STEM CELLS WORKSHOP

flash

The European Partnership for Alternative Approaches to Animal Testing

Ispra, 4-5 October 2011

STEM CELLS AND THEIR DERIVATIVES IN TOXICOLOGICAL RESEARCH PROGRAMS AND AS A POSSIBLE REGULATORY TOOL *A GAP ANALYSIS*

A workshop of the EPAA Platform on Science

Some thirty experts from academia, toxicologists, regulators and "end-users" met in Ispra on 4th-5th of October 2011 in a scientific Workshop on stem cells and their derivatives in toxicological research programs and as a possible regulatory tool to analyse current activities in the area of stem-cell based toxicity testing that are of interest for "new" safety assessments. Participants exchanged information, views and ideas and agreed on the need for a more permanent platform to keep knowledge flowing, harmonise the research efforts and facilitate collaboration. As the stem cell area is relatively new and rapidly evolving, the meeting also provided a much needed "reality check" and as such a more precise and realistic perspective as a necessary basis for a successful approach to stem-cell based toxicity testing.

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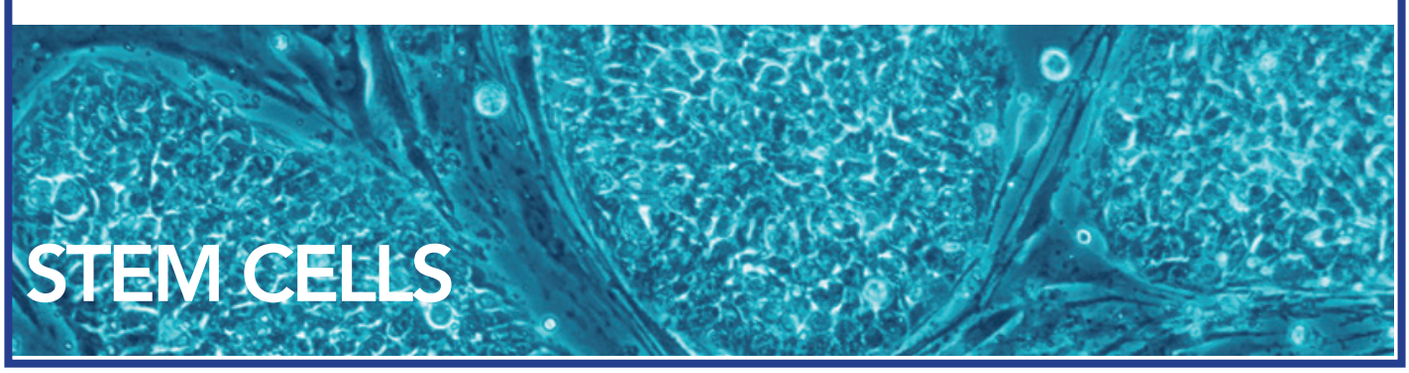
Several workshops in the past, including a meeting organised by EPAA in 2009, already examined opportunities given by stem cells in the field of safety assessments, providing fruitful indications and recommendations for existing and yet-to-come research projects. However, a comprehensive and systematic overview of all the activities currently undertaken in the area of stem-cell based toxicity testing was not yet available. The workshop therefore intended to identify opportunities to be developed and gaps to be filled by ongoing and future stem cell programmes, and to explore the possibility to build a "permanent forum" able to monitor current activities and to identify urgent needs and promising developments in such a rapidly evolving field.

Representatives of industry [M. Beilmann, Boehringer Ingelheim and B. Cochrane, Unilever], and the European Agencies [JM Vidal and B Silva Lima, EMA, and J Nouwen, ECHA] presented the views and needs of various stakeholders. One major aspect was the definition of toxicological pathways and their prospective role in risk assessment. An overview of the approaches currently undertaken in the USA was given by D. Stedman [Pfizer], providing a wider perspective on the need for a better coordinated action between Europe and the US. Other presentations described current and future European research initiatives on stem cells.

The Workshop undertook a mapping exercise of currently available information and steering directions for the future, analysing the state of the art of stem cell based safety assessments and feasible short term developments, while attempting to identify knowledge gaps and to provide indication as to where research programmes should focus on.

Major questions tackled concerned the question to know what can be expected from stem cells with respect to toxicological pathways and how many of these pathways need to be assessed, how an agreement can be reached on quality standards (induction of pluripotency, relevance and plasticity of adult stem cells, ethical standards) in the field of stem-cell related toxicity testing, and how a biomarker can be qualified as toxicologically relevant, i.e. being able to predict an adverse outcome.



The Workshop lead to several productive conclusions, but also highlighted the fact that several additional aspects require deeper analysis. The need to distinguish adaptive stress responses from pathway perturbations leading to a toxic endpoint remains a key and still unresolved issue. The concept of 'identifying toxicity pathways' was challenged and the question which stem cell based cell model, either undifferentiated or differentiated would be needed for this approach remained unresolved. Further discussions related to the degree of complexity of stem cell derived cell models in the context of organ toxicity testing, comparing 2D single cell type models with multicellular 3D organ-like models for each organ.

Major questions are whether emerging human stem cell based cell models should still be validated against the traditional animal toxicity models or whether new validation models need to be explored, and whether the available techniques are sufficient or whether new technologies will have to be developed, validated and adopted.

Recommendations for future short- and long-term activities include the following:

>>> A contemplated step must be taken in the direction of better harmonisation of research initiatives through the constitution of an international forum. This harmonisation effort should rely on common quality standards, improved communication and shared information, technologies and training;

>>> Knowledge of the basic biology of stem cells needs to be further expanded and detailed for efficient and reliable stem cell based predictive toxicity testing. In particular, further research is needed in the following fields: stem cell derived organotypic cultures (3D); relevance of stem cells for carcinogenicity assays; differentiation between adaptive response and adverse perturbation; translational aspects of stem cell use;

>>> An efficient communication network is especially needed regarding reference compounds, as a central tool to gather and share information about specific organ toxicities;

The detailed outcome of the workshop with the group's recommendations will be submitted to a peer-reviewed publication, in order to help broaden the debate to the whole scientific community. However, the first follow-up actions to set up the forum platform are already being taken.

WORKSHOP PARTICIPANTS

Mario Beilmann, Boehringer Ingelheim; Frank Bonner, Stem Cells for Safer Medicines; Susanne Bremer, JRC/ECVAM; Klaus-Dieter Bremm, Bayer; Gabriela Cezar, Stemina Biomarker Discovery; Brett Cochrane, Unilever; Paul Duffy, AstraZeneca; Roy Forster, CiToxLAB France; Jürgen Hescheler, University of Cologne; Julie Holder, GSK; Anthony Holmes, National Centre for the Replacement, Refinement and Reduction of Animals in Research (NC3Rs); Magnus Ingelman-Sundberg, Karolinska Institutet; Martina Klaric, JRC/ECVAM; Gabriele Küsters, EPAA Project management Support; Pratibha Mistry, Syngenta; Silvia Nerini-Molteni, JRC/ECVAM; Johan Nouwen, ECHA; Marc Peschanski, Institute for Stem cell Therapy and Exploration of Monogenic diseases INSERM U861 (I-Stem); Agapios Sachinidis, University of Cologne; Beatriz Silva Lima, EMA; Pablo Steinberg, University of Veterinary Medicine Hannover; Donald Stedman, Pfizer; Laura Suter-Dick, F.Hoffmann-LaRoche; Belen Tornesi, Abbott; Jean-Marc Vidal, EMA.

ORGANISING TEAM

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