RECOMBINANT DNA ADVISORY COMMITTEE

Minutes of Meeting

June 28-29, 2000

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/documents.htm>.

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
NATIONAL INSTITUTES OF HEALTH
RECOMBINANT DNA ADVISORY COMMITTEE
MINUTES OF MEETING[1]
June 28-29, 2000

The Recombinant DNA Advisory Committee (RAC) was convened for its 78th meeting at 9:00 a.m. on June 28, 2000 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 entire meeting from June 28 from 9:00 a.m. until 5:30 p.m. and from June 29 from 9:00 a.m. until 2:40 p.m. 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, Inc.
Xandra O. Breakefield, Massachusetts General Hospital
Theodore 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, Inc.
M. Louise Markert, Duke University Medical Center
Claudia A. Mickelson, Massachusetts Institute of Technology

Executive Secretary:

Amy P. Patterson, National Institutes of Health

Speakers/Principal Investigators:

Cynthia M. Dunn, University of Rochester Medical Center
Yuman Fong, Memorial Sloan-Kettering Cancer Center
Stuart H. Orkin, Harvard Medical School
Jeffrey M. Ostrove, NeuroVir Therapeutics
William F. Raub, U.S. Department of Health and Human Services
Joseph P. Salewski, U.S. Food and Drug Administration
Belinda Seto, National Institutes of Health
Jay P. Siegel, U.S. Food and Drug Administration
Lana R. Skirboll, National Institutes of Health
Karen Weiss, U.S. Food and Drug Administration
Savio L.C. Woo, American Society of Gene Therapy and Mount Sinai School of Medicine

Nonvoting/Liaison Representatives:

[11] 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.

Jeffrey M. Cohen, National Institutes of Health
Elizabeth Milewski, U.S. Environmental Protection Agency
Andra Miller, U.S. Food and Drug Administration
Philip Noguchi, U.S. Food and Drug Administration

National Institutes of Health Staff Members:

Bobbi Bennett, OD
John T. Burklow, OCPL
Sarah Carr, OD
Kelly Fennington, OD
Joe Gallelli, CC
Bob Jambou, OD
Sandra Jones, OD/CCC
Sung-Chul Jung, NINDS
Tom Kresina, NIAAA
Becky Lawson, OD
Kathy Lesh, OD
Gene Rosenthal, OD
Thomas Shih, OD
Michael Showe, OD
Sonia I. Skarlatos, NHLBI
Lana Skirboll, OD
Sharon Thompson, OD/The Kevric Company
Lucy Yang, OD

Others:

Approximately 70 individuals attended this 2-day RAC meeting. A full list of attendees appears in Attachment II.

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

Dr. Mickelson, RAC Chair, called the meeting to order at 9:10 a.m. on June 28, 2000. Notice of this meeting was published in the *Federal Register* on June 7, 2000 (65 FR 36154). Agenda items for the meeting include updates on recent events and issues in human subjects protections and gene transfer research (GTR), final review and vote on the summary recommendations of the Adenovirus Safety and Toxicity Working Group, discussion of a gene transfer protocol, report from the Advisory Committee to the Director, Working Group on NIH Oversight of Clinical Gene Transfer Research, continued discussion by the RAC Serious Adverse Events Working Group, and discussion of the criteria and the process for selecting protocols for RAC review and public discussion.

After reviewing the issues to be discussed at this meeting, Dr. Mickelson noted that during its past few meetings, the RAC has proposed several actions that would reassert and strengthen public access to information on protocols and serious adverse event (SAE) reports. At this meeting, the RAC will discuss recommendations for ensuring public access to safety information, including the importance of placing adverse event reports in context and making the content and format of the reports useful to the public and potential study participants.

II. Minutes of the March 8-10, 2000, Meeting/Drs. Gordon and Juengst

Dr. Juengst stated that the minutes of the March 2000 RAC meeting were a fair and accurate

representation of the proceedings of that meeting.

Committee Motion 1

The RAC approved a motion made by Dr. Greenblatt and seconded by Dr. Juengst to accept the minutes of the March 8-10, 2000, RAC meeting (with the incorporation of minor editorial changes) by a vote of 8 in favor, 0 opposed, and 0 abstentions.

III. Update on Recent Events and Issues in Human Subjects Protections and Gene Transfer Research

Introduction/Dr. Patterson

Dr. Patterson stated that, during the past few months, events have focused intense attention on GTR and human subjects protections, and GTR has become a lens through which the public, patients, and Members of Congress view the larger field of clinical research. The responses of the gene transfer community to these developments will be a model for other arenas of clinical research.

In February 2000, a congressional hearing was held on oversight of GTR. On May 25, 2000, the Senate Subcommittee on Public Health held a second hearing, which focused on the recommendations of the Inspector General about how to enhance human subjects protections and whether further legislation is needed to implement those recommendations. Dr. William F. Raub, Office of Science Policy, Dr. Lana R. Skirboll, Office of the Director, NIH, and Dr. Kathryn Zoon, U.S. Food and Drug Administration (FDA), testified at the second hearing for the Department of Health and Human Services (DHHS).

Dr. Patterson reviewed recent NIH initiatives related to enhanced oversight of GTR. The Office of Biotechnology Activities (OBA) has participated in an NIH Office of Extramural Research (OER) not-for-cause site visit program. These visits are being conducted to assess the level of institutions' and investigators' understanding of and compliance with NIH requirements in general and for human subjects protections and GTR in particular. Issues covered included understanding of the *NIH Guidelines for Research Involving Recombinant DNA Molecules (NIH Guidelines)* and current conflict-of-interest regulations.

One of the findings from the site visits confirmed that administrators and investigators in the academic community are confused about what should be reported to whom and when, particularly for multi-site trials and industry-sponsored trials. To further enhance the understanding and compliance of investigators with the *NIH Guidelines*, the OBA has contacted investigators, Institutional Biosafety Committees (IBCs), and institutions to reiterate the applicability, scope and requirements of the *NIH Guidelines*. OBA has also requested the submission of any previously unreported information required by the *NIH Guidelines*, including annual reports and adverse events (AEs), while noting the active exploration of harmonization of reporting requirements between the FDA and the NIH. Telephone followup is also underway.

The NIH is undertaking a number of new educational outreach initiatives, some in collaboration with the FDA, as exemplified by the recent satellite broadcast "Best Clinical Practices in the Era of Gene Therapy." As a major initiative to enhance patient safety, NIH and FDA are cosponsoring a series of patient safety symposia that will provide public forums for discussion of the most medical and scientific data from current clinical trials. The symposia will be held two to four times per year, involve leading experts in relevant disciplines, and focus on classes of research (e.g., vector, clinical indication, and patient population). The topic of the second symposium, planning for which is currently underway, will be safety issues in cardiovascular GTR.

Some Members of Congress and industry representatives have suggested to NIH that instituting national Data and Safety Monitoring Boards (DSMB) for all phases of GTR might be appropriate. The NIH is

currently assessing the feasibility and utility of one or more national DSMBs for Phase I and Phase II gene transfer clinical trials. A report on the outcome of this assessment will be provided to the RAC at a subsequent meeting.

Dr. Patterson concluded her remarks by acknowledging patient safety is the top priority for all concerned and that the challenges in GTR are not unique to this field alone. The promise to treat and perhaps cure certain diseases in the future is far too great, she concluded, for the GTR community not to rise to these challenges. The GTR field has an opportunity to be an example for other arenas of clinical research.

New U.S. Department of Health and Human Services (DHHS) Initiatives on Human Subjects Protections/Dr. William F. Raub, Office of Science Policy, DHHS

Dr. Raub reported on the efforts at the Departmental level to address the broader issues of human subject protection. He outlined five new initiatives in the following areas and noted that they relate to some of the issues raised in recent reports of the DHHS Office of the Inspector General on the system of human subjects protection.

