The TGN 1412 Phase I trial
(very preliminary draft)
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(What is TGN 1412)

TGN1412 (also known as CD28-SuperMAB) is the working name of an immunomodulatory drug which was withdrawn from development, originally intended for the treatment of B cell chronic lymphocytic leukemia (B-CLL) and rheumatoid arthritis.[1] It is a humanised monoclonal antibody that not only binds, but is a strong agonist for the CD28 receptor of the immune system's T cells.

Mice of the inbred strain BALB/c were immunized with recombinant human CD28-Fc fusion proteins and boosted with a B lymphoma cell line transfected to express human CD28. Hybridomas were obtained by fusing B cells with the hybridoma partner X63Ag8.653 and screened for reactivity with human CD28 and TCR-independent mitogenic activity. Two monoclonals called 5.11A1 and 9D7 were identified. The more active of the two, 5.11A1, is a mouse IgG1 immunoglobulin. The Complementarity determining regions of 5.11A1 were cloned into the framework of human IgG and combined with IgG1 (TGN1112) or IgG4 (TGN1412) constant regions. According to the company's Investigator Brochure, "TGN1412 is a humanised monoclonal antibody directed against the human CD28 antigen. The molecule was genetically engineered by transfer of the complementarity determining regions (CDRs) from heavy and light chain variable region sequences of a monoclonal mouse anti-humanC28 [sic] antibody (5.11A1, Luhder et al., 2003) into human heavy and light chain variable frameworks. Humanised variable regions were subsequently recombined with a human gene coding for the IgG4 gamma chain and with a human gene coding for a human kappa chain, respectively."[6] The recombinant genes were transfected into Chinese hamster ovary cells and the recombinant antibody harvested from culture supernatant.

Source: http://en.wikipedia.org/wiki/TGN1412

(How is it supposed to work?)

Naive T-cells normally require both signal 1 (the antigen receptor) and signal 2 (co-stimulation) to become fully activated. Studies of monoclonal antibodies specific for mouse, rat or human CD28 identified a so-called "superagonistic" antibodies that could stimulate T-cells without concurrent antigen-receptor stimulation. Whether this activity represents merely a "stronger" activity or a different activity is uncertain. Two antibodies specific for human CD28 were identified. The more active of the two, TGN1112 (originally called 5.11A1) belonged to the IgG1 class of immunoglobulins. TGN1412 (clone 9D7) belonged to the IgG4 class. The TCR-independent agonism of these antibodies involved binding to a specific part of the CD28 molecule called the C"D loop.[7] Once the investigators found an antibody with this property they initially wondered if it could be therapeutically useful in stimulating the immune system in immunosuppressed patients. However, in vitro and in vivo data from animal studies later suggested that administration would lead to preferential activation of regulatory T cells, leading to a net effect of T cell downregulation. On its website, the company writes: "A pronounced T-cell activation and expansion mediated by CD28-SuperMAB in animal models is accompanied by the expression of anti-inflammatory cytokines, like IL-10, rather than by the toxic cytokine storm of pro-inflammatory mediators induced by other agents that address the TCR complex.".[1] As it turned out, the results of the first trial in humans (see below) indicate that this may not always be the case.

Source: http://en.wikipedia.org/wiki/TGN1412

(Animal testing)

TGN1412 had not previously been given to humans; however, the trial was preceded by animal testing, including in non-human primates. The company claims that these did not indicate any safety issues. The US patent application states "it could be shown in a pilot study that an in vitro administration of anti-human CD28-SuperMAB induces in a rhesus monkey in vivo a profound activation of T cells, without clinically visible side effects" and goes on to say "This antibody—in spite of its strong T cell-stimulatory properties—is very well tolerated in vivo, in contrast to all other known T cell activating substances."[19]

Source: http://en.wikipedia.org/wiki/TGN1412

(Advertising for the trial)

After promising results in animal studies, ParExel advertised for volunteers for a Phase I trial.

