RS policy document 17/06

Expert Scientific Group on phase I clinical trials

The Royal Society welcomes the opportunity to contribute to the Expert Scientific Group study on phase I clinical trials which was established by the Secretary of State for Health following the severe adverse events experienced by some of the volunteers taking part in the trial of the anti-CD28 antibody TGN1412. The Society wishes to draw the Expert Group's attention to the Academy of Medical Sciences position paper *Testing Antibody Therapies*[1] which discusses some of the broad questions and issues arising from the TGN1412 trial. The Royal Society supports the conclusions of this comprehensive position paper and has focussed its response on the steps that need to be taken to optimise the safety of phase I clinical trials involving very novel biological molecules, new agents with a highly species-specific action and new drugs targeted towards the immune system. These groups of dugs offer great potential, but due to the limited previous experience of the development of such drugs, exceptional care must be taken in designing phase I clinical trials.

The aims of phase I trials (ie the first time a drug is given to humans) are to determine the initial safety profile, the maximum tolerated dose and to understand how the new drug is absorbed and metabolised in the body. Rigorous evidence-based risk assessment is required in designing phase I trials. This assessment is required in order to ensure adequate safety while avoiding over-regulation that could stifle innovation and new pharmaceutical developments.

Biological molecules with novel mechanisms of action and new agents with a highly species-specific action

As with all phase I trials, those involving novel biologicals or species-specific molecules should be informed by all available scientific knowledge of the prospective drug targets and be conducted with caution. There is very limited previous experience with novel biologicals or species-specific molecules; therefore exceptional care must be taken with initial dosing. Test dosing of a smaller dose before administration of the actual dose should occur, and suitable time intervals between each of the administrations in each test subject, and between different individuals, should be included. The Society believes that these precautions are the only way to avoid an unexpected reaction becoming unduly severe and/or affecting more than a single individual. We recommend that the regulatory authorities issue specific guidelines on how such phase I trials of very novel biologicals should be conducted, to include the precautions discussed above.

New drugs directed towards immune system targets

Targeting the immune system when developing new drugs is not inherently different to targeting other systems, as toxicities can be caused in any organ or system. However the immune response, as well as the immune status, differs between individuals and this must be factored in when planning phase I trials of novel drugs. Furthermore, many current drugs which target the immune system act to subdue it. Drugs, such as TGN1412, which stimulate the immune system require further caution due to their novel mode of action and lack of knowledge of their effects in the body. Where a 'therapeutic' effect is seen without detailed knowledge of its mechanism of action in the body, the risk of unexpected toxicity is increased and this should be taken into consideration when designing phase I trials.

For example, in addition to the region of therapeutic antibodies responsible for the targeted biological activity (called the Fab region), there is another region (called the Fc region) which interacts with cells of the innate immune system. This can have complex, and in some cases unpredictable, outcomes as the interaction can trigger a cascade of cellular and inflammatory molecules. As a result, it is crucial that all the multiple

[1] Academy of Medical Sciences (2006) *Testing antibody therapies*. Academy of Medical Sciences: London. Available online at http://www.acmedsci.ac.uk/images/project/TestingA.pdf

interactions (binding) of therapeutic antibodies with cells, and the biological consequences, are understood and documented. Given the potential multiple interactions it may be appropriate for these antibodies to be screened in preclinical development in a stepwise manner by examining first the Fab region followed by the whole therapeutic antibody (Fab and Fc regions). In this way unwanted complications in interpreting efficacy and toxicity data due to the binding of the Fc region to Fc receptors may be separated from the effect of the antibody activity per se.

The Society recommends that data from all preclinical trials using very novel immune system targets, biologicals and species-specific molecules be submitted by drug companies to the regulators. These dossiers of data can be used by the regulators to correlate better adverse events from a range of trials and make recommendations about the development of novel agents and the most appropriate preclinical tests for efficacy and toxicity. For example in the case of therapeutic antibodies, the regulators may recommend that no, or a preferred, Fc region is used.

Preclinical testing using animals

All phase I clinical studies are inherently risky; however the risk can be reduced, but not always avoided, by preclinical testing using animals. The choice of the animal species for preclinical studies is an important consideration, especially for biological and species-specific molecules. The similarity between the activity of the drug, and the distribution of the drug target, in the chosen animal species compared with humans must be considered. For small molecule drugs, differences in species specificity relating to how long the drug is exposed to the drug target and how quickly it is broken down also needs to be considered. The presence of a given biomarker (a substance in the body which changes in concentration on exposure to a particular drug) in both humans and the chosen animal species can help justify the choice of animal species used in preclinical tests.

Many proteins and functions which are highly conserved across mammals may still differ between species. It should never be assumed that, for example, close sequence homology and even 3D structural similarity of a target protein between animals and humans means that it is regulated and functions in the same way. Therefore, species-specificity of proteins or functions may have striking implications for the pharmacological effects of intervention with both small molecules and biologicals. Although there is enormous experience with small molecule drugs in this context, the rapidly expanding range of possible drug targets creates the possibility that a drug which targets a unique human function may have direct effects or unexpected side effects in humans which were not revealed by animal toxicology, even in non-human primates.

The very low level of serious adverse events in human trials indicates that the procedure of testing novel drugs in animals before progressing to phase I trials in humans is highly effective. However, the Royal Society strongly endorses the principle of the 'three Rs': to replace the use of live animals by non-animal alternatives; to reduce the number of animals used in research to the minimum required for meaningful results; and to refine the procedures so that the degree of suffering is kept to a minimum. The use of computer simulations, cell and organ cultures and the use of transgenics (including zebra fish) can be used to complement the current range of preclinical tests.

We recommend that a more prescribed set of tests, based on all the available information, including the appropriate animal species, are used in preclinical testing to contribute to effective decision making. This information would need to be continually reviewed and updated as more information is known about different classes of these new molecules.

Any inquiries about this document should be sent to
Science Policy Section, The Royal Society, 6-9 Carlton House Terrace, London SW1Y 5AG, United Kingdom
E-mail: science.policy@royalsoc.ac.uk Tel: +44 (0)20 7451 2591 Fax: +44 (0) 20 7451 2592