- Education and Training. DHHS is undertaking a major effort to improve the education and training of clinical investigators, IRB members, and associated IRB and institutional staff. NIH, FDA and the Office for Human Research Protections (OHRP) (formerly the Office for Protection from Research Risks) will work closely together to ensure that all clinical investigators, research administrators, IRB members and IRB staff receive appropriate research bioethics training and human subjects research training. Such training will be a requirement of all clinical investigators receiving NIH funds and will be a condition of the NIH grant award process and of the OHRP assurance process.

- Informed Consent. NIH and FDA are issuing specific guidance on informed consent, clarifying that research institutions and sponsors are expected to audit records for evidence of compliance with informed consent requirements. For particularly risky or complex clinical trials, IRBs will be expected to take additional measures, which, for example, could include third-party observation of the informed consent process. The guidance will also reassert the obligation of investigators to reconfirm informed consent of participants upon the occurrence of any significant trial-related event that may affect a subject's willingness to participate in the trial.

- Improved Monitoring. NIH is now requiring investigators conducting smaller-scale early clinical trials (Phase I and Phase II) to submit clinical trial monitoring plans to the NIH at the time of grant application, and will expect investigators to share these plans with IRBs. The NIH already requires investigators to have such plans and they also require large scale (Phase III) trials to have Data and Safety Monitoring Boards (DSMBs). For research on medical products intended to be marketed, FDA will also issue guidelines for DSMBs that will delineate the relationship between DSMBs and IRBs, and define when DSMBs should be required, when they should be independent, their responsibilities, confidentiality issues, operational issues and qualified membership.

- Conflict of Interest. NIH will be issuing additional guidance to clarify its regulations regarding conflict of interest, which will apply to all NIH-funded research. DHHS will also solicit public comments and hold a public consultation on August 15-16, 2000 to find new ways to manage conflicts of interest so that research subjects are appropriately informed, and to further ensure that research results are analyzed and presented objectively. These public discussions also will focus on clarifying and enhancing the informed consent process. Based on these public forums, NIH and FDA will work together to develop new policies for the broader biomedical research community, which will require, for example, that any researchers' financial interest in a clinical trial be disclosed to potential participants.

- Civil Monetary Penalties. DHHS will be pursuing legislation to enable FDA to levy civil monetary penalties for violations of informed consent and other important research practices--up to $250,000 per clinical investigator and up to $1 million per research institution. While FDA can currently issue warning letters or impose regulatory sanctions that halt research until problems are rectified, financial penalties will give the agency additional tools to sanction research institutions, sponsors and researchers who do not follow federal guidelines. As an interim step, NIH, OHRP and FDA will work more closely together to enforce and target existing penalties. More attention to continuing review—Ensure that informed consent is delivered, documented, and renewed as appropriate.

Organizational changes within the DHHS include the transfer and renaming of the Office for Protection from Research Risks from the NIH to the Office of the Secretary as the Office of Human Research Protections (OHRP). Plans are also being made to establish a new public advisory committee to provide guidance to OHRP and the Secretary on human subjects protection issues. These changes reflect the DHHS' commitment to strengthening the Federal system of human subjects protection.

In addition, Dr. Raub noted that the National Bioethics Advisory Commission is assessing the entire system by taking a broad-based look at fundamental questions of human subjects protections. Its report is expected in late 2000 or early 2001.

Dr. Raub concluded his remarks by reiterating the importance of strong and sustained efforts to reform informed consent in clinical research. Because GTR raises many fundamental questions that are common to other fields, he suggested that RAC can make critical contributions to these reform efforts.

RAC Questions and Comments

Dr. Friedmann requested clarification about the civil monetary penalties initiative. Dr. Raub explained that this new mechanism would be simpler and quicker to apply than disqualification and would provide an additional punitive measure between "clinical hold" and "disqualification." Clinical holds are quick and effective but generally temporary. Disqualification, which can result in the end of an investigator's entire career, is a lengthy process that must involve due process. A civil monetary penalty would be a clear demonstration that wrong-doing had occurred while allowing resolution of the matter, assuming FDA is satisfied that the events in question will not recur.

Dr. Friedmann raised another question about the IRB as a mechanism for investigating conflict-of-interest issues, in light of the fact that such issues could affect the IRB's own institution. Dr. Raub acknowledged the point and stated that this issue is one of the many central issues that will be discussed during the public consultation in August 2000.

To Dr. Mickelson's query about what the NIH will be doing in cases of noncompliance, Dr. Patterson responded that the *NIH Guidelines* apply not only to investigators who receive direct NIH monies for a particular trial but also to privately funded investigators conducting trials at institutions that receive NIH funding for recombinant DNA research at the bench or in the clinic. The possible consequences of noncompliance with the *NIH Guidelines* include termination, suspension, a limitation of NIH funds to the institution, and/or the requirement for prior NIH approval for any or all experiments involving recombinant DNA molecules. At present, the NIH is exploring, with its legal counsel, additional enforcement actions and sanctions that can be instituted and, after consultation with the RAC and the NIH Director, will put in place a set of graded sanctions that will be broadly disseminated to all investigators and institutions.

Dr. Aguilar-Cordova asked whether the five DHHS initiatives apply to all trials, not just to those involving GTR. Dr. Raub responded that these issues are broadly applicable to research funded or

regulated by agencies of the DHHS.

Ms. Levi-Pearl raised a question about the kinds of protections of subjects in clinical trials that are supported entirely by corporate entities not connected with an institution that receives NIH funding. According to Dr. Raub, corporate entities that are pursuing the development of a product—such as a drug, vaccine, or biologic—for introduction into commerce fall within the scope of the FDA's regulations concerning human subjects protections. Dr. Noguchi added that he believes that all gene therapy sponsors who participate in the RAC process have been following FDA requirements. Moreover, he said he was aware of very few clinical gene therapy trials in the United States that take place at an institution that does not receive NIH funding for recombinant DNA research. Dr. Cynthia M. Dunn, University of Rochester Medical Center, asked whether industry-funded research conducted at community hospitals is regulated. Dr. Skirboll responded that such research is covered under the FDA's human subjects protections regulations. Ms. King pointed out that even though most gene transfer studies are covered by the *NIH Guidelines*, there is still a major educational gap among some community hospital investigators who do not understand the role of the RAC in relation to their research.

New FDA Requirements and Activities

Overview/Dr. Jay P. Siegel, FDA

Dr. Siegel provided an overview of new initiatives underway at the FDA. Two major initiatives are a March 6, 2000 "Dear Sponsor" letter that was sent to all sponsors of gene therapy investigational new drug applications (INDs) and an inspection program in gene therapy. The FDA is also working on the following initiatives:

- Modification of the FDA's AE reporting rules to increase consistency with international requirements
- New data disclosure rules to increase the FDA's ability to release information publicly
- Guidance for use by data monitoring committees
- Plans for organizational changes to emphasize human subjects protections
- Consultations with sponsors, investigators, and institutions to devise new ways of doing business

Data reviews and for-cause inspections in the fall and winter of 1999-2000 raised concerns regarding manufacturing practices (e.g., product testing, quality control), animal safety data reporting, and clinical practices (e.g., protocol adherence, reporting, standard procedures, documentation of informed consent). The March 6 Dear Sponsor letter and the gene therapy inspectional program were designed to assess the extent of and address such concerns. The due date for data and information requested by the March 6 letter was June 6, 2000. Most sponsors responded; some responses require followup.

Specific concerns that prompted the March 6 letter included incorporating evolving requirements into older protocols; incomplete submissions to the FDA, difficulty in accessing all the information about one protocol (which may be located in several places); and quality-control issues (e.g., lack of adequate quality assurance/quality control [QA/QC] programs; manufacturing QA/QC; and clinical trial monitoring and oversight).