In February, when Rob O. saw the text message pop up on his cellphone from Parexel International -"healthy males needed for a drug trial"for £2,000 -it seemed like a harmless opportunity to make much-needed cash. www.iht.com/articles/2006/04/07/news/drug.php

Under the heading, ``What's in it For You'' the site says: ``You'll have plenty of time to read or study or just relax -- with digital TV, pool table, videogames, DVD player and now FREE Internet access! You can even just catch up on some sleep!'' The site says the study will provide ``modern medical and monitoring equipment to ensure your safety whilst on trial.'' The company used this language to recruit for the TGN 1412 trial. Goodyear says the language is deceptive, equating participation in a clinical trial to vacationing. ``I was blown away,'' he says. ``It's all about enticing people in.'' Parexel's recruiting Web site also promises payment, a free medical exam, and more. ``Free food for the duration of your stay -- and NO shopping or washing up!,'" the site says. ``I'm outraged by that cavalier language,'' Caplan says. ``That would be fine if you want to recruit someone for a summer abroad, but not for a clinical trial with uncertain risks.'' Khan, who volunteered for a different clinic trial in December and was paid 1,600 pounds, says he wouldn't do another. A friend from college alerted him to the Parexel trial, and the advertising drew him in, he says. ``If you read the advertisements, they make it look like a holiday home,'' he said. ``It makes it sound fun and relaxing. I would never do a trial again.'' www.sskrplaw.com/publications/060410.html

(Reasons for compensation)

Image of paying for education

What motivated people to volunteer for this study?

He (David Oakley) told the Mail on Sunday that he took part in the trial to raise money for his wedding in June to wife Katrina...
www.guardian.co.uk/medicine/story/0,,1838498,00.html

"He (Ryan Flanagan) told us he would be paid 2,000 pounds ($3,500) and did not think there would be any problems," Sarah Brown, a 27-year-old family friend of the Flanagans, told UK-based newspaper The Sun.
www.newstarget.com/019371.html

Khan, who was studying to be a teacher at Roehampton University in London, grew up in small town in south Wales, and has lived in London for four years. He was attracted by the offer of quick and easy income, he says. ``It's such good money for a student," Khan said. ``It goes a long way." The rights of human subjects in clinical trials are protected by independent ethics committees, which can also reject experiments or halt them if they become too risky. They make sure risks are properly disclosed, and respond to inquiries from participants with concerns about the conduct of the trial -- when participants know where to call.

(The informed consent process)

The actual consent form is at www.circare.org/foia5/tgn1412_consentform.pdf.

A critique of the consent form appears at www.sskrplaw.com/publications/060410.html. There are some pretty strong allegations here, so I want to cross check these with other sources.

When volunteers asked questions about the TeGenero study's consent form, the staff at Parexel's drug-testing facility in London's Northwick Park Hospital were dismissive, says Raste Khan, one of the participants. The 23-year-old university student was one of two people given a placebo, or dummy drug. ``The guy said, `We're in a bit of a push. Can you sign it now, and I'll explain it all to you,'" says Khan, who was interviewed in his London house on April 6. ``He didn't say anything whether the drug was going to be harmful or what it's been tested on. ``He was saying if you're ever late, you could lose 10 percent of your pay," Khan said. ``If you consume something or eat something or drink when you shouldn't, you could lose 10 percent of your pay. Most people do it because you need the money. It's a bit daunting." The 2,000 pounds, which Khan says he hasn't received, is about half of the amount of his student loan. The consent form says violations of Parexel's rules are ``misdemeanors" subject to fines. The form also says participants will get the drug or a placebo. It doesn't say that 75 percent of the subjects would get the drug. www.sskrplaw.com/publications/060410.html

Ethicists say the consent document exploited the participants' need for cash. The first page of the consent document says participants can leave the trial at ``any time without giving a reason and my rights will not be affected." On page 9, the document says, ``If you leave the study and exercise your right not to give a reason or are required to leave the study for non-compliance, no payment need be made to you." ``That's very coercive language," says Greg Koski, 56, a physician and former head of the U.S. Office for Human Subject Protection, interviewed by phone April 5. ``It's a bait and switch." www.sskrplaw.com/publications/060410.html

A few weeks earlier the volunteers had gone for some standard tests and a briefing on the trial. Nav Modi, 25, had asked the doctor if the trial was unusual or risky. "He said, 'Certainly not, because if it was risky, it wouldn't be tested on humans.' The doctors from Parexel assured us that things wouldn't go wrong. "The worst case was that we would have a headache or nausea that would be gone in a couple of hours." www.mirror.co.uk/news/topstories/2007/03/10/exclusive--one-year-after-drug-test-horror---89520-18732768/

