The London experience - The TGN 1412 Trial

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He gained his MBBS and a BMedSci degrees at Melbourne University and worked at the Royal Melbourne Hospital in various roles, including lecturing at the university, during which time he completed an MD in viral arthritis. He was then appointed Senior Medical Registrar at the Fairfield Infectious Diseases Institute, Melbourne. From 1981 to 1983, he was an NH&MRC Applied Health Services Fellow in the Division of Infectious Diseases at Stanford University in the USA.

In 1984, he was appointed Director of the Virology Department of the Institute of Clinical Pathology and Medical Research and Consultant Physician in the Infectious Diseases Unit at Westmead Hospital, and as Associate Professor of Virology at the University of Sydney until his current appointments in June 1996. He is a member of a number of State, Commonwealth and industry committees and currently Director of the Australian Centre for HIV and Hepatitis Virology Research (ACH^2).

It has been very interesting really delving into this topic. One of the things I do as the Network Director of Research in the Sydney Western Area Health Service is to report to the Chief Executive on risk management in research. We were asked by the Director General of Health to look closely at the implications of this particular trial. I think that is probably the first time the Director General of Health has written to an area health service about a clinical trial. So this is something that we have had to work on in terms of enhancing our risk management for 'first-in-human' and Phase 1 clinical trials in the Sydney Western Area Health Service.

It is really very interesting to look back at the causes of this catastrophe and to compare the official Duff Report with some of the press reports, particularly a detailed one in the *Sydney Morning Herald*, which many of you would have read recently. The two are quite different.

What actually happened?

I will first just describe what happened clinically. This was the subject of a report to the *New England Journal of Medicine*. It is very important to have this documented in the world literature and was sufficiently important to be published in that prestigious and widely read journal. I want to look at why this incident happened, whether it was unforeseen or could have been predicted, the implications for the future investigation of such incidents, and, finally, some of the implications of the Duff Report for future clinical trials.

Why this trial was a disaster for medical research

As a director of a research institute closely related to a teaching hospital, this was a potential disaster. It is extremely important that we do see our research efforts translated into the clinical arena. That is important for the progress of medicine. I am sure you have all heard the phrase, "today's research is tomorrow's medicine", and if this is not carefully looked at to achieve a balance between regulation and facilitation, it could certainly impede progress in medical discovery. That, of course, is of enormous concern to all of us, not just to me.

A collapse of ethics and science?

Was this a collapse of science and ethics, as has been portrayed in the press, or was this an unforeseen, unpredictable new event? Perhaps a little of both.

Summarising the sequence of events

In March 2006, at Northwick Park in London, a famous clinical research centre, six volunteers were injected with a monoclonal antibody *TGN1412*, active against the CD28 marker on the surface of T-lymphocytes. (I will explain what that means as we go along.)

It was made by *TeGenero*, a spin-off company of the University of Wurzburg, Germany. The scientific discoveries underlying this product of *TeGenero* are really quite substantial. This is no fly-by-night company. Very good scientists helped develop the product.

This was a Phase I 'first-in-human' trial. Phase I trials are not always 'first-in-human', but this was clearly a 'first-in-human' trial. As well as the six recipients of the monoclonal antibody, there were two who received placebo. *TGN1412* is a 'humanised' monoclonal antibody: (in order to avoid the allergic reactions which potentially occur across species with mouse antibodies, scientists try to make it as much like the human antibody as possible).

The effects of the medication

All of the patients developed fever, severe headache, low blood pressure, vomiting, oedema (generalised swelling), one sufficiently badly to be referred to as the 'Elephant Man', featured prominently in the press. This was caused by the release of protein molecules from the patient's white cells, from a particular type of white cell (the T-lymphocyte) which is absolutely crucial to our immune defences.

T-lymphocytes are the cells infected by HIV, which causes their collapse with ensuing immune dysfunction. They are also the cells that cause problems in auto-immune diseases such as rheumatoid arthritis, lupus and multiple sclerosis, where the body's immunity is affected, with these T-cells turning on themselves.

