

Recombinant DNA Advisory Committee Updates Recommendations on Gene Transfer for X-Linked Severe Combined Immunodeficiency

The National Institutes of Health Recombinant DNA Advisory Committee (RAC) has recently reviewed and amended its long-standing recommendations on gene transfer for X-linked severe combined immunodeficiency (X-SCID). The current recommendations have been in effect since shortly after the initial reports of serious adverse events that occurred in the human gene transfer studies to correct X-SCID in France (and a subsequent event in England). Faced with two new protocols submitted for review in its December 2008 and March 2009 meetings, the committee re-evaluated these recommendations, which essentially limited gene transfer trials in this disease to so-called salvage situations, i.e., to patients in whom identical or haplo-identical stem cell transplantation had failed. These recommendations were at odds with those of the Gene Therapy Advisory Committee in England, where a trial continued to accrue patients based on inclusion criteria that did not require failed previous stem cell transplantation, although it did include patients who lacked human leukocyte antigen (HLA)-identical related donors.

The two trials of relevance submitted to the RAC propose to use safety-improved retrovirus or lentivirus constructs that express the common cytokine receptor γ -chain (γ_c), which was originally identified as a component of the high-affinity interleukin-2 receptor. The first trial, reviewed at the December meeting—"Gene Transfer for SCID-X1 Using a Self-Inactivating (SIN) Gammaretroviral Vector" (overall principal investigator, Adrian Thrasher, Institute of Child Health, London)—uses a safety-improved new generation of SIN gammaretrovirus vector that lacks all enhancer-promoter elements of the long-terminal repeat (LTR) U3 region and is also devoid of all gammaretroviral coding regions. The trial as proposed sought to include children diagnosed with X-SCID who lacked HLA-identical related donors and infants with infections resistant

to medical therapy or other medical conditions that significantly increase the risk of allogeneic transplant. It was proposed as a multicenter trial with sites in Boston, Cincinnati, Los Angeles, Paris, and London. The data presented at the meeting showed reduced insertional activation activity and reduced activity in an *in vitro* bone marrow immortalization assay of the proposed construct as compared with an intact LTR backbone. The committee heard presentations from three experts in stem cell transplantation on the state of current therapies for this disease: Morton Cowan, University of California San Francisco Children's Hospital; Richard O'Reilly, Memorial Sloan-Kettering Cancer Center; and Rebecca Buckley, Duke University Medical Center. There was extensive discussion of risks and benefits of current therapies vs. gene transfer, with some RAC members emphasizing the lack of an appropriate mouse model that accurately predicts human safety as an important handicap in guiding safety considerations. One of the most contentious issues was the use of haplo-identical donors as an alternative to any form of gene transfer/therapy. Haplo-identical donors are generally available, as parents of the patient, and such transplants can be performed without conditioning. Data from single institutions show excellent survival, especially in infants younger than 3.5 months of age, although compiled data from across Europe and multiple sites in the United States show less impressive results. In addition, many haplo-identical transplant recipients need lifelong support with intravenous gamma globulin infusions, and some show gradual loss of T-lymphocyte function. During presentation of data to support the proposed gene transfer trial, Luigi Notarangelo (Children's Hospital, Boston) presented data indicating that infected patients have lower survival after transplant preceded by preparative conditioning, supporting the specific inclusion of these patients in the gene transfer trial. In the end, the RAC recommended that the trial exclude

infants younger than 3.5 months who were in good clinical condition and who had a haplo-identical (i.e., one parent) donor available. The RAC otherwise agreed with inclusion of patients who lacked an HLA-identical related donor or for whom a readily available unrelated donor could not be identified.

A related trial was presented to the RAC in the March meeting. This trial, "A Pilot Feasibility Study of Gene Transfer for X-Linked Severe Combined Immunodeficiency in Newly Diagnosed Infants Using a Self-Inactivating Lentiviral Vector to Transduced Autologous CD34⁺ Hematopoietic Cells" (principal investigator, Brian Sorrentino, St. Jude Children's Research Hospital), had inclusion criteria similar to those of the above-mentioned trial but proposed to use a lentivirus construct for gene transfer. The presented data showed reduced insertional activation and reduced immortalization *in vitro* from the proposed clinical backbone. The discussion again focused on relative risks and benefits, and the lack of a completely predictive animal model for safety studies was again noted.

At the conclusion of discussion of this protocol, the RAC deliberated on overall revisions to the previous recommendations. The proposed revisions included the statement "Gene transfer studies for X-linked SCID that propose to use integrating vectors that have been shown in preclinical studies to reduce the risk of insertional mutagenesis compared to retroviral vectors used in the original X-SCID trials that led to leukemias should be reviewed on a case-by-case basis and should, ordinarily, exclude patients who have an HLA identical related donor available for stem-cell transplantation, as this remains first line therapy." In addition, "Given the evidence

that patients who are younger than 3.5 months often have proven clinical improvement with haploidentical transplant this therapeutic option should be preferred except in special clinical circumstances." These recommendations were adopted by the RAC. Transcripts of the deliberations can be obtained at the RAC website (http://oba.od.nih.gov/rdna_rac/rac_past_meetings_2000.html).

Overall, these recommendations allow gene transfer studies in patients with X-SCID to proceed in the United States in a cautious, deliberative fashion. Clearly there are still areas that warrant continuing discussions, notably whether murine *in vivo* studies are useful for insertional safety determinations, particularly using leukemia or tumor formation as a readout; whether quantification of *in vitro* immortalization provides more accurate prediction of vector safety in humans; whether haplo-identical transplants should indeed be considered the standard for therapy in this disease; and whether—given the outcome of the previous trials—insistence on using the term "gene transfer" as opposed to "gene therapy" in these protocols is justifiable. As in all cases of new therapeutics, additional experience in humans will help clarify these issues.

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The author is sponsor of US sites for the "Gene Transfer for SCID-X1 Using a Self-Inactivating (SIN) Gammaretroviral Vector" trial. Although he is a member of the RAC, the views expressed in this column do not represent the views of the committee.

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