The goals of requesting QA/QC plans include:

- Ensuring that the sponsor has a QA/QC plan

- Encouraging sponsors to rethink the adequacy of their plans and to formalize, document, and execute those plans

- Enabling the FDA to provide feedback and assistance where needed

- Accumulating and then disseminating information regarding best practices and dangerous practices

- Assisting with inspection activities

One question to be addressed by the responses to the Dear Sponsor letter is the extent of violations of good clinical practice (GCP), such as nonsubmission of relevant information to the FDA and the IRB, not amending the protocol or Informed Consent document as agreed, and lack of standard operating procedures for conduct of the trial and for training. The FDA hopes to determine whether there are specific risk factors and possible causes for their occurrence (e.g., an inexperienced investigator) of these violations.

The gene therapy IND inspection program grew out of concerns about the GCP violations observed during for-cause inspections. The intent of this program is to find and correct errors, increase awareness among all investigators of FDA's oversight, and gather information on whether the problems were isolated or widespread, the risk factors involved, any relation of problems to conflicts of interest or investigator inexperience, and whether problems are specific to GTR.

Product Manufacturing Requirements/Dr. Philip Noguchi, FDA

Dr. Noguchi reiterated that an experimental drug or biologic cannot be administered to a human without being authorized through an IND by the FDA, regardless of where that drug is being developed.

The March 6 Dear Sponsor letter was generated because:

- Gene transfer products are becoming more complex, using various regulated biological products. The issue is how to apply today's standards to older products.

- Safety testing required years ago is deficient by today's standards.

- Inconsistent amounts of product manufacturing information are being provided in IND applications.

- Problems with manufacturing and clinical trial oversight have been found during for-cause inspections.

Dr. Noguchi outlined the following information requested by the Dear Sponsor letter:

- History of manufacturing in the facility (clinical and noncritical)
- Cross-referenced files

- Lot release and characterization of all cell banks, viral banks, and final product

- QA/QC programs for manufacturing

- Clinical monitoring plans and oversight

- Animal safety information

- Submission of yearly update reports containing the information listed above

Since these reports were due to the FDA from sponsors by June 6, 2000, a comprehensive summary of the information received is not yet available. About 60 of the 250 expected responses, have not been submitted. The FDA plans to use the information to:

- Ensure that gene therapy products are adequately tested by contemporary standards

- Determine the state of the art of manufacturers

- Reevaluate the FDA's current recommendations to determine where product testing needs to be increased or decreased, whether additional guidance is needed, and where the FDA should concentrate its limited training resources

- Review updated information regularly

Clinical Trial Monitoring Plans/Dr. Karen Weiss, FDA

Dr. Weiss presented the new clinical trial monitoring requirements that what were outlined in the March 6 Dear Sponsor letter.

For each clinical trial contained in an IND, sponsors were required to submit information detailing procedures in place to ensure:

- adequate monitoring of the clinical investigations to demonstrate the trial is conducted in accordance with regulatory requirements and Good Clinical Practices (GCPs), and the protocol; that the rights and well-being of human subjects are protected; and that data reporting is accurate and complete

- adequate oversight of the clinical investigation, as outlined in 21 CFR 312, Subpart D

- confirmation that all animal safety information has been submitted as described in 21 CFR 312.32-33

Dr. Weiss noted that this information is designed to show whether the monitoring program assesses adherence to protocol (e.g., study eligibility, treatment plan, data collection for safety and efficacy); AE reporting, including requirement timeframes (e.g., IRB with authority, sponsor or the FDA if sponsor is also the investigator, the NIH/OBA); and informed consent requirements (e.g., IRB approval of written and other informed consent materials, informed consent form signed prior to entry into study, appropriate witness documentation). The requirement that the submission of all animal data be confirmed was included in the Dear Sponsor letter because of concerns of inadequate awareness about reporting animal safety information and as a reminder about preclinical data requirements.
Dr. Weiss reported that responses to March 6 request are still being received. A review of initial responses confirms that most information has been submitted as required. She then provided a list of specific items that FDA reviewers will examine in their analysis of the responses to the Dear Sponsor letter.

Regarding inactive INDs, Dr. Weiss explained that, although some discussions continue at the FDA, it is generally agreed that if all clinical studies are closed, no new patients are being accrued, and no patients are currently receiving an investigational product, it is acceptable to place an IND on inactive status. As a result, the sponsor does not have to submit certain types of annual reports. Before any inactive IND could

be resumed, a sponsor would have to supply to the FDA the information requested in the Dear Sponsor letter. Sponsors of all INDs, including those deemed inactive, must continue with their commitments for long-term follow-up of patients that require it.

Inspections Program/Joseph P. Salewski, FDA

Mr. Salewski described the FDA's bioresearch monitoring program. Each FDA center has a program that is charged with ensuring the validity and accuracy of any data submitted to the FDA in support of any application, as well as ensuring that the rights and welfare of study subjects are protected. A series of surveillance inspections is currently under way to gather additional information about the conduct of gene therapy clinical trials.

A survey is now being conducted to obtain a clearer view of how procedures are being followed. A random sample of 30 INDs has allowed the survey to gather information from 70 investigators; 93 percent of the surveys have been completed, and five of the selected INDs have not enrolled any subjects. These investigations are currently open, so results cannot yet be shared; however, the final document will be made available to the NIH and the RAC.

RAC Questions and Comments

Ms. King expressed concern that increased attention to clinical monitoring and the resulting increase in investigator education would become an unfunded mandate; investigator-initiated trials and trials conducted or sponsored by small companies might experience financial difficulties in adhering to enhanced clinical trial monitoring requirements. Dr. Siegel pointed out that institutions must ensure that IRBs receive adequate funding. Dr. Skirboll responded that the cost of monitoring a trial is part of the cost of conducting that trial, so the NIH assumes large portions of the costs. Dr. Raub agreed that monitoring that is specific to the trial should be included in the budget for that trial. He further stated that although these requirements may not be fully funded, they are not unfunded mandates. Approximately one-third of a typical research grant reimburses indirect costs, about half of which is reimbursement for administrative costs—the category that includes IRB expenditures. The DHHS is willing to engage in discussions that would include alternatives to the current cap on reimbursements of certain parts of indirect costs. Dr. Weiss added that the FDA is aware that new emphases on ongoing requirements might significantly drive up the costs of clinical trials; however, clinical trials are expensive, and sponsors must understand the costs of conducting them correctly. Dr. Belinda Seto, OER, indicated that when she hears administrators and investigators raise this concern, she asks them to think about the costs of *not* conducting educational efforts. In general, the costs of education are minor in comparison to the costs of remedying violations that have occurred.

To Dr. Aguilar-Cordova's request for the percentage of ongoing gene transfer clinical trials that are NIH funded, Dr. Patterson responded that 157 to 160 trials in GTR are NIH funded. Dr. Noguchi added that there are approximately 200 active INDs, each of which involves one or more active trials.

Dr. Aguilar-Cordova asked how the FDA will gather statistics for, and comparisons among, trials for which the state of the art of manufacturing is evolving continuously. He also asked about the standards to which older trials will be held. Dr. Noguchi responded by stating that the FDA has developed templates for the different vector classes and will be developing specific guidance for each vector class. Older trials will need to adhere to contemporary standards, and the FDA will work with sponsors to bring their products up to those standards. If necessary, the FDA will halt an ongoing trial until the new testing procedures are in place, and it has done so already.

In response to Dr. Dunn's question about monitoring the adequacy of the IBC review, Dr. Patterson

responded that the qualifications for membership on an IBC are spelled out in broad terms in the *NIH Guidelines* and that the NIH/OBA currently reviews these IBC elements. As chair of an IBC at the Massachusetts Institute of Technology, Dr. Mickelson noted that IBCs are meant to provide a transparent and overarching review of the research that goes on within an institution so that assurances can be offered to funding agencies such as the NIH, the neighboring community, and other interested parties. The IBCs are not linked to approval or initiation of trials via the FDA but through the NIH only, and it is the *NIH Guidelines* that provide IBCs with authority.