Collapse of many bodily organs

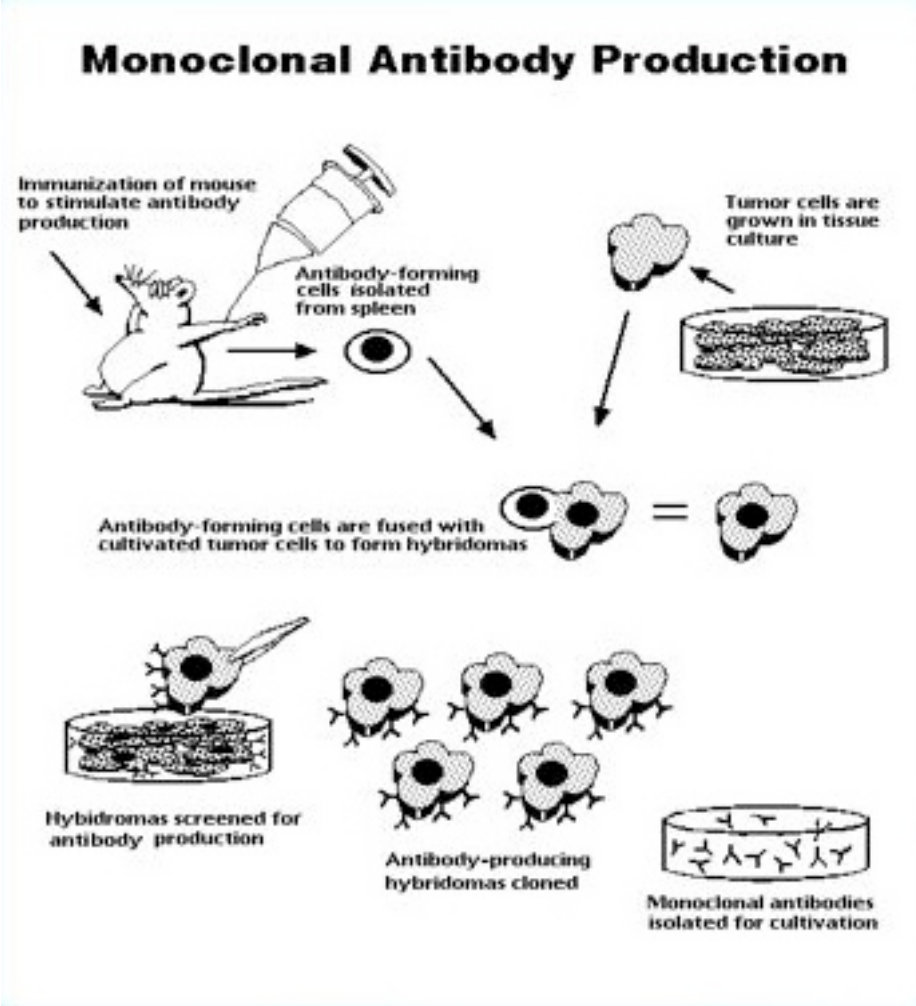
All of the recipients suffered from multiple organ dysfunction. Two required organ support in the intensive care unit, for eight and 16 days respectively, and were treated with extremely high tech medicine: steroids, plasma exchange and, in fact, an antibody against a particular receptor on the surface of those T-cells. A lot of thought went into their treatment. There is still some concern about what might happen to these men's immune systems over the next few years, whether or not they might develop cancers, auto-immune diseases etc., through this interference with their immune systems.

The consequences

The UK Medicines and Health Care Regulatory Agency (MHRA) was responsible for authorising the trial. It withdrew its authorisation and issued an international warning. *TeGenero* collapsed into insolvency. There were subsequent internal reviews by the MHRA, in conjunction with the area health service and the police, to see if anything criminal had happened, and also by the Paul Ehrlich Institute in Germany, the regulatory institute comparable with our Therapeutic Goods Administration (TGA).

