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London Drug Trial Catastrophe – Collapse of Science and Ethic

An unconventional member of a new class of drugs, all known to have caused serious side effects including deaths, has been approved for clinical based solely on unpublished animal tests. Dr. Mae-Wan Ho *and* Prof. Joe Cummins

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Drug trial that went horribly wrong

On 13 March 2006, six healthy young volunteers took part in a clinical trial and became violently ill minutes after having been injected with a d developed to fight autoimmune disease and leukaemia [1-5]. One of the two additional volunteers injected with a placebo who showed no ill recalled to newspaper reporters [2]: "The men went down like dominoes. They began tearing their shirts off complaining of fever, then some screamed that their heads were going to explode. After that they started fainting, vomiting and writhing around in their beds."

One man became especially bloated, "like the Elephant Man". All six suffered multiple organ failure, and were admitted to intensive care. The Medicines and Healthcare products Regulatory Agency (MHRA), which gave approval for the trial, immediately withdrew authorisation; and a international warning went out to prevent the drug being tested abroad.

Two weeks later, two men remain in hospital; one still in intensive care and conscious, the other said to be making good progress [6]. The cas under investigation by the MHRA. But serious questions should also be asked concerning the MHRA's approval for the trial in the first place.

A new kind of drug previously untested on humans

The drug tested, TGN1412, was developed by the company TeGenero based in Würzburg, Germany, and manufactured by Boehringer Ingelhei another company, Parexel International Corporation based in Lowell, Massachusetts, USA, was commissioned to carry out the clinical trial. Th young men were paid a small fee to participate in the experiment [1-5], according to one of them, £2 330 (US$4 070).

While Paraxel said it followed the rules for drug research, a former executive of the company, who asked to remain anonymous, expressed su that the drug was tested on so many persons at once. "It is common sense not to dose six individuals with the drug at once where there is no human experience," he said [2].

TeGenero describes TGN1412 on its website as [7] "an immunomodulatory humanized agonistic anti-CD28 monoclonal antibody that is being developed for the treatment of immunological diseases with a high unmet medical need, such as multiple sclerosis, rheumatoid arthritis and cancers". A monoclonal antibody (MAB) is an immunoglobulin protein made by the descendants of a single antibody-producing cell.

In a statement updated 24 March 2006 [8], the company disclosed that TGN1412 binds to the cell marker CD28 present on the cell surface of T lymphocytes, causing more T cells to be created. It claimed that the safety of TGN1412 was extensively tested on "rabbits and monkeys", that were no drug related deaths despite administering doses up to five hundred times the dose to be used in the phase 1 clinical trial". Neverthel pre-clinical tests, 2 monkeys experienced a transient increase in the size of lymph nodes, but TeGenero considers that not a drug related side

Family members of the human volunteers were told that a dog died in testing, TeGenero denied that TGN1412 was tested on dogs, but stated academic research which led to the initial development of TGN1412 did include testing on mice and rats.

TeGenero had applied to conduct the same test and gained approval both in the UK and in Germany, though the test in Germany had not yet and has been abandoned.

It said that the drug was given to volunteers "within a period of 2 hours", as "approved by the MHRA and the local ethics committee". TGN14 the company's "most advanced product candidate and the first to reach human testing."

What went wrong?

No one knows what caused the shocking reactions in the volunteers. An error in drug dosing or manufacture was suspected [9]. Simon Grego spokesperson for UK's MHRA, said managers at Northwick Park Hospital where the trial took place were so surprised that they called in the p to check for evidence of a crime. But MHRA and other investigations found no evidence of crime or technical error.

Was a contaminant in the MAB drug responsible? MAB drugs typically begins with extensive genetic engineering to produce the appropriate antigen, which is injected repeatedly into mice together with transgenic cells producing the protein, in order to challenge the mice to produc antibodies to the protein. The mice are then killed and the spleen cells isolated and fused with cancer (lymphoma) cells to create 'hybridoma' Clones of single hybridoma cells are then obtained to give permanent cell lines, each of which grows and secretes a single antibody protein (monoclonal antibody) continuously. 'Humanized' monoclonal antibodies would have involved additional genetic engineering to alter the monoclonal antibody protein molecule so that it would not be rejected when given to human subjects. Each step in this complicated process have introduced dangerous contaminants.

An interim report from MHRA said that the drug did not appear to have been contaminated, "or to have contained anything other than the c ingredients", said Professor Kent Woods, the chief executive of the MHRA, which regulated 350 Phase 1 clinical trials (first testing on humans UK every year. The report also cleared Paraxel, which appeared to have run the trial according to the agreed protocol, with the correct dose to the patients [10].

