as manual patch clamp but dramatically improves the throughput while maintaining the quality of data.

After providing hERG screening by conventional patch-clamp for more than 5 years, Cerep obtained Qpatch 16 in March 2007. The validation of hERG channel patch clamp assays by automated patch clamp system was carried out from April to June 2007 at Cerep. The validation study tested the effects of 10 known hERG channel blockers (reference compounds) and 16 test compounds on hERG potassium channels by Qpatch. The negative control (DMSO/water) study was also conducted. All the compounds were tested by automated (manual) patch clamp at Cerep. The results from the two different test systems were compared and reported here.