NIH Initiatives To Strengthen Human Subjects Protections/Dr. Seto, OER

Dr. Seto described the new NIH policy regarding the requirements for NIH-funded investigators to submit a monitoring plan for Phase I and Phase II clinical trials prior to the initiation of the trial. The data and safety monitoring (DSM) guidance document *(Notice OD-00-038: Further Guidance on Data and Safety Monitoring for Phase I and Phase II Trials)* elaborates on the June 1998 NIH DSM policy. The new requirement will become effective in October 2000 and is intended to augment the current requirements for safety monitoring that the NIH has in place for multi-site and Phase III trials. Dr. Seto discussed the additional guidance documents released by the NIH on June 5, 2000, regarding DSM in clinical interventions, required education in the protection of human research participants, and financial conflicts of interest and research objectivity.

There is a common understanding that Phase III trials will include DSMBs; for Phase I and Phase II trials, DSM committees do not have to take the structure of a board. However, multi-site trials should be encouraged to have a DSM committee in place and send the NIH a summary report of that committee's discussions.

The NIH currently supports thousands of clinical trials; some have hundreds of sites, and some have only one. The kind of monitoring needed for large and small trials is different. Because of the diversity of the NIH clinical trial portfolio, the principles underlying DSM center on higher risk interventions that deserve the attention of investigators and institutions and that are commensurate with the size and nature of the clinical trial. Individual NIH Institutes and Centers have flexibility with regard to how to implement the DSM policy and many have their own DSM policies. Beginning with the October 2000 receipt date, investigators for Phase I and Phase II trials must submit a detailed plan for DSM that is commensurate with the protocol. This additional guidance document does not take the place of guidelines from either the FDA or the NIH.

The required education guidance document *(Notice OD-00-039: Required Education in the Protection of Human Research Participants)* reads, "Beginning on October 1, 2000, the NIH will require education on the protection of human research participants for all investigators submitting NIH applications for grants or proposals for contracts or receiving new or non-competing awards for research involving human subjects." This policy establishes a base level of education and knowledge; key personnel in trials dealing with special populations are encouraged to have a level of education on protection of human subjects that exceeds the minimum standard.

The NIH does not plan to issue a list of "endorsed" programs, but a number of curricula are available to investigators and institutions. For example, an online tutorial, "Protection of Human Research Subjects: Computer-Based Training for Researchers" (http://helix.nih.gov:8001/ohsr/newcbt/), which was developed for the NIH staff can be downloaded at no cost and modified for use in other institutions. To facilitate education and the development of curricula, the NIH launched a Web site on bioethics in 1999, <http://www.nih.gov/sigs/bioethics/>. This site has more than 4,500 references on a broad range of relevant topics, including human subjects in research, medical and health care ethics, and the implications of genetics and biotechnology. This Web site also contains a broad set of annotated web links, including some attached to training programs.

The conflict-of-interest guidance document *(Notice OD-00-040: Financial Conflicts of Interest and Research Objectivity: Issues for Investigators and Institutional Review Boards)* discusses formation of a

new policy and the public consultation meeting on August 15-16, 2000 at the NIH. Hosted by the DHHS, "[t]his forum will afford an opportunity to discuss sharing of information on the conduct of clinical trials between IRBs and compliance offices that deal with institutional policies and procedures on investigators' conflict of interest. Other topics for discussion will include conflicts of interest pertaining to institutions, individual investigators, and IRB members."

Since 1995 the U.S. Public Health Service (PHS) has had regulations in place requiring the management of conflicts of financial interests. Although conflicts of interest at the investigator level have been widely discussed and studied, little is known about, or in place to address, conflicts of interest at the IRB and institutional levels. The August 2000 public consultation meeting should inform the NIH of additional guidance needed at all levels.

RAC Questions and Comments

Dr. Mickelson requested that Dr. Seto articulate the current NIH policy with regard to conflict of interest. Dr. Seto stated that the regulations currently place the responsibility on the institution. The NIH requires that institutions have policies and procedures in place to either reduce, eliminate, or manage a conflict of interest. When a faculty member discloses a financial involvement, NIH policy requires that the institution inform the NIH that it has either reduced, eliminated, or managed that conflict. The NIH is not informed of the nature of the financial involvement. Dr. Seto described the proactive compliance program involving 10 not-for-cause visits at institutions that have *not* been visited by the OHRP or other regulatory agencies. These visits also afford the NIH an opportunity to evaluate whether NIH policies are clear enough for others to understand. The institutions are also evaluated on their awareness of NIH policies on invention reporting, conflict of interest, and DSM. The NIH hopes that these 10 site visits will generate best practices that can then be shared with other institutions. Each year, another 10 institutions will be selected for these not-for-cause visits.

In response to Dr. Markert's concern about the educational requirement for key personnel who have nothing to do with the clinical protocol or with patients, Dr. Seto acknowledged that the educational requirement applies to only key personnel who are involved substantially in both the design and the conduct of the clinical trial. For example, an x-ray technician would not be required to participate in the program, although such personnel would not be excluded if they wished to take the course. Although this requirement is effective October 1, 2000, Dr. Seto explained that it is applied in a "just in time" fashion, meaning that grantees are not required to submit a letter indicating that they have taken the required course until the award is made. Dr. Seto also mentioned an ongoing program announcement on research ethics that the NIH has been funding since 1999. During the first year, 15 awards have been funded to develop short courses on research ethics.

American Society of Gene Therapy (ASGT) Position Statements and Policies/Dr. Savio L.C. Woo, ASGT and Mount Sinai School of Medicine

Dr. Woo, representing the ASGT for newly elected president Dr. Inder Verma, described the ASGT's positions and its recent efforts to enhance and optimize the protection of human subjects enrolled in gene therapy studies. The printed material provided to RAC members prior to this meeting represents recent policies and included the ASGT response to DHHS initiatives, the ASGT statement on SAEs, the ASGT statement on financial conflict of interest, and the ASGT ethical policy on clinical trials.

The ASGT is a strong advocate for regulatory compliance. However, from the investigator perspective, it is critically important for all Federal agencies to harmonize regulations completely. Mishaps occur when regulations are different, and Federal regulations that are not harmonized are a breeding ground for noncompliance.

The ASGT suggests that SAE data received by the OBA be identified as to their relationship to the gene transfer treatment, so the public can gain a true understanding of the safety of GTR. Unrelated SAE reports give an incorrect impression to the public. The meaning of "related" should also be harmonized between the FDA and the NIH.

Regarding financial conflicts of interest, the ASGT ethics committee produced recommendations that were adopted by the ASGT board of directors and published in the May 2000 issue of *Molecular Therapy*. In addition to Federal and institutional guidelines, the ASGT recommendations state that anyone who is directly involved with a patient should not have equity, stock options, or similar arrangements in companies that are sponsoring the trial. Whether the existence of such relationships would actually compromise the trial is irrelevant; it is the perception that is critical. ASGT has received no complaints about this policy from its members.

In response to the new DHHS initiative of May 23, 2000, the ASGT applauds the efforts to strengthen protections for human subjects and believes that these efforts should apply to all areas of medicine. The ASGT also embraces the education and training initiative. The informed consent initiative is critical; standard language should be used in Phase I studies, which precludes any promise of efficacy.

The ASGT supports inclusion of a monitoring plan in NIH submissions. Dr. Woo closed with two caveats about the cost of monitoring and the appropriateness of civil monetary penalties. Improved monitoring is important to ensure patient safety, but new plans and regulations should not incur excessive costs. Most GTR diseases do not have lucrative markets to attract investment, and the patient population will suffer if costs are increased substantially. Civil monitoring penalties may not be more effective than what is already in place. ASGT's position is that investigators and institutions should be held accountable for willful noncompliance and that institutions take immediate corrective action when they are threatened with discontinuation.

