**Title “Categorization of TdP risk dependent on compound electrophysiological response predictors”**

**Section title Context of Use**

Delayed ventricular repolarization can create a proarrhythmic environment that results in life-threatening cardiac arrhythmias including Torsades de pointes (TdP). A significant challenge in drug development and regulatory decision making is determining the proarrhythmic potential of novel compounds.

The TdP risk categorization calculator tool is used to assess the TdP risk of small molecule compounds in healthy adults to create human-relevant data for greater evidence of safety assurance for drug development and regulatory decision making.

Fitting of these results through machine learning algorithms were used to develop this open-source online calculator.

This calculator receives compound-induced input predictors:

Predictor 1, Did compound induced arrhythmias occur at any concentration? (0=no arrhythmia, 1=type A arrhythmia, 2=any other arrhythmia type)

A collection of different types of electroencephalograms

AI-generated content may be incorrect.

**Figure 1.** Representative Traces of Four Cellular Arrhythmia-Like Events Recorded in hiPSC-CMs Recorded by (left) MEA and (right) VSO platforms. The horizontal scale bar equals 1 s. We refer to type A arrhythmia as a “mild” arrhythmia-like event in the text. (Blinova et al 2018)

Predictor 2, Were drug-induced arrhythmias observed at any concentration in ≥ 40% wells. (typically in at least 2 out of 5 replicate wells) (0=no, 1=yes)

Predictor 3, Repolarization prolongation (ms) at the first drug concentration with statistically significant (p≤0.05) prolongation or shortening.

Predictor 4, Maximum repolarization change (ms) observed at any concentration.

Predictor 5, Drug concentration (folds over Cmax) at which the first statistically significant (p≤0.05) repolarization prolongation was first observed.

Predictor 6, Drug concentration (folds over Cmax) when drug-induced arrhythmias were first observed.

Predictor 7, Drug-induced repolarization change (ms) at Cmax.

And provides as outputs:

TdP risk categorization estimated from in vitro experiments on hiPSC-CMs

Model 1:

1. Low TdP Risk probability estimation
2. High or intermediate TdP risk probability estimation

Model 2:

1. Low TdP Risk probability estimation
2. Intermediate TdP risk probability estimation
3. High TdP risk probability estimation

**Section title Formulas for TdP risk categorization estimation**

**Model 1:**

* If Predictor1 = 0, .
* If Predictor1 = 1, .
* If Predictor1 = 2,

**Model 2:**

Probability of high vs low (P2a):

* If Predictor1 = 0, .
* If Predictor1 = 1, .
* If Predictor1 = 2, .

Probability of intermediate vs low (P2b):

* If Predictor1 = 0, .
* If Predictor1 = 0, .
* If Predictor1 = 0, .

**Section title Limitations of use**

While this study provides valuable insight into potential TdP risk categories it has some limitations described here (Blinova et al 2018).

1. Well-exposure analysis studies were not conducted to measure free drug concentration in hiPSC-CM experiments. Future studies should consider detailed well-exposure analysis to determine the amount of nonspecific binding.
2. The tool does not account for drug metabolites as such active drug metabolites should be investigated independently.
3. Repolarization wave can be decreased (blunted) following exposure to some compounds making it challenging to detect FPD prolongation.
4. Only acute (30 minutes) assay duration was investigated. However, chronic timepoints (e.g., days to weeks) may be of interest for specific compounds (e.g., hERG trafficking inhibitors).
5. This study was not statistically powered to investigate the effect of the electrophysiological device (platform) on the hiPSC-CM assay’s predictivity of proarrhythmic drug potential.
6. This study was conducted on spontaneous beating (non-paced) hiPSC-CMs. Utilization of field stimulated (paced) input parameters (Patel et al 2019) will require additional verification and validation.
7. To extend this tool to more complex in vitro models (e.g., co-culture, 3D, disease models) specific verification, validation and optimization will be required.

**Section title References**

Blinova 2018 PMID: 30257217

Patel et al 2019 PMID: 30912807