Moving on from TeGenero

Immunocore pioneers new safety studies

Ever since the TeGenero incident in 2006, in which six healthy volunteers nearly died in a Phase 1 clinical study in the UK, scientists have been working hard to come up with better tools for predicting the safety of novel biological therapies before they are tested in humans. TeGenero, a now defunct German company, developed a monoclonal antibody to treat leukaemia and autoimmune disease. The drug was tested safely in monkeys before it was authorised for administration to humans. At the time of the study, the six volunteers were given doses of the drug that were a tiny fraction of what had been given to the animals. Yet despite these precautions, the volunteers suffered life-threatening adverse events.

It has taken a long time to come to grips with the issues raised by the TeGenero case. In the immediate aftermath of the trial, the regulator, the Medicines and Healthcare products Regulatory Agency (MHRA), set up a special procedure for vetting novel biological therapies before they are allowed to be tested in humans. And the European Medicines Agency adopted a new guideline setting out tougher dosing standards for these drugs. Companies have been advised to examine the nature of their drug targets in humans in detail, and to carefully analyse the relevance of the animal model in working up their preclinical data packages. In general, it has been acknowledged that animal studies are not *necessarily* predictive of how biological therapies will behave in humans. But if they aren't always reliable, what are the alternatives?

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>
> *Stephen Megit*

Immunocore Ltd of the UK has provided at least one answer to this very complex question. In what is a very unusual case, the company won approval from the MHRA and from the US Food and Drug Administration in 2010 to start clinical studies of an immunotherapy for patients with metastatic melanoma on the basis of *in vitro* safety studies that did not involve any toxicity tests in animals. The Phase 1/2 trials are currently underway at three sites in the UK, and two exploratory studies have started in the US. As is customary in this field, a company's discussions with a regulator are confidential unless the company itself decides to announce the detail.

With the trials safely underway, Immunocore disclosed the results of its regulatory discussions at a conference in late 2010. *MedNous* followed this up in January 2011, and then again in April, in separate interviews with the company's senior manager for business development, Stephen Megit. Separately, the MHRA was asked to comment on the case. In a statement, the agency said that it approved the company's animal-free toxicology package following a scientific advice procedure and in accordance with a guideline on the preclinical safety evaluation of biotechnology-derived pharmaceuticals from the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (Please see box for the full MHRA statement).

Like many small companies, Immunocore has its roots in academia. It is one of two companies that grew out of a 1999 Oxford University spin-out called Avidex Ltd. Avidex was founded by Bent Jakobsen, formerly head of the immune receptor group at the Institute of Molecular Medicine in Oxford, and currently Immunocore's chief scientific officer. The immune receptor group is one of the leading international laboratories in molecular immunology and in particular, a leader in recombinant immune receptor technology. Avidex was acquired by MediGene AG of Germany in 2006, and then divested by that company two years later. Following the divestment, Immunocore was created to take over the company's T-cell receptor technology, while a second concern, Adaptimmune Ltd, was founded to develop adoptive therapies using the same technology platform.

Immunocore has developed a technology platform for producing prospective cancer treatments that is based on recombinant versions of human T-cell receptors. T cells, or T lymphocytes, belong to a group of white blood cells known as lymphocytes which play a key role in the immune system. The T-cell receptor is a molecule found on the surface of the T cell. In general, it is responsible for recognising antigens, or the substances that signal the presence of disease in the human body. Immunocore's molecules recognise antigens that are presented on a peptide complex on human cells, including cancer cells, called the human leukocyte antigen complex (HLA). The technology is expected to be uniquely effective against cancers that have a small number of HLA peptides on a cell surface, a phenomenon known as HLA down-regulation.

The product currently in human trials is a monoclonal T-cell receptor fused to an anti-CD3 single chain antibody fragment. The T cell receptor is specific to a peptide sequence from the gp100 antigen. This antigen is presented on

melanoma tumour cells by the HLA complex.

In the interview, Dr Megit said that in planning the first clinical trials, the regulatory challenge was to design a reliable preclinical test for predicting how these molecules would behave in humans. A key issue was demonstrating to the regulator that the drug's unique mode of action could only be accurately observed in fully human systems.

