RECOMBINANT DNA ADVISORY COMMITTEE

Minutes of Meeting

March 8, 2001

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
National Institutes of Health

CONTENTS

Note: The latest Human Gene Transfer Protocol List can be found at the Office of Biotechnology Activities' Web site at <http://www4.od.nih.gov/oba/RDNA.htm>.

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
NATIONAL INSTITUTES OF HEALTH
RECOMBINANT DNA ADVISORY COMMITTEE
MINUTES OF MEETING[1]
March 8, 2001

The Recombinant DNA Advisory Committee (RAC) was convened for its 81st meeting at 8:30 a.m. on March 8, 2001, at the National Institutes of Health (NIH), Building 31, Sixth Floor, Conference Room 10, 9000 Rockville Pike, Bethesda, MD 20892. Dr. Claudia A. Mickelson (Chair) presided. In accordance with Public Law 92-463, the meeting was open to the public. The following individuals were present for all or part of the meeting:

Committee Members

C. Estuardo Aguilar-Cordova, Harvard Gene Therapy Initiative
Dale G. Ando, Cell Genesys
Xandra O. Breakefield, Massachusetts General Hospital
Louise T. Chow, University of Alabama, Birmingham
Theodore C. Friedmann, University of California, San Diego
Jon W. Gordon, Mount Sinai School of Medicine
Jay J. Greenblatt, National Cancer Institute, National Institutes of Health
Eric T. Juengst, Case Western Reserve University
Nancy M. P. King, University of North Carolina, Chapel Hill
Sue L. Levi-Pearl, Tourette's Syndrome Association
Ruth Macklin, Albert Einstein College of Medicine
M. Louise Markert, Duke University Medical Center
Claudia A. Mickelson, Massachusetts Institute of Technology

Executive Secretary

Amy P. Patterson, National Institutes of Health

Ad Hocs/Speakers

Andrew George Braun, Harvard Medical School
Boro Dropulic, VIRxSYS
Cynthia Dunn, Clinical Research Institute
John J. Fung, University of Pittsburgh
Carter Van Waes, National Institute on Deafness and Other Communication Disorders, NIH

Nonvoting/Agency Representatives

Kristina C. Borror, Office for Human Research Protections, Department of Health and Human Services
Philip Noguchi, U.S. Food and Drug Administration

National Institutes of Health Staff Members

Sarah Carr, OD
Janita Coen, NHLBI
J.R. Dixon, OD
Kelly Fennington, OD

[1] The Recombinant DNA Advisory Committee is advisory to the National Institutes of Health (NIH), and its recommendations should not be considered as final or accepted. The Office of Biotechnology Activities should be consulted for NIH policy on specific issues.

Joseph F. Gallelli, CC
Robert Jambou, OD
Kathryn R. Lesh, OD
Barbara McDonald, OD
Cheryl McDonald, OD
Marina O'Reilly, OD
Alexander Rakowsky, OD
Gene Rosenthal, OD
Thomas Shih, OD
Allan Shipp, OD
Sonia I. Skarlatos, NHLBI
Lana Skirboll, OD

Others

Approximately 45 individuals attended this 1-day RAC meeting. A list of attendees appears in Attachment II.

I. Call to Order and Opening Remarks/Dr. Mickelson

Dr. Mickelson, RAC Chair, called the meeting to order at 8:30 a.m. on March 8, 2001. Notice of this meeting under the *NIH Guidelines for Research Involving Recombinant DNA Molecules (NIH Guidelines)* was published in the *Federal Register* on February 23, 2001 (66 FR 11305). The agenda included reviews of two gene transfer protocols, data management, the proposed action to amend the *NIH Guidelines* requirements for reporting and analysis of serious adverse events, a proposed plan for addressing issues related to the roles and responsibilities of Institutional Biosafety Committees, a lentiviral vector system under development for use in clinical trials, risk-containment practices for strain B of the common bacterium *Escherichia coli (E. coli)* frequently used for large-scale production processes, and the U.S. Food and Drug Administration's (FDA) proposed disclosure rule, "Availability for Public Disclosure and Submission to FDA for Public Disclosure of Certain Data and Information Related to Human Gene Therapy or Xenotransplantation."

Following a review of conflict-of-interest rules, Dr. Mickelson offered a brief summary of the March 7, 2001 Fourth National Gene Transfer Safety Symposium: Safety Considerations in the Use of AAV Vectors in Gene Transfer Clinical Trials. Several RAC members noted that this symposium was an example of how regulatory and review bodies can respond quickly to an ongoing concern within the scientific community. The Office of Biotechnology Activities (OBA) was congratulated for organizing the symposium and putting together an effective program, and Mark S. Sands, Ph.D., Washington University School of Medicine, was lauded for generating awareness among the scientific community and the public of the issues raised by his preclinical research results.

II. Minutes of the December 13 and 15, 2000 Meeting/Drs. Gordon and Juengst

Dr. Gordon noted that a few technical words were misspelled, and he provided a copy of the minutes that included those corrections.

A. Committee Motion 1

As moved by Dr. Gordon and seconded by Dr. Markert and with the understanding that any misspellings will be corrected, the RAC unanimously approved the December 13 and 15, 2000 minutes by a vote of 12 in favor, 0 opposed, and 0 abstentions.

III. Discussion of Human Gene Transfer Protocol #0101-443: Evaluation of the Safety and Effects of *ex vivo* Modification and Reinfusion of CD34+ Cells by an Antisense Construct Against HIV-1 in a Retroviral Vector

Principal Investigator:	Jeffrey C. Laurence, M.D., Weill Medical College, Cornell University
Other Investigators:	Marcus A. Conant, M.D., Dermatology/HIV Consultant; Dean L. Engelhardt, Ph.D., Enzo Therapeutics; Barbara E. Thalenfeld, Ph.D., Enzo Therapeutics
Sponsor:	Enzo Therapeutics, Inc.
RAC Reviewers:	Dr. Aguilar-Cordova, Ms. King, and Drs. Markert and Mickelson
Ad Hoc Reviewer:	John J. Fung, M.D., Ph.D., University of Pittsburgh

A. Protocol Summary

Investigators have demonstrated that the growth of HIV-1 can be blocked by the use of antisense genes. Three independent antisense sequences directed against 2 HIV-1 functional regions, tar and tat/rev, have been embedded into separate cloned human U1 RNA genes. This triple U1/HIV-1 antisense cassette was incorporated into a Moloney murine leukemia virus derived vector (HGTV43) used to transduce CD34+ cells. Preclinical data suggested that the presence of the anti-HIV-1 genetic antisense RNA in CD4+ cells would be sufficient to manage HIV-1 levels in infected subjects.

