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Patient-Specific Stem Cells and Cardiovascular Drug Discovery

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The pharmaceutical industry faces numerous challenges in the development of novel compounds. Phase II clinical trial success rates are at a five-year low of 22%, and the average number of preclinical programs needed to produce a single new drug has increased from 12 to 30 between 2007 and 2012 alone ¹. As a result, the average new drug requires over \$1.8 billion dollars and 12 years from time of discovery to commercial launch ². If drug development is to remain commercially viable in the future, the current model for drug discovery and development must undergo a fundamental shift. To counteract these high attrition rates and increased costs, drug developers need to be able to predict and identify potential efficacy and safety issues as early as possible during the drug discovery process. Doing so will enable more attention to be focused on programs with optimal chances of progressing through end-stage clinical trials rather than costly failures.

Since the discovery of human induced pluripotent stem cells (iPSCs) in 2007, this technology has been used to model diseases, interrogate drug response and toxicity, and create multiple cell types for therapeutic transplantation. To create iPSCs, somatic cells are first isolated from patient tissues, such as skin from punch biopsies, peripheral blood, lipoaspirate, cord blood, and amniotic fluids. Through ectopic expression of pluripotency transgenes (e.g., Oct4, Sox2, Nanog, and c-Myc), these somatic cells become similar to embryonic stem cells (ESCs). Because this technology does not involve embryo destruction, it can bypass the ethical controversy associated with ESCs. Similar to ESCs, these iPSCs possess the ability to “self-renew” (i.e., can divide indefinitely) and are “pluripotent” (i.e., can differentiate into cell populations of all three germ layers, including cardiomyocytes,

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pancreatic beta-islet cells, hepatocytes, and neuronal cells). Several studies have now shown that iPSC-derived cardiomyocytes (iPSC-CMs) derived from patients with various cardiovascular diseases, including familial dilated cardiomyopathy, familial hypertrophic cardiomyopathy, LEOPARD syndrome, Timothy syndrome, and long QT syndrome, can simulate clinically observed phenotypes *in vitro*.

Recent advances in iPSC-CMs present an important opportunity to overcome the current limitations of pre-clinical drug discovery. Unlike existing animal and *in vitro* cell expression models, iPSC-CMs represent a more physiologically relevant system in which biochemical, electrophysiological, genomic, and mechanical properties are similar to those of primary human cardiomyocytes³. Importantly, iPSC-CMs are able to exhibit certain disease processes at the single cell level, making them an attractive option for phenotypic and top-down drug screening cascades. Patient-specific iPSC-CMs also represent a new model for personalized medicine as they can exhibit “patient in a dish” disease phenotypes. Coupled with advances in next-generation sequencing technologies, patient-specific iPSC-CMs may help to accelerate the investigation of molecular mechanisms for cardiovascular disorders that are resistant to treatment and to identify novel therapeutic targets for these diseases (Figure 1).

After approval, approximately 4% of drugs released to market are subsequently withdrawn by the FDA because of safety issues. Cardiac toxicity is a leading cause of drug attrition during pharmaceutical development and drug withdrawal after market release, accounting for approximately 40% of all drugs withdrawn due to safety concerns⁴. These high-profile withdrawals have led to increased regulatory scrutiny, including mandatory pre-clinical drug screening policies to detect potential for drug-induced arrhythmia, QT prolongation, and Torsades de Pointes (TdP). The primary reason cardiotoxic effects are not detected earlier in the drug discovery process is the inability to access patient heart tissue at the preclinical stages of pharmaceutical development. Current FDA-mandated methods to screen for drug safety rely on artificial expression of single cardiac ion channels in genetically altered human and animal cell lines, or whole animal heart and Purkinje fiber assays⁵.

However, these *ex vivo* toxicity screening assays have significant limitations for human translation and do not always accurately predict the potential toxic effects of these drugs in patients. For instance, individual responses to pharmacological therapy differ significantly among diverse patient populations (e.g., isosorbide dinitrate/hydralazine combination is specifically indicated for African Americans with congestive heart failure)⁶, and current early stage drug screening methods do not take these genetic differences into account.

Recently, developments in phenotypic toxicity profiling methods that take advantage of patient-derived iPSC-CMs have made it possible to overcome the weaknesses of current *in vitro* and *in vivo* screening assays used in the pharmaceutical industry. For example, Liang et al. demonstrated that a panel of patient-specific iPSCs can be used to detect differences in cardiotoxic responses resulting from inter-patient genetic diversity and susceptibility to cardiac arrhythmia⁷. Patient-specific iPSC-CMs may also play an important role in drug repurposing or repositioning⁸. This approach aims at finding a therapeutic use of a drug or drug candidate for a disease other than that for which it was originally developed.

Combining phenotypic-based iPSC technology with high-throughput screening assays using libraries of approved drugs could result in new indications for existing FDA-approved compounds.

While iPSCs hold promise for drug discovery and development, significant hurdles must be overcome before iPSC-based technologies are widely accepted within the pharmaceutical industry, including technical difficulties associated with generating and analyzing iPSCs and iPSC-CMs. One major challenge is the ability to reliably produce mature cardiomyocytes that can accurately mimic physiology of the adult human heart. A second challenge is use of iPSC-CMs to model disease at the organ level, where additional cell types such as smooth muscle, endothelial cells, and fibroblasts, constitute the heart. There has been significant progress in these areas, with many groups conducting research aimed at the maturation and co-culture of iPSC-CMs using novel techniques such as 3-dimensional organ constructs.

In summary, by providing a more powerful platform for the identification of novel cardiovascular therapeutic targets and compounds, iPSC-CMs may help to foster efficient productivity in the pharmaceutical research and development process. By shifting attrition to the earlier preclinical stages of the drug development process, these cell lines could expedite early identification of lead drug candidates and potentially accelerate the screening of cardiotoxic and off-target effects of these pharmacological agents.

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Figure 1.

Patient-specific iPSC-CMs make an ideal platform for phenotypic drug discovery assays because of their capacity to recapitulate cardiac phenotypes. Coupled with current advances in high-throughput screening technologies, patient-specific iPSC-CMs will accelerate our ability to investigate the molecular mechanisms of cardiovascular disorders that are resistant to current pharmaceutical treatments and to identify novel therapeutic targets for these diseases.