**Cardiotoxicity In Silico Prediction: Validation Results of a Multiscale Simulation Model (eTOX VII)**

**Abstract**

The Cardiac Safety Research Consortium (CSRC) established the eTOX initiative to develop a validated model for in silico assessment of cardiovascular risk. This study reports validation results of a multiscale simulation model (eTOX VII) combining hERG, ion channel, chemical space, and in vitro methods. The model was trained on public data, so predictions of proprietary drugs could be validated. Predictions were compared to experimental data from nonclinical and house compounds.

**Methods**

**Comprehensive in vitro pro-arrhythmia assay**
- Validation of pro-arrhythmia risk in vitro, screening for hERG blockers, ion channel effects, and non-cardiac effects on cardiac ion channels.
- Testing Cardiac Safety Research Consortium (CSRC) hERG, IC50.
- Assessed to answer the IC50 guideline and to simulate the clinical through QT (GT) study.

**Multiscale in silico prediction system**
- Assessed the effect of drugs on the cardiac ion channel currents (Cav1.2, ICaL, EAD).
- Assisted in silico prediction systems for drug candidates that showed the highest potential for cardiac arrhythmia.
- The model was trained on public data, so predictions of proprietary drugs could be validated.

**In SIlico prediction results**
- From all in vitro Pirkhine fiber tests, 449 drug candidates (small molecules) were screened and classified based on AED effects, QT interval changes, and proarrhythmic effects.
- Positive AED change: active (IC50 > 10 µM) or low pacing (0.25 Hz).
- Equivocal AED change: active (IC50 > 10 µM) and low pacing (0.25 Hz).
- Parameters that were used to clearly classify the predicted risk in silico models:
  - QT change at 5 µM > 1.1
  - QT change at 10 µM > 1.1

**Validation results**
- Optimal drug candidates without proarrhythmic liability were identified.
- Identification of drug candidates with proarrhythmic liability was achieved.

**Conclusion**
- Validation results demonstrated the proof of concept of in silico approach.
  - In silico: predicted hERG blockers.
  - In vitro: predicted non-cardiac effects on cardiac ion channels.
  - Factors which have an impact on the results should be taken into account in clinical development.
  - Rapid assessment of drugs in silico is a challenge.

**References**


**Keywords**
- Cardiac Safety
- In Silico Prediction
- Multiscale Simulation Model
- eTOX VII