

**National Institutes of Health
Recombinant DNA Advisory Committee (RAC)
Building 31, Conference Room 10
Bethesda, Maryland
September 24-25, 1998
Final Agenda¹**

September 24, 1998

I.	Call to Order and Opening Remarks/Mickelson	9:00 a.m.
	Tab 2033 Notice of Meeting, September 2, 1998 (63 FR 46801) (Page 190)	
II.	Introductory Remarks/Dr. Lana Skirboll, Associate Director for Science Policy	9:05 a.m.
III.	Minutes of the June 18-19, 1998, Meeting/Macklin, Ando	9:10 a.m.
	Tab 2037 June 18-19, 1998, Minutes (Page 467)	
IV.	Chair's Statement Regarding <i>In Utero</i> Gene Transfer Discussion/Mickelson	9:15 a.m.
	Impetus for submission of "Pre-Protocols"	
	Tab 2031 Prototypic Protocol entitled: <i>In Utero Gene Transfer for the Treatment of ADA-Deficient SCID</i> (Page 7) Pls: French Anderson, et al, Gene Therapy Laboratories	
	Tab 2032 Prototypic Protocol entitled: <i>In Utero Gene Transfer for the Treatment of Alpha-Thalassemia</i> (Page 91) Pls: French Anderson, et al, Gene Therapy Laboratories	
	Tab 2036 Reviews from RAC Members: (Page 339) --Ando, Chow, Gordon, Greenblatt, Juengst, King, Macklin, Markert, McIvor, Mickelson	
	Reviews from Ad Hoc Consultants: (Page 402) --Andrews, Buckley, Cohen, Deisseroth, Karson, Parkman, Zallen	
	Tab 2042 Anderson's Response (Page 427)	
	Tab 2043A Zanjani's Response (Page 576)	
	Tab 2043B Ad Hoc Comments/Walters (Page 581)	
	Tab 2043C Public Comments (Page 591)	
	Tab 2043D Public Comments/Additional (Page 594)	
	Tab 2034 Appendix M, <i>Points to Consider</i> (Page 667)	
	Tab 2043E Zhao's CV (Page 192)	
	Tab 2043F RAC Comment/Levi Pearl (Page 697)	
	Tab 2943G Public Comments (during & after meeting) (Page 701)	
	Tab 2043H Newspaper Articles (Page 721)	
	Tab 2045I Public Comments (after meeting) (Page 724)	
	Tab 2045J Newspaper Articles (Page 728)	
	Brief Overview	
	- Scope of <i>NIH Guidelines</i> (published 1976 to present), including 1990 inclusion of <i>Appendix M</i> (somatic cell gene transfer)	
	- Summary of somatic cell gene transfer experience to date - clinical phases, disease targets, patient populations, biologic versus clinical efficacy	

¹All times on this agenda are estimates. The actual time for consideration of an item may be earlier or later than indicated.

Format for September 24-25, 1998, RAC Discussion of "Pre-Protocols"

Objectives of RAC Discussion

- Provide a context for identification of scientific, safety, ethical, legal, and social issues for subsequent deliberation at the Gene Therapy Policy Conference (GTPC) tentatively scheduled for January 7-8, 1999, and future RAC meetings
- Develop guidance for investigators and institutional review bodies, e.g., Institutional Biosafety Committees (IBCs) and Institutional Review Boards (IRBs)
- Provide a forum for public dialogue on relevant issues
- Initiate and coordinate interagency discussions and policy development

V. **Development of the Human Fetal Immune System -- Overview/Buckley** 9:25 a.m.

VI. **In Utero Hematopoietic Stem Cell Transplantation - Experience to Date/Buckley** 9:35 a.m.

- Preclinical
- Clinical

VII. **Risk Assessment - General/Ando** 9:55 a.m.

Specificity of DNA integration - relative likelihood of occurrence, availability of sensitive assays to monitor for, and potential adverse consequences (maternal, fetal, close contacts, health care providers, or environmental) related to:

- Rearrangement
- Recombination
- Random integration, e.g., insertional mutagenesis, susceptibility to other diseases, fetal germ-line integration (relationship to level of mitotic activity at proposed gestational age)
- Replication-competence

Potential pathogenicity

Immune response - relative likelihood of occurrence and potential adverse consequences related to an immune response (maternal or fetal) to:

- Transferred cells
- Delivery vehicle
- Gene insert

(Break) 10:45 a.m.

