

Molecular Therapy

An Integrated Funding Mechanism for Clinical Trials in Human Gene Therapy

The American Society of Gene Therapy (ASGT) has recommended to the National Institutes of Health (NIH) the development of a new, goal-oriented and milestone-driven, integrated funding mechanism to support clinical trials in human gene therapy. The concept was initially proposed by ASGT in 2006 and was subsequently discussed with representatives of the Office of Biotechnology Activities (OBA) and other institute officials in December 2008. The concept arose in the context of well-defined mechanisms to support hypothesis-driven basic research in gene therapy by the R01 or P01 mechanisms, which are adequate to support preclinical development, including the design and testing of specific vectors and their evaluation in relevant animal models. The proposal also seeks to build on the valuable program established by the National Heart, Lung, and Blood Institute (NHLBI) to make selective core resources available to the gene therapy community. However, current mechanisms for carrying out other aspects of clinical trials require multiple individual grants to fund various aspects of further product development necessary for initiation of early-stage clinical trials, which is inefficient and significantly retards progress toward clinical application of gene transfer.

Following the re-expression of interest in ASGT's proposed funding mechanism in December 2008, our President, David Bodine, appointed a working group to develop the proposal further. Co-chaired by ourselves, it included Jean Bennett, Barrie Carter, Odile Cohen-Haguener, Ken Cornetta, Helen Heslop, Kathy High, Don Kohn, Francis Szoka, Sam Wadsworth, and David Williams. The group held several meetings by telephone to develop the proposal, which was submitted to Jacqueline Corrigan-Curay, the Interim Director of the OBA, in late March 2009 after it had been reviewed and approved by the ASGT Board of Directors. On 7 April, we met with the Trans-NIH Gene Therapy Group, chaired by Sonia Skarlatos, to discuss the proposal.

Our recommendation was that eligibility for funding by the new mechanisms require definitive

scientific proof of concept for a particular application using the actual vector design and sequence proposed to be taken to a clinical trial. In this context, scientific proof of concept is taken to mean (i) demonstration of successful delivery and gene expression (or knockdown) by the relevant route of delivery and (ii) utilization of appropriate animal models to demonstrate correction or amelioration of the disease. Such animal studies should also provide evidence of the absence of significant toxicity and therefore the potential tolerability of the intervention in the proposed future clinical application.

We suggested an integrated single review of proposals by a panel constituted by experts in product development, disease-specific clinicians, and gene therapy experts, so that there is adequate expertise to evaluate the preclinical data, the proposed product development plan, and the relevance of the gene therapy approach in the setting of current therapeutic options for a particular disease. We noted that successful peer review should lead to approval of all the required funding, with the funds to be released in a milestone-driven manner as proposed by the investigators and reviewed by the panel. The funding mechanism should support the following: (i) Good Manufacturing Practice production of the vector and relevant safety testing required for product release, (ii) all additional preclinical studies required to complete a preclinical package for safety and toxicity, as well as to support clinical trial design and dosing for filing the Investigational New Drug (IND) application, (iii) costs associated with preparing and filing an IND or other regulatory and administrative documents, and (iv) costs of designing and conducting the clinical trial and of supporting oversight and regulatory filings. Further, our proposal suggested that applications should generally include documentation of pre-IND interactions with the US Food and Drug Administration that support the feasibility of the proposed approach. Each proposal should include an established external advisory committee of three to five experts to help shape it and evaluate its progress.

We have been extremely encouraged by the enthusiasm shown toward this proposal by the OBA officials and the Trans-NIH Gene Therapy Group, particularly the identification of relative advantages and disadvantages of various funding mechanisms that could be used for such support. Of particular interest to ASGT is the existing cooperative agreement mechanism, which seems to provide the most flexibility for such clinical trial applications and the greatest opportunity for effective interaction between grantees and the NIH staff. Members of the working group suggested several programs in various institutes that might serve as a model for further development

of our proposal. At the suggestion of Dr. Corrigan-Curay, the OBA is considering a policy conference to examine more fully the issues that we have raised. We held a meeting with NIH officials at the ASGT annual meeting in San Diego and agreed to a follow-up discussion later this year.

Arthur Nienhuis

ASGT President (2007–2008)

Theodore Friedmann

Member, Editorial Board