

Lecture: free communications

Improved toxicity prediction for safety assessment of drugs during preclinical drug development using relevant hepatic and cardiac cell lines

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Preclinical drug testing for efficacy and safety represents a lag phase in drug development where most time is spend. With strict regulations and exigent requirements from the regulatory authorities such as the FDA and EMEA, it is not only a challenge but sometimes a problem for the pharmaceutical industry which has to kill thousands of potential drug molecules due to safety concerns.

Lately huge progress has been achieved for the safety issues and side effects monitoring and understanding of toxicity mechanisms of drugs. However, the methods of safety assessment have been lagging behind. This has led to an urgent need to improve the preclinical testing so as to avoid late drug attrition and clinical trial failures where most of pharmaceutical costs are concentrated. In addition, post-marketing withdrawal due to side effects is becoming a nightmare for the pharmaceutical industry. This is despite the extensive use of animal test systems which shows that these systems have poor clinical relevance.

Better cell based assays incorporating human relevant cells such as the hESC derived cells as well as innovative non invasive assays in an integrated approach hold a great promise for the improvement of toxicity prediction. We present here a novel integrated approach of a kinetic respiration assay (Deshpande et al., 2005) and the techniques of metabolome and flux analysis (Gouder et al., 2006) for toxicity assessment of drugs and NCEs (new chemical entities). We are applying these techniques to reference cell lines namely Hep G2 and HL-1 but these techniques are applicable to more human relevant cells that is the human embryonic stem cell derived hepatocytes and cardiomyocytes within our European projects namely; Vitrocellomics and Invitroheart.

References

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