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ANABIOS BIOMARKER QUALIFICATION UPDATE

Biomarker Qualification Goal

AnaBios intends to qualify a Pro-Arrhythmia Score based Biomarker derived from an ex-vivo human AP-based assay for the purpose of preclinically identifying the pro-arrhythmia risk of drugs, with specific focus on Torsade de Pointes (TdP) type arrhythmias

Biomarker Definition

The Biomarker will constitute a Pro-Arrhythmia Score, which will be a numerical value calculated from several parameters measured from ex-vivo AP recordings in human ventricular tissues. The Pro-Arrhythmia Score will determine and define the safety margin with respect to TdP / pro-arrhythmia potential of the tested drug.

Biomarker Context of Use

The Pro-Arrhythmia Score will be used at the preclinical stage of drug discovery to assess the TdP pro-arrhythmia risk of a test article, in order to facilitate clinical development and risk management planning, and support benefit-risk analysis, as well as enable regulatory decision making.

Background

Cardiac safety remains the leading cause of drug development discontinuation and withdrawal of marketed drugs. Consequently, International Council on Harmonization regulatory guidelines (S7B and E14) and various cardiac models have been established for evaluating the pro-arrhythmic potential of novel drugs at the preclinical stage. However, these models have low specificity (high rate of false positive signals) and low sensitivity (high rate of false negative signals). Thus, the limited predictivity of the current models has stimulated a quest for more reliable platforms based on the use of human tissues and/or cells that will better characterize human pro-arrhythmia risk of therapeutics. For human cardiac tissues and cells to have practical utility in preclinical cardiac safety assessment, the development and validation of methodologies would be essential, which could provide human cardiac tissue of high and consistent quality, and assays, which could provide predictive data.

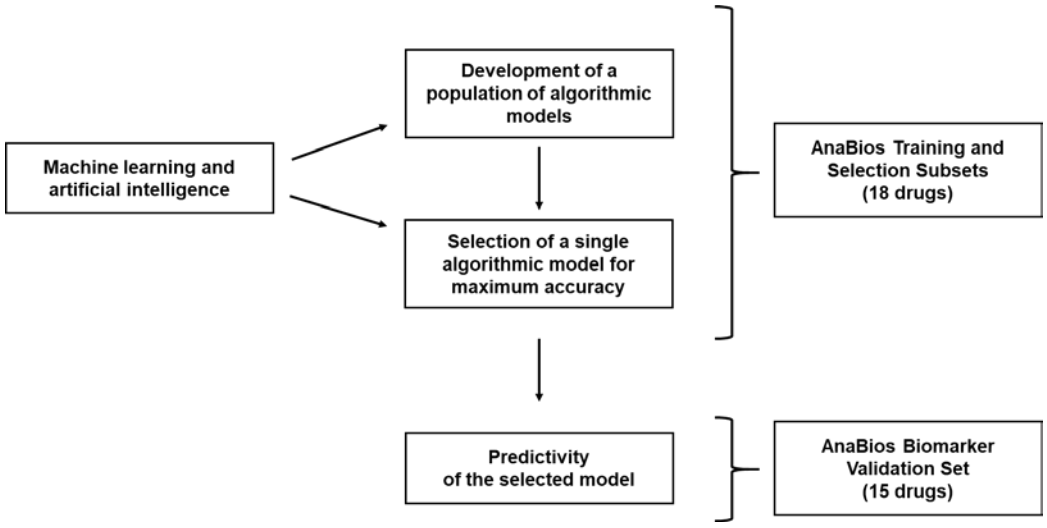
Summary of AnaBios activities

AnaBios has developed procedures that consistently allow the procurement and experimental interrogation of adult human cardiac tissues (Page et al., 2016; Qu et al., 2018) and adult human cardiomyocyte preparations (Nguyen et al., 2017). The Page et al. study was the object of our initial Phase 1 of Biomarker Qualification program and was performed in collaboration with an industry consortium (AbbVie, Roche and Novartis) and the FDA Biomarker Qualification Review Team (Study Report and Raw Data Tracings were received by the FDA Team on October 31 and November 7, 2016 respectively). In this study, AnaBios validated an ex-vivo human action potential (AP)-based model with 5 drugs (3 pro-arrhythmic and 2 non-pro-arrhythmic). The compounds were each blinded and tested at 3 rising concentrations in a total of 15 ventricular trabeculae derived from 5 hearts. A time control was included for each heart tested (n=20 hearts total). The results of this study can be summarized as follows:

- Human tissue action potential recordings are electrophysiologically stable.
- The assay can correctly identify safe drugs devoid of pro-arrhythmic risk.
- The assay can correctly identify the torsadogenic potential of known pro-arrhythmic drugs.
- The assay can accurately and reliably be executed with a small sample size derived from 2 hearts.

Additionally, AnaBios performed a more extensive ex-vivo human AP study in collaboration with Amgen (Qu et al., 2018) and the effects of 15 drugs were assessed (8 pro-arrhythmic, 5 non-pro-arrhythmic and 2 discovery molecules). Each drug was tested blindly with 4 rising concentrations in a total of 4 human ventricular trabeculae derived from 2 hearts. To characterize the pro-arrhythmic risk of each drug, a Pro-Arrhythmia Score was calculated as the weighted sum of percent drug-induced changes compared to baseline in multiple AP parameters. Moreover, a ratio that relates each testing drug concentration to the human therapeutic unbound C_{max} was used to understand the translation of the AnaBios ex-vivo human AP-based model to known human outcomes. Scores for sensitivity (88%), specificity (80%), positive predictive value (88%) and negative predictive value (80%) at a ratio of 10x the known free effective therapeutic concentration were derived and indicated an excellent performance.

To further refine the Pro-Arrhythmia Score algorithm developed during the Amgen study (Qu et al, 2018), AnaBios has been collaborating with an experienced machine learning and artificial intelligence software company, Liquid Biosciences. The 18 reference drugs described in Page et al. and Qu et al. were divided into Training and Selection subsets. The Training subset was used to evolve a population of algorithmic models. The Selection subset was used to select a single final model with the best accuracy from the evolved population models. For the Validation phase required for our Pro-Arrhythmia Biomarker Qualification, it is our intention to validate this final model against data derived from 15 newly blinded compounds tested in our ex-vivo human AP assay. The predicted outcomes, Torsadogenic versus Non-Torsadogenic risk at various multiples of the free effective therapeutic plasma concentration, will be assessed against actual known clinical TdP/pro-arrhythmia risk. The figure below provides a flowchart summary of our refined Pro-Arrhythmia Score development and Pro-Arrhythmia Biomarker Qualification testing process.



Action Plan

1) AnaBios plans to submit the Validation Study plan.
2) Upon receiving feedback from FDA Biomarker Qualification Review Team, AnaBios will incorporate suggestions and revisions to the plan, as appropriate.
3) AnaBios will conduct the validation data collection and analysis.
4) AnaBios will submit the data, and results analysis to the FDA Biomarker Qualification Review Team for review and evaluation.