**National Institutes of Health**
**Recombinant DNA Advisory Committee (RAC) Symposium and Meeting**
**December 8-10, 1999, Bethesda, Maryland**
**Final Agenda[1]**

****Please Note Location for Each Day****

---

**December 8, 1999 - RAC Symposium**
**National Institutes of Health**
**Building 10, Masur Auditorium**

---

**I. Call to Order/Mickelson ..... 8:00 a.m.**

**NIH Opening Remarks/Patterson ..... 8:05 a.m.**

**II. Keynote: Adenovirus Biology, Pathophysiology and Adaptation to Gene Therapy ..... 8:10 a.m.**

Adenovirus Molecular Biology and Disease ..... 8:10 a.m.
Marshall Horwitz, M.D., Albert Einstein College of Medicine

Adaptation of Adenovirus for Gene Transfer ..... 8:25 a.m.
Inder Verma, Ph.D., Salk Institute

**III. Examples of Adenovirus-induced Pathophysiology ..... 8:40 a.m.**
**Moderators:** Claudia Mickelson, Ph.D., Massachusetts Institute of Technology
Inder Verma, Ph.D., Salk Institute

The Interplay Between Adenovirus and Pro-Inflammatory Cytokines ..... 8:45 a.m.
Linda Gooding, Ph.D., Emory University

Receptors and Signaling Events in Adenovirus Cell Entry ..... 9:00 a.m.
Glen Nemerow, Ph.D., Scripps Research Clinic

Adenovirus-Induced Hepatotoxicity ..... 9:15 a.m.
Robert Warren M.D., University of California, San Francisco

Disseminated Intravascular Coagulation ..... 9:30 a.m.
Margaret Rick, M.D., NIH

Toxicity Experience with Adenoviral Vectors at Baylor College of Medicine
Estuardo Aguilar-Cordova, Ph.D., Baylor College of Medicine. ..... 9:45 a.m.

Helper-Dependent Adenoviral Vector -- Development, Performance and Safety ..... 10:00 a.m.
C. Thomas Caskey, M.D., Merck & Company, Inc.

---

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

**IV. Safety and Toxicity Data from Clinical Trials Using Adenoviral Vectors ..... 10:15 a.m.**

**Moderators:** Claudia Mickelson, Ph.D., Massachusetts Institute of Technology
Inder Verma, Ph.D., Salk Institute

| | | |
|---|---|---|
| Tab 2103D | Crystal, Cornell Medical Ctr/*Human Gene Therapy* | Page 1245 |
| | Meeker, Genzyme Corp/Slides | Page 1337 |
| | Dreiling, Rhone-Poulenc Rorer Gencell/Slides | Page 1340 |
| | Horowitz, Schering Plough/Statement & Slides | Page 1343 |

Summary of Phase I Studies with Adenoviral Vectors at Penn ..... 10:20 a.m.
James Wilson, M.D., Ph.D., University of Pennsylvania

Safety of Local Delivery of Low and Intermediate Dose Adenovirus Gene Transfer Vectors to Individuals with a Spectrum of Comorbid Conditions. ..... 10:35 a.m.
Ronald Crystal, M.D., Cornell Medical Center

David P. Meeker, M.D., Genzyme Corporation ..... 10:50 a.m.

JoAnn Horowitz, Ph.D., Schering-Plough ..... 11:05 a.m.

Ad5CMV-p53 (RPR/INGN 201) - Global Safety Assessment ..... 11:20 a.m.
Lyndah K. Dreiling, M.D., Gencell/Rhone-Poulenc-Rorer

Viral Cancer Therapy with ONYX-015 ..... 11:35 a.m.
David H. Kirn, M.D., Onyx Pharmaceuticals

*TBA* ..... 11:50 a.m.

*Lunch Break* ..... 12:05 p.m.

Panel Discussion ..... 1:05 p.m.

Public Comment ..... 1:35 p.m.

Working Group Discussion ..... 1:50 p.m.

| | | |
|---|---|---|
| Tab 2097 | Comment from Public | Page 1074 |

**V. End of Session/Mickelson ..... 3:00 p.m.**

**December 9, 1999 - RAC Meeting**
**National Institutes of Health**
**Building 10, Masur Auditorium**

**VI. Opening Remarks/Mickelson ..... 8:30 a.m.**

| | | |
|---|---|---|
| Tab 2087 | Notice of Meeting | Page 10 |
| | Proposed Actions | Page 11 |
| Tab 2094 | Rules for Conflict of Interest (FACA) | Page 1030 |
| Tab 2103F | Amended Notice of Meeting | Page 1399 |
| | Addenda to RAC Roster | Page 1401 |

**VII. Discussion of Severe Adverse Event on Human Gene Transfer Protocol #9512-139 entitled: *A Phase I Study of Adenoviral Vector Mediated Gene Transfer to Liver in Adults with Partial Ornithine Transcarbamylase Deficiency (OTC)* ..... 8:45 a.m.**

