Research and Reviews: Drug Delivery

Current Developments in Toxicology and Drug Metabolism

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Perspective

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DESCRIPTION

The application of PSC in drug toxicology and safety pharmacology has enabled significant progress to be made in this area. In particular, the availability of hPSC brings us closer to bridging the gap when translating pre-clinical data to the clinical setting, an issue that has and continues to play a key role in the development of ADRs. Much work have demonstrated such progress through the use of these novel model systems, with some good correlations between *in vitro*, *in vivo* and clinical data, providing greater confidence in the predictive power of these novel stem cell-based model systems. Furthermore, the application of iPSC for disease modeling is an attractive proposition, while its potential as an alternative source of undifferentiated stem cells for use in mechanistic studies of disease states will serve to reduce derivation of hPSC from embryos.

Recently, the ability to directly convert from one cell lineage to another through lineage reprogramming or transcription factor-based trans-differentiation has been demonstrated in a number of studies. Reports include the direct conversion of human fibroblasts and hepatocytes into neuronal cells, the bi-directional trans-differentiation of pancreatic cells into hepatocytes, and HepG2 cells into pancreatic-like cells which have been shown to produce insulin. This technique is particularly advantageous over the traditional method of inducing pluripotency in somatic cells initially before differentiation into a different lineage, as it avoids the potentially tumorigenic state of PSC, as well as contamination within the reprogrammed population of cells by residual undifferentiated PSC. As described

earlier, this approach also provides an alternative source of human cell types which could ultimately reduce significantly or remove the need for sourcing ESC from human and animal embryos.

The advent of PSC in combination with state-of-the-art analytical techniques have provided drug toxicology and safety pharmacology an incredibly rich resource and a large window of opportunity to carry out experiments that a decade or two ago would have been deemed unimaginable. These new systems require further refinement and optimization but most importantly, should be fully validated. Limitations of these systems should also be identified. Current and future validations of *in vitro* models for drug toxicity are likely to differ in accordance with the demands of which they are designed to meet. Within the area of developmental toxicity, attempts to validate the EST by several working groups that have been established solely for this purpose such as ReproTech have collectively demonstrated that further refinement of this test for the screening of xenobiotic-induced developmental toxicity is required. Independent assessments of reference compounds with known toxicities using the EST have shown varying predictive accuracies of the EST method between laboratories. As such, there is yet no fully validated EST protocol that has been approved for regulatory registrations and risk assessments of NCE. However, modified versions of the EST according to the requirements of the user have been developed and are routinely used within the pharmaceutical industry as a tool to facilitate in the decision making on compounds during the early stages of drug discovery and development. There is still however great interest in the development of a fully validated EST that is suitable for regulatory registrations and risk assessments. To assist in achieving this, a number of optimization strategies have been suggested by the pharmaceutical industry, academia and regulatory authorities. One such suggestion with reference to the original EST protocol is to drive the differentiation process from ESC into different lineages instead of generically driving the differentiation process toward a cardiac phenotype. Through this, the predictive power of the EST could be increased as the endpoint during the differentiation process will have more relevance depending on the compound(s) being tested as previously demonstrated with Thalidomide.

Similar to the current situation in the developmental toxicity arena, no hPSC-based *in vitro* cardiotoxicity assay has been formally validated yet, as some of the official test development criteria, such as the biological relevance of the hPSC-CM model, is not fulfilled (OECD). Although the hPSC-CM model with its fetal phenotype has been shown to predict the electrophysiological alterations similar to clinically detected electrocardiographic changes, the full impact on the toxicological response to cardio-toxicants, especially non-electrophysiological cellular cardiotoxicity, is not ascertained. A full characterization of the hPSC-CM against the gold standard of human primary cardiomyocytes in terms of functional assessment, as well as standardization of an agreed and reproducible differentiation protocol are still needed before formal validation of models using hPSC-CM can be considered. Similarly, for the purposes of toxicology research and screening of NCE by the pharmaceutical industry using hPSC-CM, reproducibility of the expressed phenotype is important and the detection of a panel of agreed markers will serve as internal validation of the hPSC-CM-based assay.