

Stem cell technology improves discovery hit rates

Cellular Dynamics International develops and markets human induced pluripotent stem cells and differentiated cells to the pharmaceutical industry and academic researchers for drug discovery, toxicity testing and basic research. The company launched its first human iPSC-derived product, iCell Cardiomyocytes, with endothelial cells, neurons, and hepatocytes soon to follow, all of which have the potential to improve pharmaceutical hit rates out of discovery and reduce the risk of rare adverse events that have been observed with some pharmaceuticals.

Founded in 2004 by Dr James Thomson, a University of Wisconsin-Madison pioneer in human embryonic stem cells, and Tactics II Ventures, a Wisconsin-based private equity fund, Cellular Dynamics International, Inc (CDI) is a developer and marketer of next-generation stem cell technologies for drug development and personalised medicine applications. The company uses human induced pluripotent stem cells and their ability to differentiate into any cell type as drug development tools. In addition, the company is a specialist in iPSC technology for the production of pluripotent stem cell lines from adult tissue.

Qualifying therapeutic discovery projects

In November of last year, CDI was awarded a total of \$977,915 for investments in four qualifying therapeutic discovery projects. The company is using the grant money to

advance the development of its programmes in hepatocytes, neurons, endothelial cells, and the creation of multiple induced pluripotent stem cell (iPSC) lines.

Human-induced pluripotent stem cells (hiPSC) are a particular type of human stem cell. Stem cells hold the potential to give rise to any cell type in the body, and unlike embryonic stem cells, which are generated during very early stages of the development of a fertilised egg, hiPSCs are generated by reprogramming fully differentiated mature cells, such as skin or various blood cells, back to a stem cell state. hiPSCs can be generated from virtually any donor, thus enabling researchers to perform relevant mechanistic studies of normal and diseased cellular processes in a native human cellular environment for the first time. CDI says such an advance will drastically alter the way in which research is performed and translated to better the human condition.

The isolation and cultivation of human embryonic stem cells was first published by Dr Thomson in 1998, while the creation of hiPSCs was simultaneously and independently reported by the laboratories of Dr Thomson and Dr Shinya Yamanaka in 2007. The first commercial application of hiPSC technology was the launch of CDI's iCell(R) Cardiomyocytes in late 2009.

"iCell Cardiomyocytes are the first commercial product developed from human iPS cells and are gaining wide acceptance in industrial and academic research programmes," says Chris Parker, CDI's chief commercial officer. "They beat spontaneously in vitro and exhibit the electrophysiological and biochemical properties of normal human heart cells, thereby creating significant advances over current cardiac cell models. By providing a relevant human model, this cellular tool is designed to aid basic research and drug discovery by enabling more precise drug targeting and greater compound efficacy as well as increased predictability of toxicity screens. As iCell Cardiomyocytes are an in vitro test system, they can be utilised early in the development pipeline to weed out ineffective and potentially toxic compounds prior to significant time and resource investment."

Early drug discovery

The initial applications of iCell Cardiomyocytes have been in pharmaceutical drug development across both the discovery and toxicity/drug safety areas. For example, several companies are studying cardiac hypertrophy and metabolic diseases and ways in which these processes can be therapeutically modulated. A variety of technology platforms, including high-content imaging, cell-based biochemical assays, label-free reporting and electrophysiological techniques, are being used to uniquely assess potential cardiotoxic effects of drugs under development. Traditionally, each technology platform would have used a



The key to the mass production of iPSCs and differentiated cell types is to develop a process that is automated, scalable and standardisable. Cellular Dynamics has industrialised this process to produce iPSC-derived cells in the quantity, quality, and purity required by pharma researchers.

surrogate cell model best suited for that particular platform. However, iCell Cardiomyocytes have multi-platform utility, thus enabling more relevant and meaningful data compilation from fully functional human cardiomyocytes.

"Human iPSC-derived technology has a very broad application in drug discovery and basic research," says Parker. "In drug discovery, the technology will provide human cellular environments to validate drug targets, compound efficacy and compound safety. Additionally, access to human cell types obtained from healthy and targeted disease populations will enable studies in the appropriate human cellular environment, lessen the need for surrogate non-human models, and facilitate the translation of laboratory data to the clinic.

