Cytotoxicity Monitoring for Safety Assessments: iPS Cardiomyocytes and Cancer Cells

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Question: Human stem cell-derived cardiomyocytes (hiPSC-CMs) have recently proven to recapitulate key features of cardiac electrophysiology in vitro. Here, we show a thorough overview of the Comprehensive In-vitro Proarrhythmia Assay (CiPA) initiative compounds, and their effects on the impedance and extracellular field potential (EFP) signal of diverse spontaneously beating hiPSC-CMs. We also demonstrate alternative application of impedance for cell cytotoxicity and proliferation assays.

Methods: Diverse cell types were monitored using a 96-well hybrid screening instrument that combines impedance (or cell monolayer resistance) with MEA-like EFP recordings, under physiological conditions (temperature, humidity and CO₂), which enabled short and long-term recordings without using an incubator. Changes in the impedance signal indicate effects on cell contractility, cell morphology and proliferation over prolonged periods of time, giving a crucial advantage of this technique over standard cytotoxicity assays. The EFP parameters provide information about the electrophysiological activity of the beating network of cells.

Results: We focus on concentration-dependent effects of compounds such as nifedipine, pentamidine, dofetilide, E4031, isoproterenol and mexiletine on the impedance and EFP of hiPSC-CMs. In addition to data obtained from spontaneously beating cells, we also demonstrate optical stimulation of hiPSC-CMs, with an advantage over electrical stimulation due to the highly precise timing and simultaneous delivery of the light stimulus to all cells of the beating network. Optogenetic approach delivered optical pacing of hiPSC-CMs in a range from 1Hz to 3Hz, and impedance and EFP traces adapting to the paced beat rate were compared. In addition, we describe the development and optimization of a label-free cell monitoring assays using impedance measurements. These assays provide reproducible results for toxicity screens of adherent, proliferating (e.g. cancer) or non-proliferating cells. We focus on the data obtained from testing the concentration dependent effects of chemotherapeutic drugs on cancer cells and their proliferation patterns as well as of cytotoxic and hepatotoxic drug effects using diverse cellular models.

Conclusion: In summary, our data and technical innovations strengthen the importance of testing compounds in assays complementary to patch clamp electrophysiology, to provide an all-inclusive safety and toxicity compound profile.