"Basically, the TCR end [of the drug] only binds to human proteins and rather unfortunately, the anti-CD3 end only binds to human T cells," the executive said. The company's first step therefore was to contact a special group that had been set up at the MHRA, post-TeGenero, to handle these matters. "We knew we would have to go through the EAG [expert advisory group] because we ticked most of the boxes for a very high risk product," Dr Megit recalled.

"The approach that we actually took with them was to basically go through the scientific rationale of all of the options that were available. The options were basically, to do no animal tox studies but base [the clinical trial application] all on assays against human cells, or to go away and make a surrogate molecule that would work in an animal," he said.

The disadvantage of a surrogate molecule

The company didn't think a surrogate molecule administered to animals would yield any meaningful information. This is because the process of making the surrogate would alter the ratio between the molecule's constituent parts, which is to say, the T-cell receptor and the anti-CD3 antibody fragment. Also, the company was worried about the time that it would take to produce such a molecule.

"There was absolutely no way in the world that you could go away and generate a species-specific homologue that had exactly the same binding characteristics as the drug you actually wanted to take into the clinic," Dr Megit commented. After careful deliberations, the MHRA agreed.

The upshot was that the company conducted a battery of tests on human cells. These included cross-reactivity tests against a panel of primary human cells as well as cytokine release experiments. The company also tested the ability of hormones called corticosteroids to block the activity of the drug. This was to demonstrate that if something did go wrong in a human trial, there would be a procedure for dealing with it.

Discussions with the MHRA covered all the bases, and approval was granted within a matter of months to start a clinical trial in the UK. Immunocore subsequently presented the same data to the FDA and got approval to start an exploratory programme of the melanoma treatment there. Exploratory, or Phase 0 studies, usually involve very limited human exposure.

Trials in both countries got underway in 2010 without any difficulties, and as of 5 April 2011, things were proceeding according to plan.

The company is conducting studies at three sites in the UK – Oxford, Cambridge and Birmingham – in order to establish a tolerable intravenous dose of the drug and then assess the effect of this dose on pharmacodynamic markers when given repeatedly to a larger group of patients. In line with the new European guideline on first-in-human studies, the patients were started at the smallest dose thought likely to have a biological effect. This standard is called MABEL or the minimal anticipated biological effect level. The company expects to have data from the UK studies, including some efficacy results, by June of 2012.

In the US, Immunocore is conducting two exploratory studies to, among other things, look for efficacy. "What we are doing in the US is putting a very high dose into a small metastatic lesion to look for signs of efficacy and to look for biomarkers," Dr Megit said.

"The exploratory IND will give us an indication if firstly, the drug is working as expected and secondly, what immunological read-outs will show us that it is working.

"We can then use that information to analyse the UK patients who are getting the drug systemically for signs that the drug is working at an earlier stage, than you otherwise would do," he added.

Statement from the MHRA

The MHRA, like all Regulatory Authorities, accepts that biotechnology derived products have to be developed on a "case by case" basis and recommends that companies consult for advice on the appropriateness of their development programmes before conducting unnecessary and potentially misleading studies.

The nonclinical development programme developed by Immunocore was in accordance with the International Regulatory Guideline ICH Topic S6 - Preclinical Safety Evaluation of Biotechnology-Derived Pharmaceuticals (CPMP/ICH/302/95). This guideline states that safety evaluation programmes should include the use of relevant species only. The company conducted appropriate studies to be able to conclude that there was no relevant species other than man.

The company conducted a rigorous series of *in vitro* safety studies and then approached appropriate Regulatory Authorities for scientific advice. The MHRA agreed with the approach adopted by the company and accepted a clinical trial design which involved an extremely low starting dose and very cautious dose escalation steps with appropriate safety monitoring.

While it is very unusual that no relevant animal species was identified for this product, biotechnology derived products are almost always developed with a much reduced package of animal studies due to their specificity.

MedNous interviewed Dr Stephen Megit in Abingdon, UK on 24 January 2011 and again by telephone on 5 April.