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Pharmaceutical toxicology: Designing studies to reduce animal use, while maximizing human translation

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ABSTRACT

Evaluation of the safety of new chemicals and pharmaceuticals requires the combination of information from various sources (e.g. *in vitro*, *in silico* and *in vivo*) to provide an assessment of risk to human health and the environment. The authors have identified opportunities to maximize the predictivity of this information to humans while reducing animal use in four key areas; (i) accelerating the uptake of *in vitro* methods; (ii) incorporating the latest science into safety pharmacology assessments; (iii) optimizing rodent study design in biological development and (iv) consolidating approaches in developmental and reproductive toxicology. Through providing a forum for open discussion of novel proposals, reviewing current research and obtaining expert opinion in each of the four areas, the authors have developed recommendations on good practice and future strategy.

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1. Introduction

Traditionally, evaluation of the safety of new chemicals and pharmaceuticals requires regulatory studies in animals to protect human health and the environment. Given their importance, the utility of animal models for prediction of human safety should be regularly reviewed as advances in both scientific understanding and technical methods evolve. This practice is essential to ensuring

Abbreviations: 3Rs, replacement, refinement and reduction of animals in research; ACSA, Agricultural Chemicals Safety Assessment; ADA, anti-drug antibody; CNS, central nervous system; DBS, dried blood spot; DART, developmental and reproductive toxicity; DRF, dose range finding; ECG, electrocardiograph; EFD, embryofetal development; EPA, environmental protection agency; ePPND, enhanced peri-postnatal toxicity study; GLP, Good Laboratory Practice; hERG, human Ether-a-Go-go Related Gene; ICATM, International Cooperation on Alternative Test Methods; ICH, International Conference for Harmonisation; ILSI-HESI, International Life Sciences Institute Health and Environmental Sciences Institute; IND, investigational new drug; JET, jacketed external telemetry; LLNA, Local Lymph Node Assay; mAb, monoclonal antibody; NHP, non-human primate; NRC, National Research Council; OECD, Organisation for Economic Co-operation and Development; PD, pharmacodynamic; PK, pharmacokinetic; PPND, peri-postnatal toxicity study; TK, toxicokinetic.

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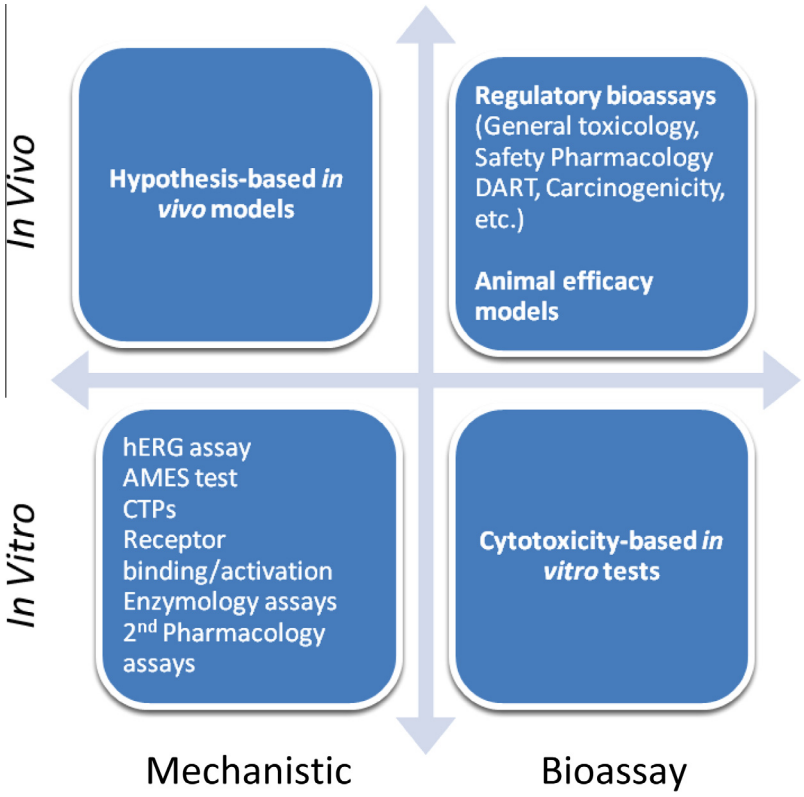

Fig. 1. Examples of *in vitro* and *in vivo* methods. Specific biological mechanisms and holistic bioassays are represented separately. hERG, human Ether-a-Go-go Related Gene; CTPs, phosphocholine cytidylyltransferase; DART, developmental and reproductive toxicity.

appropriate animal use in toxicology studies, with the continued goals of not only improving their predictive value but also reducing overall animal use and enhancing animal welfare.

Generally, risk assessment can be viewed as a process by which information from various sources (e.g. *in vitro*, *in silico*, and *in vivo* studies) is combined to characterize a particular chemical or molecular entity. Ideally, chemical and drug development would be front-loaded with experiments that can definitively select safe compounds as quickly as possible. As data accumulates to support the predictive validity of *in silico* and *in vitro* studies for human safety, these techniques will enable compounds to be deselected earlier in development, thereby limiting the need for animal testing. The replacement, refinement, and reduction of animals in research (the 3Rs) is a well-established concept, originally described in 1959 (Russell and Burch, 1959). Throughout the 1960s and 1970s, the idea that there may be alternatives to animals in research continued to increase in visibility, until finally gaining significant momentum during the 1980s when governments, academia and industry became more involved (Stephens et al., 2001). However, it is only now 50 years since the initial publication that the 3Rs are truly coming of age, with growing recognition of their benefits and widespread efforts to identify new opportunities for implementation.

In order to identify opportunities to further reduce animal use and improve efficiency in drug development, an international workshop was convened to catalyze discussion on various related themes, including: (1) accelerating the progress and uptake of *in vitro* methods, (2) incorporating the latest science into safety pharmacology assessments, (3) optimizing designs for rodent studies to support the development of biologicals, and (4) consolidating various approaches and endpoints in developmental and reproductive toxicology. Representatives from international pharmaceutical companies, contract research organizations, and regulatory agencies also discussed potential concerns around regulatory acceptance when making decisions using novel, rather than traditional approaches. In the 12 months since the workshop, drawing on the expertise of the authors and others present, we have worked towards some practical solutions to common challenges with implementing and improving 3Rs practices in these various areas. Further, expert advice on how new ideas and approaches may be effectively integrated into the constantly evolving model of drug development is discussed. Although this paper is focused on the pharmaceutical industry, participants from the agrochemical industry have also participated, and we have also drawn on their experiences to identify cross-sector parallels.

2. Predicting human toxicology using *in vitro* methods; can we accelerate progress?

There are multiple drivers for the development of new *in vitro* approaches to replace animal bioassay testing including scientific and technological advances, increased focus on animal welfare, and legislative changes. Position papers in Europe and the US (Schumann, 2002; EEC, 1986; Louhimies, 2002), European legislation for the testing of chemicals and cosmetics (EEC, 1976; REACH, 2006) and establishment of validation centers for alternative test methods illustrate the interest in this area from the international community of scientists, regulators and government agencies. Additionally, the European Medical Agency (EMA) recognized the increased use of *in vitro* methods with a recent revision of their concept paper on the replacement of animal studies with *in vitro* tests (EMA, 2012). One purpose of this paper was to more clearly define the process for regulatory acceptance of alternatives, including the need for formal validation studies on some occasions but proof of scientific validity on others.

The intended goal of this section is to provide expert opinion on the smooth integration of appropriate *in vitro* tests into current

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