RAC Questions and Comments

In response to Ms. Levi-Pearl's query about whether the ASGT's ethics committee had defined "indirect financial interest," Dr. Woo reported that the indirect aspect of financial interest had been debated for a long time. Finally, the committee agreed that it was trying to put out an overall ethical statement, and it would not be possible for the ASGT policy to spell out the specifics of what would and would not be acceptable. The ASGT's objective is that anyone who interacts directly with a patient should have the patient's interest in mind; the Society will use its persuasive power to convince its membership to adhere to that high ethical standard.

Dr. Aguilar-Cordova asked whether the ASGT could participate in this discussion with other institutions such as the NIH, the FDA, or the OHRP, since it is a valuable source of scientific advisory expertise. Dr. Woo stated that the ASGT has submitted its recommendations to the NIH, the OBA, the FDA, and other agencies and has been advocating those positions to the responsible agencies on behalf of the entire GTR community.

Dr. Markert mentioned another aspect of the conflict-of-interest discussion—the case in which an investigator conducting a trial for a rare disease makes an invention and stands to profit if it works. Dr. Woo indicated that a policy statement such as the ASGT's cannot cover all instances. However, Federal regulations allow investigators to benefit financially through patented inventions and licensing; ASGT is concerned with the investigator who has equity positions in a company that sponsors the trial and who also conducts the trial.

Dr. Skirboll thanked Dr. Woo for his past leadership of the ASGT. She reiterated that NIH appreciates

ASGT's participation in the policy development process.

Clinical Investigator Training Program: Principles and Models/Dr. Cynthia M. Dunn, University of Rochester Medical Center

Dr. Dunn outlined some principles for clinical investigator training in the ethical conduct of clinical research and described the components of the University of Rochester's (UR) mandatory training and testing program and the events that led to its development. In 1996, a UR undergraduate student participating in a study as a "normal, healthy" volunteer died as a direct result of participation. Shortly before this incident, the FDA had cited the UR IRB for being under-resourced and its staff undertrained. Since the study in which the death occurred was federally funded, the OHRP investigated and found weaknesses in UR's human subjects protections program. UR's president responded by forming a blue-ribbon committee—the Committee on the Conduct of Human Subjects Research. After studying other prominent institutions' programs, the Committee found significant deficiencies in UR's program and concluded that UR should institute an intensive training program for all investigators in the ethical conduct of research with human subjects.

The training program is intended to aid researchers in the understanding of regulatory requirements and the ethical principles on which they are based. The program also highlights some of the especially sensitive ethical issues (e.g., vulnerable subjects, perception and research, role as researcher vs. health care provider) in clinical research. The program incorporates biomedical and behavioral issues relevant to the conduct of research involving human subjects, and the course manual focuses on the topics, regulations, and guidelines most pertinent to academic research, including the following modules:

- Historical perspectives on human subjects research
- Ethics and Federal regulations
- Roles and responsibilities of institutions in human subjects research
- Roles and responsibilities of the investigator and the study process
- FDA-regulated research issues
- Behavioral research issues
- Publication of study results
- An examination

Successful completion of this program (a score of 85 percent or higher on the exam) is a prerequisite for IRB approval of a new or ongoing study, regardless of funding source. The program is currently required for clinical investigators involved in more than minimal risk research, IRB administrative staff members, and IRB members and is being extended to study coordinators who administer consent. The UR is planning to offer a training program to other institution staff members who may meet subjects as they are checking in and during other miscellaneous encounters.

The training program has been well-received at the UR, with support at the highest levels. Whether the program has improved research at the UR is difficult to measure. Passing the final exam in this program is like obtaining a driver's permit—it forces drivers to learn the rules of the road but does not guarantee good driving. Nonetheless, the UR program has raised the standards for protecting human subjects—for

its researchers and for those at other institutions. The UR has made its training program available to individual investigators. The manual can be obtained through CenterWatch, Inc. at <http://www.centerwatch.com>.

RAC Questions and Comments

Ms. King asked why the UR program is limited to investigators involved in more than minimal research. Dr. Dunn responded that implementing the has been administratively intense (approximately 400 investigators have completed it thus far). In the future, some type of program might be developed for minimal-risk research. Recertification is required every 3 years.

In response to a question from Dr. Mickelson, Dr. Dunn said that at this point, the UR IBC members have not been required to take this course.

In response to Dr. Juengst's question about how the UR funds this training program, Dr. Dunn stated that this large expense comes out of the university's budget. Four years ago, the UR's human subjects protections program had a budget of $150,000; the current budget is more than $1 million. The money was not easily acquired, but it represents the recognition of the cost of *not* providing this program. Dr. Dunn stated that she keeps copies of the UR's past warning letters and the resulting press coverage to remind people of the value of funding the program.

Dr. Patterson asked how many other institutions have adopted similar programs and whether the UR anticipates modifications or augmentation of the current training program in light of recent events in GTR. Dr. Dunn noted that six other institutions have adopted the UR program, two of which have made the program mandatory on their campuses. More than 15,000 copies of the UR training materials have been distributed to public and private institutions and organizations. The UR is in the process of adding a section on GTR, including information on IBC review, and conflict of interest issues.

To Dr. Friedmann's question about whether the UR program targets training opportunities for genetic counselors, Dr. Dunn indicated that it does not specifically address that area. Dr. Friedmann further indicated that the genetic counseling community will be critical for the future of the gene transfer field; currently there is no such training for genetic counselors, and such training is needed.

Dr. Skirboll asked what happens when someone fails the exam at the end of the UR program. Dr. Dunn explained that an individual can retake the exam; so far, no one has failed the second exam. While the individual is in the process of passing the exam, no new protocol can be submitted, and an ongoing protocol can be suspended to new enrollment. If someone fails the exam twice, the person must undergo more intensive education.
In response to the questions asked by Drs. Patterson and Mickelson about clinical and data management endpoints, Dr. Dunn explained that the number of subject complaints has decreased since the UR instituted this program. The UR has also stepped up its internal auditing program and has found that the appropriate INDs are in place, which had not always been the case.

Recommendation

Dr. Markert recommended that this training would be useful for RAC members as they first become members of the Committee. Dr. Patterson stated that the OBA is planning a 1-day intensive training for new RAC members about the scope and content of the *NIH Guidelines* and other items; additional suggestions for the content of that training should be forwarded to her.

IV. Data Management/Dr. Greenblatt

Dr. Greenblatt reported that a total of 402 protocols had been submitted to the OBA; 14 new protocols were submitted to the OBA since the past reporting period, 13 of which were exempted from full review by the RAC. One protocol, *A Phase I Study of the Safety, Tolerability, and Activity of the Intrahepatic Arterial Injection of Escalating Doses of NV1020, a Genetically Modified Herpes Simplex Virus, in Patients With Hepatic Metastases of Colon Carcinoma*, will be reviewed at this RAC meeting.

Of the 402 protocols, 37 are gene marking, 363 are for gene transfer, and 2 are non-therapeutic. In terms of disease targets for the 363 gene transfer studies:

- 33 were for infectious diseases (principally HIV/AIDS).
- 49 were for monogenic diseases (cystic fibrosis [CF] was the most frequent).
- 36 were for other diseases (coronary artery disease and peripheral artery disease were the most frequent).
- 245 were for cancer.

SAEs

A total of 921 SAEs were reported during the reporting period February 11 to June 1, 2000. Many of these had been previously sent to the OBA in response to the special request for data on advenoviral vectors for the December 1999 RAC symposium. Most (76 percent) occurred prior to January 1, 2000. Of the 921, 103 (10.4 percent) were classified as unexpected and possibly associated with the study agent. Several of the protocols involve administration of vectors that contain genes for angiogenic factors, such as fibroblast growth factor (FGF-4) and vascular endothelial growth factor, which cause the formation of new blood vessels. The protocols are testing whether administration of these factors will result in new blood vessel formation and, thereby, mitigate disease. The SAE data shows that in three protocols (#9902-238, #9804-243, and #9811-271), patients given those vectors developed tumors.