Treatment with monoclonal antibodies (MABs)

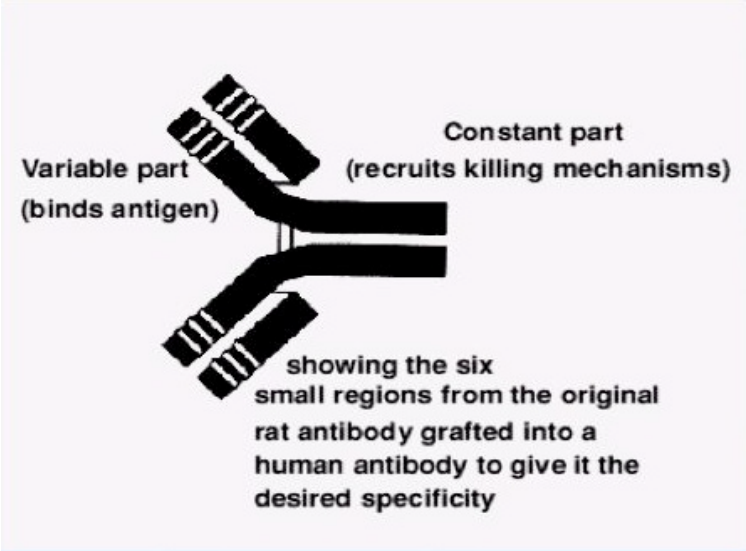
We are using monoclonal antibodies a lot in medicine these days. They are made by injecting mice with the protein or the cell against which we want to develop the antibody Because that cell will, of course, die pretty quickly, Nobel medallist scientists, Kohler and Milstein, fused the antibody-producing lymphocytes with a tumor cell - a myeloma cell, a type of primitive white blood cell. - In this way, the fused cell is immortalised and produces these antibodies forever; one can then purify them.



Because they are highly targeted at a particular protein or cell they are called 'monoclonal'. They are quite pure and don't cause as many side-effects as ordinary antibodies.

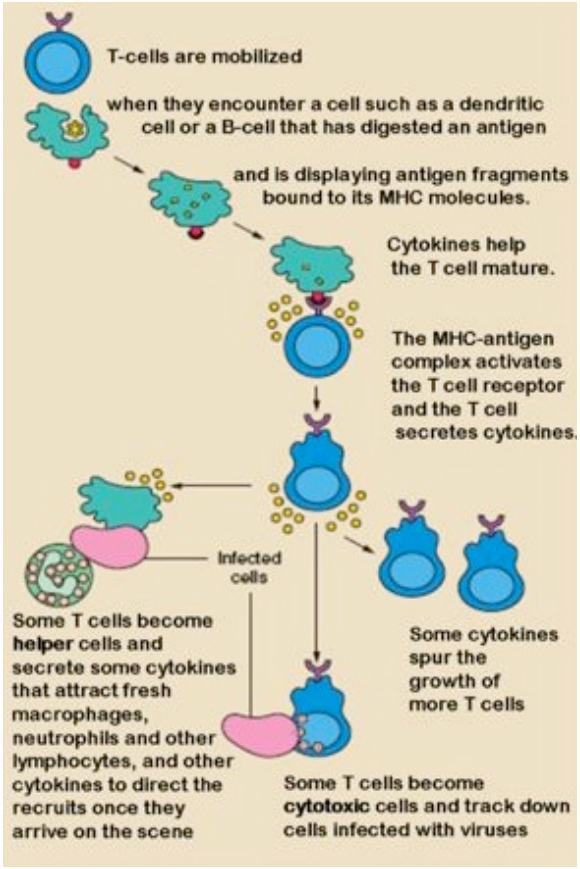
Changing mice antibodies into human antibodies

The problem is that they are mouse antibodies. If you consider the structure of the antibody and try and create a human backbone and then just put a few mouse bits at the business end, you have overall a human antibody with just the important target areas of the mouse antibody incorporated at the end. [6] That reduces the likelihood of allergic cross-species responses against the mouse protein.



