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GM Ice Cream Coming

**FDA in Drug Trials Controversy -
Widespread Accusations of Corporate Links**

RNAi Gene Therapy Nightmare

POON

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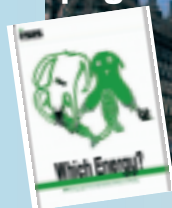
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Cover: *Bury my heart in the deepest blue* by Li Poon, Canada

Lessons from TGN1412

It is five months since the catastrophic clinical trial of the drug TGN1412. All six victims have survived so far, but according to recent reports their future is bleak. According to laboratory tests and medical reports seen by the International Herald Tribune, they are suffering from severely damaged immune systems and are likely to suffer immune problems for the rest of their lives. One is showing early signs of cancer.

This would be a tragic situation however it came about, but there is overwhelming evidence that it could and should have been avoided. Two major investigations and statements made by many scientists with experience in monoclonal antibody drugs have confirmed our initial suspicion that a cytokine storm, which caused the violent illnesses, was by no means totally unforeseeable as has been claimed (see London Drug Trial Catastrophe - Collapse of Science and Ethics; Warnings on FDA Approved Monoclonal Antibody Drugs; Post Mortem on the TGN1412 Disaster; Science in Society 30). It was a risk that ought to have been anticipated, and the body responsible for regulating drug trials, the Medicines and Healthcare products Regulatory Agency (MHRA) has shown itself to have a dangerously limited view of its responsibilities.

In the light of what *was* known at the time of the drug trial, we need to ask some serious questions.

The role of the company that developed the drug

Why did TeGenero, the company that developed TGN1412, not realise this was a potentially hazardous trial and ensure that it was carried out under conditions that would reduce the risk to an acceptable level? There is nothing in the protocol for the trials or in the information given to the volunteers to suggest they did.

It's not that they didn't know about cytokine storms. On the contrary, they state on their website: "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."

In other words, it is not at all unexpected that a drug of this kind should cause a

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cytokine storm. The special feature of CD28-SuperMAB is that it does not, at least not in the animals it was tested on. Like all monoclonal antibodies, however, it cannot be used in humans in its original form. It has to be genetically modified to make it immunologically acceptable to humans, which means that the drug used in the trial is inevitably different from the one that was tested on animals.

Thus, when the trials began, TGN1412 was known to be one of a class of drugs that can cause cytokine storms. The drug it was derived from did not do this in the animal tests and TGN1412 had not done it when tested in monkeys; if it had there would have been no question of testing it in humans. In the light of this, it is astonishing that TeGenero did not feel the need to be especially cautious, especially in view of the recognized species specificity of such drugs.

Parexel did not even follow the simple and relatively common practice of giving the drug to only one volunteer first and waiting long enough to see there were no untoward reactions before proceeding. And the doctors in the intensive care unit at Northwick Park have said that it was hours after the volunteers reached them that the Parexel team informed them of the possibility of a cytokine storm. Only then did they begin to treat their patients with high doses of steroids to blunt the immune response.

Other companies have been more prudent. In May this year, the BBC reported that Dr Harsukh Parmer, the Director of Discovery Medicines for AstraZeneca had said his company is also developing drugs of this kind. He had added that when working with monoclonal antibodies, the company carries out a wider range of tests than normal before proceeding to human trials. Even then, they begin by putting ultra low concentrations just under the skin, rather than straight into the blood stream.

The role of UK drug trials watchdog

What exactly is the role of the UK Watchdog MHRA (Medicines and Healthcare products Regulatory Agency)? In its investigation, it found no errors in the manufacture of the drug or in the way it was given to the trial participants. It concluded that, "an unpredicted biological action of the drug in humans is the most likely cause of the adverse reactions in the trial participants." It said that the agreed protocol had been followed, but made no comment about whether the protocol had been appropriate for a trial of this sort of drug.

The MHRA does make some criticisms, but none that it considers material to the disastrous outcome. It found that Parexel, the company that carried out the trial, had failed to check that TeGenero's insurance actually covered the volunteers. The MHRA does not, however, explain why it did not verify this as part of its approval of the protocol, as one would expect. The counter staff at my local Post Office, for example, demand to see my third party liability insurance when I pay the

annual tax on my car. In fact, the volunteers were insured but only for a total of £2 million, which may well be considerably less than the compensation they will be awarded. Someone should have checked this before the trial; nobody did.

Damning reports by Expert Scientific Group and by drug industry

There have been two substantial reports since that produced by the MHRA. One is by an Expert Scientific Group (ESG) set up by the UK Department of Health, and the other is by a joint task force of the UK BioIndustry Association (BIA) and the Association of the British Pharmaceutical Industry (ABPI). These reports are comprehensive and damning, in complete contrast to that of the MHRA.

The BIA/ABPI report states:

"...there are sufficient signals in the publicly available data, and in historical precedents, to indicate that a very cautious approach is appropriate when assessing the risk, the starting dose and the study design with first-in-human studies with a potent agonist antibody such as TGN1412."

What they are saying is that it was obvious to many scientists both in universities and in industry that special care is required in clinical trials using any drug like TGN1412.

