

Molecular Therapy

A “Vector Drain” in US Gene Therapy Development?

There is now a significant track record for novel vectors that have been designed and tested in animal models in the United States to be first tested in the clinic abroad. The double-copy vector design developed by E. Gilboa and colleagues in New York¹—and later the LASN vector designed by A.D. Miller and colleagues in Seattle²—were used in the first successful clinical studies in adenosine deaminase deficiency performed in Milan, Italy.^{3,4} The MFG vectors developed in the laboratory of R. Mulligan at the Whitehead Institute in Cambridge, Massachusetts,⁵ led to the first success in the treatment of X-linked severe combined immune deficiency in Paris.⁶ The first tissue-restricted lentiviral vectors, exemplified by the TNS9 vector developed in New York,⁷ are now under clinical investigation in Paris, using a similar vector constructed in Boston⁸ and manufactured at the National Gene Vector Laboratories (NGVL) at Indiana University. No trial has yet been funded by the National Institutes of Health (NIH) to support a clinical study that aims to treat the severe hemoglobinopathies in the United States.

These observations lead one to question why clinical gene therapy protocols seem to be lagging in the United States. Dan Wright, Senior Scientific Advisor and Program Director for Hematology Research at the NIH’s National Institute of Diabetes and Digestive and Kidney Diseases convened a one-day meeting on 14 January 2008 to identify and discuss both the challenges involved in bringing gene therapy approaches to clinical trials and the key barriers that are encountered in such work. The meeting was attended by a cadre of researchers who have successfully moved basic studies into the clinic, as well as representatives from multiple NIH institutes and the US Food and Drug Administration. Important questions were addressed, such as whether this phenomenon is due to a greater fear of gene therapy in the United States or the collapse of funding for translational research and clinical trials, or whether it is part of a greater trend to delocalize therapeutic trials outside the United States.

The answers to these questions are multifactorial and complex and have received much attention

in our editorial pages and from the American Society of Gene Therapy (ASGT) (see editorials in the April and November 2006 and January 2007 issues of *Molecular Therapy*).^{9–11} These include the recent constriction of the NIH budget, in addition to the fragmented and redundant nature of funding and regulatory oversight needed to develop a clinical trial—particularly one involving gene transfer technology. These two barriers—funding fragmentation and regulatory redundancy—have been cited elsewhere, including in a letter from the ASGT to NIH Director Elias Zerhouni in late 2006. The recommendations of the ASGT also included strong support for the continuation of the NGVL.

Despite the best intentions of individual institutes at the NIH, and those of individual leaders such as Dan Wright, it would seem that these recommendations have not had a significant impact on the NIH approach. Throughout the day of discussions, it became apparent that the NIH structure does not lend itself to the type of long-term (i.e., over the standard 4- to 5-year funding cycle) and single review with milestones for release of money advocated by the ASGT, and therefore little effort seems to have been made toward developing such an approach. Admittedly this would require significant rethinking and inter-institute collaboration, and perhaps even legislative action by Congress to “un-handcuff” the NIH. Discouragingly, there are few signs that ASGT and/or the NIH can muscle such dramatic changes. In fact, the recent loss of NGVL funding, which primarily resulted from a lack of trans-institute NIH support, points in the other direction.

Thus, we continue to urge both the ASGT leadership and the NIH to focus on these key issues. Failing this, it is clear that US researchers will continue to have difficulty in sharing in the tremendous advances toward the clinical use of gene transfer technology being enjoyed by our colleagues abroad.

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