Investigator: Mark Batshaw, M.D., Children's National Medical Center, D.C.
Co-Investigator: James Wilson, M.D., University of Pennsylvania
Contact: Philip J. Cross, University of Pennsylvania

| | | |
|---|---|---|
| Tab 2089 | RAC Minutes on OTC Protocol, 12/4-5/95 | Page 158 |
| | Article on Adenovirus, *Human Gene Therapy Journ*, 9/20/98 | Page 169 |
| | Article on OTD, *Medical Intelligence*, 10/13/88 | Page 177 |
| | Protocol, *Human Gene Therapy Journal*, 9/20/99 | Page 182 |
| | Report of Serious Adverse Event, 9/20/99 | Page 201 |
| | ORDA Ltr to RAC, IBC, FDA, OPRR, 9/21/99 | Page 204 |
| | FDA Ltr to ORDA, 9/30/99 | Page 212 |
| | ORDA Ltr to PI, 10/1/99 | Page 213 |
| | Current Informed Consent Document, Rec'd 11/18/99 | Page 220 |
| Tab 2103D | Zoon, FDA/Slides | Page 1365 |
| | Pilaro, FDA/Slides | Page 1370 |
| | Eggerman, FDA/Slides | Page 1373 |
| Tab 2103E | Members, Adenovirus Adverse Event Working Group | Page 1376 |
| | Wilson/Overheads | Page 1377 |
| | PI Serious Adverse Event Report, 9/20/99 | Page 1379 |
| | IBC Serious Adverse Event Report, 12/2/99 | Page 1382 |
| | PI Response to OBA, 12/7/99 | Page 1394 |
| Tab 2103H | OTC Protocol | Page 1406 |
| | Article--Adenoviral, *Human Gene Therapy Journ,* 7/20/98 | Page 1746 |
| | Article--Adenovirus, *Human Gene Therapy Journ,* 11/20/99 | Page 1758 |
| | Article--Adenovirus , *Microb & Molecul Biol Rep,* 9/99 | Page 1773 |

Clinical Aspects of Ornithine Transcarbamylase Deficiency
Arthur Beaudet, M.D., Baylor College of Medicine ..... 8:45 a.m.

Principal Investigator's Presentation of Ornithine Transcarbamylase Deficiency Protocol ..... 9:00 a.m.

Food and Drug Administration Comments ..... 10:30 a.m.
Kathryn Zoon, Ph.D., CBER/FDA

RAC Working Group Comments on Human Gene Transfer Protocol #9512-139 ..... 11:15 a.m.

Public Comment ..... 12:15 p.m.

*Lunch Break* ..... 12:30 p.m.

RAC Working Group Recommendations on Adenovirus-Safety and Toxicity ..... 1:30 p.m.
- Preliminary Findings and Conclusions
- Time Line for Issuance of Final RAC Report

Discussion Co-Chairs: Mickelson and Horwitz

Public Comment ..... 3:00 p.m.

**VIII. Data Management/Greenblatt ..... 3:30 p.m.**

| | | |
|---|---|---|
| Tab 2088 | Protocol List | Page 17 |
| | Protocols Not Requiring Full RAC Review | Page 68 |
| Tab 2098 | Safety Reports and Adverse Events | Page 1077 |
| | Amendments and Updates | Page 1084 |

**IX. Minutes of the September 2-3, 1999, Meeting ..... 3:40 p.m.**

Reviewers: Greenblatt, Juengst

| | | |
|---|---|---|
| Tab 2099 | RAC Minutes/September 1999 | Page 1094 |

**X. *End of Session* ..... 3:45 p.m.**

---

**December 10, 1999–RAC Meeting**
**National Institutes of Health**
**Natcher Building 45, Room E1 & E2**

---

**XI. Opening Remarks/Mickelson ..... 8:30 a.m.**

**XII. Current Issues in Adverse Event Reporting and Proposed Action ..... 8:35 a.m.**

Working Group: Chair: Macklin
Members: McIvor, Ando, Mickelson, King, Verma

| | | |
|---|---|---|
| Tab 2087 | Proposed Actions | Page 11 |
| Tab 2093 | FDA Support Letter on Public Review, 9/30/99 | Page 1021 |
| | FDA Letter to IND Sponsors & PIs, 11/5/99 | Page 1022 |
| | Letter from Walters, et al., 11/5/99 | Page 1024 |
| | ORDA's Serious Adverse Event Reporting Form | Page 1026 |
| | ORDA's Letter on Reporting Adverse Events, 11/22/99 | Page 1027 |
| Tab 2096 | Comments from Public | Page 1061 |
| Tab 2103A | Public Comments | Page 1169 |
| | Draft Serious Adverse Event Reporting Form | Page 1177 |
| Tab 2103C | Public Comments | Page 1186 |
| | --Biotechnology Industry Organization | |

| | | |
|---|---|---|
| | --Perry, Systemix | |
| | --Beall, Cystic Fibrosis Foundation | |
| | --Pelliccione, Schering Corporation | |
| | --Spiegel, Schering-Plough Research Institution | |
| | --Woo, American Society of Gene Therapy | |
| | Articles | Page 1211 |
| | --Morgan, *Blood* | |
| | --Walters, National Academy Press | |
| | --Aguilar-Cordova, *Nature Medicine* (#1) | |
| | --Aguilar-Cordova, *Nature Medicine* (#2) | |
| | Noguchi, FDA | |
| | --Background Information | Page 1232 |
| | --FDA Standard Operating Procedures & Policies | Page 1240 |
| Tab 2103D | Weiss, FDA/Slides | Page 1367 |
| Tab 2103F | Charge of ACD Working Group on NIH Oversight Clinical Gene Transfer Research | Page 1400 |

FDA Presentation on Adverse Event Reporting
Karen Weiss, M.D., CBER/FDA ..... 8:45 a.m.