A phase I clinical trial was initiated in which peripheral blood stem cells (PBSC) from HIV-1 infected research participants were transduced with HGTV43 and reinfused. Results from the clinical protocol demonstrate long term (6-12 months) survival of antisense RNA in a low number of bone marrow stem cells as well as in the peripheral blood mononuclear cells (PBMC) and CD4+ fraction. Since this low number of transduced PBMC has remained constant over a number of months, these data support the conclusion that stable engraftment of some of the antisense RNA-producing PBSC has occurred. Finally, there is no evidence that multiple infusions led to increased levels of engraftment.

This protocol is a continuation of the trial reported above. The investigators propose to increase the number of CD4+ cells producing anti-HIV-1 genetic antisense RNA. The investigators propose to isolate a population of PBSC from HIV-1 positive participants previously treated with G-CSF. After this isolation, the participants will receive a treatment of immune conditioning using mycophenolate mofetil (MMF). The PBSC will be transduced with HGTV43. After the transduction is complete, the participants will be irradiated in an outpatient procedure (600cGy, TBI), and the transduced cells containing the antisense genes will be re-infused into the HIV-1 participant. The end points of this study are the safety of the procedure and the extent of engraftment and proliferation of the engineered cell population. The study will enroll up to 6 participants.

B. Written Comments From Preliminary Review

Seven RAC members recommended that the protocol warranted public discussion. Ms. King and Drs. Markert and Mickelson submitted written reviews, as did *ad hoc* reviewer Dr. Fung, to which the investigators responded in writing and during this meeting.

Dr. Aguilar-Cordova raised a concern about the potential for high risk to the participants if radiation increased viral load simultaneous with reducing the immune response. He also asked which chemotherapeutic agent would be used and its effect on HIV Long Terminal Repeat (LTR) expression. Another issue of concern was the stability of the integrated vector. The vector contains three repeat sequences which increase the potential for recombination. He requested that the investigators provide more information about the packaging cell line.

In order to calculate the risk/benefit ratio, Ms. King requested more information on the effects of total body irradiation (TBI): potential for improved engraftment vs. immune suppression. Regarding the informed consent document, Ms. King noted that the potential benefit to participants was overstated, the statement of the risk of bone marrow suppression should be emphasized, an autopsy request should be included, an

appropriate financial disclosure statement should be added, and the document should be rewritten in second person.

Dr. Markert asked about the effect of irradiation on existing peripheral T cells and the thymus since these are sources of T-cell renewal in adults. If the thymus is damaged prior to or during irradiation, the participant would be unable to regenerate functional T cells. She recommended that only participants with proper thymic function should be enrolled and that, if the first two participants' subsequent test results show the thymus has been damaged such that T cells cannot be made, the study should be halted. She asked that the vector facility be properly audited to ensure that Good Manufacturing Procedures are followed, that procedures be performed on participants in a clinic rather than a physician's office, and that a Data and Safety Monitoring Board (DSMB) be established.

Dr. Mickelson focused on concerns about whether the use of the proposed conditioning/ablation treatments would significantly increase the risks associated with trial participation for this patient population. She also questioned whether using TBI would increase the risk of neoplasia, or the rate of appearance of HIV variants, thus affecting the efficacy of concurrent drug therapies. Because of these possible effects, she asked why TBI was selected rather than high-dose chemotherapy. She also questioned the low efficiency of transduction of CD34+ cells and which differentiated cell types might express the antisense RNA after engraftment.

Dr. Fung expressed concerns about the lack of information in the preliminary data regarding multiple-dose subjects, the effect of TBI on HIV replication, the use of immunosuppressive agents in an autotransplant, and the use of human serum for the isolation of CD34+ cells.

C. RAC Discussion

Several issues were raised by RAC members during discussion in addition to those expressed by the initial reviewers:

- Dr. Markert asked why the researchers used fetal calf serum in this protocol.
- Dr. Friedmann expressed concern that the vector construct may be prone to genetic rearrangements.
- Ms. Levi-Pearl commented that the informed consent document did not disclose information regarding whether the investigators have financial interests with the sponsor.
- Dr. Markert suggested that investigators use an immunoscope prior to and after the procedure to provide useful immunologic information about thymic function. The DSMB could use these comparative data to keep track of subjects' immune status and to decide whether to halt the trial.

D. Investigator Response

Regarding the concern about administering product in a physician's office, Dr. Conant responded that his office is set up to respond to severe hypotension and other immediate reactions, and provides both nursing staff and appropriate equipment. He agreed with Dr. Markert's suggestion of starting the trial with two subjects and then asking a DSMB with immunology expertise to review those results before proceeding. As to testing subjects for thymic function, Dr. Conant expressed his belief that only a small percentage of patients would be excluded as a result of thymic dysfunction, but agreed to implement that test. In response to Dr. Mickelson's question about using radiation therapy instead of chemotherapy, he stated that chemotherapy would be more detrimental than the low-dose radiation therapy proposed for this trial.

Dr. Laurence stated that the level of radiation proposed is standard treatment at New York Hospital's transplant unit and has been approved for treating cancer patients who are HIV positive. In response to Dr. Fung's questions about the proposed immunosuppressive regimen, Dr. Laurence responded that it is a mild, immune-conditioning regimen and that MMF appears to be an effective anti-HIV agent that

synergizes with other anti-HIV drugs. Dr. Conant noted mycophenolic acid is also useful in arresting differentiation of the transduced CD34+ cells following readministration to the participant. Dr. Laurence also indicated that fetal calf serum would be replaced with human serum to avoid possible antibody formation.

In response to Dr. Aguilar-Cordova's suggestion to use Southern blot analysis on target clones to check for rearranged vectors in the transduced cells, Dr. Engelhardt stated that the investigators have assayed by amplification of the insert rather than performing Southern blots on transduced cells.

E. Public Comment

No public comments were offered.

F. RAC Recommendations

Dr. Mickelson summarized the RAC recommendations as follows:

- A DSMB should be used to review the thymic function data and other safety information to determine whether the study should continue or what the next steps should be. At least one immunologist should be involved as immunologic adverse events may well occur. For research subject safety, this expert input on the review of safety data and protocol design is important.
- Southern Blot analysis should be conducted to assess vector construct stability in both the vector producing cells and the transduced cells.
- With regard to the informed consent document, the partial ablation radiation and pre-conditioning regimen should be clarified and this explanation should be moved forward to a more prominent position in the document. Also, the informed consent document should disclose whether the investigators have financial interests in Enzo Therapeutics, Inc.
- In order to diminish the host immune rejection response, xenoproteins such as fetal calf serum should be replaced with human or autologous proteins where possible.

