The Use of Human Tissues and Cells in Biomedical Research: The Unusual Suspects

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Summary — There are compelling reasons to search for alternatives to the use of animals in medical and pharmaceutical research. Aside from the obvious animal welfare issues, both the well-established differences between animal models and humans, and the inherent inter-individual variability in human biological responses, indicate that human-based alternatives are urgently required. However, any such alternative must out-perform the animal-based alternative, otherwise there will be little or no uptake and adoption by end-users. Data obtained from inbred animal models is often highly reproducible, and is therefore attractive to researchers in the fields of biomedical and pharmaceutical research. The inter-individual variability observed during human volunteer and human tissue-based studies is often considered to be problematic, and has been highlighted further with the advent of the ‘omics’ technologies which generate large biological datasets. However, the variability in both baseline data and response to pharmacological or toxicological challenge observed in human tissues potentially contains a veritable gold mine of information, which may be critical for the advancement of drug discovery.

Key words: DNA microarray, human tissues, primary cell culture, systems biology.

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Introduction

Animals and, in particular, rodents, have long been the main experimental models for pharmaceutical and toxicological research. There are many reasons for this and, when taken at face value, the use of animals makes considerable scientific sense. The use of inbred rodent models in a controlled, pathogen-free environment, often generates data that are reproducible and reliable. The response to toxic or pharmacological challenge is robust, and the degree of inter-animal variability is fairly low. Therefore, it is not surprising that animal-based testing is considered to be integral to the majority of drug discovery programmes, and is essential for the regulatory approval of new medicines and toxicological studies. Indeed, the numbers of rodents used in biomedical research has risen in recent years, primarily due to the increase in the use of transgenic mouse models of human disease (1). This increase reflects the desire to improve the test bed for new drugs. It has been suggested that, in combination with microarray gene expression assays, metabolomics and proteomics, new rodent models of human disease will provide much more-comprehensive and relevant information with regard to the pharmacological effects of a candidate drug (2, 3). Despite these initiatives, the massive increase in research and development (R&D) budgets and the directives set out in the Food and Drug Administration’s Critical Path document (4), the registration of new molecular entities for therapeutic use is considerably lower per annum than in previous decades. The moribund state of the drug pipeline is clearly a major problem. When this is allied to the high-profile recall of potential blockbuster drugs, such as Vioxx, Rimonabant and Avandia, and the fact that many drugs fail to progress to the market due to lack of efficacy in humans, the conclusion must be that drug discovery, development and safety are not best served by strategies based on animal testing.

The Need for Human-based Alternatives

Basic differences between human and rodent metabolism

Perhaps the most compelling reason for the use of human subjects and tissues in medical research is that, in a significant number of experimental paradigms, rodent metabolism and responses to pharmaceutical intervention are not sufficiently similar to those observed in humans to act as a scientifically useful model. Work in our laboratory during the 1990s and early 2000s focused on the effects of