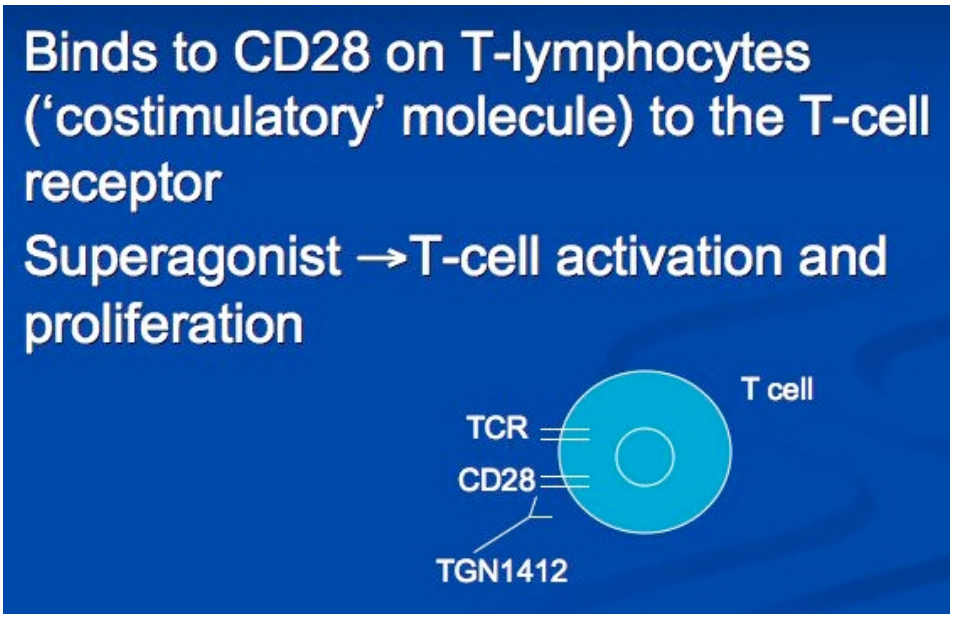
The T-cells

When a virus, a bacterium or an antigen enters the body, it interacts with a cell called an antigen presenting cell (shown here in green), which then presents the antigen to these T-lymphocytes (shown here in blue). These T-lymphocytes can respond by proliferating, by multiplying or by producing proteins called cytokines. Cytokines are the essential messengers of the immune system and are very powerful proteins indeed, capable of both good and bad actions. If present in excess, they can produce an extremely nasty 'superagonist' reaction; this is, in fact, what happened.



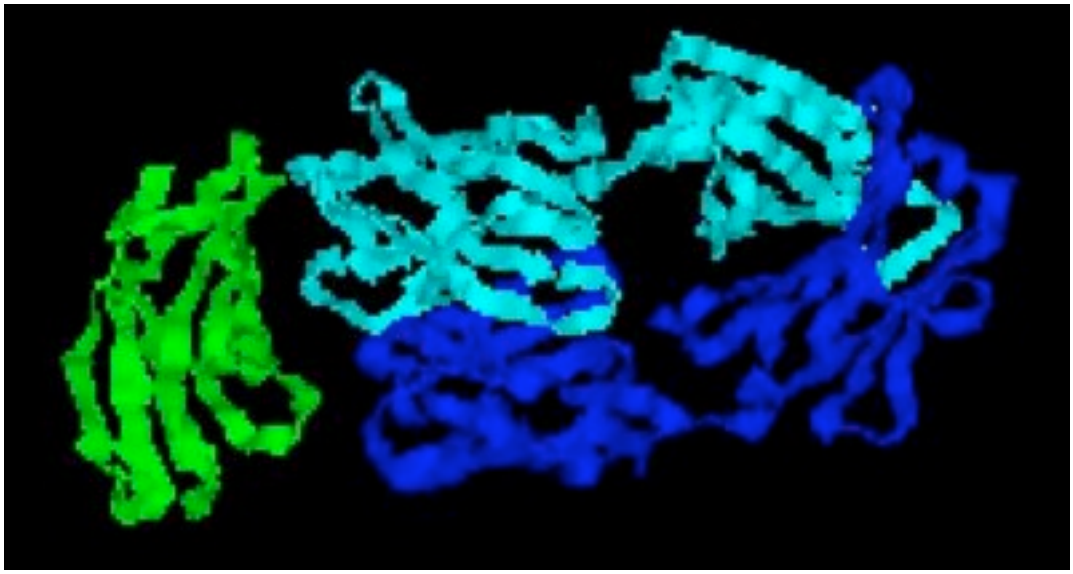
What the scientists wanted

A T-lymphocyte has two essential receptors or proteins. Stimulating both of them results in a proliferation of the T-lymphocytes and the production of cytokines. What the scientists hoped to do was to target only one particular receptor 'CD28'.