G. Committee Motion 2

It was moved by Dr. Aguilar-Cordova and seconded by Dr. Markert that the recommendations expressed the views of the RAC and, following review by the RAC members and ad hoc reviewers, would be reiterated in a letter to the investigators and sponsor. The vote was 13 in favor, 0 opposed, and 0 abstentions.

IV. Optimization of HIV-1 Vectors Containing an Anti-HIV Antisense Payload for Gene Transfer into HIV-Infected Individuals/Boro Dropulic, Ph.D., VIRxSYS

Dr. Dropulic presented a lentiviral vector, VRX496, being developed for use in *ex vivo* gene transfer into HIV patients. The vector is derived from HIV-1, and does not encode any viral proteins. Expression of an antisense RNA to HIV-1 envelope is controlled by the HIV LTR, limiting expression only to HIV infected cells also expressing Tat and Rev. The clinical goal would be to interfere with wild type (wt)-HIV *in vivo* to decrease the viral load set point and to increase CD4 T-cell survival in order to postpone the development of acquired immune deficiency syndrome. Because the vector consists of only HIV-1 sequence, it may have safety advantages since it would introduce no new sequences into possible recombinants between the vector and wt-HIV-1; therefore, any replication-competent recombinants generated would not have the potential to be more pathogenic than wt-HIV.

In vitro results were presented showing the efficiency of human CD4 cell transduction and inhibition of HIV replication in challenged transduced cells. Biodistribution studies were performed in a mouse NOD/SCID model injected with transduced human T cells.

Dr. Dropulic also outlined the design of the clinical trial that is expected to be mounted. It would involve *ex vivo* transduction of CD4 T cells isolated from the research participant. Before re-administration, the cell product would be assayed for the presence of helper RNA or DNA. Research participants in this incremental dose-escalation trial would be monitored for differential viral load, CD4 count, and replication competent retrovirus (RCR).

A. RAC Discussion

Dr. Aguilar-Cordova asked why a vector that did not mobilize well was being pursued since mobilization should amplify the inhibitory effect while a vector without that capability would not have any advantage over MLV based retroviral vectors. Dr. Dropulic agreed that mobilizing vectors would have increased efficacy, but the vector was chosen for its safety features. He suggested that an HIV-1 derived vector would be more effective because the vector HIV RNA would track intra-cellularly to the sites of wt-HIV-1.

Dr. Mickelson and Dr. Friedmann asked about potential problems with toxicity or immune responses to the vector pseudotyped with the Vesicular Stomatitis Virus G (VSVG) envelope. Dr. Ando pointed out that because of the potential for recombination, the choice of envelope is not trivial and assays for RCR are limited in their sensitivity. Dr. Dropulic described the lot release criteria involving polymerase chain reaction (PCR) detection of helper RNA or DNA sequence and cell assays to look for any potential replication-competent virus.

Dr. Markert suggested that participants should be followed with an immunoscope to test for immune diversity. Dr. Dropulic responded that in the animal studies for which preparations are currently under way, immunoscopic analysis of the cells will be performed and cells will be tested by fluorescence-activated cell sorter for various receptors. Dr. Markert indicated that the new cytokine assays might result in allergies.

B. Public Comment

No public comments were offered.

V. Discussion of Risk-Group Designation for Strain B of *E. coli*/Drs. Ando and Mickelson

Dr. Ando explained that the University of Florida requested a definition of the risk-group classification for *E. coli* B strain be developed. Strain B is widely used in industry for fermentation and large-scale manufacturing of proteins because of the increased stability of cloned sequences compared with that of *E. coli* K-12.

Dr. Mickelson suggested that all *E. coli* strains could be placed into Risk Group 1 (RG1), nonpathogenic organisms, provided they lack virulence genes, contain deletions in metabolic genes so they are dependent on laboratory media, and do not make any known toxins. She explained that certain *E. coli* strains, such as K-12, are exempt from the *NIH Guidelines* because they meet a fourth criterion: inability to colonize the human gut. Rather than making decisions on a strain-by-strain basis, she suggested the generation of a general statement outlining the characteristics required for *E. coli* strains to be designated RG1 under the *NIH Guidelines*. Dr. Patterson indicated that a strawman proposal for this had been developed which could be put forward as a proposed action.

In the interim, a letter will be drafted in reply to the University of Florida's request that its strain of *E. coli* be considered RG1, as long as it does not contain toxins or virulence factors and there is metabolic dependence on laboratory media. Drs. Ando and Mickelson will work on the wording of the letter and distribute it to RAC members for review before sending.

Proposed language to amend the *NIH Guidelines* will be brought to the RAC at its next meeting and will then be published in the *Federal Register* for a public comment period. Dr. Mickelson offered the following general phrasing of the amendment language: If a strain can be shown not to produce any of the known bacterial toxins, does not contain any of the known major virulent factors for *E. coli*, and it carries

deletions in the metabolic genes that make it dependent on laboratory media, then those strains should be considered as Risk Group 1 *E. coli* for both large-scale and laboratory work.

A. Committee Motion 3

It was moved by Dr. Gordon and seconded by Dr. Markert that the strain of *E. coli* proposed by the University of Florida be considered Risk Group 1 and that draft language be developed to amend the *NIH Guidelines*. The vote was 12 in favor, 0 opposed, and 1 abstention.

VI. Proposed Action To Amend the *NIH Guidelines* Requirements for Serious Adverse Event Reporting (SAER): RAC Discussion and Vote/Dr. Macklin

Dr. Macklin called on Dr. Patterson and Mr. Allan Shipp, OBA.

A. Dr. Patterson

Dr. Patterson presented an overview of the Proposed Action that would amend the *NIH Guidelines* to enhance the reporting of safety information, its assessment, and its communication to the scientific community and the public. There are four elements to the proposal: (1) harmonization of the scope and timing of SAER to create one set of reporting criteria to both the NIH and FDA; (2) public access to safety information that will not be considered trade secret; (3) protection of research participant privacy in SAER; and (4) establishment of a national data assessment board. The Proposed Action establishes one set of reporting criteria for researchers to follow for both NIH and FDA and will provide enhanced and systematic analysis of safety data across all trials that will be presented publicly to inform about the design and conduct of ongoing and future clinical trials.