Although it is not possible to attribute treatment with these vectors to the development of cancer because one of the patients had a familial history of colon cancer, Dr. Greenblatt pointed out that there is enough of a theoretical possibility that these factors could stimulate the growth of already existing tumors to warrant exclusion of patients with cancer. He indicated that, according to Dr. Noguchi, the FDA regards cancer is an exclusion criterion in these studies. He also pointed out the importance of consent forms for these protocols containing a statement about the possibility that these vectors may stimulate tumor growth.

Amendments and Updates

The OBA received 90 amendments since the past reporting period. Most of the amendments were minor, involving such matters as adding new study sites or new investigators, informing the OBA of protocol clarifications (mostly protocol inclusion criteria), changing dose modifications, and notifying the OBA that the protocols were closed or that the IND had been withdrawn. The OBA also received several updates concerning replication-competent retrovirus in transduced CD34+ cells, which were later determined to have resulted from contaminating DNA in the assay and not from the presence of replication-competent retrovirus.

OBA was also notified of the following updates:

- Protocol #9810-268, *Treatment of Patients With Stage 4 Renal Cell Carcinoma With B7-1 Gene-Modified Autologous Tumor Cells and Systemic IL-2*, reported that of 11 evaluable patients, one patient had a partial response and one a minor response.

- Protocol #9902-284, *Phase 1 Multi-Center, Single-Treatment, Dose-Escalation Study of Factor VIII Vector for Treatment of Severe Hemophilia A*, reported that the trial was placed on clinical hold by the FDA because a single PCR assay indicated the presence of retroviral vector in a semen sample from one patient; repeat of the assay on the same sample was negative, and the conclusion was that the initial result was a false positive.

- Protocol #9902-290, *Phase 1 Trial of Immunization Using Particle-Mediated Transfer of Genes for gp100 and GM-CSF Into Uninvolved Skin of Patients With Melanoma*, reported that the study was stopped because of vector plasmid contamination with a small portion of the simian immunodeficiency virus *nef* gene.

RAC Questions and Comments

Dr. Markert asked Dr. Greenblatt whether he found useful the additional approximately 750 SAE reports submitted to the NIH (and not required to be submitted to the FDA). Dr. Greenblatt responded that the reports are difficult to analyze without a database and that it would be easier to detect possible trends if the unrelated AEs were excluded. He said that it is difficult and sometimes almost impossible to assign attribution on a single event, especially when, as with some of the cancer trials, patients are receiving 10 or more different drugs concurrently.

Dr. Patterson offered some general observations about the attribution of an SAE to the experimental product. When an SAE first occurs, most investigators and sponsors err on the side of caution and label it "possibly associated." After lab test results and followup clinical evaluations are reviewed, the initial assessment can be refined. Some of the followup reports to SAEs labeled "possibly associated" and "unexpected" indicate that these events are relabeled "unrelated" or "unassociated." Regarding the database, Dr. Patterson reported that the first version of this database will be beta-tested on the Web this summer. However, this is a pilot; the NIH wants to engage industry, investigators, the public, RAC and other user groups to help identify the kinds of queries that might be performed using this database. A controlled medical vocabulary will be used. Advancing the field will be directly proportional to the quality of information submitted and analysis that is conducted on these data. Dr. Mickelson further explained that the goal is to have the large functional database online by the end of this year.
With regard to the report about a plasmid vector contamination in Protocol #9902-290 Dr. Noguchi reported that the FDA is now requiring that all plasmid vectors be sequenced in their entirety.

In response to Ms. Levi-Pearl's question about whether the SAE reports come directly to the NIH/OBA or through the FDA, Dr. Noguchi stated that they come directly to the NIH/OBA. He explained that if the information comes from the FDA, NIH/OBA is bound by FDA rules and cannot make the information public, whereas if the information comes directly to the NIH/OBA, it can be discussed publicly at RAC meetings.

Dr. Mickelson reiterated the importance of post-mortem examinations and the data they can provide.
Dr. Gordon then noted that there are unique issues about how to handle post-mortem examinations in a setting in which many unexpected AEs are taking place that have no medical precedent. Interpretation of post-mortem examinations within GTR will be a unique challenge.

Recommendations

Dr. Gordon recommended that a future RAC meeting include a presentation on the possible association of the development of tumors and growth factors. National Cancer Institute (NCI) experts in angiogenesis could assist in planning such a presentation. The December 2000 safety symposium on cardiovascular gene transfer research will provide an opportunity for further exploration of this and other issues.

Ms. Levi-Pearl recommended that the RAC be provided with information about the date on which the SAE occurred. This information could be part of the new database.

V. Discussion of Human Gene Transfer Protocol #0005-396: *A Phase I Study of the Safety, Tolerability, and Activity of the Intrahepatic Arterial Injection of Escalating Doses of NV1020, a Genetically Modified Herpes Simplex Virus, in Patients With Hepatic Metastases of Colon Carcinoma*

Principal Investigator:	Dr. Yuman Fong, Memorial Sloan-Kettering Cancer Center
RAC Reviewers:	Drs. Ando and Breakefield and Ms. King
Ad hoc consultant (Written Review Only):	Robert Warren, M.D., University of California, San Francisco

This protocol was selected for review by almost all RAC members because it is the first arterial administration of a replication-competent vector, because of the potential safety issues, and because of the novel route of administration. The principal investigator (PI) and sponsor representative provided a 15-minute presentation of this protocol, the reviewers discussed their concerns with time allotted for responses, and the RAC and the public presented additional questions.

Background/Protocol Summary

In the United States, more than 50,000 patients per year develop colon cancer that then spreads to the liver. Surgery offers these patients a one-third chance of cure, but the majority of patients have few effective treatment options. The average time to disease progression is 6 to 9 months, and overall survival is 12 to 18 months.

The primary objective of Protocol #0005-396 is to assess the safety and tolerability of single and multiple administrations of several doses of NV1020 in patients with colorectal metastases to the liver. The secondary objectives are to assess antitumor activity, immune reaction, and shedding of NV1020. NV1020, the virus used in this study, has been modified from HSV-1, which causes cold sores. HSV-1 is widespread in the human population, and infections are usually mild or asymptomatic. Occasionally HSV-1 can cause systemic illness and/or brain disease, but this usually occurs in newborn babies or in adults with poor immunity. HSV-1 disease can be controlled effectively with prescription antiviral drugs such as acyclovir or foscarnet. NV1020 has been extensively tested in animal models that mimic HSV disease in humans. These studies include tests in mice, rats, and owl monkeys. Owl monkeys are extremely sensitive to HSV infection; exposing these animals to HSV creates a resemblance to HSV infection in immunocompromised humans.

Studies of NV1020 have shown that the virus can kill or slow the growth of multiple types of cancer. In mouse models, injections of NV1020 directly into a tumor significantly inhibited tumor growth and prolonged survival compared with controls. NV1020 also has been shown to retard the development of liver tumors in a rat model of liver cancer.

To ensure that NV1020 would be safe if it were to migrate to the brain (the most sensitive organ for HSV

disease), NV1020 was injected into the brains of mice. Studies show that NV1020 is at least 5,000 times safer in the brain than wild-type HSV-1. Mortality has been observed in mice injected with high doses of NV1020, either into the brain or by infusion through the portal vein. However, direct injection of high doses of NV1020 into the liver of mice caused only mild illness at the time of infection and resolved quickly. The livers appeared completely normal when observed microscopically 1 month later.

Toxicity has also been studied in owl monkeys injected with NV1020 through the hepatic artery, the same route to be used in the clinical trial. Monkeys did not develop clinical signs or symptoms. Although viral DNA could be detected in other organs of the body, no infectious virus could be isolated. The starting dose for the proposed Phase I clinical trial is approximately 3,000 times lower, on a per-weight basis, than this no-effect dose in owl monkeys.

Dr. Fong explained the rationale for choosing this study group:

- Colorectal cancer is a common disease.
- Tumors are sensitive *in vitro*.
- Even advanced disease is often confined to the liver.
- Patients with measurable disease often have good performance status.
- Patients will be undergoing surgery.
- The liver has a dual blood supply.
- The hepatic artery is easily accessible angiographically.

