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

SUMMARY MINUTES
Meeting #32, May 9, 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

TEMPORARY VOTING MEMBERS
Daniel R. Salomon, M.D., Acting Chair
Lori P. Knowles, M.A., L.L.M.
Thomas F. Murray, Ph.D.
Robert K. Naviaux, M.D., Ph.D.
Edward A. Sausville, M.D., Ph.D.
Eric A. Schon, Ph.D.
Eric A. Shoubridge, Ph.D.
Jonathan Van Blerkom, Ph.D.

GUESTS/GUEST SPEAKERS
Robert Casper, M.D., Ph.D
Jacques Cohen, Ph.D.
Susan Lanzendorf, Ph.D., H.C.L.D.
Stephen Rose, Ph.D.

FDA PARTICIPANTS
Jesse Goodman, M.D.
Deborah Hursh, Ph.D.
Scott Monroe, M.D.
Malcolm Moos, M.D., Ph.D.
Philip Noguchi, M.D.
Jay Siegel, M.D.

EXECUTIVE SECRETARY
Gail Dapolito

COMMITTEE MANAGEMENT SPECIALIST
Rosanna L. Harvey

The summary minutes for the May 9, 2002 meeting of the Biological Response Modifiers Advisory Committee were approved on July 18, 2002.

I certify that I attended the May 9, 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 9, 2002

The Biological Response Modifiers Advisory Committee (BRMAC) met on May 9, 2002 at the Gaithersburg Hilton, Gaithersburg, Maryland . In open session, the committee discussed 1) updates of CBER research programs in the Division of Monoclonal Antibodies and the Division of Therapeutic Proteins, and 2) ooplasm transfer in assisted reproduction. The committee also recognized, in a short ceremony, service to the committee by retiring member, Dr. Edward Sausville.

A closed session was held on May 9. This portion of the meeting was closed to permit discussion and review of confidential information under 5 U.S.C. 552b(c)(4). Approximately 125 persons attended the public meeting each day.

Daniel Salomon, M.D., Acting Chair, called the meeting to order. Representatives from the Divisions of Therapeutic Proteins and Monoclonal Antibodies provided updates of research programs in the Laboratories of Gene Regulation and Immunobiology. A closed session followed to allow discussion of a report of a review of individual research programs in the Center for Biologics Evaluation and Research.

The committee then reconvened in open session. The chair introduced the members and consultants and the executive secretary read the conflict of interest statement into the public record, stating that members of the committee with an appearance of a conflict of interest, 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 of ooplasm transfer between human oocytes as a method to treat female infertility and the safety issues facing the FDA in regulating this type of germline transmission.

Guest experts provided information on:

- ?? cytoplasmic transfer in humans and the birth of children after ooplasmic transplantation
- ?? a mouse model to study the transmission and segregation of mitochondrial DNA
- ?? mitochondrial function and inheritance patterns in early human embryos
- ?? ethical issues in human ooplasm transfer experimentation

The chair then commenced the open public hearing. Representatives from the American Society for Reproductive Medicine and the American Infertility Association addressed the committee regarding regulation by FDA of ooplasm transfer in humans.

Following the open public hearing, the committee began deliberations of questions posed by the FDA related to the safety of ooplasm transfer in humans.

The committee discussed animal data assessing the following risks of ooplasm transfer to offspring:

1. mechanical damage to oocyte cytoarchitecture
2. inadvertent transfer of chromosomes, chromosome fragments, or other cellular constituents
3. enhanced survival of abnormal embryos, increasing the likelihood of children born with significant birth defects
4. risks associated with heteroplasmy

The committee agreed there are significant safety issues related to # 2 and # 3 and that existing animal and clinical data are insufficient to adequately address these safety concerns. The committee stressed the need to better characterize the cellular constituents that are transferred.

The committee also agreed there was sufficient ICSI experience related to #1 to indicate this is an acceptable risk. A majority of the committee stated, that based on available animal data, the mixing of mitochondrial populations (heteroplasmy) by this procedure does not present a major safety concern. However, some committee members expressed concern about the long-term risks of heteroplasmy. Many metabolic diseases appear later in life and available animal data do not address this adequately.

The committee discussed animal and clinical data assessing the risks of ooplasm transfer to the mother:

The committee stated that risks to the mother that might be different than those incurred with established ART procedures or risks to future fertility or the ability to engage in subsequent ART procedures can only be determined by a formal clinical trial. There are not sufficient animal or clinical data to determine these risks at this time.

The committee discussed if available safety data were sufficient to support further clinical investigations and/or if further nonclinical experimentation was considered appropriate:

The committee stated that the presentation of additional data supporting a lack of contaminating nuclear or viral DNA in the ooplasm for transfer and a viable plan for long term follow-up of children born after the procedure to develop scientific data on possible longer term effects of mitochondrial mixing were sufficient to allow a small clinical trial to go forward under IND. The committee suggested that the potential of animal models to advance the testing of this procedure be explored actively in parallel with clinical trial efforts.

The committee discussed clinical issues including trial design, patient selection criteria, informed consent and long term follow-up of offspring:

The committee clearly stated that the scientific data reviewed by the experts supporting the rationale for proposing a benefit of ooplasm transfer in infertile couples were not convincing.

Thus any clinical trial would require a design adequate to begin testing this procedure's real benefit. For example, uniform selection criteria of patients and enrollment of patients that had failed alternative in vitro techniques for infertility at the same study centers rather than from outside centers where procedure success rates and techniques might not be comparable. The committee agreed long-term follow-up was a necessary component of a clinical trial and stated informed consent should include detailed information on long-term follow-up and what data currently exists on mictochondrial mixing.

This completed the discussion of safety and clinical issues related to ooplasm transfer as a method to treat female infertility. 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.