(Initial administration of the drug)

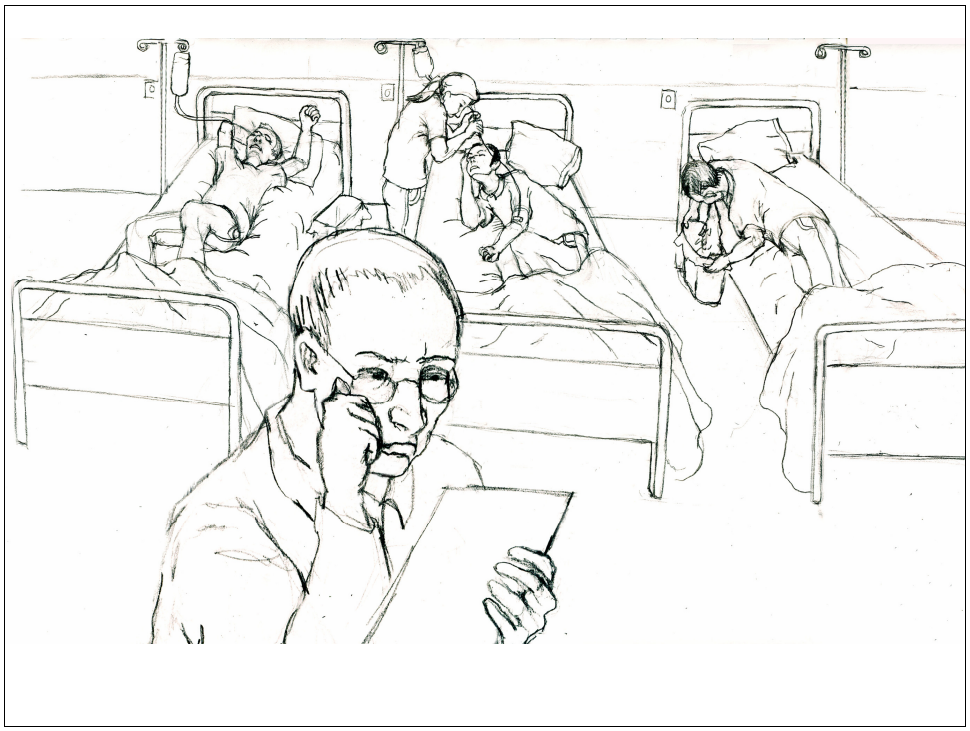
The trial began at 8am. David was the first to be injected and the others followed at 10-minute intervals.

Source: www.mirror.co.uk/news/topstories/2007/03/10/exclusive--one-year-after-drug-test-horror---89520-18732768/

The volunteers knew the test had gone wrong within 20 minutes, Khan says. The men started to undress, even though the ward was cold, he says. They were grabbing their heads, and their breathing became erratic. Khan was sent to the canteen as nurses and doctors tried to relieve the men's pain. Khan says the man in the next bed pleaded for assistance. `Horrible Scream' ``It was a horrible scream," Khan says. ``He was begging for help, saying `Doc, my head is killing me. My back is killing me.' He was moving around like a snake, arching his back." www.sskrplaw.com/publications/060410.html

Within minutes of the last volunteer getting his TGN1412, the first injected recruit had begun to complain of a severe headache, backache, fever and pain. He tore his shirt off and yelled he was burning. 'An Asian guy next to me started screaming and his breathing went haywire as though he was having a terrible panic attack,' said one of the volunteers, Raste Khan, who had been given a placebo. 'They put an oxygen mask on him but he kept tearing it off. He was shouting "Doctor, doctor, please help me!" He started convulsing, shouting that he was getting shooting pains in his back. People were fainting and coming back to consciousness. It was terrifying. I kept expecting it to happen to me at any moment. But I felt fine and didn't know why.' www.guardian.co.uk/medicine/story/0,,1734446,00.html

