Predicting QT Prolongation: Assessing hERG and Other Cardiac Ion Channels Early

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The prediction of clinical QT prolongation through preclinical assays has been under debate due to the lack of correlation in identifying drug candidates producing adverse cardiovascular events in human. Although QT prolongation has been associated with IKr block, hERG inhibition has been considered a weak biomarker in detecting proarrhythmic risk. Focus has extended beyond the standard hERG assay to include compound interactions with alternative cardiac ion channels in more complex assays involving cardiac cells, tissues, whole organ or whole animal.

These sensitive assays are required to elucidate events which lead to QT prolongation such as triangulation, reverse-use dependence, dispersion of repolarization, beat-to-beat instability, etc. In compliance with the ICH S7B guidelines (Oct. 19, 2005), repolarization assays are recommended in conjunction with the hERG assay for a more complete early cardiovascular safety strategy.