Advancements in the Use of iPS Cell-Derived Systems for In Vitro Disease Modeling and Phenotypic Screening

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Abstract

Cellular Dynamics International (CDI) is the world’s largest producer of fully functional, terminally differentiated cell types derived from human induced pluripotent stem (iPS) cells. The quality, quantity, and purity of iCell® Cardiomyocytes, Endothelial Cells, Hepatocytes, and Neurons have been the driving force for adoption of this technology in the scientific community. The use of iCell products has helped to overcome many limitations of current in vitro cellular models, including limited supply, culture instability, poor representation of the disease state, and genetic background variability. Such advantages are illustrated in a rapidly growing list of publications highlighting the utility and predictivity of iCell products for various high throughput screening (HTS) applications.

To demonstrate the impact of iCell products in the drug discovery and development space, we present here examples of assay miniaturization, transduction optimization, and high content imaging-based phenotypic assays. With respect to disease modeling, we have utilized iCell Cardiomyocytes to simulate cardiac hypertrophy in vitro with a diverse array of endpoint readouts — including analysis of both gene expression and protein production of the biomarker, BNP. We have also optimized the delivery of shRNA oligonucleotides into iCell Neurons to develop unique systems for modulation studies at the gene-specific level. Finally, we share a published case study where researchers at GlaxoSmithKline screened a focused chemical library against iCell Neurons for compounds that blocked Aβ1-42 toxicity (Xu, X., et al. 2013: Stem Cell Res. 10: 213–227). This example, in addition to the other work presented here, provides an excellent paradigm for how iPS cell-derived terminal cell types offer a high level of consistency from experiment-to-experiment that is both scalable and on par with the complex human biology for which they are able to recapitulate. Implementation of iCell products into routine workflows should both accelerate the understanding of and yield more predictive information on drug activity in the human body.

Relevant Neuronal Model for Alzheimer’s Disease

Researchers at GSK used iCell Neurons to establish a cellular model of Alzheimer’s Disease. Neuronal loss was induced by exposure of the cells to an insult of Aβ1–42 aggregates. CDK2 was validated as an important signaling target for rescue of toxicity using known inhibitors and shRNA against CDK2. This model system was further utilized to identify novel modulators of this neurodegenerative disease in a focused drug screen.

Phenotypic Screening and Cardiac Hypertrophy

The HTS community is constantly striving to combine new technologies with advanced cellular systems and simplified assay workflows. However, the availability of a high-content relevant cell-based assays or disease-specific models that accurately represent the human condition is insufficient. Quality, and purity needed for a drug discovery campaign is severely lacking. Featured here is an in vitro disease model of cardiac hypertrophy using iCell Cardiomyocytes, as well as the development of a phenotypic assay in 384-well format that is suitable for screening. Understanding and manipulating the many complex mechanisms underlying cardiac hypertrophy has enormous therapeutic impact for cardiac dysfunction and heart disease.

HTS-Compatibility

iCell Neurons and iCell Cardiomyocytes can be used in large-scale HTS applications as they can be utilized in high-throughput screening (HTS) for drug discovery and development. HTS-optimized cell lines are amenable to 96-well plates or 384-well plates with high-throughput screening (HTS) applications. Ca2+ Handling data is presented for both FLIPR, 96- and 384-well Molecular Devices. XF Analyzer, 96-well (Seahorse Biosciences) and Malteso MEA, 46-well (Axion Biosystems)

RNai as a Tool for Discovery

Genetic manipulation techniques in primary neuronal cultures are especially inefficient and often toxic. In fact, neurons are considered one of the most difficult and resistant cell types for introduction of siRNA oligos. We have successfully utilized the Accell siRNA reagents (Thermo Scientific) to knockdown target gene expression as measured by quantitative real-time PCR (qPCR). These data lay the foundation for downstream investigation into the roles of specific genes in neuron development and functionality.

Summary

CDI’s core competencies are the reprogramming, engineering, and differentiation aspects of iPS cell technology. However, in order to help promote the use of iCell Products to routine laboratory workflows, the benefits and utility of using these human cell types must be demonstrated. The data presented in this poster illustrate such advantages, including a scalable and consistent cell source, compatibility with a variety of HTS formats and applications, high quality data with robust and reproducible results, and an ideal system for phenotypic screening. Furthermore, these examples highlight the potential new opportunities that iCell Products can offer for drug screening efforts in the future.