The ESG report contains a list of 19 recommendations. Some, such as being far more careful in trials of novel drugs, are already "best", if unfortunately not universal practice. They also recommend far more transparency and the sharing of information on the results of phase one clinical trials in general and Suspected Unexpected Serious Adverse Reactions (SUSARs) in particular.

Fragmentation of the pharmaceutical industry a factor not considered

One factor not considered by these Reports is that the pharmaceutical industry, like other industries, has become fragmented. The major companies do not carry out all their research in house. Many new products originate in small firms and are only taken up by the big companies when they are past the early stages of development.

There are some advantages to this, but it has meant that the clinical trial of TGN1412 involved four companies: TeGenero, who developed it, Boehringer, who produced the samples used in the trial, Parexel, who conducted the trial, and an unnamed company that had carried out the trials on monkeys. As with the British railway system after privatisation, it appears there was no one with an overview of the entire process, no one with overall responsibility. Were the people at Parexel who designed the trial fully aware of the nature of the drug they were testing? If they were, they said nothing about it in the information they gave to the volunteers.

It also makes it harder for the victims to get adequate compensation. TeGenero has filed for insolvency, whereas a major pharmaceutical company would have the resources to pay whatever damages are



awarded. Merck may be badly hurt by the Vioxx scandal but it is highly unlikely to go under.

A new regulatory body is needed

As we write, six previously healthy young men are facing lifetimes of immune-system related illness and the distinct possibility of early death. Despite what the experts in the field are saying, those responsible for the trials insist that they did everything properly, that what happened was completely unforeseeable. The regulatory body that should have intervened continues to back them up, also in the face of all the evidence.

The regulation of drug trials in the UK is clearly inadequate, and the problem is made worse as the pharmaceutical industry becomes increasingly international. The Food and Drug Administration in the USA is currently embroiled in several drug trial scandals amid widespread accusations of conflicts of interests in a high proportion of its scientific advisory panels (this issue). More and more trials are being carried out in third world countries where regulation is less stringent; Parexel, for example, is expanding its operations in Latin America.

The World Health Organisation is in the process of setting up an International Clinical Trials Registry so that the information from trials anywhere in the world can be accessed (WHO Registry of Clinical Trials, S/S 30). There must also be internationally agreed standards for trials. And as a first step, the UK must get its own house in order.

The MHRA sees its task only as verifying that the right boxes have been ticked on a standard protocol, and it doesn't do even that very well. After the incident, it had nothing to say beyond that what had happened had been unpredicted, when there is a consensus among the experts that it should have been anticipated.

Clinical trials are too important and potentially too hazardous to be regulated in such a casual manner. We need a new regulatory body with the scientific expertise to look critically and independently at all the trials that are submitted to it and the authority to reject any that do not satisfy the strict requirements.



Geocrop
circle,
Courtesy of
Greenpeace

French company granted permit to grow vaccine maize crops

We were astonished to discover that maize modified with human genes for producing monoclonal antibodies had been approved for commercial planting in France since 2005, as stated by the French company Meristem Therapeutics on its website: "MERISTEM® has successfully expressed in transgenic corn several recombinant monomeric IgA sequences derived from tumor specific IgG for a partner. One of these recombinant plant-made monomeric Ig A 1 has been produced and GLP-purified at the gram-scale...Our partner has showed [sic] that IgA s produced in corn have interesting biological activity such as lung, breast and pancreatic cancer tumor regression in animal models...In April 2005, MERISTEM was granted their first authorization for field production of these antibodies."

A large number of monoclonal antibodies (mAbs) for treating diseases are being developed, eight of these, for treating cancers, are among those approved by the United States Food and Drug Administration (FDA). All of the approved cancer therapy mAbs are associated with severe side effects, frequently resulting in death. One mAb tested in London recently hit the headlines for weeks, as it made all six healthy volunteers violently ill (London Drug Trial Catastrophe - Collapse of Science and Ethics, Post Mortem on the TGN1412 Disaster SiS30).

Producing mAbs in maize is bound to contaminate our food supply with the mAbs as well as the human or humanized genes coding for the antibodies. Yet transgenic crops with these drugs are being tested in secret locations (Drug Trial Catastrophe & Safety of Secretly Tested Pharm Crops, SiS30) and unsuspecting members of the public are exposed without their knowledge or consent.

Cancer vaccines are tested and used for preventing or treating cancers. The mAbs are employed as therapeutic vaccines to treat developed cancers, and despite their toxic side effects, can provide control of cancers that are not too far advanced. Both prophylactic and therapeutic cancer vaccines have been produced in plants, all too often in food crops.

EU funds major programme in transgenic vaccines and antibodies in crops plants

The European Union (EU) has promoted and funded a major programme to produce vaccines and therapeutic antibodies in crop plants such as maize. Officially, the first clinical trials are targeted for 2009, but may start well before that date.