"In addition to CDI's first human iPSC-derived product, iCell Cardiomyocytes, three additional cell types and a service will be launched in the near future: human iPSC-derived hepatocytes, neurons and endothelial cells; as well as the derivation of speciality iPSC lines. The current iCell Cardiomyocytes product will give rise to additional line extensions such as pure populations of cardiomyocyte sub-types – atrial, nodal or ventricular cells—as dictated by customer demand and needs," he says.

Technology collaborations

CDI recently completed a two-year early access collaboration with Roche Pharmaceuticals that is now transitioning into a standard supply agreement. Several additional agreements are well underway and are being expanded to encompass the other hiPSC products.

Last September, CDI formed a partnership

with ACEA Biosciences to bring early and accurate prediction of potential cardiotoxic side effects to the drug discovery process. The partnership combines CDI's iCell Cardiomyocytes with the xCELLigence™ RTCA System developed by ACEA and Roche Applied Science.

CDI supplied purified human iCell Cardiomyocytes to ACEA for the evaluation experiments. In these experiments, the xCELLigence RTCA Cardio System was used to measure the effects of cardiac compounds with known electrophysiological and/or biochemical actions as well as drugs withdrawn from the market due to cardiac liability. The evaluation has been completed, and the platform is in external beta testing at several pharmaceutical and academic institutions and will be made commercially available soon.

The xCELLigence RTCA system encompasses a series of instruments that utilises specially fabricated microtitre plates containing microelectrodes for real-time dynamic monitoring of cell behaviour under label-free conditions. A number of cell-based applications, including cell proliferation and cytotoxicity, cell adhesion, cell migration, and invasion and receptor-mediated signaling, have been developed on the xCELLigence platform, which provides a label-free, easy-to-use, fast analysis system for monitoring basic cell health and cardiomyocyte function.

In June of last year, CDI and Promega entered into a research collaboration to combine bioassays with human cardiomyocytes to improve prediction of unintentional and detrimental side effects that have previously remained undetected until late in the development process or after release of the drug to the general public. CDI

validated a panel of cell-based cytotoxicity assays from Promega that use iCell Cardiomyocytes. Promega's multiplexed biomarker assays for cytotoxicity and cell viability can be used to identify known toxic agents with similar sensitivity. CDI and its pharmaceutical collaborators have begun validating such assays in order to incorporate them into their routine discovery programmes.

"Ultimately, the combination of these two technologies from Promega and CDI is expected to provide more biologically predictive data and drive the development of safer and more effective drugs," says Parker.

Continuing to meet pharma's needs

"Pharmaceutical customers recognise the importance of using human models to perform their studies but up until recently, human cell models that exhibited true human biology *in vitro* were difficult to come by," says Parker. "We have several pharmaceutical customers who've validated *in-vitro* cardiotoxicity assays using iCell Cardiomyocytes, which have correlated well with previous data from cardiotoxicity studies in animal-based models.

"The stem cell space currently has several companies that utilise either embryonic human stem cell or animal iPSC models. However, CDI is the only company to date that has been able to supply pure human iPSC-derived product at the quantity, quality and purity needed by the pharmaceutical industry. The basic premise of commercialising hiPSC technology is to enable access to human-based test systems. From a drug discovery perspective, this will enable quicker development of safer and more effective drugs. CDI will continue to utilise its manufacturing infrastructure in responding to the needs of the pharmaceutical industry by providing innovative and cutting-edge stem cell tools," he concludes.

Further information

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Meet Chris Parker of CDI



Chris Parker is responsible for sales, marketing and business development for Cellular Dynamics International and brings more than 20 years of experience in the life science industry to the company. As a Vice President at Affymetrix, he managed all aspects of sales

and marketing for the Global Pharmaceutical Business Unit and led the sales efforts that grew Affymetrix to more than \$350 million per year in revenue within eight years. Prior to his position in the Global Pharmaceutical Business Unit, he was responsible for market development of Affymetrix's genetics business and flagship products. His background also includes serving on the drug discovery services team at Amersham Pharmacia and more than a decade of research in molecular and cellular biology in the Department of Human Oncology at the University of Wisconsin-Madison, Comprehensive Cancer Center. While there, he worked with notable investigators, including V. Craig Jordan, to develop important cancer drugs such as Tamoxifen.