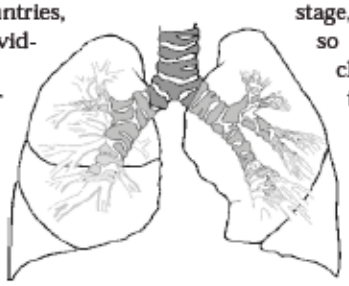
## New TB vaccines to be tested

The incidence of tuberculosis (TB) is on the increase, particularly in Russia and other states of the former Soviet Union (*Lancet* 358, 1513; 2001), and also in countries such as the United Kingdom (*Thorax* 56, 173; 2001). The rise is due to the spread of TB strains that are resistant to drugs and to co-infection in HIV patients. Fortunately, two clinical trials of new TB vaccines are imminent; these will be the first since the introduction of BCG (Bacille Calmette–Guerin) 80 years ago.

Helen McShane, Wellcome Clinician Scientist Fellow at the John Radcliffe Hospital, Oxford, is leading one of the studies. Her group is beginning a Phase I safety and immunogenicity trial in the UK using BCG first and then boosting immunity with a new vaccine (MVA85A) engineered from attenuated vaccinia virus that expresses the 85A antigen. If these studies are successful, McShane will run a parallel study in a TB endemic area such as Africa.

BCG has been administered to 3 billion people worldwide. "It protects well against disseminated disease in childhood, but is not effective against adult pulmonary disease, which is where the burden of mortality lies," says McShane, adding "We don't know yet whether the new vaccine will boost the immune response to BCG if the BCG was given many years before. That's one of the things we need to test." The Netherlands and the United States have never recommended routine BCG immunization. Sweden stopped recommending it in 1975 and Czechoslovakia in 1986. In all of these countries, BCG is used for at-risk individuals only.



Meanwhile, plans for human trials of a second TB vaccine are attracting criticism. Célio Silva, of the University of Sao Paulo, Brazil, helped develop the vaccine and is leading the trials due to start next year. The DNA-based inoculation is injected into muscle and triggers cells to express Hsp65, a heat-shock protein taken from *Mycobacterium leprae*, a bacterium similar to *Mycobacterium tuberculosis*.

The collaboration, backed by the Sequella Foundation and supported by British immunologist, Doug Lowrie, hope that this method will work therapeutically to treat people with multi drug-resistant strains of TB. But immunologists have voiced concerns that the treatment could trigger an autoimmune response, as the *M. leprae* protein shows 55% homology with the equivalent mammalian protein. Ian Orme, from Colorado State University, has publicly opposed the treatment, but is now reserving judgement: "I'm very pleased to see that the field is finally getting to the clinical trials stage, since a new vaccine is so badly needed." He declined to comment further on Silva's trials pending the publication of his own research into the vaccine, which is believed to report negative effects in mice.

The group has defended its work, citing successful safety testing in mice, guinea pigs, monkeys and cattle. "None of the extensive studies of this DNA vaccine in normal animals have given any indication of such a problem," says Lowrie. "Experts… have tested it and found no harmful effects in either initiating or exacerbating autoimmunity."

**Jeremy Thomson, London**

## Fifteen-year follow up for gene therapy patients

The group that advises the United States Food and Drug Administration (FDA) on aspects of gene therapy has recommended that patients taking part in trials of the technique be subject to a 15-year follow-up period and that trial data should be more efficiently recorded by a federal agency.

The Biological Response Modifiers Advisory Committee (BRMAC) was charged with determining the long-term safety risks of gene therapy to patients and how this differs between vector classes. "We're not thinking of, for example, the acute release of inflammatory cytokines after injection of adenovirus as happened in the Gelsinger death. We were charged with looking at what will happen between 1 and 20 years post-injection," BRMAC chair, Daniel Salomon, told *Nature Medicine*.

Daniel Salomon

"We agreed that integrating vectors, such as retroviruses, would cause a true danger if they integrated into an area where there is a regulatory gene sequence, that is, insertional mutagenesis…and we figured 15 years monitoring would be needed for this set of patients. We also reasoned that *ex vivo* treatment of cells would probably be less risky than *in vivo* because with the latter, it's more difficult to control the cells you target. Another issue is the use of replication-competent viruses, which need the same length of follow-up."

Although proper records have not been maintained to date, it is estimated that there have been 200 gene-therapy trials involving almost 1,000 patients, most of whom have been terminal cancer patients. But it is not known how many of these people are alive today or why they died. A database has been set up in the last year by the FDA and NIH to monitor patient information.

Involvement in clinical trials necessitates intense monitoring for the duration of the study, which typically includes at least a 1–5-year post-evaluation period that entails physical monitoring. It is follow-up after this time that BRMAC is addressing. "We decided that trial sponsors should be responsible for sending out a yearly health survey to patients," says Salomon. "If patients report disease then the sponsor would pursue this. Carcinogenicity, autoimmunity, neurologic and hematopoetic disorders are the main areas of focus."

Whereas industrial sponsors already budget for and accommodate long-term follow-up in post-marketing surveillance, such lengthy monitoring creates problems for principle investigators who, for example, might rely on standard five-year NIH grants. Salomon says that additional funding mechanisms may need to be created so that the proposed regulations do not dampen research in the field.

**Karen Birmingham, London**