Using food crops for prophylactic and therapeutic vaccines

Transgenic Maize with Monoclonal Antibodies Grown in France

Prof. Joe Cummins, Dr. Mae-Wan Ho and Prof. Peter Saunders say this amounts to an illegal massive clinical trial of monoclonal antibodies known to cause severe side effects including death (Warnings on FDA Approved Monoclonal Antibody Drugs, SiS30). They call for banning transgenic crops producing pharmaceuticals and the withdrawal of EU funding for such projects.

is a very risky undertaking. The synthetic transgenes incorporated into food crops are approximations of the original genes, frequently resulting in proteins with altered amino acid sequences and with sugars added to the protein (glycosylation patterns) totally different from those in the original mammalian cells. Apart from the intended and unintended side effects of the vaccines on human subjects, the glycosylation pattern of a protein is an important determinant of its immunological activity. The scientific community has been rudely reminded of that recently when tests were carried out on a transgenic pea (Transgenic Pea that Made Mice Ill, SiS29). A previously harmless bean protein transferred to pea acquired new glycosylation patterns, provoking dangerous inflammation of the lungs and general food sensitivities.

Mass clinical trials without informed consent

Growing transgenic crops producing pharmaceuticals in secret locations amounts to conducting mass clinical trials without informed consent, thereby contravening the current EU directive 2001/20/EC on clinical trials of medical products, which sets out the requirement for informed consent and product identification and labelling. In the case of the transgenic maize, the use of male sterility traits or de-tasselling is not sufficient to protect the public. People and animals will be exposed to plant material in the form of dust and debris; and the grain and corn kernels will escape as volunteers to spread the transgenes. Diseased or decaying transgenic cobs or plant residues will release vaccines and transgenes to contaminate surface and groundwater.

It is imperative that those potentially exposed to transgenic vaccines or other transgenic pharmaceuticals should be informed of the locations and the full nature of crops grown commercially or field tested, both currently and at any time previously. People who suffer adverse health or other impacts from exposure to the transgenic plants must be given appropriate compensation.

Meanwhile, we propose that all EU funding should be withdrawn from projects using crop plants for transgenic vaccines and other pharmaceuticals, and an immediate ban should be imposed on all further environmental releases of such crops. We have time and again pointed out that the production of transgenic pharmaceuticals should only be allowed in plant/animal tissue culture under strictly contained conditions.

Please circulate this paper widely, forward it to your MEPs and relevant regulatory bodies in the European Parliament and European Commission

Should not be approved, major gaps in risk assessment
Prof. Joe Cummins and Dr. Mae-Wan Ho

USDA Proposes to Deregulate Its Own Transgenic Plum

This report was submitted to the USDA on behalf of the Independent Science Panel

Transgenic plum for plum poxvirus resistance

The United States Department of Agriculture (USDA) announced that its Animal and Plant Health Inspection Service (APHIS) has received a petition from its Agricultural Research Service (ARS) seeking non-regulated status for a transgenic plum designated transformation event C5, genetically engineered to resist infection by plum poxvirus (PPV).

It is worth mentioning that the transgenic plum petition is the first temperate transgenic tree to be petitioned for non-regulated status. Petitions for a number of transgenic trees are certain to follow in short order including transgenic forest trees, which would be really disastrous for the world's forests (GM forest trees, the ultimate threat, *SiS 26*).

A version of the same petition was first submitted to the USDA in 2004, and the current petition open for public comment is a revised version submitted in March 2006, together with an updated environment assessment. The most salient feature of the revised petition and assessment is that the gene for the viral coat protein was found not to produce a viral protein but to initiate a process called post-transcriptional gene silencing associated with a small inhibitory RNA, a short sequence of RNA which can be used to silence gene expression.

The proposed commercial release is the patented plum variety "Honey Sweet" plum developed jointly by USDA, Institut National de la Recherche Agronomique, Paris, France and Cornell University. The plum tree has the plum poxvirus (PPV) coat protein gene incorporated to provide resistance to the major plum pest PPV. The female parent of the plum is "Bluebyrd" (named for Senator Robert Byrd), while the pollen parent is "unknown". The plant is not self fertile, a pollinator is required. The variety is propagated by bud grafting to standard rootstocks. The plum fruit is a typical drupe in which the skin and flesh of the fruit contain only maternal genes; the seed embryo and endosperm contain both paternal and maternal genes. The seeds of the transgenic plum are viable and could produce viable plants. A non-transgenic plum tree pollinated by the transgenic plum will give fruits that will not contain the PPV gene in their flesh, only the seed would. All the plums produced on transgenic tree, however, fruit and seed, would be transgenic, regardless of the status of the pollinator.

The transgenic plum contains the PPV coat protein gene along with the selectable markers NPTII (Kanamycin resistance) and GUS (β -Glucuronidase). There are multiple copies of the PPV coat protein gene linked at the insertion site. The genetic modification of the plums was done using a gene cassette containing the NPTII gene driven by the relatively weak *nos* promoter from *Agrobacterium* and terminated by the *nos* terminator. The PPV-CP was driven by the cauliflower mosaic virus (CaMV) promoter and transcription was terminated by the *nos* terminator from *Agrobacterium*.



Chinese jade figure with peach