

One drug trial, six men, disaster...

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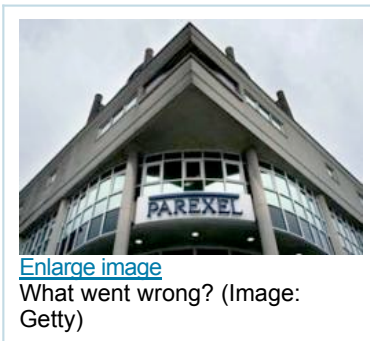
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AT 8 o'clock on the chilly morning of Monday 13 March, eight healthy young men were injected as part of a drug safety trial. The volunteers were all paid for their participation, but no one suspected what lay in store. Within minutes six of them were reportedly writhing in pain, tearing at their clothes, screaming and retching. The two others waited in terror for their turn, but they were in luck: they had been given placebos and escaped.



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What went wrong? (Image: Getty)

It is unprecedented for such serious and rapid symptoms to appear in all volunteers given a drug in a phase I trial, its first human test for safety. All six men, reportedly suffering from multiple organ failure, were transferred from the clinical trials unit run by the US-based company Parexel at Northwick Park Hospital in London to the hospital's intensive care unit. As *New Scientist* went to press, four of them were conscious, three of whom no longer needed organ support. Two were still in a critical condition. How could such a horrific reaction have occurred?

The drug, called TGN1412, was being developed by TeGenero of Würzburg, Germany, to treat leukaemia and certain autoimmune diseases such as rheumatoid arthritis, in which the body's immune system turns upon its own tissue and attacks it. It was intended to work by stimulating immune cells called T-cells to multiply in a way that would eventually dampen down the immune system. But published studies examined by *New Scientist* suggest that its action on T-cells, far from having the intended effect, led to the violent and uncontrolled reactions seen in the drug trial.

TGN1412 is a monoclonal antibody, a class of drug designed to bind to a specific target in the body, usually a protein receptor on the surface of a cell where it either activates the cell by mimicking a naturally occurring molecule, or blocks the receptor, preventing other molecules from binding to it. Such antibodies have been used safely to treat such diseases as lymphoma.

TGN1412 works in a different way to most monoclonal antibodies. When it binds to a receptor called CD28 on the surface of T-cells, it does so in such a way as to strongly stimulate the T-cells to multiply, without the usual need for a second specific signal from a different receptor. Because of this modus operandi, TGN1412 is classified as a "super-agonist" (see Diagram).

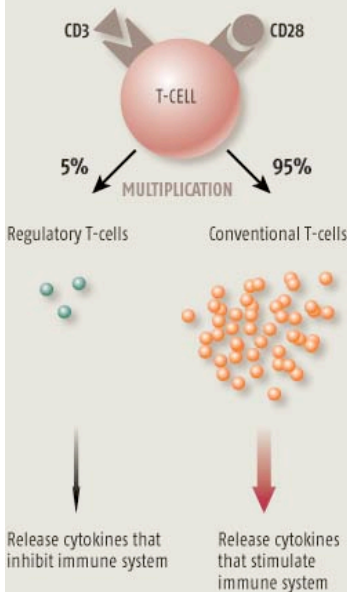
Earlier trials in animals suggested that as well as boosting total T-cell numbers, TGN1412 was particularly effective in increasing the number of regulatory T-cells in the body. Unlike normal T-cells, the regulatory cells dampen down the immune response rather than stimulate it. Changing the balance of T-cells in this way could counter the overactive immune system associated with autoimmune disease, the researchers thought.

Initial experiments conducted by TeGenero looked promising. Company founder Thomas Hüning and his colleagues published a review last year in

HOW T-CELLS RESPOND TO ANTIBODIES

Normal response

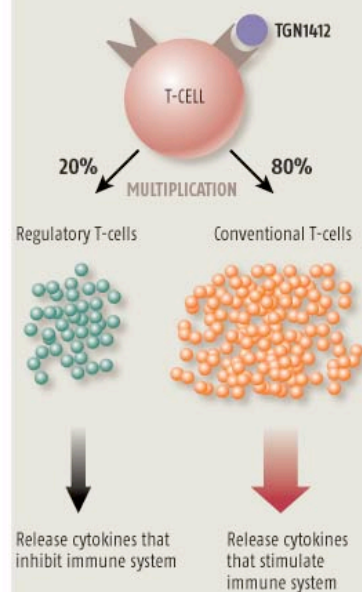
The CD3 and CD28 receptors must both be stimulated for the cell to multiply



How T-cells respond to antibodies

Response to "super-agonist"

The CD28 antibody alone stimulates the cell to multiply. This produces larger quantities of both types of cells, but especially regulatory T-cells



Annals of the Rheumatic Diseases (DOI: 10.1136/ard.2005.042564) which reports that the highest dose of the drug boosted regulatory T-cells from 5 per cent of all T-cells to 20 per cent in healthy mice and rats. It also boosted overall T-cell numbers 20-fold. Similar results were seen in rabbits and monkeys, the company says. Two out of 20 monkeys had swollen lymph nodes, indicating that extra T-cells were being produced as expected, but there was no suggestion of the violent reaction seen in the six men.