In that way, they hoped to stimulate the proliferation or multiplication of these T-lymphocytes in a useful fashion, without stimulating them to produce nasty proteins or cytokines.

This is the molecule against which the antibody was directed. It was, in fact, the scientist who was the principal of *TeGenero* who solved the three-dimensional structure of this particular protein.



He showed that this particular antibody could bring two molecules of this particular receptor together and could trigger mouse T-cells to multiply or proliferate, without producing cytokines. His plan was to expand and to activate certain types of T-cells, ('regulatory T-cells' which dampen down the immune system) which could be important in controlling auto-immune diseases, such as rheumatoid arthritis, lupus and multiple sclerosis.

Was there any evidence of safety?

Although this is potentially dangerous in that the positive or stimulating cells might also be stimulated, not just the negatively or inhibitory reacting cells, they had good evidence in mice and monkeys that there was no major toxicity. All that happened was a little swelling in the lymph nodes in the latter.

What happened in humans?

In humans, unlike in mice and monkeys, the antibody stimulated the effector T-lymphocytes, (the wrong ones) producing a lot of cytokines, resulting in what is called a 'cytokine storm', (This is what happens in bird 'flu in humans: it has a 50 percent mortality, with death due to a cytokine storm in the lungs). These subjects suffered a cytokine storm in the general circulation, not the lungs. They are somewhat fortunate to have been close to an intensive care unit (ICU) and to have been treated so well.

Was there contamination?

After the event, the reasons for the problems were investigated. It was originally thought that maybe there might have been a contaminant in the antibodies. A common one consists of traces in the cell walls of bacteria in which these medicines are grown, but that was found not to be the case. The toxicity was due to the intrinsic activity of the preparation itself. We don't know why this was not observed in mice or monkeys.

Are monoclonal antibody medications risky?

Of around 355 currently in development, 18 have been granted approval by the United States Food and Drugs Administration (FDA) for use in cancer and immunologic diseases. They are usually pretty much a last resort. Doctors usually use them in the treatment of lymphoma, but not often as first line treatment. They are also used (anti-TNF antibodies) as part of the treatment of severe rheumatoid arthritis. Significantly, there are warnings with all of these medications to be wary of allergic side-effects. TGN1412 is potentially even more dangerous.

Was the trial conducted correctly?

There were a number of potential criticisms leveled at the trial. One was that *Paraxel*, a contracted clinical research organization (CRO), a private organisation rather than academic investigators, conducted the trial. It was said that the CRO should have been more aware of the possibility of a cytokine storm. Another criticism was that the subject recruitment and informed consent was not sufficiently stringent, in that little was said on the web site about risk. In addition, people have been critical of the testing site being too far away from an established ICU and that no ICU had been warned about the potential for harm in a trial like this. What about the dose? The dose was in fact 500 times less than the safe dose in monkeys. What we don't know, however, is if that safety margin is transposable to humans.

However, it was generally agreed that *major mistake* was the almost simultaneous testing of six volunteers without scaling the dose up from a very low level and the six patients' being injected over a shorter period than had been approved by the MHRA.

The investigations

The MHRA investigated *TeGenero* and *Paraxel* and found everything pretty much in order. The Paul Ehrlich Institute in Germany looked at the manufacture by the reputable German company, Boehringer Ingelheim, at the testing, storage and distribution of the medication. They found no evidence of anything other than this being an unpredicted biological action in humans. The press and plaintiff lawyers were less forgiving, as one can see from various web sites.

