

## Use of Animal Models: Pharmaceutical Perspective John C Waterton PhD

Translational Sciences, AstraZeneca, Alderley Park, Macclesfield, Cheshire UK

Why do pharmaceutical companies use animal models in their research? In the vast majority of cases (let us exclude here research on veterinary medicines), the answer is simple. We use animal models, often before the first trials in man, *to test hypotheses which we cannot at that point test ethically in man*. Article 12 of the declaration of Helsinki<sup>1</sup> states that “Medical research involving human subjects must ... be based on ... as appropriate, animal experimentation” implying clearly that the drug developer should gain insight from suitable animal models before exposing humans to the investigational substance.

Important hypotheses that can be tested using MR in animal models include the following:

1. We can test the hypothesis that a novel drug target may be relevant in human disease. We may explore the effect of a prototype or positive control molecule in an animal model which with pathology relevant to the human disease, before we even start a medicinal chemistry project.
2. When we have our candidate drug, or perhaps a shortlist of several candidate drugs, we can test the hypothesis that the candidate drug has a dose-dependent effect on the modulation of the target, and of the disease phenotype, in an appropriate animal model.
3. We may perform MR of animals in investigative toxicology studies. All substances are toxic at a sufficiently high dose. However, before our first human trials, we may use MR to test the hypothesis that adverse effects are benign or reversible at high doses, and are not evident at clinically relevant doses.
4. For the drug developer, the most important use of animal models is almost certainly in the discovery, development, and evaluation of imaging biomarkers proposed for use in phase 2 clinical trials. Of compounds entering clinical development, approximately 90% fail to become approved medical products. The drug developer's aim therefore, following Popperian logic, is not to prove the hypothesis that the drug will be a useful medical product, but to disprove the hypothesis, so that the project can be stopped, futile exposure of patients to ineffective investigational therapies can be avoided, and resources can be used more productively elsewhere. The characterisation of biomarkers and their confounds to support a Stop decision typically involves a large portfolio of both animal and human imaging, and is probably the most important role of MR in drug development. Evaluation of an imaging biomarker not only involves cross-sectional and longitudinal studies and reproducibility assessment in humans, but also response to intervention, and imaging-

---

<sup>1</sup> “Medical research involving human subjects must conform to generally accepted scientific principles, be based on a thorough knowledge of the scientific literature, other relevant sources of information, and adequate laboratory and, as appropriate, animal experimentation. The welfare of animals used for research must be respected”. WMA Declaration of Helsinki - Ethical Principles for Medical Research Involving Human Subjects. 2008

histopathology correlation in animals. It is very difficult in many musculoskeletal diseases to provide convincing correlations in humans between dose-dependent changes in the imaging biomarker, and dose-dependent changes in the underlying histochemical markers to give molecular evidence of the desired pharmacology. Imaging-histopathology correlation is, of course, much easier to do in well-designed animal studies where the model exhibits important aspects of the human pathology, than in human patients. Moreover, in designing a trial using an MR imaging biomarker, to calculate statistical power we need some estimates of the effect size. Such data of course unavailable if the drug has never been given to humans: however we can often get good estimates of the effect size through animal experimentation, to help guide clinical trial design.

It is important to recognize that no animal model perfectly predicts responses in man, indeed no response in a human population or human individual perfectly predicts response in another population or individual. However animal models which exhibit relevant aspects of the human pathology, particularly when good positive and negative control interventions are available, allow our biomarkers to be selected and evaluated, and clinical trials to be designed, with much more confidence than if no animal data are available, and help avoid unnecessary exposure of patients investigational drugs and doses.