Safeguards of this protocol include:

- A low starting dose (5,000 times less than the lowest effective dose seen preclinically).
- Dual blood supply of the liver
- Direct perfusion of only half of the liver
- A long period of inpatient monitoring
- Availability of acyclovir
- Involvement of the infectious diseases specialists at the clinical trial site
- Review of data with a gene therapy committee prior to multidose testing

RAC Discussion

Drs. Ando, Breakefield, and King were the primary reviewers of the protocol. They submitted written reviews which were shared with the investigators prior to the meeting.
Dr. Breakefield's written review focused on the degree to which efficacy has been demonstrated in a preclinical model of liver metastases; the investigators' claim of similarity of the NV1020 virus to herpesvirus vector G207; interpretation of the relative toxicity of the virus prepared by different methods in Aotus monkeys; insufficiency of data presented regarding the replication of NV1020 in tumor cells compared with normal liver cells in culture; toxicity and safety in Aotus monkeys, including insufficiency of data concerning the extent of NV1020 attenuation compared with wild-type virus; subject inclusion and eligibility criteria concerns; duration of subject sequestration; and concerns about drug control of herpes simplex virus type 1 (HSV-1) encephalitis.

Dr. Breakefield focused her oral comments on the nature of the virus and the toxicity data. This protocol is one of the first to use a replication-competent herpesvirus in humans, and the virus is being administered via the hepatic artery, which in the case of adenovirus, can cause severe toxicity. Her specific concerns related to (1) the difference between G207 and NV1020 in terms of attenuation and the fact that NV1020 is a more potent virus; (2) whether R7020 and NV1020 are identical, especially since much of the provided data are related to R7020 and not NV1020; (3) researchers' ability to detect wild-

type virus at a reasonable rate; (4) owl monkey data showing differential toxicity depending on how the virus is prepared; (5) mice toxicity data that varied depending on the route of administration and that showed extensive liver bleeding and necrosis; (6) whether the vaccination trial showed reactivation of wild-type virus; and (7) conditions under which there would be concern about the infectability of liver cells.

Dr. Ando's written review focused on whether preclinical studies exist that show that the intrahepatic arterial injection of the virus will affect an established hepatic metastasis; alternative treatment options for these patients; questions surrounding chemotherapy pump placement and the timing and coverage of the costs of chemotherapy; prescreening tests for immune competence; the effect of preexisting immunity to HSV on vascular delivery and efficacy/safety; aggressiveness of the dose escalation of patient cohorts; and separating this protocol into two studies—a single-dose study and a multiple-dose study.

Dr. Ando's oral comments centered on: (1) insufficient data about liver-associated necrosis or damage, based on half-log increments; (2) use of half-log vs. arithmetic increments, with the latter providing better safeguards; (3) whether the patients will receive chemotherapy and who will pay for the pump to deliver those treatments; (4) inclusion in the consent form of the potential for total lymphoid irradiation complications; (5) testing for minimal CD4 counts to ascertain immune competence; (6) inclusion of a table of systemic AEs and lab abnormalities in grades 1 through 4; and (7) breaking this study into two trials, the first of which would establish the safety and side effects of chemotherapy in combination with multiple doses of NV1020.

Ms. King's written review focused on statements in the informed consent form about the potential for direct benefit to subjects; differences in statements of the goals of the study among the consent forms, the protocol, and the Appendix M responses; confusing language in the consent forms about the risks of NV1020, which could mislead potential subjects; and inappropriate word choices in the informed consent, such as "patient" and "treatment" which should be replaced with more appropriate terms such as "subject" and "NV1020 injection."

Ms. King's oral comments centered on the informed consent form. Her concerns included: (1) limiting enrollment to subjects without extrahepatic metastases; (2) overstatement of the potential for direct benefit to subjects; (3) use of "patient" and "treatment" language, which should be changed to "subject" and "receiving the NV1020 injection," respectively; (4) the existence of adequate preclinical data; and (5) separating this trial into two trials (a concern similar to that of Dr. Ando).

RAC Questions and Comments

Responding to one of Dr. Breakefield's questions about the relationship between R7020 and NV1020, Dr. Richard J. Whitley, co-investigator at the University of Alabama, Birmingham, explained that NV1020 is a clonal derivative of R7020 developed as an HSV-1 vaccine candidate. He discussed the use of R7020 into humans and his concern about delivering a genetically engineered replication-competent virus into a host that subsequently becomes immunocompromised. (The original experiments with R7020 were being conducted at the time that HIV was first being identified.) To alleviate this concern, Aotus monkeys were immunized with as much virus as possible (10^7) by four routes—intravaginally, subcutaneously, intraorally, and intracerebrally. The monkeys exhibited no signs of disease from the injected virus. The researchers then immunosuppressed the monkeys to determine whether the researchers could reactivate R7020 and cause disease. Disease did not occur in this experiment, nor did it in a second experiment in which researchers first immunosuppressed the animals and then gave them the same quantities of virus by the same four routes. With that degree of confidence, the researchers believed they had an attenuated virus that was safe for human studies.

Dr. Fong addressed some of the questions posed by the RAC reviewers. He explained that, although the

livers of these subjects are diseased, the hepatocytes and all other cells in the livers usually function normally nonetheless; the researchers know this through study of liver regeneration, magnetic resonance spectroscopy, and a wide range of metabolic studies. Dr. Fong also addressed the other concerns stated of RAC reviewers, including:

- Dr. Fong stated that third-party payers are willing to pay for salvage/regional chemotherapy by pump.
- Dr. Fong agreed with the RAC reviewers' concerns regarding dose-escalation. He explained that at some point, using clinical parameters, the researchers will move to an arithmetic progression rather than continue at the half-log dose escalation.

- All of Ms. King's concerns about informed consent form/process will be incorporated. A revised version of the consent form had not yet been provided to the RAC; since it must be approved by 27 local committees, Dr. Fong wanted to wait until after the RAC meeting to be able to incorporate all the changes at one time. Dr. Fong prefers to change "patient" to "patient/subject," because he believes there is an element of the doctor-patient relationship in this trial. The researchers will provide a copy of the revised consent form to the RAC.

- In most patients considered for salvage/regional chemotherapy, disease can be found only within the liver.

- Even with all possible scanning, 10 to 15 percent of patients will have some small amount of disease outside the liver that is not visible through scanning and that only becomes detectable after these patients have been operated on (which occurs after the first administration of virus). These 10 to 15 percent of patients will not be removed from the study because they will already have suffered the greatest risk—administration of the virus—and continuation on protocol would be more beneficial.

Dr. Aguilar-Cordova stated that most patients are HSV serum positive but questioned how the researchers will handle seronegative patients. Dr. Fong responded that it is unknown whether seronegative patients will experience higher toxicity, which is why this trial is starting at such a low dose of virus. Seronegative patients will not be ruled out because they might have the most positive responses. Researchers will keep track of titre levels and will correlate them with toxicity.

Dr. Friedmann questioned the efficiency of regional injection and whether the liver's other lobe would become infected. Dr. Fong answered that some circulating virus is found during the first 30 to 40 minutes after injection, indicating that something is being delivered to other organs. Some blood vessels cross from one side of the liver to the other. By injecting the virus directly into one side of the liver, researchers believe they will deliver more virus to that side compared with the other, an effect that is difficult to demonstrate in animals.

In response to Dr. Aguilar-Cordova's concern about the maximum number of wild-type doses that could be administered, Dr. Fong stated that any contamination would occur either during manufacturing or recombination within the patient. The dose being delivered would not have high levels of wild-type virus. No one has administered wild-type herpes virus on a voluntary basis. These viruses are extremely stable, and the researchers indicated that they could not imagine how wild-type viruses would appear. Dr. Noguchi pointed out that no one can state with certainty that this event would never happen.