The proposed Gene Transfer Safety Assessment Board (GTSAB) would function as a mechanism for collecting, analyzing, and publicly reporting safety information across all trials. As such, it would facilitate early recognition of trends; report findings, conclusions, and aggregated trend analyses for public discussion at RAC meetings; and inform research participants, clinical investigators, basic scientists, Institutional Review Boards (IRBs) and Institutional Biosafety Committees (IBCs), and the public. The GTSAB would operate in an analytic and advisory capacity and would not supersede or replace the responsibilities of FDA or local review bodies in the day-to-day review of, and real-time response to, safety information. Approximately 15 members would make up this new Board, with outside experts in relevant fields constituting the majority of its membership; other members would include two RAC members, and NIH and FDA members. The board would meet quarterly in closed sessions prior to RAC meetings and provide reports to the RAC as well as publish periodic summary reports and cumulative trend analyses.

Dr. Patterson also reported on the status of the development of a national database for gene transfer clinical research. Using a controlled reporting vocabulary, this relational database will include product descriptors, elements of clinical trial design, and safety and toxicity data. It will be query capable and Web based. As an analytic tool for FDA, NIH, and advisory boards, this database will facilitate the evaluation and analysis of safety information from all gene transfer clinical trials. Reports from the database will inform diverse user groups such as IRBs, IBCs, local DSMBs, investigators, research participants, and the general public. Currently, the basic data structure and software design are nearing completion, and a draft common adverse event (AE) reporting form acceptable to both NIH and FDA staffs has been completed. The next steps include obtaining input from other user groups to finalize system software and training investigators and sponsors in the use of controlled vocabularies.

B. Mr. Shipp

Mr. Shipp summarized the public comments on the Proposed Action for SAER. Thirty-four sets of comments were received: two from professional associations, one from a scientific association, three from industry associations, six from patient groups and associations, three from academic officials, four from pharmaceutical and biotechnology companies, and the remainder from individuals. According to those comments, the prohibition of submission of individually identifiable patient data was supported

universally. Public access was also generally favored although there were differing views about the definition of confidential commercial information. Regarding the timing and scope of SAER, the majority of comments favored harmonization; however, industry and the National Hemophilia Foundation believe that no raw SAEs should be reported to the RAC, but rather that the RAC should rely on FDA for that information. A majority of respondents stated their belief that the RAC and the proposed GTSAB can serve a unique and necessary role in the public dissemination of safety and ethical information regarding gene transfer research (GTR) given that FDA is bound by confidentiality restrictions.

C. Public Comment

1. Abbey S. Meyers, National Organization for Rare Disorders (former RAC member)

Ms. Meyers described one role of the RAC as informing a public fearful of gene transfer research. In the wake of the Jesse Gelsinger tragedy and problems with genetically modified foods, public trust is eroding. The proposal is necessary to prevent the rejection of gene therapy as is happening with agricultural biotechnology. Gene therapy will fail if the public withdraws its trust in research, the researchers and the government's ability to protect the people. She urged the adoption of the proposed action and suggested that industry needs to realize that gene therapy is not just about money; it is about lives.

2. Stephan E. Lawton, Biotechnology Industry Organization (BIO)

Mr. Lawton began with assurances that BIO supports the reporting and analysis of safety data. However, they interpret the proposed action as, for the first time in the history of DHHS, compelling the submission and revelation of confidential commercial information to the public. This would make information accessible to competitors and could constitute a significant risk to smaller biotechnology companies, particularly in their ability to attract venture capital. He requested an invitation to work with the RAC/NIH on the proposed action prior to its approval.

Dr. Mickelson requested clarification of BIO's position in light of the fact that this same type of information has been requested, released, and discussed by the RAC for a decade. Mr. Lawton replied that some of the information requested in Appendix M could be of advantage to competitors; therefore, they objected to not being able to label it trade secret. Dr. Patterson reiterated that the proposal refers to a set of data that has already been requested for 10 years with the provision that it not include confidential commercial information. If it is marked as such, decisions will be made on a case-by-case basis allowing for dialogue with the investigator. She emphasized the need to be true to the spirit of the proposal to which Mr. Lawton requested again to work with NIH on the letter of the proposal.

3. Rosemary Quigley, Council of Public Representatives (COPR)

By speakerphone, Ms. Quigley expressed her concerns about the adequacy of research subject protection and the need for patient access to information necessary for truly informed consent. COPR strongly supports adoption of the proposed action as drafted. In order to protect participants and advance the nascent field of GTR, she stressed the importance of reporting all adverse events when there is any possibility of association with the gene transfer product. The creation of the GTSAB was endorsed as a necessary complement to the reported raw data that may become available under the FDA proposal. She stated her appreciation that in addition to the RAC review of protocols, NIH would now take the responsibility for the informed dissemination of SAE information. Regarding the BIO statement, COPR views public disclosure of SAEs and discussion of the analyzed data as assistance, not a hindrance, to industry.

4. Paul Gelsinger, Citizen

Mr. Gelsinger stated his belief that a major reason for his son's death in a gene transfer clinical trial was the financial pressure upon medical research that caused money to become more important than the welfare of clinical trial participants. He urged researchers to properly report all AEs and to allow NIH to

discuss and review events related to GTR, and that FDA be allowed to release more information to the public. He stated that this proposed action is an appropriate step toward getting GTR on the correct path.

5. W. French Anderson, University of Southern California/American Society of Gene Therapy (ASGT)

Speaking on behalf of ASGT, Dr. Anderson stated that ASGT is very much in favor of the Proposed Action and the proposal to allow FDA to be more open regarding SAE reports. Although he expressed support for the spirit of these proposals, he was concerned that, in the enthusiasm to implement them, certain aspects could cause problems, so he suggested working with BIO and other individuals.

6. Alan Milstein, Attorney

Mr. Milstein queried the RAC about the meaning of Mr. Lawton's statement that "we can work out" the concerns of the biotechnology industry. He was apprehensive that negotiations might result in the removal of the requirement for public disclosure of SAEs.

D. RAC Discussion

Issues discussed included the following:

- Dr. Skirboll clarified the following points: SAEs would be submitted to NIH in a manner harmonized with FDA submission. The GTSAB analysis would not occur in public, but the reports generated would be publically discussed by the RAC. As with any raw data that come to NIH, this data would also be publicly accessible if requested under the Freedom of Information Act (FOIA). Should there be any substantive changes to the proposal, it would have to be brought back to the RAC for another vote. Because the *NIH Guidelines* can be amended if necessary, further changes may be made should the FDA public disclosure rule become regulation.

- Ms. King reminded everyone present about the language in Appendix M of the *NIH Guidelines* about proposals not containing trade secrets or confidential commercial information; she reiterated that nothing in the Proposed Action changes that language, which has been in effect for about 10 years, and she suggested that RAC discussion center on aspects of the Proposed Action other than the wording found in Appendix M.

