



NATIONAL HEMOPHILIA FOUNDATION

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MASAC Document #212
(Replaces MASAC Document #127)

The following recommendation was approved by the Medical and Scientific Advisory Council (MASAC) on November 10, 2012, and adopted by the NHF Board of Directors on November 11, 2012.

MASAC DOCUMENT REGARDING RISKS OF GENE THERAPY TRIALS FOR HEMOPHILIA

The National Hemophilia Foundation (NHF) has recognized the importance of the development of gene transfer and stem cell research to cure bleeding disorders. To this end, NHF has supported collaborative relationships between gene and stem cell researchers, the National Institutes of Health (NIH), and individuals with bleeding disorders. Additionally, this support has been funded by generous donations from the bleeding disorders community, including support from the NHF “It’s Time for a Cure” campaign, which has resulted in numerous research grant awards to advance gene and cell cures. The knowledge gained from preclinical and clinical research has contributed to an iterative process that has incorporated sequential changes as new data are obtained and are integrated into new solutions to overcome existing hurdles.

A human clinical trial for hemophilia B, reported by Nathwani and colleagues in December 2011 (1) provides the first evidence of successful gene replacement of a clotting factor. The observed factor IX expression was not only measurable in all study participants, but also persisted for more than two years, with expression ongoing, and was associated with decreased clinical bleeding and/or decreased dependence on prophylactic factor IX infusions. There were no serious adverse events in the trial, although as in a previous trial (2), asymptomatic immune-mediated inflammation of the liver was observed at the highest dose level, resulting from an immune response directed at the vector. This successful trial used a self-complementing adeno-associated virus serotype 8 vector to deliver the factor IX gene to the liver. Underlying advances that were incorporated into this trial have been supported by the research award programs of NHF in a variety of research laboratories (see footnote).

The Medical and Scientific Advisory Council (MASAC) of NHF continues to emphasize the careful consideration of advances in gene therapy to quantify and mitigate the risks to patients and others, including evaluation in informative animal models. MASAC supports human clinical trials that proceed with appropriate risk/benefit analysis and risk reduction. MASAC encourages iterative research efforts to pursue adequate gene expression to achieve an absence of joint and other spontaneous bleeding without concern for hepatic and other injury.

MASAC re-iterates the ongoing relevance of the “MASAC Recommendation for Conducting Gene Transfer Clinical Trials in Persons with Bleeding Disorders” (MASAC recommendation #136), addressing appropriate preclinical safety evaluations and safe conduct of human clinical trials.

Thus MASAC recommends that existing NHF resources leverage communications that document the existing positive results in hemophilia gene therapy and support continued momentum and options for clinical trial participation. Effective communication should continue to be provided to the bleeding disorders community

through the NHF HemAware publication, at the NHF Annual Meeting, and at the NHF-sponsored Workshops on Novel Technologies and Gene Transfer for Hemophilia.

REFERENCES:

1. Nathwani AC, Tuddenham EG, Rangarajan S, et al. Adenovirus-associated virus vector-mediated gene transfer in hemophilia B. *New England Journal of Medicine*. 2011; 365(25): 2357-65.
2. Manno CS, Pierce GF, Arruda VR, et al. Successful transduction of liver in hemophilia by AAV-Factor IX and limitations imposed by the host immune response. *Nature Medicine*. 2006; 12(3): 342-7.

FOOTNOTE: Specific strategies that were incorporated into the successful hemophilia B human clinical trial to increase efficacy and decrease risk that were advanced through NHF research grant support:

NHF Career Development Awards:

- 2000 Research Focus: *Immunology of AAV.FIX in Liver*
- 2001 Research Focus: *Alternative serotype AAV vectors for Hemophilia B gene therapy*
- 2002 Research Focus: *Factors responsible for hepatocyte permissiveness to AAV vectors*
- 2003 Research Focus: *Self-complementing (sc)AAV vectors to improve efficacy and safety of FIX gene therapy*

NHF Judith Graham Pool Fellowship Awards:

- 1998 Research Focus: *AAV Hemophilia gene therapy vectors*
- 2004 Research Focus: *Development of self-complementing scAAV AAV5 vectors for FIX gene therapy*
- 2005 Research Focus: *Proficient AAV vectors for hemophilia B*

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