nature

14 November 2002 Volume 420 Issue no 6912

The trials of gene therapy

The news that a child in a gene-therapy trial has developed cancer has cast a cloud over the technique. But this has more to do with the field's chequered history than the particular circumstances of this tragic case.

"Oh no, not again!" That was the reaction of many observers of gene therapy last month, after researchers in Paris announced that a child given a pioneering treatment for severe combined immunodeficiency disease (SCID) had succumbed to a leukaemia-like disease (see *Nature* **419,** 545; 2002).

Just three years ago, the death of 18-year-old Jesse Gelsinger, in a trial of a gene therapy for a liver defect that causes a dangerous build-up of ammonia, threw the field into crisis — with good reason. Gelsinger died of an inflammatory reaction to the viral vector used to deliver the corrective gene, and serious faults were soon found in the way that the trial, at the University of Pennsylvania in Philadelphia, had been conducted. Patients had been inadequately informed of the potential risks, despite evidence of problems at high doses of the vector in animal experiments. And when signs of liver stress emerged in some patients, regulators weren't informed.

As these facts sunk in, questions began to be asked about the reporting of adverse events in other trials, and gene therapists embarked on a bout of soul-searching. Perhaps, some acknowledged, the field had been too eager to rush into the clinic.

The present case, in which a retroviral vector's site of insertion into the genome seems to have activated a cancer-causing gene, has come as a further blow. And given recent history, it's understandable that authorities in France, directly responsible for the affected trial, and the United States, where the Gelsinger debacle has left painful memories, should move quickly to suspend such trials.

However, a closer examination of the French case reveals important differences to the Gelsinger case that should convince regulators to proceed once more with SCID trials, albeit more cautiously.

First, there has been no suggestion that the investigators are at fault. Cancer triggered by 'insertional mutagenesis' was always recognized as a risk of gene therapy using retroviral vectors, and the parents of patients enrolled in the SCID trials were informed of this possibility. The researchers involved are now pursuing studies to investigate the risks facing the other patients they have treated (see page 116). And although a definitive risk assessment isn't possible, the results should be promptly communicated to regulators and the patients' parents.

Perhaps the most important difference to the Gelsinger case is that, whereas SCID gene therapy is a potential life-saver for children who otherwise face an extremely bleak outlook, the Gelsinger trial was a safety study in adults of a treatment designed for young children. Gelsinger and the other volunteers did not stand to gain any therapeutic benefit. In trials of drugs for life-threatening conditions, on the other hand, severe adverse events do sometimes occur, and may be tolerated if the benefits outweigh the risks. It is in this light that the current SCID setback should be viewed.

This is not to say that changes are unnecessary. Procedures for obtaining informed consent from the parents of future SCID gene-therapy patients must be adjusted to stress that cancer caused by insertional mutagenesis is now a tangible, rather than a theoretical, risk. Regulators must also reconsider the wisdom of using retroviral vectors, particularly where genes are introduced to mark populations of cells for study, rather than for their intrinsic therapeutic effects.

The challenge for gene therapists and regulators is to show that the field can respond appropriately to a serious adverse event in an otherwise successful clinical trial. It is unlikely to be the last: such setbacks are inherent to the development of new medical treatments. ■

Frameworks can be too rigid

There are lessons to be learned from scientists' responses to the European Commission's latest research programme.

When asked about their experiences with the European Commission's Framework research programmes, scientists tend to roll their eyes. Baffling bureaucracy and the programmes' overt socioeconomic objectives have been deterring many of the continent's best researchers.

The Sixth Framework Programme, worth 17.5 billion euros (US$17.7 billion) over the next five years, was highlighted this week with great fanfare at a major conference in Brussels. So is it likely to be any more popular than its predecessors?

The programme's underlying vision is an end to the fragmentation of European research. It aims to unite to an unprecedented degree the best groups in the fields that are most relevant to European citizens. Take breast-cancer research: the idea is that geneticists, molecular biologists, clinical researchers, biotech and pharmaceutical companies, and whoever else is relevant, will pool their expertise into an overarching research consortium with the goal of defeating the disease.

It sounds a laudable aim, but the concept fails to consider the role of competition as a driving force in science. Mega-collaboration is not always the best solution to a tough intellectual problem. And the demands of managing huge research networks can detract from scientific creativity and hypothesis-driven enquiry.

Fortunately, however, the European Commission has received a great deal of indirect feedback about its plans. Rather then setting the programme in stone, and simply issuing a series of narrowly defined 'calls for proposals', the commission has this time invited scientists to submit 'expressions of interest' — condensed proposals outlining what researchers think are the most fruitful scientific opportunities (see http://eoi.cordis.lu/search_form.cfm).

The response was overwhelming, with some 15,000 proposals being submitted. These submissions do not just represent a goldmine of scientific ideas. Their sheer number, and the fact that many do not envisage huge collaborative efforts, also provides a clear indication that Europe's research community is not willing to accept the idea that a few large networks fit all.

How exactly this exercise in consultation translates into formal calls for proposals, scheduled for 17 December, remains to be seen. But it is not too late for the European Commission to adapt its vision, and accept that, in some cases, thinking small is the best approach. ■

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