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## Commercialization of ES/iPS cell drug screening technology

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*Chikafumi Yokoyama, CEO, ReproCELL, Japan*

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Embryonic stem cell (ES cell) and induced pluripotent stem cell (iPS cell) have been attracting a lot of attention. ES/iPS cells have two key advantages as a cell source: pluripotency to develop into various types of cells and the capacity for indefinite in-vitro expansion in a normal state. The combination of these two basic characteristics unleashes enormous potential for many new applications.

The ES/iPS cell business can be divided into four fields: research reagents, drug discovery tools, personalized medicine, and regenerative medicine. The growth of the research reagent market has accelerated since the invention of human iPS cell in 2007 by Prof. Shinya Yamanaka in Kyoto University. Some countries, including Japan, have set strict guidelines to use human ES cell because of the ethical issues related to the destruction of embryos. However, since iPS cells are derived from adult cells, the ethical issues are less contentious. Moreover, iPS holds the promise of autologous cell therapy for patients. These compelling advantages mean the number of researchers involved in iPS cell is growing quickly.

The application of stem cells to drug discovery is emerging rapidly. ReproCELL offers cardiotoxicity assay services using

cardiomyocytes derived from ES cells (from 2008) and iPS cells (from 2009). This is the first commercially available stem cell drug discovery services, and is the subject of this article.

Human ES/iPS cell technology will bring a paradigm shift in drug discovery technology in future, because various types of functional cells derived from human ES/iPS cells can be supplied infinitely. Currently, immortalized cell lines and animal derived-primary cells are usually used in drug discovery process. However, the former lose the characteristics of normal cells, and therefore, their ability to be usefully screened for specific functions, while the latter are difficult to supply to mass production scale and suffer large lot-to-lot variation. Human ES/iPS cells are the only cell source which can be developed into various types of human functional cells including cardiomyocyte, neuron, hepatocyte, and insulin secreting beta cells. Cell-based assays using these human differentiated cells will change the drug discovery process significantly.

Personalized medicine is a future target of drug discovery technology. iPS technology has enormous potential in this area. Individual iPS cells, obtained from individual somatic cells, have the potential to be differentiated to any type of functional cells. In general, metabolizing enzyme levels vary widely in individuals, and the rates of drug metabolism also vary. If an individual's hepatocyte can be derived from iPS cells, it could be used to test the metabolism of various commercially available drugs to define an appropriate prescription.

Regenerative medicine is the most promising application in ES/iPS cell field. The clinical trial by Geron Corporation is set to be a significant breakthrough in 2009.

**Drug discovery technology using ES/iPS cells**

R&D costs in pharma companies are currently growing, consuming 15-20 percent of total revenues. The reasons for this increased cost per drug are mainly due to a higher rate of attrition of candidates drugs. As regulatory agencies raise safety standards, poor toxicity profiles are increasingly seen as a liability that has to be better managed. If the efficacy and toxicity of the drug candidate could be predicted more accurately at earlier stages of drug development, overall R&D cost and drug development period can be reduced significantly. Human ES/iPS cells have enormous potential to impact on this issue.

Drug-induced QT interval prolongation (DIQTIP) leading to serious ventricular arrhythmias poses a major safety concern for the development and use of new drug candidates. Candidate compounds in clinical development have been dropped as a result of DIQTIP and many marketed drugs have been withdrawn. This significant safety issue has caused regulatory agencies such as the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) to require pharmaceutical companies to implement safety studies to minimize the risk of QT interval prolongation.

Several preclinical models are available to evaluate compound's potential to cause DIQTIP: the most widely used are an in vitro hERG (human ether a-go-go-related gene) assay and animal-based QT prolongation assays. However, these assays are usually performed in late stages of preclinical development, due to cost and resource limitation. To predict potential QT prolongation in early drug development, we set out to establish a new assay system using cardiomyocytes derived from human ES/iPS cells. The patch-clamp based hERG assay is most widely used for this purpose and its use is regulatory mandated.

However, the hERG assay can be inaccurate (false positives and false negatives) because it does not take account of non-hERG cardiac ion channels and does not measure the overall effect of a compound on cardiomyocyte function. ReproCELL has developed QTempo (QT prolongation Examination with Myocardia derived from Pluripotent cell), a significantly improved assay that incorporates spontaneously beating cardiomyocytes derived from monkey, human ES cells and human iPS cells. To validate QTempo, beating cardiomyocytes were placed on micro-electrode arrays and challenged with reference compounds known to cause clinical DIQTIP. Compounds tested included E-4031, astemizole, rofecoxib, dofetilide, flecainide, lidocaine, quinidine and terfenadine sotalol.

All compounds could be assayed using QTempo at drug concentrations equal to, or lower than, those reported for the hERG assay. For example, verapamil, which does not prolong QT interval in-vivo but generates a false positive in the hERG assay, was correctly scored negative for DIQTIP in the QTempo assay.

The QTempo assay is more predictive of clinical outcome because it more closely reproduces clinical mechanisms involved in potential regulation of cardiac action: it is not limited to a single ion channel, and is built around beating cardiomyocytes. Data output for QTempo resembles the familiar ECG and is readily understood by clinicians as well as specialist scientists. Large numbers of beating cardiomyocytes derived from hiPSC can be generated for this system allowing parallel HTS screening of drugs. QTempo is a valuable tool for the more accurate prediction of clinical cardiotoxicity.Cardiotoxicty assay is the first commercialized technology for ES/iPS cell drug discovery.