Editorial

Stem cells technologies in toxicology assessments

During the last decade, stem cells have been the subject of increasing scientific interest because of their utility in numerous biomedical applications. Stem cells are able to renew themselves, they can be continuously cultured in an undifferentiated state or giving rise to more specialized cells of the human body such as blood, bone marrow, liver, heart, and nerve cells, etc. Therefore, stem cells are an important tool for developing in vitro model systems from all species including man to test xenobiotics and improve the relevance of toxicity in human.

The articles presented in this volume focus on the use and application of stem cells in drug and chemical safety assessment. The purpose of publishing this special issue in the journal Toxicology is to acquaint the toxicology community with the advances in stem cell technology and its use in safety assessment, a theme which was, inter alia, eloquently analyzed and discussed at the EUROTOX 2008 Congress, held in Rhodes, Greece.

Given the reality of the inadequacies in existing concepts of the mechanisms of chemical toxicities and of the various assays to predict toxicities from current molecular, biochemical, in vitro and animal bioassays, recently (in NAS Report, “Toxicity Testing in the 21st Century: A Vision and a Strategy”) attention has been drawn to a renewed examination of what needs to be done to improve our current approach for better assessment of potential risk to human health. The Academy report provides a major paradigm-challenge to the present concepts of how chemicals induce toxicities and how these various mechanisms of toxicities can contribute to the pathogenesis of some human diseases, such as birth defects and cancer. This report supports the use of human embryonic and adult stem cells, grown in vitro under simulated “in vivo niche conditions”.

More specifically, while tissues contain a few stem cells, many progenitor/transit cells and terminally differentiated cells, it should be obvious that both embryonic and adult stem cells would be critical “target” cells for toxicity testing. The ultimate potential for in vitro testing of human stem cells will to try to mimic a 3-D in vitro microenvironment on multiple “organ-specific and multiple genotypic/gender” adult stem cells. The role of stem cells in many chronic diseases, such as cancer, birth defects, and possibly adult diseases after pre-natal and early post-natal exposures (Barker hypothesis), demands toxicity studies on stem cells. Alteration of gene expression (“toxico-epigenetic”) and of the quantity of stem cells during development is a legitimate endpoint of these toxicity studies. If the future utility of human stem cells proves to be valid, the less relevant, expensive and time-consuming rodent and 2-D human in vitro assays will be eliminated.

The ethical dilemma on the use of toxicity tests based on human embryonic stem cell lines (hESCs) is still under debate since no harmonization within Europe on the use of hESC lines has been achieved yet. A mutual acceptance of toxicity tests based on hESCs for regulatory applications is therefore challenging. Recent reports on the establishment of induced pluripotent stem cells (iPSC) are pointing to a way out of this dilemma, since these cells have apparently very similar characteristics as hESCs and per se could serve as a basis for the development of toxicity tests. A careful scientific comparison between pluripotent cells of different origin is now needed in order to make final judgments. In any case, the development of reliable and relevant in vitro toxicity tests based on human pluripotent cells requires additional validation of several critical parameters.

Nowadays research projects developing hESC-based toxicity tests at EU level and their possible use within the European Legislations relevant to safety assessments of industrial chemicals (REACH) and Cosmetic ingredients are ongoing. These projects will provide preliminary insights in additional quality assessments needed for iPSCs. Designs and applications for clonogenic assays have been used to detect myelotoxicity induced by chemicals, drugs, food and environmental contaminants. Myelotoxicity describes bone marrow failure due to adverse effects of xenobiotics on hematopoiesis, a complex system in which pluripotent hematopoietic stem cells (PHSCs) differentiate into many highly specialized hematopoietic cells (PHSCs) and the progenitor cells, on one hand, and the stromal cells, which constitute the hematopoietic environmental niche, on the other hand.

Primary hepatocytes and transformed liver cell lines, stem cells either isolated from embryos or adult tissues or obtained by reprogramming somatic cells are emerging as a new potential source of unlimited numbers of hepatocytes. Currently, only hepatocyte-like cells expressing low levels of liver-specific markers, especially drug metabolizing and detoxifying enzymes, are usually obtained, making them at present unsuitable as metabolically competent cells for toxicity studies. The only exceptions are some hematoma cell lines, particularly the HepaRG cell line that can differentiate from a bipotent progenitor stage to attain the functional capacity of normal adult hepatocytes in primary culture without losing the indefinite growth property of transformed cells.

Studies demonstrated that stem cells derived from other tissues could home to and/or participate in the regeneration of liver tissue, raising the possibility that stem cell-based therapies may be developed for effective treatment of liver diseases. A clinically attractive approach is to use granulocyte colony-stimulating factor...
(G-CSF) to mobilize bone marrow stem cells (BMSCs) to the circulation. The intermittent G-CSF treatment provoked the initiation of endogenous hepatic tissue regeneration in response to CCl4 injury and ameliorate its fibrogenic effects.

Stem cell technology combined with emerging surface nano/micro-technologies provides a new tool for better understanding of the mechanisms involved in cell-fate decisions and compound-induced adverse reactions. Stem cell technology will provide state-of-the-art development of modern multiparameter bio-tests based on interactions between neural stem cells derived from human cord blood and bioengineered surfaces. Bioengineered surfaces on protein microarrays and microelectrode array chips provide a novel approach to the multiparameter bio-tests by adding important information on the sensitivity of certain molecular pathways and functional cellular responses to selected neurotoxins.

The selected papers in this special issue demonstrate the use and application of stem cells in drug and chemical safety assessment and reflect the present state of the art in stem cell technology.