More and more, the suspicion has turned onto TGN1412 itself, which may have triggered the T cells to release a toxic flood of cytokines (cell signalling molecules), or the T cells may have attacked the body's own tissues, leading to multiple organ failure [9, 11]. But MHRA, TeGenero a Paraxel all maintained that the volunteers' reactions were "unforeseeable". TeGenero's chief scientific officer Thomas Hanke issued a statem

17 March: "Extensive preclinical tests showed no sign of any risk."

Henke told *Science* magazine that a rodent version of TGN1412 was tested extensively at high doses in rats and mice, with no ill effects; and TG itself was given to 20 cynomolgus monkeys in an unpublished study, after it was shown that their T cells were activated in the same way as hu cells, with no significant adverse effects other than a brief increase in lymph node size. Simon Gregor of MHRA said that they have gone back files and there was nothing in the documentation that would cause them to think there was a concern.

We do not know what the documentation contained, but disagree that the problems were "unforeseeable".

The problems should have been anticipated

At least one drug, CTLA4 monoclonal antibody, which binds to a different cell marker, have caused side effects in human trials, including skin and gut reactions, which were controlled with steroids.

In fact, there are over 355 MAB drugs in clinical development, and the US Food and Drug Administration (FDA) has granted approval to18 so f mainly for cancer treatment and control of immune system disorders. *There is warning posted on every one of the approved drugs*, as one of us readily discovered and compiled the list ("Warning on FDA approved monoclonal antibodies", this series). So it is difficult to believe that the problems were unanticipated as claimed.

On the contrary, the problems associated with MAB drugs are widely recognized. One drug approved for treating multiple sclerosis (MS) was associated with several deaths from brain infections, probably because it blocked immune cells migrating to the brain to fight infections. That was voluntarily suspended pending further studies. The other MAB drugs approved are almost without exception associated with severe side effects, in many cases including death. These drugs provide, in most instances, treatment of last resort for terminal or highly debilitating diso For that reason, the risk of administering the treatment has been deemed acceptable provided that consent for treatment is truly informed. I

The problems associated with up-regulating the immune system are also well known, and include inflammation of the eye, skin, gut, pituitary along with cases of hepatitis and loss of skin pigmentation [12]. A humanized MAB used to treat colon cancer caused 17 percent of the cancer patients to experience adverse immune events [13]. Initiation of such adverse events in susceptible patients could be detected by first admini a low dose of the drug, so those patients could be removed from further treatment with high doses [12]. In the London drug trial, the dose administered to all six volunteers must have been sufficiently high to cause all of them to become critically ill.

Another factor that should have made those involved in the London trials much more cautious is that the drug tested was unusual even amor monoclonal antibody drugs.

Superagonist monoclonal antibodies are unconventional

Soon after the first monoclonal antibodies were raised against the cell surface molecules of white blood cells in the later 1970s, researchers h realised that they could be used to change immune responses, potentially for therapeutic purposes. The majority of the antibodies block imm functions or augment them when used in conjunction with other reagents. A much smaller subset of antibodies activate white blood cells autonomously, and are defined as superagonists [14, 15].

Natural activation of T cells requires both the T cell antigen receptor (TCR) and T cell marker CD28 to be stimulated by specific ligands (diffusi signal molecules), causing the TCR and CD28 respectively to become cross-linked and clump together on the cell membrane. What happens downstream is not well understood, but is thought to involve cross talk between the clumped TCR and CD28 patches at the cell membrane.

In experimental systems, the natural ligands of TCR and CD28 can be replaced by specific MABs.

There are two types of MABs that bind to CD28 to stimulate T cells, conventional MABs that depend on simultaneous stimulation of TCR, and superagonist MABs that can give full activation of T cells without TCR stimulation. Researchers from TeGenero working with other laboratori showed that superagonist and conventional rat and human CD28-specific MABs bind at different sites, and that the superagonist binding site conserved across the evolutionary divide separating rodents and humans [14]. They also claimed previous research in the rat model showed t superagonist CD28 MABs were highly potent stimulators of T cell proliferation *in vivo* without apparent toxicity, and were ready to exploit th for therapeutic purposes.

Animal tests consist of "unpublished data"

Although TeGenero claimed to have carried out extensive animal testing of TGN1412, it provided no scientific papers on the tests. A review pu by TeGenero in 2005 [15] referred solely to "unpublished data" as far as animal testing was concerned.

