Biological Response Modifiers Advisory Committee
Food and Drug Administration
Center for Biologics Evaluation and Research

SUMMARY MINUTES
Meeting #32, May 10, 2002
Hilton Hotel, Gaithersburg, MD

COMMITTEE MEMBERS
Bruce R.Blazar, M.D.[+]
Katherine A. High, M.D.[*]
Joanne Kurtzberg, M.D[+]
Alison F. Lawton[+]
Richard C. Mulligan, Ph.D.
Mahendra S. Rao, M.D., Ph.D.
Alice Wolfson, J.D.
[+] Not attending
[*] Recused

TEMPORARY VOTING MEMBERS
Daniel R. Salomon, M.D., Acting Chair
Martin Dym, M.D.
Terence Flotte, M.D.
Jon W. Gordon, M.D., Ph.D.
Eric T. Juengst, Ph.D.
Thomas F. Murray, Ph.D.
R. Jude Samulski, Ph.D.

GUESTS/GUEST SPEAKERS
Valder Arruda, M.D., Ph.D
Linda Couto, Ph.D.
Mark Kay, Ph.D.
Stephen Rose, Ph.D.

FDA PARTICIPANTS
Philip Noguchi, M.D.
Anne Pilaro, Ph.D.
Jay Siegel, M.D
Daniel Takefman, Ph.D.

EXECUTIVE SECRETARY
Gail Dapolito

COMMITTEE MANAGEMENT SPECIALIST
Rosanna L. Harvey

The summary minutes for the May 10, 2002 meeting of the Biological Response Modifiers Advisory Committee were approved on July 18, 2002.

I certify that I attended the May 10, 2002 meeting of the Biological Response Modifiers Advisory Committee and that this report accurately reflects what transpired.

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Gail Dapolito
Executive Secretary

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Daniel R. Salomon, M.D.
Chair

FDA BIOLOGICAL RESPONSE MODIFIERS ADVISORY COMMITTEE
SUMMARY MINUTES
Meeting #32, May 10, 2002

The Biological Response Modifiers Advisory Committee (BRMAC) met on May 10, 2002 at the Gaithersburg Hilton, Gaithersburg, Maryland . In open session, the committee discussed issues related to the potential for inadvertent germline transmission of gene transfer vectors.

Daniel Salomon, M.D., Acting Chair, called the meeting to order and introduced the members and consultants. The executive secretary read the conflict of interest statement into the public record. This statement identified members who recused themselves from the committee discussion and members of the committee with an appearance of a conflict of interest, who were issued waivers to participate. Copies of the waivers are available from the FDA Freedom of Information Office.

The FDA provided an introduction to the topic with a general outline of the potential for integration of the different vectors currently under development for gene transfer and the routes of administration most likely to result in dissemination to the germ cells.

Guest experts provided information on:

- ?? the biology of Adeno-associated virus (AAV) vectors and the ability of wild-type vs. recombinant AAV vectors to integrate
- ?? biology of germ cell development and potential routes of exposure to gene transfer vectors in treated subjects
- ?? current data on the ability of a variety of gene transfer vectors to transduce germ cell in animal models
- ?? Avigen, Inc. presented the results of tests performed on two subjects treated with a recombinant AAV vector expressing the Factor IX gene. Results from PCR analysis on whole semen are positive for vector-specific sequences for at least 12 weeks

The chair then commenced the open public hearing. A representative of the National Hemophilia Foundation addressed the committee providing the NHF perspective on continuation of an AAV Factor IX liver-directed gene transfer trial to treat hemophilia patients. A hemophilia patient who participated in a Phase I AAV gene transfer trial provided a patient perspective concerning the risks of germline transmission in this trial. A representative of Avigen, Inc. addressed the committee concerning Avigen's goals and proposal for an AAV-mediated liver-directed gene therapy in hemophilia B patients.

Following the open public hearing, the committee began deliberations of questions posed by the FDA related to the potential for inadvertent germline transmission of gene therapy vectors.

The committee discussed the utility of semen fractionation to test for vector sequence:
The committee recommended against testing of fractionated semen samples due to the inability of semen fractionation techniques to provide pure sperm fractions. The committee suggested that sponsors of gene transfer trials monitor whole semen for extended periods of time. The committee stressed the need for quantitative assays to detect vector sequences in order to determine whether the amount of detected vector diminishes or remains constant.

The committee discussed if a clinical hold is warranted when semen samples test positive for vector sequence or should enrollment be allowed to continue with appropriate modification to consent documents:
The committee agreed that it was not necessary to place a trial on clinical hold until semen samples became negative for vector sequence. The committee stressed protocols (vs informed consent forms) be adequately designed such that samples are available for testing and advice given to research participants about sperm banking and the use of barrier contraception until semen fractions become negative. The committee agreed that informed consent documents, provided to study participants, include an adequate discussion of the potential for inadvertent germline transmission.

The committee discussed situations in which clinical development of a gene transfer agent might proceed in the absence of the ability to monitor semen for evidence of germline alterations or the presence of vector gene sequences:
The committee considered gene transfer studies in individuals where collection of adequate semen samples was impossible (females) or difficult (small samples size in males). The committee agreed gene transfer product development should not be limited to male subjects, however the committee stated issues related to gender equity in gene transfer clinical trials were not appropriate topics for this meeting. The committee noted that currently there are no non-invasive means to monitor female research subjects for inadvertent germline transmission and charged the gene transfer research community with developing appropriate animal models in this area.

The committee discussed appropriate regulatory actions if vector sequences are persistently detected in semen:
The committee agreed that if semen samples tested positive for vector sequences for periods extending out to 1 year, then a working assumption could be made that permanent germline modification probably occurred. Further trials should be halted while a series of studies were initiated to prove a gene transfer occurred. These studies could include testicular biopsy and/or sequencing of sperm DNA to document genomic insertions. Should studies prove gene transfer occurred, a discussion is needed to 1) consider ways to prevent the birth of a transgenic child and 2) consider the whole issue of germline gene transmission in the context of the current state-of-the-art of therapeutic gene delivery at that time (i.e. risk vs. benefit).

This completed the discussion of safety and clinical issues related to the potential for inadvertent germline transmission of gene transfer vectors. The meeting was adjourned at this time.

For more detailed information concerning the open session presentations and committee discussion summarized above, please refer to the meeting transcripts available on the FDA website at http://www.fda.gov/ohrms/dockets

All external requests should be submitted to the Freedom of Information office.