BIO-FI: LEVERAGING THE POWER OF BIOLOGICAL BIG DATA FOR ADVANCED ANALYTICS AND MODELING OF CHEMICAL AND BIOLOGICAL THREATS

Ai-enabled In Vitro Cardiotoxicity Assay Of Hipsc-cardiomyocytes, 2nd Iteration Goal: Increase Human Response Predictivity From 90% To 95%

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We've report initiation of our second AI training/development iteration to achieve ≥95% predictivity of cardiotoxicity on 350 perturbagens (toxins and drugs) with known clinical responses, after having published 90% predictivity on 125 drugs with known clinical responses screened on human induced pluripotent stem cell (hiPSC)-derived cardiomyocytes (CMs) (Pfeiffer, et al., 2016, PMID: 27095424). This was the most accurate prediction of human arrhythmia of any approach, and thus demonstrated sufficient data quality. Now we're multiplexing single-cell readouts of action potentials, contraction, mitochondrial health, and endoplasmic reticulum (ER) stress with the original calcium transients. The multiplexed data will enable prediction of comprehensive cardiotoxicity by adding myopathy, and may provide the mechanism of action cellular subsystem in which the target resides.

Our approach develops in vitro AI training sets from clinically active perturbagens and screens them on hiPSC models along with negative controls. Many non-drug toxins like ingested tetrodotoxin have known human responses, are target-selective, and make excellent perturbagens. We screen on the high throughput (HT, robotic) Kinetic Image Cytometer®, which performs high-speed single-cell video cytometry of fast-acting cells such as myocytes and neurons. It produces about 50 TB of raw data from 7,000 experiments (i.e., perturbagens/concentrations/wells in microtiter plates) on 10 million cells per day. In this iteration, we'll screen 63,000 wells in 384-well microtiter plates and produce about 0.5 PB of raw data on 94 million cells.

Neurotoxicity may be more relevant to biowarfare toxins and we are developing analogous hiPSC-neuronal models. However, hiPSC-neuronal model development trails hiPSC-CM model development because brain function is more complex, and models require multiple cells types (e.g., neurons, microglia and astrocytes) for quality data and high predictivity. Still, cardiotoxicity is a relevant biowarfare target organ we're already reusing many of the same techniques for neurotoxicity. And medically, cardiotoxicity causes about 25% of toxicity-related drug discovery failures and is dose-limiting for many anti-cancer therapeutics. So reduced cardiotoxicity would increase clinical trial success rates and, especially for cancer, directly improve efficacy. The number of cancer survivors may exceed 22.1 million by 2030 and their risk of cardiovascular death may soon exceed that of the cancer itself (K. Miller, et al., 2019). A recent FDA-authored review reported that there are no effective in vitro tools to predict myopathies (X. Yang, T. Papoain, 2018). Animal studies, which are low throughput and costly, have historically detected only ~70% of human-relevant toxicities (H. Olson, et al., 2000). There is thus an unmet need for development of in vitro cardiotoxicity assays to aid selection of uHTS hits and inform lead development.

This high throughput cardiotoxicity assay has the potential to better predict agents that may cause myopathy and arrhythmia and may also predict the primary subcellular system in which the target resides. As potentially the first AL/ML-enabled screen to have produced sufficient data quality for high predictivity of human responses, it may also contribute to the development of systematic methodologies to leverage the power of biological big data for advanced analytics and modeling of chemical and biological threats.

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