

## Oversight and monitoring of clinical research with gene therapy in Australia

*The NHMRC has set up the Gene and related Therapies Research Advisory Panel (GTRAP) to oversee gene therapy research*

The cornerstone of clinical research involving humans in Australia is the HREC (Human Research Ethics Committee). All studies must be approved by an HREC at the investigators' institute(s). The demands on these committees are considerable, particularly when cutting-edge technology is involved. This was the situation in 1994 when the National Health and Medical Research Council (NHMRC) formed GTRAP (Gene and related Therapies Research Advisory Panel). The function of GTRAP was to provide the NHMRC, researchers, clinicians and HRECs with advice on medical, scientific and technical issues related to gene therapy,<sup>1</sup> a novel form of treatment that had just been introduced in the United States. Its use in Australia — to treat severe combined immunodeficiency (SCID) — is described in this issue of the Journal (*page 458*).<sup>2</sup>

The NHMRC, through its Australian Health Ethics Committee, required that HRECs not give final approval for a gene therapy trial unless that trial had also been reviewed and approved by GTRAP. In Australia, gene therapy requires both local HREC and national GTRAP oversight. The reason for this was the novelty of the treatment, which does not involve traditional drugs or chemicals, but cells that have been genetically modified.

Risks such as insertional mutagenesis, now tragically seen after gene therapy of SCID-X1, were known in the early 1990s to be possible.<sup>3</sup> Another concern was the unintentional involvement of germ cells, although the original targets for gene transfer were somatic cells. Genetic errors in somatic cells would harm the patient, but those in germ cells could be passed on to future generations.

GTRAP works closely with the Therapeutic Goods Administration (Australia's equivalent of the US Food and Drug Administration [FDA]), the Office of the Gene Technology Regulator and the Australian Health Ethics Committee through members in common. The "and related" component of GTRAP's title reflects the growing use that will be made of cellular therapies in clinical practice. The NHMRC has recently expanded the GTRAP terms of reference to include cell therapies in the broader sense, given the future possibility that genetically engineered stem cells (or xenotransplants) will be trialed in clinical research. This move parallels the Therapeutic Goods Administration's proposed new regulatory framework for tissues and emerging biological therapies.<sup>4</sup> Because of the inherent uncertainty surrounding these novel therapies, GTRAP requires that all treated patients (or their families) be contactable should problems develop in the longer term. All studies require the sponsors or investigators to provide annual reports, notifications of adverse events, and a final report on completion of the study.

GTRAP's current position on trials of gene therapy for X-linked SCID or other therapy involving potential risk combinations (retroviral vectors and stem cell targets) is similar to that followed by the FDA, outlined in this issue of the Journal (*page 440*).<sup>5</sup> For SCID-X1, this means that gene therapy can still be considered as an option if there are no alternative treatments, such as a suitable allogeneic bone marrow transplantation, or if such transplantation has failed. In the case of the potential risk combinations outlined above, gene therapy could continue after review of the risk–benefit analysis, ongoing monitoring which now would need to include 6-monthly integration-site analysis

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(analysis of the patient's cells to detect any potential oncogenic events early), and inclusion in the patient information sheet and consent form the information that acute leukaemia has occurred in children as a complication of gene therapy.

In Australia, the clinical investigator and sponsor of two ongoing gene therapy studies involving SCID-X1<sup>2</sup> and HIV, respectively, placed their studies on voluntary clinical hold when two cases of leukaemia were reported in children who had received gene therapy for SCID-X1. Since then, the SCID-X1 clinical study has remained on voluntary hold. The HIV study, which uses a retroviral vector targeted to haemopoietic stem cells, came off voluntary hold when reassessed by GTRAP. This reassessment included a review of the risk-benefit analysis, implementation of the additional monitoring requirement, and rewording of the consent documents, as described above. Following the report of a third leukaemia complication, the HIV study, which is also being conducted in the United States, has continued pending further advice from the FDA as well as GTRAP. At present, there are no additional scientific data available to GTRAP that would require a clinical hold on the HIV study, although the patient information sheet and consent forms must again be changed to reflect three, rather than two, leukaemia cases.

More information on GTRAP (including a list of all gene therapy studies undertaken in Australia) can be found on the NHMRC website ([www.nhmrc.gov.au/research/gtrap.htm](http://www.nhmrc.gov.au/research/gtrap.htm)).

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**Competing interests:** As Chair of GTRAP, Professor Trent is paid an allowance.

- 1 National Health and Medical Research Council. Gene and related Therapies Research Advisory Panel (GTRAP). Available at: <http://www.nhmrc.gov.au/research/gtrap.htm> (accessed Mar 2005).
- 2 Ginn SL, Curtin JA, Kramer B, et al. Treatment of an infant with X-linked severe combined immunodeficiency (SCID-X1) by gene therapy in Australia. *Med J Aust* 2005; 182: 458-463.
- 3 Balicki D, Beutler E. Gene therapy of human disease. *Medicine* 2002; 81: 69-86.
- 4 Therapeutic Goods Administration. Proposed regulatory framework for tissues and emerging biological therapies. Available at <http://www.tga.gov.au/bt/prtisreg.htm> (accessed Mar 2005).
- 5 Thrasher AJ. Gene therapy: great expectations? [editorial] *Med J Aust* 2005; 182: 440-441. □