A Cardiac Risk Algorithm to Predict the Probability of Drug-Induced Torsades de Pointes with Novel Anti-TB Agents

Alexander Berg, PharmD PhD FCP
Associate Program Director, Quantitative Medicine
Role of the Critical Path Institute

• Act as a trusted, neutral third party
• Convene scientific consortia of industry, academia, and government for pre-competitive sharing of data and expertise
  ✓ The best science
  ✓ The broadest experience
  ✓ Active consensus building
  ✓ Shared risk and costs

• Goal is to generate robust “drug development tools” that can be used with confidence by Sponsors and trusted by Regulators

*Multiple companies within each sector
CPTR’s Mission and Focus

• **CPTR Partners and Members:** A collaboration co-founded in 2010 by the Bill & Melinda Gates Foundation, TB Alliance, and C-Path.
  – Consortium of 8 pharma / 18 diagnostic companies, 26 academic institutions, 20 NGOs, and 5 governmental bodies.

• **Mission:** The Critical Path to TB Drug Regimens (CPTR) is a cross-sector initiative that aims to speed the development of safer and shorter duration anti-tuberculosis (TB) drug regimens and rapid drug susceptibility tests. CPTR will accomplish this by focusing on:
  – **Improving Regimen Selection**
  – **Accelerating Regimen Development**
  – **Influencing Regimen Deployment**
  – **Facilitating Improved Trial Infrastructure and Network**
Many anti-TB drugs are considered to be potentially pro-arrhythmic given the propensity for hERG inhibition and QTc prolongation

- **Challenge:** QTc prolongation does not necessarily translate to a high risk of potentially fatal arrhythmias, particularly Torsade de Pointes (TdP)

**Anti-TB Drugs**

- QTc prolongation

  - High Risk of TdP

  - hERG vs. other ion channel inhibition?
  - QTc vs. other ECG changes?
  - Therapeutic vs. supratherapeutic dosing?
  - Monotherapy vs. combination regimens?
To address these uncertainties, CPTR is developing a model-based Quantitative Systems Toxicity (QST) platform for progressive cardiac risk assessment throughout discovery and development.
The “Cardiac Risk Algorithm” was developed linking *in vitro* ion channel inhibition data to observed TdP risk using outputs derived via through the use of the Simcyp Cardiac Safety Simulator®

- Algorithm based on CredibleMeds® classifications for 96 compounds with known TdP risk across multiple structural and therapeutic classes
- Validated against 12 additional compounds, including moxifloxacin

---

**Drug Concentrations (0 – 500 uM)**

**Human Heart Left Ventricle Cell Model**

- hERG *in silico* (QSR)
- hERG *in vitro* (measured)
- other ion currents *in silico* (QSR)
- other ion currents *in vitro* (measured)
- IKs, INa, ICaL

**Population Representative Virtual Female Subject**

**EM Window**

- EM Window (EMW) = time gap between the end of electric and mechanical systole
- Index of Cardiac Electrophysiological Balance (iCEB) = QT/QRS

**Cell Contractility**

**Action Potential** (APD90)

**pseudoECG** (QT, QRS)

**• QT prolongation**

**• iCEB**

**• J-Tpeak, Tpeak-Tend**

**CredibleMeds® TdP +/- Classification**

**Machine Learning**

**Cardiac Risk Algorithm**
The Cardiac Risk Algorithm is an alternating decision tree utilizing the EMW and iCEB outputs from the CSS at various drug concentrations

- The model correctly classified the TdP propensity of 85 out of 96 learning set compounds
  - High specificity (96%) with moderate sensitivity (71%)
  - 10 of 12 validation set compounds were correctly classified

- Notably, application to both bedaquiline and moxifloxacin resulted in correct classification (TdP(-) and TdP(+), respectively)
Limitations of the Cardiac Risk Algorithm are primarily related to the iterative development strategy and placement in the QST framework

- The current algorithm is sufficient for monotherapy assessment only
  - Reflects placement in the discovery / early development stages of the QST where focus is on novel drug characterization prior to regimen design

- Effects of non-drug factors (e.g., physiological variability) affecting torsadogenicity were not incorporated during algorithm development
  - Could still be incorporated in simulations to estimate “what if” scenarios

- Algorithm converts an estimated TdP probability to a binary +/- output using probability threshold of 0.5 (near optimal per ROC analysis)
  - However, misclassified compounds in the learning set exhibited a TdP (+) probability near the cutoff threshold (range = 0.34 to 0.54)
  - Thus it is recommended that the TdP +/- classification be considered in the context of the algorithm-estimated TdP probability
Full details on the Cardiac Risk Algorithm will be provided in an open-access paper, with an anticipated publishing date of early 2018.

As with any quantitative drug development platform, the Cardiac Risk Algorithm is intended to evolve with additional data:

- Updates to clinical TdP risk classification and *in vitro* data for reference compounds will be incorporated with future iterations.
- Further research will investigate extension to include physiological variability and extrinsic factors, specifically drug combinations, as well as incorporation of alternative classification schemes (i.e., trinary [low/medium/high] risk stratification).
Next Steps for QST Framework

• Beyond Cardiac Risk Algorithm refinement, CPTR is conducting further work to generate a robust QST framework for cardiac risk assessment
  – Late stage assessment focused mechanistic PK-PD models (i.e., PBPK-pseudoECG)

• PBPK-pseudoECG model extension to intrinsic and extrinsic factors that may influence TdP risk
  – Prediction of TdP risk for PK and/or PD DDIs, particularly for anti-TB regimens

• Predictive performance of PBPK-pseudoECG models for known drugs (e.g., MOXI) when used as monotherapy
  – Work nearly complete, pending publication
Conclusions

• CPTR has developed a Cardiac Risk Algorithm for use in discovery and early development programs, with emphasis on TB

• By using outputs from the Simcyp Cardiac Safety Simulator®, the Cardiac Risk Algorithm is able to convert in vitro ion channel inhibition data to estimates of clinical TdP risk for a new or repurposed drug with good predictive performance

• The Cardiac Risk Algorithm will continue to be refined as a component of a broader quantitative systems toxicity (QST) platform for cardiac risk assessment of novel anti-TB drugs and regimens
Acknowledgements

- C-Path:
  - Debra Hanna
  - Klaus Romero
  - Lindsay Lehmann

- SIMCYP:
  - Sebastian Polak
  - Nikunjkumar Patel

- BMGF:
  - Dave Hermann
Thank you!

Alexander Berg PharmD PhD FCP
Associate Program Director, Quantitative Medicine