Within one hour, they were screaming in agony, with fevers and excruciating headaches. One said it felt like rockets in his brain. Rob says: "There was a sense the staff just wanted to get it over with." Four minutes after restaurant manager Nino Abdelhady's had his jab, his life became a screaming, agonising nightmare. "Everything just fell apart" as the drug ripped through his body like wildfire, he says. The drug was destroying their immune systems and shutting down their vital organs. Sixteen hours later, the volunteers were finally moved into intensive care. Shocked to the core, it was Nino's girlfriend, My fanwy Marshall, who described him as the "Elephant Man."
www.mirror.co.uk/news/topstories/2007/03/10/exclusive--one-year-after-drug-test-horror---89520-18732768/



The first inkling that doctors were facing an unprecedented medical crisis began with a call to the critical care unit at Northwick Park Hospital last Monday afternoon. Patients on the seventh floor were having strange reactions to a new drug, they were told. Some were having breathing difficulties, others were losing consciousness. The news triggered alarm, but nothing more. The unit's six beds were already occupied by patients who were too ill to be moved. So a separate bay was taken over and the first patients rushed down. It was then that staff realised the nature of the calamity they were up against. Within minutes, the bay was filled with the writhing bodies of young men screaming for help. Consultants were summoned from their homes. All were baffled. Even the team who had administered the test drugs could not explain why the men were slipping in and out of comas, why their heads had puffed up to twice their normal sizes, why some were vomiting, or why some were in such pain. Their only real comfort was provided by an experienced nurse who supervised the installation of drips and ventilators. www.guardian.co.uk/medicine/story/0,,1734446,00.html

The men, who had been contracted by the US drug testing company Parexel to test the anti-cancer drug TGN1412, were put on ventilators. Then some began showing signs of kidney failure. Blood filtration units were brought it to clean out their veins and arteries. Relatives were called and told to expect the worst. Only a miracle would see them through, one was told. www.guardian.co.uk/medicine/story/0,,1734446,00.html

(Patient in coma)

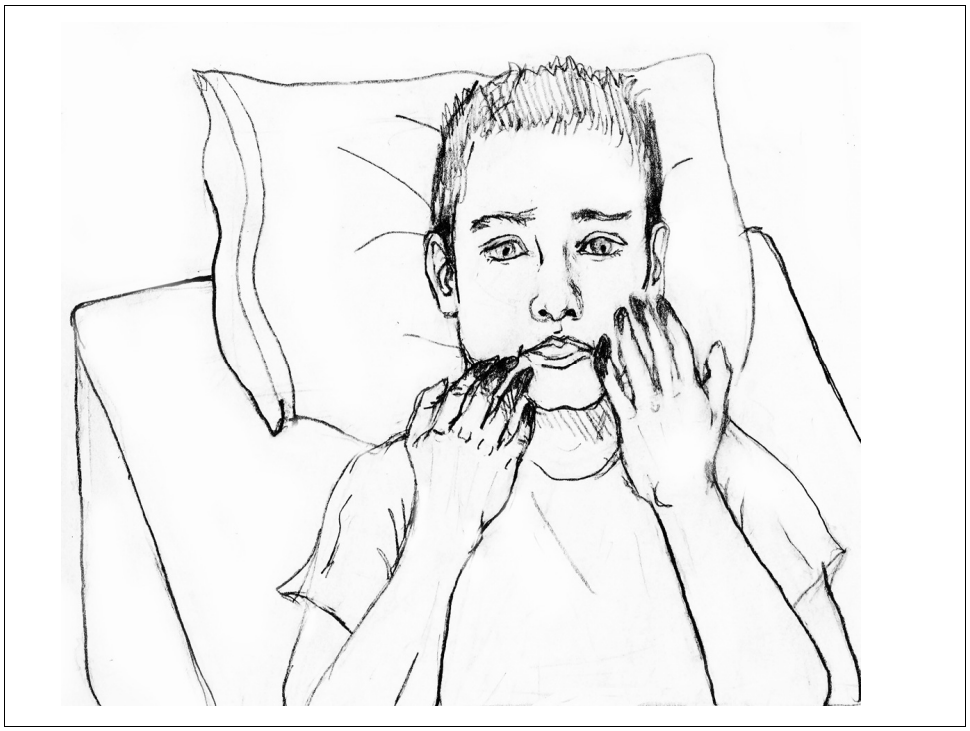
(Cytokine storm)

What caused such an extreme reaction in these patients? An article in the New England Journal of Medicine suggests that TGN 1412 may have induced a cytokine storm.