- Dr. Markert stated that GTR is not particularly high risk in relation to other research; however, the Proposed Action is necessary to allay the public perception of it as such. Another misconception is that the GTSAB would be reviewing individual SAEs. In actuality, it would review data in the aggregate. Individual review of SAEs could continue to be the responsibility of the local DSMBs. Dr. Markert also noted that a database of raw SAE information on the Web that can be accessed by anyone may be a disservice to the public. Dr. Patterson and Dr. Greenblatt explained that while analysis of the data would be available, the raw data and the preanalysis would be sheltered behind a firewall. Raw data would be available only through FOIA requests to OBA.

- Dr. Jay P. Siegel, FDA, explained that FDA does assess AE in a manner similar to that proposed for the GTSAB, but FDA recognizes that this potential duplication of effort is currently necessary due to the restrictions on public disclosure by FDA. In the event that FDA's disclosure rules are loosened, it would be appropriate to review the coordination of FDA and NIH efforts. Dr. Siegel described some of the issues related to the review of safety data, particularly noting that the aggregate assessment of safety data is a complex process. He further noted that the GTSAB will likely review a database that is somewhat different from the one FDA reviews because of disclosure issues. Dr. Siegel reiterated FDA's position that periodic overview of SAE data in the public domain is a positive development, and that FDA will work with the GTSAB and will continue to work with OBA and the RAC.

- Dr. Aguilar-Cordova brought up the suggestion by ASGT and others that SAEs be reported in their clinical context. He suggested a possible role for the GTSAB in organizing Gene Transfer Policy

Conferences (GTPCs), and properly disseminating the information put forth at these conferences to the public, investigators, and sponsors.

- Dr. Gordon stated that creation and utilization of the GTSAB and AE database are essential. A usable database in the hands of experts can bring forth important trends in GTR that may prevent an SAE and identify potentially promising areas.

- Dr. Breakefield agreed with Dr. Aguilar-Cordova's comments about the necessity of having mechanisms in place so that knowledgeable people from different sectors of GTR can meet quickly and efficiently, analyze SAE data, and release the analysis publicly. She explained that the existence of more safety nets means a better chance of detecting a potential problem before it becomes serious.

- Dr. Friedmann commented that while the proposal may be imperfect, it does address many of the important issues in the GTR field. He advocated approving the proposal as it is, implementing it, and then being flexible in dealing with problems as they arise. He stressed the importance of the interaction among Government, academia, and industry as being necessary to move the gene transfer field forward.

- Dr. Macklin reminded RAC members that policies rarely include operational details; fine-tuning those details occurs during implementation. She also stated that overlapping responsibilities are not necessarily negative if they result in improved protection of human subjects participating in frontier research areas such as GTR.

- Dr. Greenblatt declared his strong support for the creation of the GTSAB, stating that it would represent a significant improvement over what is currently available and that it has value to patient-subjects and to science. He pointed out that the GTSAB would be reevaluated after two years.

E. Committee Motion 4

It was moved by Dr. Gordon and seconded by Ms. Levi-Pearl that the RAC recommend the Proposed Action to amend the *NIH Guidelines* to the NIH Director with the understanding that the details will be worked out. The vote was 11 in favor, 0 opposed, and 1 abstention.

VII. Discussion of Human Gene Transfer Protocol #0101-445: Clinical Protocol for Wild-Type p53 Gene Induction in Premalignancies of Squamous Epithelium of the Oral Cavity via an Adenoviral Vector

Principal Investigator:	Gary Clayman, M.D., University of Texas M.D. Anderson Cancer Center
Sponsor:	Introgen Therapeutics, Inc., represented by Deborah R. Wilson, Ph.D.
RAC Reviewers:	Drs. Aguilar-Cordova, Breakefield, Chow, and Macklin
Ad Hoc Reviewer:	Carter Van Waes, M.D., Ph.D., National Institute on Deafness and Other Communication Disorders, NIH

A. Protocol Summary

For a discrete group of patients with preneoplastic lesions of the oral cavity, no meaningful treatment exists other than conventional surgery. Surgery does not address the multifocality, high incidence of recurrence, and second primary lesions involving aerodigestive tract sites. Biochemoprevention approaches have demonstrated disappointing results; in more than 50% of patients, lesions become malignant. Biomarker studies have suggested that patients with mutant p53 and genetic instability were at greatest risk of disease progression. The objective of this protocol is to directly modify the precancerous cell to express large quantities of an exogenously introduced, normal tumor suppressor gene product that

may reverse the premalignant process by inducing apoptosis in the cancer predisposed cells, allowing for repopulation with normal genotype epithelial cells. The goal is to determine the transduction efficiency of adenoviral mediated wild-type p53 gene transfer in reversing oral premalignancies.

Patients will receive an injection of the Ad5CMVp53 vector and oral rinse on day 1 followed by twice-daily oral rinses on days 2-5, additional lab work, research blood draws and photo documentation for the completion of one cycle. The study cycle will be repeated on a monthly basis for a period of 6 months. A total of 12 patients will be entered into the phase I dose escalation study with 33 patients anticipated to be entered into the phase II study. Biopsies of normal and preneoplastic tissue are performed at pretreatment and two hours following the first oral rinse of the 1st and 6th cycles. Alternative biologic endpoints will also be monitored through the collection of serum and urine. Maximal transduction rate will be determined by immunohistochemistry of p53 and downstream gene products.

B. Written Comments From Preliminary Review

Three RAC members recommended that the protocol warranted public discussion. Drs. Breakefield, Chow, and Macklin submitted written reviews, as did *ad hoc* reviewer Dr. Van Waes, to which the investigators responded in writing and during this meeting.

Dr. Aguilar-Cordova raised no safety concerns. He noted that adenoviruses are relatively unstable at low pH and queried the investigators about the effect of saliva on the adenovirus.

Dr. Breakefield focused on the novel route of administration (oral rinse), which is difficult to model in animals and may have toxic consequences to organs such as the larynx. Because premalignancies were targeted, she was also concerned about the risk-benefit ratio since it was not clear how well the vector would be able to transduce the target cells by this route and, if it did, whether the transduced cells would undergo apoptosis. Given that smoking and alcohol consumption predispose squamous cell carcinomas of the oral cavity, she asked whether participants would be counseled about these risks. Dr. Breakefield also inquired about the stability of the adenoviral vector in saliva, how the saliva will be monitored for shed virus after vector administration, and how SAEs associated with the oral tissues and larynx would be monitored.

