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European Journal of Cancer 40 (2004) 783–784

European Journal of Cancer

www.ejconline.com

Introduction

Preclinical models in cancer drug discovery and development

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The continued clinical need for new cancer medicines and recent advances in molecular pathology have resulted in unprecedented levels of activity in both the academic and commercial drug-development communities. Methods such as high-throughput genomic and proteomic analyses, and high-throughput compound screening and structure-based drug design, are identifying a large number of drug targets and the molecules that act on these. However, the complexities of the cell and intact organisms are such that it is not yet possible to progress directly from cell-free, or indeed *in vitro* cell culture-based, assays to clinical trials. Hence preclinical models of human cancer are needed to prioritise and select potential drug candidates for investigations in man. There are at least three important reasons for this circumstance. First, while patients are open, to an astonishing degree, to receiving investigational interventions, ethical approaches that would avoid exploiting their altruism should help provide some basis for at least the possibility of value and the likelihood of safety for the individual while participating in such clinical research. Unfortunately, no cell-free or cell culture-based assay can yet provide this information. Secondly, a molecule active in a cell-free or purely cell-culture system is not a 'drug', the historical distinction resting in that the fact that *bona fide* drugs possess the capacity for 'pharmacological action at a distance' across the boundaries of the route of administration, stability in the circulation, metabolising systems, and elimination routes encountered in organisms. Thirdly, from a pragmatic and economically important point of view to those who must apportion resources for drug discovery, no ultimately successful cancer treatment used today is without robust activity in at least some model of cancer treatment.

The current volume contains a series of articles that describe, and evaluate the strengths and weaknesses of, contemporary preclinical models used in cancer drug development, both *in vitro* and *in vivo*. These models are intended to define whether a particular potential therapy has activity against tumours with the appropriate drug target, and whether or not activity might be expected in patients at tolerated doses. With the advent of 'molecularly targeted therapies', this issue of the *European Journal of Cancer* is particularly timely because the models that have been used in the development of cytotoxic drugs will need re-evaluation and refinement as clinical-laboratory correlates, and discrepancies, between activity and toxicity emerge with these new drugs. However, is it already clear that the screening of molecularly targeted therapies in unselected preclinical models cannot substitute for rational development programmes based on pharmacodynamic and pharmacokinetic parameters.

The use of *in vivo* models raises important animal-welfare issues. Regulatory authorities in certain venues currently require evidence of activity in a preclinical *in vivo* model at a tolerated dose before clinical trials are sanctioned, and as described above from both an ethical and a scientific viewpoint this stance can be justified. There is a duty of care to patients who are often terminally ill and there must be a realistic expectation of a therapeutic index. However, the refinement of models, a reduction in numbers of animals used and the replacement of *in vivo* models with *in vitro* systems where possible is a goal that should be pursued in parallel with the development of new agents; scientifically they are complementary aims.

Lastly, the editors of this volume would like to express their gratitude to their good friends and colleagues who have contributed outstanding and authoritative papers in a timely manner. Access to, and the interpretation of, data from preclinical models is often perceived as a bottleneck in drug development and it is hoped that this volume might go some way to relieving this limitation, thereby expediting the identification of better anticancer treatments. In fact, we hope that our colleagues in industry and academia would embrace the

* Tel.: +1-301-496-8720; fax: +1-301-402-0831.

0959-8049/$ - see front matter Published by Elsevier Ltd.
doi:10.1016/j.ejca.2004.01.010

pursuit of well-described and reproducible activity in an appropriate animal model as an important and worthy goal that portends a subsequent successful clinical development pathway. Indeed, in the ideal case the preclinical experience would be an exact representation of, and serve as a basis for, the design of initial clinical studies with a new agent, providing a platform for clear decision-making to drop or pursue with vigour the compound's development either before or as early clinical experience emerges.