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Using Stem Cells in Toxicological Assessments

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Introduction

An increasing number of regulations around the world support and require *in vitro* toxicity testing in order to replace animal studies and to obtain more predictable results under *in vitro* conditions [1]. Towards this direction, stem cells and their use in *in vitro* pharmacological and toxicological studies are gaining increasing scientific interest [2,3]. Stem cells have the capacity for self-renewal and generation of differentiated cells, such as cardiomyocytes, hepatocytes, neurons, and muscle cells. In the field of toxicology, stem cell studies mainly focus on target organ toxicity and developmental toxicity.

Animal studies present limitations such as cross-species extrapolation and metabolic differences between species. Furthermore, there is always a concern regarding ethical issues. On the other hand, human stem cell technology has a high potential to overcome disadvantages of animal testing, which do not always reflect human toxicity.

Stem cell sources could be classified into 2 main groups: embryonic and non-embryonic. Embryonic stem cells are good predictors for prenatal developmental studies, while non-embryonic stem cells are more suitable for disease modelling [4].

Stem cells are important targets for environmental toxicants. At the genomic, proteomic and epigenomic levels, environmental toxicants such as pesticides, tobacco smoke, heavy metals and radiation can affect changes associated with ageing in stem cells [5].

There is an increasing need for validated, *in vitro*, alternative methods for regulatory purposes. Recently, the EPAA (European Partnership of Alternatives to Animal Testing) organized a workshop on stem cell models and stressed that stem cell studies need further multidisciplinary work [6]. The European Union Reference Laboratory for alternatives to animal testing (EURL-ECVAM) has validated mouse embryonic stem cell use in embryotoxicity screening [7]. The mouse embryonic stem cell test (mEST) is based on the determination of cardiomyocyte differentiation and on the comparison of cytotoxicity differences between mEST and 3T3 fibroblasts [8].

It is ofcourse self-evident that studies on human embryonic stem cells could better represent and help us understand the pharmacological effects and toxicological exposures in humans. However, until today, ECVAM has not approved any human embryonic stem cell based test. In order to obtain human embryonic stem cells, a human embryo has to be destroyed. Therefore, ethical reasons constitute the main limitation towards the development of human embryonic stem cell techniques and their use for toxicity assessments and regulatory applications.

However, it seems that induced pluripotent stem cells (iPSC) could be a good alternative to human embryonic stem cells. Gurdon and Yamanaka received the Nobel Prize in 2012 with their discovery that mature cells could be converted to stem cells [9]. Induced pluripotent stem cells could be derived from differentiated, mature, specialized cells by manipulating pluripotency genes [10]. iPSCs from patients suffering from the disease of interest seem to be a promising tool for understanding pathology in the cell model. During the last years, iPSCs have been used in disease modelling and the discovery of disease-specific biomarkers.

Pluripotent cells from different origins must be evaluated and compared to each other in terms of representing *in vitro* toxicity. It is critical to standardize reprogramming protocols and culture conditions and to characterize stem cells with pluripotency markers [11]. Hepatocytes play a crucial role in the metabolism of chemicals and drugs and iPSCs seem to be promising for use in hepatotoxicity studies. Reprogramming iPSCs to hepatocyte-like cells is a challenging issue, as genetic and epigenetic abnormalities may take place. Currently, primary hepatocytes and some transformed cell lines, such as HepaRG cells, seem to be the most appropriate cell models for hepatotoxicity testing. However, there is a potential for using iPSC-derived hepatocytes in several fields, such as drug screening and *in vitro* disease modelling. Producing large numbers of metabolically suitable liver cell lines for use in pharmacological and toxicological studies [12,13] seems to have an increasing scientific interest.

Neurotoxicity studies present many challenges and it seems that stem cells are quite promising in this field. Stem cells are

able to differentiate into functional and metabolically active neurons, oligodendrocytes and astrocytes under *in vitro* conditions. The development of validated, stem cell-based neurotoxicity models will improve studies in different fields, such as developmental neurotoxicity, neurodegenerative medicine and drug-induced neuropathy [14,15].

Cardiotoxicity is an important and frequent adverse effect of chemical exposure or drug treatment. However, preclinical tests may fail to demonstrate cardiotoxicity. Due to limitations in preclinical tests, new models are of scientific interest. iPSC-derived cardiomyocytes seem to be a good model for studying drug cardiotoxicity and validation studies are currently underway to assess stem cell technologies for such applications [16,17].

Isolated cell culture models do not represent vascularisation and immunological parameters and it is therefore hard to extrapolate data obtained from these studies to humans. On the other hand, three dimensional cell cultures are good models for studying target organ toxicity. Future progress in the 3D human stem cell-based models will greatly contribute to the development of more predictable models in the field of toxicology [14]. Such advancements in stem cell technologies will allow the development of novel *in vitro* methods for early testing of drugs and chemicals, and will enable the reduction of animal studies.

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