Dr. Chow also focused on the route of administration and the targeted disease. She expressed concern about the possible effects of the oral rinse and the 10 percent acetic acid prerinse on nontarget tissues in the oral cavity as well as possible accidental exposure to the epithelial cells lining the airway and the esophagus. Since a control arm using a placebo oral rinse is not proposed, Dr. Chow wondered how investigators would know whether any observed effect was due to the intralesional injection of the virus, the oral rinse, or both.

Dr. Macklin focused on recruitment of participants, how and where it would occur and who would be doing it. She also expressed concerns about the route of administration and the inability to model it in animals prior to human trials. She questioned whether compliance with a 30-minute oral rinsing regimen would be possible, and pointed out that possible harm could result from swallowing or aspirating the virus solution. Overall she expressed concern about the risk-benefit balance, suggesting that the uncertainty of potential benefits may not outweigh the potential harms. In the informed consent document, the terms “patient,” “treatment,” and “doctor” should be replaced with terms that reflect the experimental nature of the process.

Dr. Van Waes also centered on the use of a new patient population and delivery method. He asked for the percentage of dysplasias that have p53 mutations, the frequency with which lesions with p53 mutations progress to carcinoma, why p53 mutation is not an eligibility requirement, and whether preclinical studies have been performed to support the hypothesis that wt-p53 can efficiently induce apoptosis of premalignant cells and repopulation of normal epithelial cells. He also asked about the rationale and safety of the oral acetic acid rinse, whether acetic acid is a carcinogenic agent in subjects using tobacco and alcohol, and why intralesional injection without the rinse is not being performed first. Dr. Van Waes also suggested that the consent document include a description of the rinse and instructions for research subjects to abstain from oral contact with others.

C. RAC Discussion

Ms. Levi-Pearl requested that the informed consent document include financial disclosure information.

Dr. Macklin commented on the "therapeutic misconception" and the need for a clearer distinction in the protocol between the role of researcher and that of a personal physician.

Dr. Van Waes requested that the investigators amend the eligibility criteria to make it clear that they are recruiting participants who have failed other therapies and who have widespread or diffuse disease involvement.

Dr. Friedmann asked the researchers to explain why leukoplakia is not part of the study, and to describe the fate of all the administered adenovirus, particularly whether it survives in the trachea.

D. Investigator Response

Dr. Clayman clarified that the protocol is directed toward participants who have failed other standard or experimental treatments. Fifty percent of patients diagnosed with premalignancy progress to the malignancy within 6 months.

In regard to the delivery route, preclinical studies showed no toxicity in mice receiving an equivalent oral dose. Also there have been other trials involving intratumoral injection in which participants have been found to shed the same vector in saliva without ill effect. A 30 minute oral rinse is standard in other treatments for head and neck squamous cell carcinoma patients. The use of the 10 percent acetic acid did not significantly change the pH of the oral cavity, and ingested adenovirus p53 is neutralized by the stomach's pH of 1.

Dr. Clayman explained that leukoplakias are not necessarily premalignant. They can be benign long-term processes that do not progress to malignancy.

E. Public Comments

No public comments were offered.

F. RAC Recommendations

Dr. Mickelson summarized the following RAC recommendations as follows:

- To revise the eligibility criteria to ensure that only patients with diffuse and refractory premalignancies are enrolled.
- With regard to the informed consent document:
    - To include a financial disclosure for the investigator and any sub-investigators (and if any financial conflict of interests, to give details);
    - To replace the word "patients" with "subjects" or "research participants" since this is clinical research rather than provisional medical care; and
    - To revise the informed consent document to reflect the changes agreed to during the preliminary review (e.g. 30 minute oral rinses would occur in a clinical setting where biohazard containers are available).

G. Committee Motion 5

As moved by Dr. Breakefield, the RAC vote on the recommendations was 9 in favor, 0 opposed, and 2 abstentions.

VIII. Proposed Plan for Addressing Issues Related to Institutional Biosafety Committees/ Allan Shipp, M.H.A., Office of Biotechnology Activities; Cynthia Dunn, M.D., University of Rochester Medical Center; and Andrew George Braun, D.Sc., Harvard Medical School

The issues for discussion were as follows: (1) Should the *NIH Guidelines* be amended to clarify when an institution conducting recombinant DNA research may use an offsite IBC, defined as an IBC at another institution or a commercial IBC? and (2) Pending such an amendment, should an interim policy be put into place to promote clarity and consistency in the interpretation of the current *NIH Guidelines*?

OBA proposed to hold a conference in fall 2001 on a range of issues pertinent to IBC function. Conference participants will discuss such matters as the origin of IBCs, the meaning and necessity of local review, the importance of community consultation, the role of IBCs relative to IRBs, the relationship of IBCs to Federal agencies, and specific questions directly germane to the offsite IBC question. By opening a dialog on these matters, the conference will inform the development of any necessary amendments to the *NIH Guidelines.*

A. Mr. Shipp

Mr. Shipp presented an overview of the membership, procedures, and functions of IBCs as defined in the *NIH Guidelines*. The need to review the current policy has been prompted by two types of queries to OBA. Researchers from institutions that do not have adequate resources to set up their own IBCs would like to use IBCs from neighboring institutions. Investigators who are conducting multisite trials have requested the use of commercial IBCs to coordinate review of the research across sites. A policy interpretation is needed that will optimize subject and community protections and research advancement.

A strawman proposal that included two scenarios was put forth for RAC approval. In scenario A, if an institution or its clinical site conducting GTR were to receive NIH support for recombinant DNA research, it would have to set up a local, institutionally accountable, fully compliant IBC. In scenario B, if an institution or its clinical site did not receive NIH support for recombinant DNA research, but the sponsor of the research did receive NIH support, the site would have to set up its own local, compliant IBC or hire an offsite IBC by contract, with OBA approval. Alternatively, the sponsor IBC could conduct the review, or the sponsor could hire an IBC by contract, with OBA approval. To be acceptable, an offsite IBC used under contract would have to meet the fundamental requirements specified in the *NIH Guidelines* including:

- A majority of the members (three or more) must fulfill the expertise requirements specified in the *NIH Guidelines* (but the expert members need not reside at or be affiliated with the site).
- At least two members must be from the community surrounding the IBC and represent its interests with respect to health and protection of the environment, and these members must be able to consult promptly with other IBC members.
- There must be periodic inspections of the site by the IBC members who have expertise in the type of research being conducted.
- The IBC must be able to be convened as promptly as necessary (which may be done by teleconference).

