

Molecular Therapy

ASGT advises NIH on funding of gene therapy trials

As noted in our November 2006 editorial¹, an ad hoc American Society of Gene Therapy (ASGT) committee appointed by Theodore Friedmann and led by Arthur Nienhuis has studied the complicated issue of NIH funding of gene therapy trials. The recommendations of this committee have been adopted by the ASGT Board of Trustees and have now been sent to the leadership of the NIH and to at least eleven NIH Institute Directors.

The committee, of which I was a member, suggests that there are two major barriers to the initiation of trials in the setting of an academic medical center. First, there are multiple, overlapping, and incompletely harmonized levels of regulatory review, both locally and nationally, that extend the length of time and effort required for protocol development and ultimate approval. Second, the funding mechanisms available, mainly individual (RO1) and program project (PO1) research grants awarded for four to five years, are increasingly difficult to obtain and may be ill suited for funding clinical trials that generally need a much longer period for development and implementation. As a consequence, multiple individual grants are needed to fund various aspects of the process, such as vector production, toxicity studies, and the actual conduct of the clinical trial. The multiple and redundant rounds of peer review for these grants may have diverging outcomes, thereby making it difficult to complete all the steps needed to initiate and complete the trial. These obstacles have seriously dampened the enthusiasm of many academic centers to invest in the infrastructure necessary to carry out sustained efforts in gene therapy.

The committee recommended to the NIH that a new structure be devised for a funding commitment through which all the resources necessary for product development and initial clinical testing be made available with a single review decision. The review panel convened to make this key “go/no-go” decision regarding individual trials should comprise experts in product development, disease-specific clinicians, and gene therapy experts, so that there is adequate expertise to evaluate the preclinical data, the product development plan (which should include realistic milestones that must be reached to release

each segment of funding), and the relevance of the gene therapy approach in the setting of current therapeutic options for a particular disease. Representatives from relevant institutions should participate in this review. Regulatory approval would not need to be obtained before review but would be anticipated to be a defined milestone for release of funds for the clinical trial.

Once the preclinical development of a study is completed, support is needed for at least three well-defined subsequent phases to successfully initiate a clinical trial: (i) clinical vector production, (ii) toxicity testing of the vector backbone, transgene, and clinical vector preparation, and (iii) conduct of the clinical trial. These three phases should be supported by a single review and funding process rather than additional and separate rounds of grant applications, review, and funding. As noted earlier, awards should be determined by critical peer review that evaluates the preclinical evidence supporting the clinical trial and its design. The committee felt that a contractual mechanism would seem advantageous, in that the full amount of money necessary for conduct of all three phases could be awarded at the onset, with money released for each successive phase only when the prior one has been successfully completed with results that support the following step. Formal milestones would have to be established to ensure appropriate progress, but significant flexibility should be allowed in the timeline, given the complex and arduous process of regulatory review and the possibility that unforeseen events might delay the trial. Ideally, once funds are awarded, their release would not be subject to the vagaries of additional and new peer review but would be given timely administrative review.

With respect to vector production, the committee noted the strong track record of the National Gene Vector Laboratory (NGVL). Over the past eleven years, the NGVL has manufactured 36 gene therapy vectors for use in clinical trials. There are currently five vectors in production at NGVL centers, with an additional three vectors in production at outside centers under the direction of the NGVL. Eighteen academic institutions have received

NGVL-manufactured vectors. To date, 310 subjects have been treated. All academic investigators, not just those receiving NGVL vector services, are eligible to participate in the NGVL Archiving and Repository Program, NGVL Clonality Testing Services, AAV Database, and Pharm/Tox Database. The committee recognized that the field must continue to benefit from access to core laboratories such as the NGVL, which have infrastructure support that allows ongoing development of specific vector systems, independent of the actual production of individual lots for clinical trials. The committee strongly urged that the NGVL program be continued. The committee also noted, however, that an alternative would be to allow each investigator awarded funding to contract directly with academic centers, including NGVL Centers, with proven capabilities to make vectors. Recognizing that the current system of independent NGVL peer review of proposed projects adds another level of complexity to the

initiation of clinical trial, the committee further proposed that NGVL peer review be eliminated.

This series of recommendations represents a welcome proposal for a unified approach to the review and funding of gene therapy clinical trials after preclinical proof of principle is completed. Such a unified approach to clinical trial development would address the impediments widely recognized in the current multiple funding mechanisms and would probably facilitate the sustained effort required for successful development and implementation of gene therapy clinical trials. We strongly urge the NIH to consider seriously these recommendations made by the ASGT.

David A Williams

Editor-in-Chief

REFERENCE

1. Williams, D.A. (2006) NIH funding of gene therapy trials. *Mol. Ther.* **14**: 607.

ASGT celebrates its 10th anniversary, and a new publisher for *Molecular Therapy*

To celebrate the 10th anniversary of the ASGT, the Society will present a special celebratory symposium at its annual meeting in Seattle in June 2007. This anniversary will be devoted to advances in the field of gene therapy and a presentation of important challenges and future directions for basic and clinical applications. Speakers will include Sir David Weatherall of the University of Oxford and past Regius Professor at Oxford, Malcolm Brenner of Baylor College of Medicine, Maria Grazia Roncarolo of the San Raffaele Telethon Institute for Gene Therapy in Milan, and David Baltimore, President of Caltech. The symposium will be one of the highlights of what promises to be an outstanding meeting. The ASGT now has over 2,000 members and continues to attract more than 2,000 registrants to its annual meeting.

Concurrent with the anniversary, this issue of *Molecular Therapy* is the first published by our new publishing partner, Nature Publishing Group (NPG). Rob Frederickson and I want to thank the staff of our previous publisher, Elsevier Science, for a productive relationship that saw *Molecular Therapy* grow to become the

preeminent gene therapy journal. We would like to thank this year's retiring Associate Editors (Barrie Carter, Theodore Friedmann, Donald Kohn, John Rossi, and Jude Samulski) and welcome the new Associate Editors (Hildegund Ertl, Loren Field, Mark Kay, Ernst Wagner, and James Wilson) to the journal.

In the coming months we will continue the tradition of rapid review and time-to-first-decision and, with help from NPG, will continue to strive to enhance the appearance and production quality of the journal. We look forward to a very productive relationship with our new publisher. As many authors already know, one immediate benefit of the move to NPG is the elimination of the fee for submission of articles. We have also instituted reduced charges for color pages, and active ASGT members will now benefit from reduced page charges. We are extremely pleased with the journal's fresh new look. Under NPG, the journal will continue to enjoy the same editorial independence and management.

David A Williams

Editor-in-Chief