It was this boost to T-cell numbers overall which may hint at what went wrong in the human volunteers, according to some experts contacted by *New Scientist*. Three years ago, Hünig and his colleagues reported that when rats whose immune system had been completely destroyed were given an injection of TGN1412 along with a small dose of normal T-cells, their T-cell population was fully restored in just three weeks (*Blood*, vol 102, p 1764). Both ordinary T-cell and regulatory T-cell function were restored.

Michael Ehrenstein of University College London, who studies the role played by regulatory T-cells in rheumatoid arthritis, believes a similarly dramatic expansion of overall T-cell numbers may have occurred in the six men. "One explanation is that instead of acting on regulatory T-cells, they just activated all the T-cells," says Ehrenstein. "They would attack anything and everything," including the body's vital organs.

Thomas Hanke, TeGenero's chief scientific officer acknowledges that overall T-cell numbers increased when TGN1412 was tested on animals, but points to the even greater boost to regulatory T-cells. "We also observed that regulatory T-cells responded particularly well to CD28 super-agonist treatment," he told *New Scientist*. There were no drug-related side effects in the animal models, and this gave them confidence in the drug.

"Since we did not see any clinically relevant adverse events we were very convinced that in general it would be very well tolerated," Hanke says. He adds that the drug was also tested in human cells outside the body, where it activated both regulatory and conventional T-cells in a similar way to what had been seen in rats and mice with no ill effect.

Exactly what happened to make the six men given TGN1412 so ill remains to be discovered. One clue may come from a study of the chemical structure of the CD28 receptor targeted by TGN1412 by Andrew Martin of University College London and colleagues. In humans, 15 amino acids on the receptor come into contact with TGN1412. In rabbits, mice and rats at least two of these amino acids are different, which might explain why TGN1412's effect on humans and animals was so different. "These could easily account for several orders of magnitude in the binding affinity of the antibody for CD28," Martin says. In monkeys, one amino acid is different, slightly changing the shape of the receptor. This could obstruct proper binding, again reducing the effect of the drug in monkeys compared with humans.

Meanwhile, the UK Medicines and Healthcare products Regulatory Agency, which was responsible for approving the trial, has begun an inquiry that could take weeks to complete. Meanwhile, it defends its decision to give the trial the go-ahead. "The preclinical data showed absolutely no cause for concern about safety," its spokesman told *New Scientist*. "We have gone back and looked at it, and if we looked at it again, we would have made the same decision."

Suspicion also falls on accidental overdose

While TGN1412 is the prime suspect for triggering the disastrous reactions in the six patients it was given to, other possible causes are being investigated. One is overdose, another possibility is contamination.

Investigators will be checking that the company conducting the tests did not inadvertently give the volunteers more of the drug than intended. Another possibility is that we do not fully understand what constitutes an overdose of TGN1412, even though the dose specified for the trial was just 0.2 per cent of that considered safe in animals.

Contamination by bacteria, fungi or some other agent is another possibility, and could explain some of the symptoms reported. Bacteria, especially *Escherichia coli*, can cause catastrophic blood poisoning, or "septic shock", prompting the immune system to react by producing massive inflammation and a profusion of inflammatory cytokines, such as tumour necrosis factor, which can rapidly cause death through multiple organ failure.

Andy Coghlan**T-cell successes gave no hint of trouble**

Previous attempts to fight disease by altering the balance of T-cells have had some success, and none has caused any side effects remotely as serious as those seen with TGN1412.

A team led by Steven Rosenberg of the US National Cancer Institute in Bethesda, Maryland, tried invigorating the immune system in patients with skin or kidney cancer by giving them an antibody to block the CTLA4 receptor found on all T-cells. This receptor does the opposite of the CD28 receptor, and prevents T-cells becoming activated, so blocking it sets the immune system free to fight cancer cells.

Results published last September in the *Journal of Clinical Oncology* (vol 23, p 6043) show that melanomas receded in 13 per cent of patients, disappearing completely in two of them. "Two-thirds of the patients had no side effects at all," Rosenberg says. Side effects in the other third were not serious, came weeks rather than minutes after treatment, and were easily managed, occurring locally rather than throughout the body. Of the 41 kidney cancer patients, six showed benefit from treatment with the anti-CTLA4 antibody.

Another success has been in people with diabetes who received an antibody to CD3, another receptor found on all T-cells. The idea was to block the CD3 receptor, not stimulate it, but the aim was the same as TeGenero's: to coax regulatory T-cells into multiplying, which in turn would prevent the body's other T-cells from attacking and destroying beta cells in the pancreas which produce insulin.

The six-day treatment, reported in *The New England Journal of Medicine* (vol 352, p 2598), worked well in patients who started with 25 to 40 per cent of the beta cells. "At 18 months, there was no further decline in their insulin-producing cells," says Bart Keymeulen of the Free University of Brussels in Belgium, who coordinated the trial. "It was keeping their disease stable," he says - a 48-month follow-up will be published soon. There were no serious side effects, other than flu-like symptoms and transient reactivation of a virus.

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