OBA's ongoing concerns about offsite IBCs included those related to research that occurs in "doc-in-the-box" settings (e.g., in a doctor's office), managing the risks of certain classes of vectors, adequate training of personnel, and ensuring institutional accountability.

B. Dr. Dunn

Dr. Dunn described offsite or independent IBCs as only overseeing GTR clincal trials at biosafety levels 1 or 2. Members must have the required expertise but need not be affiliated with the site. Membership will include a biosafety officer, and infection control specialist from the local community to inspect the site. She cited the trend in which clinical research is shifting from academic medical centers to smaller sites

that may not have the professional expertise to support their own IBCs. Independent IBCs could combine the benefits of local review—community awareness and familiarity with the research environment—with that of central coordination—greater access to expertise, and decrease in conflicts of interest because there would be no direct connection to the clinical site. Dr. Dunn urged OBA to issue a clarification statement indicating that compliance with the *NIH Guidelines* regarding IBCs is not dependent on whether the IBC is constituted internally or independently.

C. Dr. Braun

Dr. Braun noted that he was speaking for himself, not as a representative of Harvard University.

IBCs were originally established so local communities could become more aware of research in their neighborhoods; therefore, meetings should continue to be open to the public, whether the IBC is internally or externally constituted. At most institutions, serving on an IBC is a difficult job that is rarely rewarded properly. Members are motivated by the interesting work, and knowing that they are working for the good of their institution, their field, and their own consciences. It is unclear whether commercial IBCs could be expected to display the same degree of devotion to their work.

However, some aspects of outside IBCs would be useful: highly specialized knowledge could be made available to small institutions, economies of scale would occur when people work full time on one issue, the potential for conflict of interest among academic colleagues would decrease, and improved cooperation among different sites in the same protocol may occur if a single IBC oversaw the biosafety issues at those multiple sites.

A possible drawback to commercial IBCs would be the creation of a situation in which members have greater loyalty to their employer than to the sponsor, the institution at which the research is being conducted, or the research participants. Also if clinical studies were removed from local IBC responsibility, service on the local IBC would be less interesting, resulting in more difficultly in getting volunteers to serve on the local IBCs.

Dr. Braun summarized his view that outside IBCs can provide a useful role in certain circumstances related to the need to provide expertise in human gene tranfer protocols for small clinical establishments. Because there is no substitute for local knowledge or experience, the RAC should strongly encourage clinical sites to establish their own IBCs.

D. RAC Discussion

Dr. Friedmann asked for basic information about the Western Institutional Review Board (WIRB). Dr. Dunn responded that the WIRB is an independent company that was established in 1968 to conduct IRB reviews. WIRB members are paid honoraria by either the clinical site or the sponsor on a per-review basis, whether or not the study is approved.

Dr. Juengst pointed out that the definition of "community member" as a local biosafety officer and an infectious disease expert differs from the type of community member added to an academic IBC: a lay person representing the perspective of the surrounding community. Dr. Dunn responded that the community members are familiar with community attitudes, but they are not necessarily lay members. Dr. Mickelson reiterated the concern that the community-member representation should include lay persons from the public.

Dr. Breakefield suggested the possible establishment of regional IBCs to which institutions would contribute expertise. Another important topic for the proposed fall 2001 meeting, for both independent and institutional IBCs, would be a method of public notification of IBC meetings.

Dr. Aguilar-Cordova suggested that the discussion also include how IBCs function for an institutionally affiliated (but geographically distant) research site, especially in light of how community members are involved in the IBC process.

Dr. Patterson asked the RAC for guidance about whether OBA should adopt the proposed strawman

interim policy, adhere to a strict interpretation of the *NIH Guidelines* on this topic, or make decisions on an *ad hoc* basis until the conference. She also asked whether decisions should take into account the level of risk involved.

Dr. Friedmann preferred to postpone major decisions until more information could be learned during the policy conference. However, Dr. Dunn noted that, if the RAC does not make a decision about the use of independent IBCs before the fall of 2001, sponsors seeking to establish IBC review would be prohibited from using investigative sites outside of academic institutions.

Dr. Macklin suggested that the RAC reject a narrow interpretation of IBCs as being "at the clinical site" in favor of IBCs that provide the most expertise. Dr. Breakefield stated that certain protocols would lend themselves more easily—and with more "comfort" within the community—than the use of independent IBCs. Dr. Aguilar-Cordova agreed that not having a strict interpretation of "at the site" for IBCs would be an acceptable interim stance so that OBA could make case-by-case analyses until after the fall 2001 IBC meeting.

Dr. Braun and Dr. Mickelson objected to the statement in the strawman proposal that the meetings of an independent IBC be allowed to be held by teleconference because teleconferencing would defeat the purpose of allowing public participation and involvement.

E. Public Comment

Dr. J. Tyler Martin, representing Valentis, suggested the need for a "scenario C" to cover sites and sponsors that voluntarily submit to RAC review.

F. Vote of the Committee

As moved by Ms. Levi-Pearl and seconded by Dr. Aguilar-Cordova, the RAC accepted the outline of the strawman proposal until such time as the proposed IBC conference is held with a friendly amendment regarding teleconferencing. The vote was 7 in favor, 3 opposed, and 0 abstentions.

IX. Data Management/Dr. Greenblatt

Dr. Greenblatt reported that 24 new protocols were submitted to OBA during the December 1 to March 1 reporting period; 22 were exempted from public review by the RAC. Of the 449 total protocols, 38 are classified as gene marking, 409 as gene transfer, and 2 as nontherapeutic in normal volunteers. A breakdown of the 409 GTR protocols indicates that:

- 280 were for cancer.
- 50 were for monogenic diseases (cystic fibrosis was the most frequent).
- 35 were for infectious diseases (all but 1 for HIV).
- 44 were for other diseases (coronary artery disease and peripheral artery disease being the most frequent).

A. Amendments and Updates and Adverse Events

During the reporting period, 37 amendments and updates were submitted to OBA including annual updates, eligibility criteria updates, and site additions. Three responses to Appendix M-I-C-1 following the initiation of the clinical investigation were also received.

Of the 206 serious or unexpected reports submitted to OBA, 160 were initial reports and 46 were followups; 25 percent of these occurred prior to 2001. Of the 38 reports classified as serious, possibly

associated, and unexpected, 22 were initial reports and 16 were followups.

Dr. Greenblatt described one report in which a research participant received adenoviral p53 gene transfer for ovarian cancer and died a week after receiving the vector. The preliminary autopsy noted severe peritonitis which was possibly related to treatment. However, the final autopsy attributed death to the complications of extensive metastatic carcinoma, changing the AE from possibly related to unrelated.