The review referred to studies in rats and mice given superagonist anti-CD28 MABs, in which a transient but significant increase in overall T ce numbers was found, without unleashing a toxic "cytokine storm"; and the researchers concluded that, "the lymphocytosis induced by CD28 superagonists appears to be benign and well tolerated." A dose range 0.5mg/kg to 5mg/kg body weight led to a transient increase in the prop of T regulatory cells from 5 to 20 percent, while absolute cell numbers increased up to 20 fold. Low doses of anti-CD28 MABs (0.5m/kg body v per rat) appeared to expand T regulatory cells without inducing overall T cell increase; hence it was concluded that CD28 superagonist stimul *vivo* leads to the preferential expansion and strong activation of naturally occurring T regulatory cells over other T cells.

The review claimed that: "Efficacy of CD28 superagonist therapy has so far been evaluated in animal models of both peripheral and central ne system inflammation as well as in a model of human rheumatoid arthritis." These animal models showed that CD28 superangonist "prevente least greatly mitigated clinical symptoms when given prohylactically – that is, before the animals showed signs of clinical disease (unpublishe data)." And, "even after the onset of clinical symptoms therapeutic CD28 superagonist administration rapidly stopped disease progression ar induced remission." Consequently, for "successful therapy, as for Treg cell expansion, low doses of CD28 superagonist (0.5mg/kg body weig were sufficient (unpublished data)."

The fallout

The dust from the catastrophe has far from settled. It has left the scientific and medical community stunned, and serious soul searching bega almost immediately in the aftershock.

UK's top science journal *Nature* reported the trial under the headlines, "London's disastrous drug trial has serious side effects for research", predicting tighter restrictions on clinical research and closer scrutiny of the private companies that carry out the majority of clinical trials [16].

The report raised a number of key questions: Was informed consent adequate? Were the right subjects recruited for the trial? Were the right given? Did the company carrying out the trial behave responsibly? Some observers say that the company TeGenero should have been more ca about the drug as it bypasses the immune system's natural control mechanism; as immunologist Angus Dalgleish of St. George's Medical Scho London said, "all hell can break loose".

Parexel International, the company contracted to do the clinical trial, operates in 39 countries. Ethicists in the United States have called for th careful scrutiny of a newly loosened set of rules for making and testing drugs in human trials, as well as the lucrative business of contract rese organizations (CROs) such as Paraxel. Bioethicist Art Caplan is concerned that CROs are tacitly encouraged not to focus on protecting human subjects. He said CROs are often told by pharmaceutical companies to "just get us the data on the deadline", and "don't get asked questions how that's being done." The Association of CROs boasts that CROs conduct clinical trials 30 percent more quickly than the pharmaceutical companies that hire them.

The London drug trial episode came in the wake of 11 otherwise healthy people who tested positive for tuberculosis in Montreal, Canada, afte were paid to volunteer for research conducted by a private company. The volunteers apparently caught TB from an infected subject they'd b housed with as part of the study paid for by a Canadian company, but conducted by the CRO SFBC International.

Writing in the *Philadelphia Daily News*, Caplan expressed doubt that informed consent and safety were given the priority required to protect t human volunteers taking part in such studies [17].

"The recruitment of the participants into the British trial certainly left much to be desired ethically." Caplan wrote. The website recruiting vol said almost nothing about risks, but went on and on about good pay, free medical care, free food and "plenty of time to read or study or just with digital TV, pool table, video games, DVD player and free internet access."

The other CRO, SFBC International, has problems beyond Montreal. The company's major facility for housing subjects in long-term studies in had received numerous safety and fire-code violations. When subjects went public with complaints, at least three of them said they SFBC offi bullied them and threatened them with deportation.

Twenty years ago, Caplan said, most clinical research was conducted in academic medical centres, and most research was paid for with gover money. Now, private CROs running studies for pharmaceutical and device companies are a $14 billion industry in the United States alone. A lo research is done using poor people or students, sometimes in the United States, but often in Europe, India and Southeast Asia.

The role of the regulatory agency should also come under careful scrutiny. Why did the MHRA allow the tests to be carried out simultaneousl six volunteers? Did it have all the information available when it approved the trial? Did it make sure that informed consent was adequate?

In Germany, the local public prosecutor in Würzburg is investigating whether any criminal wrongdoing was involved [16]. The Paul Ehrlich Inst which authorises human trials of biological drugs, announced it will tighten regulation of the first tests of such drugs in people. Johannes Löv president of the Institute based in Langen, asked why six people were treated at the same time, instead of starting with one. He said his Insti will start requiring sequential rather than simultaneous administration of 'high risk' monoclonal antibodies such as TGN1412, which activates t immune system.

Have the standards of science and ethics both collapsed in the new ethos of the "knowledge economy" that promotes wealth creation abov else?