ESCAPING CASTALIA

How effective are our preclinical animal models? A new series of articles in *Nature Reviews Drug Discovery* this year will aim to rationally assess this increasingly criticized area of drug discovery research.

As *Nature Reviews Drug Discovery* enters its fourth year, we have been considering which articles that we have published so far have generated the greatest reaction within the drug discovery community. Prominent among these is a Perspective by the late David Horrobin, published 2 years ago, in which he argued for a much more critical assessment of the assumption of congruence between animal models of disease and the corresponding human condition[1]. Researchers who accepted this congruence without question were compared in some ways to the scholars of Castalia — a fantasy, isolated state within the real world — in Herman Hesse's novel *The Glass Bead Game*. In Castalia, these scholars are persuaded that the highest intellectual achievement is to play the extremely complicated and challenging 'glass bead game', but unfortunately playing the game makes no contribution to the real world. By becoming preoccupied with gaining knowledge based on animal models of disease whose relevance to the human condition is unproven, Horrobin suggested, we are in danger of "creating a modern glass bead game that bears as little relation to real medicine as did Hesse's Castalia to the reality of the surrounding world".

Horrobin has not been the only scientist to raise concerns recently about the usefulness of some animal models of disease. In another article that has stimulated much debate — 'Why we're losing the war on cancer— and how to win it', published in *Fortune* early last year[2] — several leading cancer researchers were strongly critical of the mouse models that are widely used in preclinical cancer drug development, suggesting that millions of dollars are being wasted each year because of the poor correlation between efficacy in these models and efficacy in human disease. Such problems have also been recognized by the US FDA, which identifies better animal models as an important area for future focus in its 2004 'Critical Path' white paper[3]. In addition, the agency highlights the benefits that might be gained from analysing the vast amounts of data they possess that could link animal toxicity data with human outcomes. Such analyses could improve the predictive power of preclinical safety models, and therefore reduce costly failures that result from unexpected toxicities, and might also allow the elimination or replacement of existing tests that are not found to be useful.

Given these rumblings of dissent, a thorough investigation of the potential and limitations of some of the well-established and emerging animal models used in preclinical research seems timely and appropriate. With this in mind, this month, we start a series of articles on the use of model organisms in drug discovery. The first of these articles, on page 35 of this issue, considers how the zebrafish, which has proved highly valuable in understanding development, could also be useful in target validation and toxicological studies owing to its suitability for high-throughput phenotyping. Subsequent articles will explore issues such as what is being done to develop cancer models to address the problems highlighted in the *Fortune* article.

Despite such problems, we should of course not forget the many key advances in biomedical science that have resulted from animal research. The value of such advances is clearly evident in the groundbreaking career of the Nobel laureate Sir John Vane, who died in November 2004. A strong advocate of the need for animal research, his many important contributions to drug discovery, such as elucidating the pharmacology of aspirin and stimulating the development of angiotensin-converting enzyme inhibitors for treating hypertension, are honoured in our first obituary on page 10. By analysing how best to improve animal research, our article series aims to facilitate further advances, and to help avoid this research becoming trapped in what Horrobin described as "a self-consistent but ultimately irrelevant Castalian game".

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1. Horrobin, D. F. Modern biomedical research: an internally self-consistent universe with little contact with reality? *Nature Rev. Drug Discov.* **2**, 151–154 (2003).
2. Leaf, C. Why we're losing the war on cancer—and how to win it. *Fortune* 9 Mar (2004).
3. Innovation or Stagnation? Challenge and Opportunity on the Critical Path to New Medical Products [online], <http://www.fda.gov/oc/initiatives/criticalpath/whitepaper.pdf> (2004).