A **cytokine storm** is a potentially fatal immune reaction consisting of a positive feedback loop between cytokines and immune cells, with highly elevated levels of various cytokines.[1] A cytokine storm is a potentially fatal immune reaction consisting of a positive feedback loop between cytokines and immune cells, with highly elevated levels of various cytokines.[1]

When the immune system is fighting pathogens, cytokines signal immune cells such as T-cells and macrophages to travel to the site of infection. In addition, cytokines activate those cells, stimulating them to produce more cytokines. Normally this feedback loop is kept in check by the body. However, in some instances, the reaction becomes uncontrolled, and too many immune cells are activated in a single place. The precise reason for this is not entirely understood, but may be caused by an exaggerated response when the immune system encounters a new and highly pathogenic invader. Cytokine storms have potential to do significant damage to body tissues and organs. If a cytokine storm occurs in the lungs, for example, fluids and immune cells such as macrophages may accumulate and eventually block off the airways, potentially resulting in death.

Source: http://en.wikipedia.org/wiki/Cytokine_storm



Now, more than a month after the incident, doctors frankly don't know whether the adverse effects are reversible, especially for 20-year-old trial volunteer Ryan Wilson, who is the lone volunteer still hospitalized. Wilson had slipped into a coma for three weeks after taking the drug, and after awakening, discovered that he may lose parts of his fingers and toes, which had turned black because of his reaction to the drug. "I'm told it's like frostbite and my fingers will just fall off," Wilson told the UK's News of the World recently. In addition to being in a coma for nearly a month, Wilson also suffered from heart, liver and kidney failure, septicemia, pneumonia and dry gangrene. Marshall says her boyfriend -- a previously healthy, 28-year-old bar owner in London -- had changed beyond recognition immediately after taking TGN1412. "I went in expecting to see his smiley face and curly, black hair, but he was completely lifeless," she says. "He's like a shell of who he is. He can't even move his eyelids. The machine is pumping out of his lungs. His chest is puffed out. His face is puffed out like the Elephant Man. A day ago, I was talking to him and he was fine, and now they are saying he could die at any moment." www.newstarget.com/019371.html

Today Rob, 32, has been told he is suffering from post-traumatic stress. His blood, he says, is "not how it was" and his immune system remains damaged. He's had a recurring rash on his legs and arms that feels as though someone's stabbing him hard with pins. "You end up being paranoid about the smallest things, thinking, 'God, what if it's cancer.'"
www.mirror.co.uk/news/topstories/2007/03/10/exclusive--one-year-after-drug-test-horror---89520-18732768/

Oakley, from Ealing, west London, has been told by doctors that he is showing 'definite early signs' of lymphoma.
www.guardian.co.uk/medicine/story/0,,1838498,00.html

(TeGenero response)

Yesterday Dr Thomas Hanke, TeGenero's chief scientific officer, defended the decision to use healthy volunteers. 'We had early evidence [from animal studies] that the effect of the drug depends on the status of the patient, so it dampens the immune response for patients with auto-immune disease and it boosts the response for the other group [with cancer]. We are so terribly sorry it went so wrong. We are devastated by the tragic events that have happened.' www.guardian.co.uk/medicine/story/0,,1734446,00.html

It said the life-threatening inflammation of the men's tissues and internal organs were "most likely" caused by an unexpected biological effect that had not been detected in animal tests of the TGN1412 drug, manufactured by TeGenero. "We are satisfied that the adverse incidents which occurred were not as a result of any errors made in the manufacture of TGN1412, its formulation, dilution or administration to trial participants," the agency's chief executive, Professor Kent Woods, said.
http://society.guardian.co.uk/health/story/0,,1783076,00.html

(Rapid infusion)

One of the criticisms of the TGN 1412 trial was that the drug was infused too rapidly, in a matter of minutes, when it should have done over a much longer time frame. (Source needed).

(Simultaneous administration)

Another criticism is the near simultaneous administration of the drug. A waiting period after the first administration to see what develops would have put only one patient at risk. (Source needed)

(Excessive compensation)

Others have criticized the excessive compensation offered for this trial (Source needed)

(Unrealistic portrait of research)

Image of injection equalling a tropical vacation.

(Novel mechanism of action)

A final concern raised by the TGN 1412 trial is that drugs using a novel and untested mechanism of action need to be monitored more carefully (Source needed)