

# Molecular Therapy

## NIH Recombinant DNA Advisory Committee Continues to Ponder Adverse Event Associated With AAV Gene Therapy Trial

**A**t the 3 December 2007 meeting of the National Institutes of Health Recombinant DNA Advisory Committee (NIH RAC), additional information concerning the death of a study participant in the Targeted Genetics gene therapy trial was presented (see previous editorial in *Molecular Therapy*<sup>1</sup>). The trial evaluated the effects of delivery of an adeno-associated virus (AAV) vector to rheumatoid arthritis patients. The therapy involved intra-articular injection of an AAV2 vector encoding a fusion of the IgG1 Fc and tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ) receptor. This fusion is identical to the construct utilized to manufacture the TNF- $\alpha$  antagonist drug etanercept (Emberl). The therapeutic vector being studied, TgAAC94, was developed by Targeted Genetics for local instillation into affected joints as an alternative potential therapy in this disease. The trial has been reopened after review of details of the event by the independent Data Safety and Monitoring Board and the US Food and Drug Administration.

The case has received a great deal of publicity, and in some cases the lay media made a rush to judgment that the gene transfer itself was a cause of the unfortunate death of one of the study participants. At the December 2007 NIH RAC meeting, an update was presented by Targeted Genetics, and additional details of the autopsy results and postmortem laboratory evaluations were provided to the committee and the public. The committee's interim opinion, as discussed in the open public session and widely reported, although not yet finalized, is that the subject's death was primarily a result of an infection with disseminated histoplasmosis, bleeding complications, and multiorgan failure. Her risk for such an adverse event was her systemic rheumatoid arthritis therapy, not the gene therapy agent. Indeed, the committee felt that the intra-articular injection of the gene therapy transfer vector was very unlikely to have played any significant role in the serious adverse event.

The discussion included a considerable amount of retrospective analysis of study design details,

most prominently the lack of pre-stored specimens to examine the potential immunological response, particularly T-cell responses, to the vector or viral proteins included in the vector. The focus on T-cell responses was due to the lack of sufficient available data to determine whether the patient had an immune response as well as to the ongoing concern that viral vectors may elicit such a response, thus reducing efficacy or, potentially, causing side effects. However, there was no clinical evidence of an immune response, and the systemic exposure to the vector in this patient proved to be several orders of magnitude below the doses that elicited what was apparently immune-mediated transaminitis in the recently reported coagulation factor IX hemophilia trial. As is nearly always the case when complex clinical trials are performed, the experience of performing the trial itself leads to improvements in study design. In this case, among other items, changes may include more blood draws, a greater effort to monitor intercurrent illnesses that might alter the response of the subject to the test therapy, a focus on assays that will help distinguish transgene effects from other concurrent interventions, and development of logistics that would enhance communication between the research personnel and the caregivers responsible for the intercurrent medical care of study participants.

Going forward, a very important aspect of many AAV trials—and perhaps even selected retrovirus vector trials—will be the need for or advantage of immune suppression to prevent immune-mediated elimination of transgene-expressing cells. Thus, the topic of more complete analysis of the immune responses is timely.

Although they are helpful, in my opinion these other aspects of the committee's deliberations perhaps obscured somewhat the main message: the investigation of this serious adverse event yielded a large body of data, and none of these data suggested that the vector or transgene were implicated in the unfortunate death of the study participant. The dilution of this message was reflected in the lay

press's response to these deliberations. For example, *BioWorld Today* (4 December 2007) published the news of the RAC deliberations with the headline "NIH Panel Won't Rule Out Gene Therapy in Trial Death."

It is clear that the NIH RAC provides an important public forum for the consideration and discussion of all aspects of gene therapy trials. As we become aware of an additional leukemia in the X-linked severe combined immunodeficiency trials in London and Paris, this role takes on added importance because of the clear overall success of this therapy in the case of pediatric immunodeficiency diseases. The scrutiny of these trials is critically important, not only for investigators but also for continued education of the public about this still nascent therapeutic modality. The latter is crucial because there clearly still exists a poor public perception of gene therapy even though hundreds of trials have been conducted safely and the track record of this modality

compares favorably with that in other areas of early-phase human clinical trials. In the setting of early human clinical trials, we must accept that side effects will occur. However, progress is clearly being made in some diseases, and with persistence and continually improving reagents and trial design it is reasonable to expect that this progress will continue in the future.

#### ACKNOWLEDGMENT

Although I am a member of the NIH RAC, the opinions expressed in this editorial are my own and do not represent the opinion of the committee.

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#### REFERENCE

1. Williams, DA (2007). RAC reviews serious adverse event associated with AAV therapy trial. *Mol Ther* **15**: 2053–2054.