Platform for High-Throughput Cardiotoxicity Drug Screening

Technology Summary

This technology is an optical dynamic clamp (ODC) platform that enables light-activated current generation in iPSC-derived cardiomyocytes, making them a suitable platform for cardiotoxicity screening.

Technology Overview

Cardiovascular toxicity is a leading cause of drug development failure and market withdrawal across multiple drug classes including anti-cancer, antibiotics, antidepressants, and antipsychotics. Drug safety regulations mandate cardiac testing of all drug candidates. Current platforms for preclinical cardiotoxicity screening largely rely on nonhuman models that do not faithfully recapitulate human physiology. Induced pluripotent stem cell-derived cardiomyocytes (iPSC-CMs) are a renewable source of human cardiomyocytes for preclinical studies and can be derived from target patient populations. However, iPSC-CMs exhibit low levels of the inward rectifier potassium current, leading to an immature electrophysiological phenotype and limiting their relevance to adult arrhythmogenesis. Electrode-based dynamic clamp (EDC) is used to inject current and produce more adult-like electrophysiology in iPSC-CMs, but this technology does not scale for high-throughput applications.

Inventors:
David J. Christini
Trine Krogh-Madsen
Bonnie Quach
Emilia Entcheva

Location:
Weill Cornell Medicine

Patents:
Filed

Licensing Contact:
Donna Rounds
(646) 962-7044
djr296@cornell.edu

Cornell Reference:
D-7882

Cornell inventors developed an optical dynamic clamp (ODC) which uses light to deliver the current necessary to induce adult-like action potential morphology in iPSC-CMs in a precise and contactless manner. Similar to EDC, ODC is able to inhibit spontaneous activity, allowing for accurate measurement of AP characteristics. These results are consistent at different frequencies and in the presence of ion-channel modulators, validating the use of ODC as a platform for high-throughput cardiotoxicity drug screening.

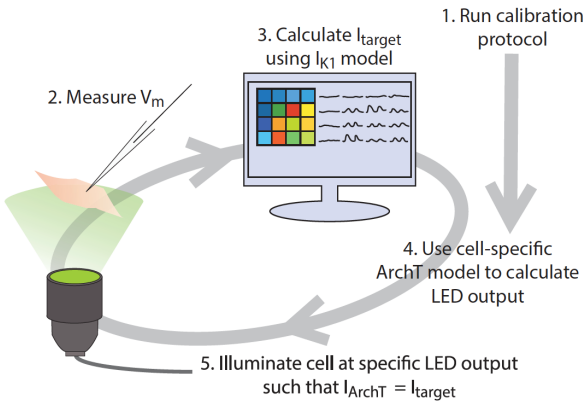

Figure 1: *Schematic of ODC system. A calibration protocol is executed before implementing the ODC system.*

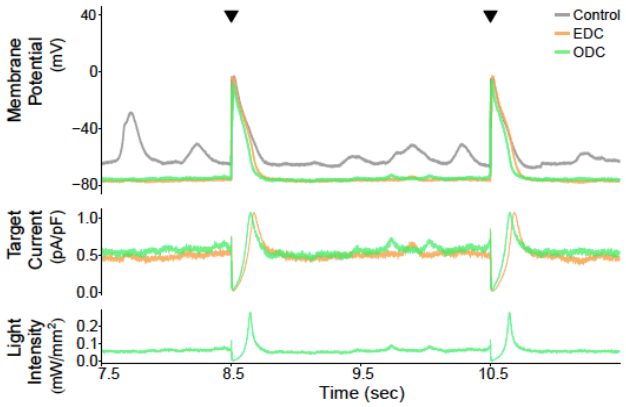

Figure 2: *Two stimulated Action Potentials (AP) in a test cell showing effects of adding target current by EDC and ODC.*

Executive Summary

Potential Applications

- High-throughput screening of drugs for cardiotoxicity
- Platform for future development of a contactless dynamic clamp

Advantages

- Optical input enables high-precision contactless control of the target current
- Compatible with a variety of cell formats, including clusters and monolayers

Publications

- Quach et al. "Light-Activated Dynamic Clamp Using iPSC-Derived Cardiomyocytes." *Biophysical J.* 2018.
- PCT Patent Application: WO/2020/072427. "Kits and methods for performing optical dynamic clamp on excitable cells." Published Apr 9, 2020.