The MHRA then refused to authorise any further Phase I trials unless there was an expert opinion on safety, until an expert scientific group had handed in its report. This expert group, appointed by the Secretary of State for Health, was chaired by Gordon Duff. The terms of reference were to plan for the future whatever was necessary for the transition from pre-clinical to phase I trials with these biological molecules with highly species specific actions and with new agents targeted at the immune system and to decide what is needed for the authorisation of such trials.

The Duff Report

It is very interesting that Duff, in his introduction to this crucial report, which should be read by everybody involved in Phase I trials or in their regulation, stated that it is very important to optimise safety without stifling innovation or raising unnecessary barriers to development of new medicines. Exposure to new medicines always will involve some risk. He also noted that, up until this trial, Phase I trials had a very good safety record and that such universal and severe side-effects were unprecedented.

The group recommended that, in looking at the assembly of pre-clinical data for 'first-in-humans' trials, the application must be science-based and assembled by experts and that it should be reviewed, on a case by case basis, by experts. There should be an open access data-base of pre-clinical information. It proved quite difficult to get such information out of *TeGenero* and *Paraxel*. This information should be shared world-wide and should include failed trials. We do now have data-bases of failed trials, but those with safety problems should be added to the world data-base. The regulator should seek advice from independent research-based experts. They also recommended setting up an expert advisory group within the UK regulatory bodies.

Duff recommended a broader approach to dose calculation, including calculations of the saturating levels of doses for the cells being targeted; the lowest (cautious) dose should be used; slower infusions should be used; and the dosage should escalate sequentially, ie starting low in one patient, waiting and then moving up to the next higher dose for the next patient, with appropriate intervals.

Healthy or sick volunteers?

Many Phase I trials are sometimes conducted on volunteer patients with terminal illness. Duff discussed this in terms of a possible benefit to those patients. If a cancer patient is likely to benefit from a Phase I trial, they might then be maintained on the Phase I medication. Such an approach could perhaps justify patient volunteers.

Accreditation

As far as the clinical environment was concerned, Duff suggested a national accreditation system for principal investigators in 'first-in-human' trials; pre-arranged emergency provisions with the local intensive care unit; well-trained staff with well-defined standard operating procedures; the secondment of postgraduate clinical investigator trainees to 'first-in-human' centres; and perhaps specialist centres for 'first-in-human' Phase I trials. Some do exist in Australia, at the Prince of Wales Hospital and at the Baker Institute in Melbourne.

What of the role of the MHRA?

Criticisms were raised about the actions of the MHRA which had approved the original trial protocol. Why were the infusions not better staggered, why was there not better informed consent and should not their investigation have been independent rather than in-house?

The response in NSW

The area health services were notified by a Director General's letter about the trial. Area chief executives were asked to be aware of, and to take responsibility for Phase I trials in their jurisdiction. This had a direct effect on me. Our Scientific Advisory Committee of our Health Research Ethics Committee considered this as a special category, which should not only consult an experienced expert internally in any Phase I trials, but should also have, as an external referee, an expert in the field. We set up a process for consideration of their reports by the executive of the committee which would be passed on to the Human Research Ethics Committee, as well as being reported to the Chief Executive.

We have conducted six 'first-in-human' trials in the last two years. As they are increasing and often involve cell therapy or therapy with monoclonal antibodies, all of what happened in London is highly relevant.

Monoclonal antibodies in modern medicine

MAB therapy is now a common part of cutting-edge medicine. Because MABs are proteins, this is a bit like transfusion medicine. MABs are used in the treatment of lymphomas, rheumatoid arthritis and macular degeneration (a common cause of blindness). It is very important, for reasons of safety, to premedicate with antihistamines, corticosteroids and paracetamol, and to have available medications such as adrenalin and bronchodilators and look at long infusion times. None of this appears to have been done in the London trial.

Ethical issues

Should private or academic clinical research organizations be running these trials? Should they be run in the third world? Should poverty stricken people, like students (!), be recruited? Should subjects be paid more if there is an increased risk? There are no unequivocal answers to these questions.

In general, we need to consider how to further reduce harmful side-effects in clinical trials and to monitor right through into Phase IV (release onto the market as a prescription-only medication), as we have seen with *Vioxx* and other medications only recently.