X. Food and Drug Administration's Proposed Disclosure Rule/Dr. Noguchi

Dr. Noguchi described FDA's proposed disclosure rule, "Availability for Public Disclosure and Submission to FDA for Public Disclosure of Certain Data and Information Related to Human Gene Therapy or Xenotransplantation," which was published for comment in the January 18, 2001 *Federal Register*. The purpose of the rule is to allow FDA to participate fully in public discussions about GTR and xenotransplantation. While the proposed rule would maintain the confidentiality of information about research participants, trade secrets, and confidential commercial information, it proposes to disclose:

- Product and participant safety data and related information;
- Name and address of the sponsor;
- Clinical indications to be studied;
- A protocol for each planned study, including abstracts, statement of objectives, names and addresses of investigators, names and addresses of official contacts for local review bodies, criteria for subject selection and exclusion, and description of the treatment that will be administered to subjects, as well as the clinical procedures, laboratory tests, or other measures to monitor safety and minimize risk;
- Written informed consent documents;
- Identification of the biological product and method of production;
- Investigational new drug (IND) safety reports;
- Information submitted in the annual report;
- Regulatory status of the IND; and
- Other relevant data and information.

A. RAC Comments

Dr. Greenblatt asked Dr. Noguchi how this information would be made available to the public. Dr. Noguchi responded that the sponsor will submit redacted information with each official submission to FDA. The redacted information will then be sent to FDA's public dockets, which are publicly available on the Internet and updated daily. Dr. Greenblatt expressed concern that the proposal, if implemented, will make all raw SAE data available, which the RAC has previously stated may not be in the public interest. Considering that this rule would be a major departure from past FDA policy, he asked whether Congress would allow it to take effect. While acknowledging the possibility of Congressional opposition, Dr. Noguchi indicated that the proposed rule is consistent with law enacted in 1902 that ensures public confidence in medical therapies involving biological products.

Dr. Friedmann, Ms. King, and Ms. Levi-Pearl commended FDA for taking this significant step toward greater transparency. Dr. Aguilar-Cordova queried how this proposal would relate to the OBA-proposed database. Dr. Noguchi responded that the proposal is intended to augment the OBA database, and the information released publicly by FDA would be available for inclusion in the OBA database.

Ms. Levi-Pearl urged anyone with an opinion about the proposal to provide public comment during the

comment period. Dr. Noguchi also encouraged comments and noted that the deadline is mid-April 2001.

B. Public Comments

1. Dr. Andrew Braun, Harvard Medical School

Dr. Braun suggested that the raw data for SAEs need a denominator—the total number of people studied so that the number of SAEs can be put into context. If this background is not provided, reported numbers may be misleading.

2. Jo Ann Blake, Citizen

Ms. Blake asked whether SAE data such as that described by Dr. Greenblatt will link directly back to the original document in FDA records. If the proposed rule changes are implemented, Dr. Noguchi responded that this would be possible.

C. Committee Motion 6

As moved by Dr. Breakefield and seconded by Ms. King, the RAC voted unanimously (9) to support the implementation of FDA's proposed disclosure rule because it will further the RAC's mandate and is in the public interest.

XI. Chair's Closing Remarks/Dr. Mickelson

Dr. Mickelson thanked the RAC members and indicated that the next RAC meeting is scheduled for June 14-15, 2001.

XII. Adjournment/Dr. Mickelson

Dr. Mickelson adjourned the meeting at 5:25 p.m. on March 8, 2001.

[Note: Actions approved by the RAC are considered recommendations to the NIH Director; therefore, actions are not considered final until approved by the NIH Director.]

Amy P. Patterson, M.D.
Executive Secretary

I hereby acknowledge that, to the best of my knowledge, the foregoing Minutes and Attachments are accurate and complete.

Date:

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Chair

Attachment I
Committee Roster

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Attachment II
Attendees

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John Bishop, FDA
Eda Bloom, FDA
Adwoa K. Boahene, *The Blue Sheet*
Parris R. Burd, Maxygen
Andrew Byrnes, FDA
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Joy A. Cavagnaro, Access BIO
Yung-Nien Chang, VIRxSYS
Janice Chappell, DirectGene
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Aleta Crawford, University of Florida
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Steve Eckert, NBC News
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Abbey S. Meyers, National Organization for Rare Disorders
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Gail M. Miller, Centocor

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Tom Staton, NBC News
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Margaret Taleff, Centocor
Barbara E. Thalenfeld, Enzo Therapeutics
Dianna Thomsen, King & Spalding
Melissa A.B. Tice, Schering-Plough Research Institute
Jennifer Washburn, writer/journalist
Michael J. Werner, Biotechnology Industry Organization
Patricia D. Williams, TheraSolutions
Carolyn Wilson, FDA
Deborah R. Wilson, Introgen Therapeutics
Gary L. Yingling, McKenna & Cuneo

Attachment III
Abbreviations and Acronyms

AAV	adeno-associated virus
AE	adverse event
AIDS	acquired immunodeficiency syndrome
ASGT	American Society of Gene Therapy
BIO	Biotechnology Industry Organization
CC	Clinical Center, NIH
COPR	Council of Public Representatives
DNA	deoxyribonucleic acid
DSMB	Data and Safety Monitoring Board
E. coli	*Escherichia coli* bacterium
FDA	U.S. Food and Drug Administration
FOIA	Freedom of Information Act
GTPC	Gene Therapy Policy Conference
GTR	gene transfer research
GTSAB	Gene Transfer Safety Assessment Board
HIV-1	human immunodeficiency virus type 1
IBC	Institutional Biosafety Committee
IND	investigational new drug
IRB	Institutional Review Board
LTR	long terminal repeat
MMF	mycophenolate mofetil
NHF	National Hemophilia Foundation
NHLBI	National Heart, Lung and Blood Institute
NIH	National Institutes of Health
NIH Guidelines	*NIH Guidelines for Research Involving Recombinant DNA Molecules*
OBA	Office of Biotechnology Activities
OD	Office of the Director, NIH
PBMC	peripheral blood mononuclear cells
PBSC	peripheral blood stem cells
PCR	polymerase chain reaction
PI	principal investigator
RAC	Recombinant DNA Advisory Committee
RCR	replication competent retrovirus
RG	risk group
RNA	ribonucleic acid
SAE	serious adverse event
SAER	serious adverse event reporting
TBI	total body irradiation
VSVG	Vesicular Stomatitis Virus G
WIRB	Western Institutional Review Board
wt-HIV	wild-type human immunodeficiency virus