Patient Privacy and Confidentiality
Lana Skirboll, Ph.D., NIH/OSP ..... 9:05 a.m.

RAC Discussion of Proposed Action ..... 9:25 a.m.

Public Comment ..... 11:00 a.m.

RAC Conclusions ..... 11:45 a.m.

*Lunch Break* ..... 12:00 noon.

**XIII. Discussion on Human Gene Transfer Protocol #9906-322 entitled: *NGF Ex Vivo Gene Therapy for Alzheimer's Disease*** ..... **1:30 p.m.**

Investigator: Mark Tuszynski, M.D., Ph.D., University of California at San Diego
Reviewers: Chow, Mickelson, King
*Ad hoc:* Wilma Friedman, Columbia University

| | | |
|---|---|---|
| Tab 2091 | ORDA Summary | Page 345 |
| | ORDA Letter to PI on RAC Public Review | Page 349 |
| | RAC Members Recommendations | Page 350 |
| | Review from Chow, Mickelson, King, Friedman | Page 352 |
| | Protocol | Page 366 |
| Tab 2100 | PI's Response to Chow, Mickelson, King, Friedman | Page 1126 |
| | King/Additional Comments | Page 1155 |
| Tab 2103B | PI Response #2 to King's Additional Comments | Page 1178 |

**XIV. Discussion on Human Gene Transfer Protocols #9910-342 and #9910-343 entitled: *Phase I Trial to Evaluate the Safety of H5.020CMVPDGF-B for the Treatment of a Diabetic Insensate Foot Ulcer* and *Phase I Trial to Evaluate the Safety of H5.020CMVPDGF-B and Limb Compression Bandage for the Treatment of Venous Leg Ulcer (Trial A)* ..... 2:30 p.m.**

Investigator: David J. Margolis, M.D., University of Pennsylvania
Sponsor: Philip J. Cross, Institute for Human Gene Therapy, University of Pennsylvania
Reviewers: Markert, Ando, Macklin

| | | |
|---|---|---|
| Tab 2092 | ORDA Summary | Page 591 |
| | ORDA Letter to PI on RAC Public Review | Page 597 |
| | RAC Members Recommendations | Page 598 |
| | Review from Markert, Ando, Macklin | Page 602 |
| | Protocol #9910-342 | Page 608 |
| | Protocol #9910-343 | Page 688 |
| Tab 2101 | Sponsor's Response to Markert, Ando, Macklin | Page 1160 |
| Tab 2103G | Margolis Slides | Page 1402 |

**XV. Other RAC Issues ..... 3:30 p.m.**

**XVI. Chair's Closing Remarks/Mickelson ..... 4:55 p.m.**

**XVII. Future Meeting Dates, Announcements/Mickelson ..... 4:59 p.m.**

| | | |
|---|---|---|
| Tab 2095 | RAC/March 9-10, 2000, NIH, 31C, CR10 | Page 1051 |

**XVIII. Adjournment/Mickelson ..... 5:00 p.m.**

**********

- **For Your Information**

| | | |
|---|---|---|
| Tab 2094 | RAC Follow-up | |
| | --#9902-284/Ragni, ORDA Letter to PI, 9/29/99 | Page 1031 |
| | --#9902-284/Ragni, PI Letter to ORDA, 9/30/99 | Page 1034 |
| | --#9905-317/Mendell, ORDA Letter to PI, 9/29/99 | Page 1044 |
| | FDA Guidance for Retroviral Vectors, 11/3/99 | Page 1048 |

- **Human Gene Transfer Protocol #9908-334 entitled:** ***A Phase I Study of FGF2-Fab' Modified Adenovirus Vector Mediated Intraperitoneal Delivery of Herpes Simplex Virus Thymidine Kinase (HSV-TK) Gene and Intravenous Ganciclovir in Previously Treated Ovarian and Extraovarian Patients***

Investigators: Ronald D. Alvarez, M.D., Mack N. Barnes, M.D., David T. Curiel, M.D., University of Alabama at Birmingham

Reviewers: Breakefield, McIvor, Levi-Pearl

| | | |
|---|---|---|
| Tab 2090 | ORDA Summary | Page 232 |
| | ORDA Letter to PI on RAC Public Review | Page 235 |
| | RAC Members Recommendations | Page 236 |
| | Review from Breakefield, McIvor, Levi-Pearl | Page 237 |
| | Protocol | Page 242 |
| Tab 2102 | PI e-mail/Protocol Withdrawn | Page 1167 |

**********

**Visit the OBA Web site at:**
http://www.nih.gov/od/oba/

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

**********