VIII. **Preclinical Research Design Issues - General/Chow** 11:00 a.m.

- Characterization of the biological system
- Model systems for assessing biologic efficacy

IX. **Clinical Research Design Issues - General/Markert** 11:20 a.m.

Rationale for Candidate Diseases

- Natural history and range of clinical expression of disease
- Objective/qualitative measures of disease activity - ability to predict meaningful assessment of clinical results
- Availability of alternative therapies - advantages and disadvantages compared to *in utero* gene transfer
- Anticipated risks versus benefits - maternal and fetal

Correlation between phenotype and genotype as a reliable predictor of disease severity

Technical considerations: volume, dose, and route of administration

Assessment of clinical efficacy

- X. **Ethical, Legal, and Social Issues (ELSI) in Prenatal Gene Transfer - Overview/Walters 11:50 a.m.**
Including, but not limited to:
- Role of the genetic counselor
 - Recruitment practices
 - Enrollment criteria
 - Maternal and fetal interests
 - Whether to proceed to clinical trials
 - Risk benefit analyses
- (Lunch) 12:30 p.m.
- XI. **Informed Consent Issues/Zallen, Macklin, Juengst 1:30 p.m.**
Including, but not limited to:
- Fetal--Child Issues/Zallen**
- Prenatal diagnosis – accuracy and predictive value
 - Assessment of fetal benefit versus risk
 - Long-term follow-up – purpose, methods, duration, and frequency of evaluation
 - Importance of post-mortem analyses
 - Statement regarding provision of necessary medical care and related costs
 - Is there a need for an advocate for the fetus?
 - Privacy
- (Break) 2:45 p.m.
- Maternal Issues/Macklin**
- Assessment of maternal benefit versus risk
 - Maternal follow-up – purpose, methods, duration, and frequency of evaluation
 - Statement regarding provision of necessary medical care and related costs
 - Is there a need for an unbiased counselor?
 - Privacy
- Paternal Issues/Juengst**
Societal Issues/Juengst
- End of Session 5:00 p.m.

September 25, 1998

- XII. **Opening Remarks - Brief Summary of September 24, 1998, Discussion/Mickelson 8:30 a.m.**
- XIII. **Pre-Protocol Candidate Diseases – Clinical Overview/Buckley, Cohen 8:40 a.m.**
- Severe Combined Immunodeficiency caused by Adenosine Deaminase Deficiency (SCID-ADA)/Buckley
 - Alpha Thalassemia/Cohen
- (Break) 10:30 a.m.

- XIV. **Preclinical Research Design Issues -- Specific Clinical Indications/Mclvor** 10:45 a.m.
 - SCID-ADA
 - Alpha thalassemia

- XV. **Clinical Research Design Issues -- Specific Clinical Indications/Marker** 11:45 a.m.
 - SCID-ADA
 - Alpha thalassemia

- (Lunch) 12:45 p.m.

- XVI. **Ethical, Legal and Social Issues (ELSI) -- Specific Clinical Indications/Macklin** 1:45 p.m.

Including, but not limited to:

 - Provision of care and coverage of costs associated with maternal medical care in the event of research related injury
 - Provision of care and coverage of costs associated care in the event of partial correction resulting in the viable birth with one or more disabilities
 - Risk benefit analyses
 - Informed consent
 - Inadvertent germ-line transmission

- (Break) 3:00 p.m.

- XVII. **Data Management Update/Greenblatt** 3:15 p.m.
 - Tab 2035 Safety Reports, Adverse Events, Amendments, & Updates (Page 205)
 - Protocol List (#8810-001 through 9809-265)
 - Protocols not Requiring Full RAC Discussion
 - #233, 248, through 263
 - (Protocols # 245 and 246 will be resubmitted)
 - (Protocols #264 and 265 currently under review)

- XVIII. **Other RAC Issues** 4:15 p.m.

- XIX. **Chair's Closing Remarks/Mickelson** 4:40 p.m.

- XX. **Future Meeting Dates, Announcements/Mickelson** 4:45 p.m.
 - Tab 2041 GTPC Tentatively Scheduled for January 7-8, 1999 (Page 574)
 - RAC Scheduled for March 11-12, 1999, NIH, 31C, CR10

- XXI. **Adjournment/Mickelson** 5:00 p.m.

- For Your Information**
- Tab 2038 *Human Gene Therapy Article on In Utero* (Page 527)
- Tab 2039 ORDA's letter to PIs and/or Sponsors regarding RAC's June 1998 Discussions of Protocols #232, 235, 236, 237, 238, 244, 247 (Page 543)
- Tab 2040 Biodistribution Studies--Follow up (Page 568)
- Letter from Gay/Chiron Corporation

 Visit the ORDA Web site at:
<http://www.nih.gov/od/orda/>

For current information on Guidelines, Protocols, Principal Investigators, Meetings, and information about upcoming Gene Therapy Policy Conferences