Dr. Jeffrey M. Cohen, OHRP, reiterated the importance of subjects understanding that they are participants in an experiment from which they may not derive any direct benefit. Phase I decisions are made in the interest of science and not necessarily in the best interests of individual subjects. Investigators should separate their roles as researchers from their roles as physicians.

Dr. Friedmann asked how useful it would be to have proof of the concept of regional delivery, not

necessarily using the same vector. This might be an important safety measure, but no experimental proof yet exists. Dr. Fong responded that vasculature in nonhuman animals makes it difficult to thread a catheter into only one side of the liver. Researchers do know that some substances can be delivered successfully to one tumor or to one side of the liver; the question is whether this delivery can also be accomplished with viruses.

Dr. Woo asked whether mice can be given acyclovir at $5x10^7$ to prevent death. Dr. Fong responded that no toxicity has been observed from any level of acyclovir, and death can be prevented for almost all animals.

Dr. Friedmann reiterated his concern about using the issue of regional distribution as a selling point for safety; he suggested deleting it because it is an experimental question. The researchers agreed to do so.

Public Comments

No public comments were offered.

Recommendations

RAC members offered the following recommendations to be included in the letter to the investigators:

Stratify subject population according to the status of serum neutralizing antibodies against NV1020. The virus should not be administered to serum negative subjects until the first group of serum positive subjects has been treated; data from serum positive subjects should not be used as the basis for dose-escalation of the serum negative subjects.

Develop a monitoring plan to detect any harbingers of toxicity including cytokine profile and liver function tests, e.g., alanine transaminase (ALT), in order to determine when to change the dose escalation from the logarithmic to arithmetic increments. The plan should include polymerase chain reaction (PCR) monitoring of cerebral spinal fluid for virus in subjects with any signs of neurologic dysfunction.

Determine the specificity of the test for the presence of a wild type virus in the preparations to be administered to subjects and continue studies to determine the maximum safe dose of wild type in suitable animal models. Consult with the FDA pharmacology/toxicology staff on the level of wild type virus contamination that is permissible in the trial.

Consult with the FDA pharmacology/toxicology staff with regard to the adequacy of the preclinical data, especially in view of a sharp threshold effect in mice and a 50% toxicity record in Aotus monkeys. Perform additional toxicologic studies in nonhuman primates, e.g., Aotus monkey, if so indicated.

Address the issue of liver toxicity of the virus. A test should be performed to determine the extent to which the virus replicates in human liver cells compared to replication in the target tumor cells; the investigators indicated that such a test has been planned pending the delivery of the hepatocyte cell culture.

Discuss with Dr. Robert Warren, University of California at San Francisco, about hepatic administration of an adenovirus and the monitoring plan to detect any harbinger symptoms such as hypotension, in the dose escalation study.

Consult with Ms. King regarding amendments to the informed consent document. Ms. King noted four areas of concern including potential for direct benefit, emphasis on tumor effects outside the liver, clarity of risk descriptions for NV1020, and potentially misleading consent form language.

Committee Motion 2

A motion was made by Dr. Aguilar-Cordova and seconded by Dr. Markert to include the above RAC recommendations in a letter to the investigators. This motion passed by a vote of 11 in favor, 0 opposed, and 0 abstentions.

VI. Final RAC Review of Summary Recommendations of the Adenovirus Safety and Toxicity Working Group/Dr. Mickelson

Dr. Mickelson reviewed the Working Group's summary document titled "Consideration of the Final Draft Recommendations." RAC approval is needed to develop this summary into a full report.

Recommendations

RAC members made the following recommendations:

- The informed decisionmaking item (#6) states, "Patient advocates should be part of the informed consent process"; this wording needs more discussion, as this may affect the *NIH Guidelines*. GTR should not be treated differently from other research areas. The informed consent process should be left to the discretion of the OHRP. Change "should be part of the informed consent process" to "may be part of the informed consent process" and change "patient advocates" to "participant advocates."

- The data and information item (#7) should ask for harmonization as much as possible. A common format would make it easier to assess the information.

- The study controls item (#4) uses the term "controls," which can imply scientific robustness. If there are only 12 subjects, for example, this term might be misleading. This item should state that the use of controls should be meaningful. The phrase "whenever possible and practical" should be removed.

- Each appearance of the word "patient" should be changed to "research subject."

Dr. Patterson suggested a process for finalizing the recommendations whereby a small number of RAC members would serve as final reviewers for each of the seven items in these final draft recommendations. The OBA will incorporate the final reviewers' comments and then circulate the revised recommendations to the entire working group (which is composed of 18 to 20 members and includes most of the RAC members). The working group must report back to the RAC with its final report. Volunteers to review each of the seven major points were as follows:

Clinical trials using adenoviral vectors—Drs. Mickelson and Gordon

Standards—Drs. Aguilar-Cordova, Gordon, Greenblatt, and Noguchi

Vector systems—Drs. Aguilar-Cordova, Steve Bauer (FDA), Friedmann, Gordon, and Noguchi

Study controls—Drs. Aguilar-Cordova, Breakefield, and Gordon

Clinical monitoring—Drs. Aguilar-Cordova, Ando, Friedmann, Gordon, and Noguchi/Weiss

Informed decision-making—Dr. Gordon, Dr. Juengst, Ms. King, Ms. Levi-Pearl, Dr. Macklin, and Dr. Markert

Data and information—Drs. Ando, Gordon, and Mickelson

Committee Motion 3

Moved by Dr. Juengst and seconded by Ms. King, the RAC approved proceeding with this working group draft, with the suggested changes as listed in the recommendations above, by a vote of 11 in favor, 0 opposed, and 0 abstentions.

Committee Motion 4

Moved by Dr. Gordon and seconded by Dr. Aguilar-Cordova, the RAC approved the process of reviewing the final draft by the above-listed volunteers by a vote of 11 in favor, 0 opposed, and 0 abstentions.

VII. Day One Closing Remarks/Dr. Mickelson

Dr. Mickelson thanked the participants and adjourned the first day of the June 2000 RAC meeting at 5:30 p.m. on June 28, 2000.

VIII. Day Two Opening Remarks/Dr. Mickelson

Dr. Mickelson opened the second day of the June 2000 RAC meeting at 9:05 a.m. on June 29, 2000. The agenda for this day focused on examining the roles of the RAC and the NIH.

IX. Role of the NIH in Gene Transfer Research: Looking to the Future

Report From the ACD Working Group on NIH Oversight of Clinical Gene Transfer Research/Dr. Stuart H. Orkin, cochair, Harvard Medical School

Constituted before Dr. Harold Varmus left his position as Director of the NIH, the ACD Working Group met four times and engaged in many conference calls and e-mail sessions. Dr. Orkin provided an overview of the ACD Working Group's charge and focused his remarks on two main aspects—protocol review and AEs. He then commented on other items in the final report that were not part of the ACD Working Group's initial charge.

The ACD Working Group was charged with answering the following four questions:

1. Is the current NIH framework for oversight and public discussion of clinical GTR appropriate, especially with regard to the respective roles of the RAC and the NIH?

2. Are current NIH mechanisms adequate for coordination of the oversight of clinical GTR with the FDA, the OHRP, IRBs, and IBCs?

3. Are additional NIH measures needed to minimize risk associated with clinical GTR?

4. What should the NIH role be with regard to reporting, analysis, and public discussion of SAEs?

Dr. Orkin noted that the strength of the ACD Working Group was that the membership cut across many different areas—laboratory research, clinical research, public interest, ethics, the FDA, and industry. Unanimous agreement was difficult to obtain. The interim report of the ACD Working Group was presented to Dr. Ruth Kirschstein, Acting NIH Director, a few weeks ago at a Director's meeting.

ACD Working Group principles were constituted by the group as follows:

- The field of human GTR should meet the highest ethical and scientific standards.

- Human subjects who participate in clinical gene transfer should receive maximum possible protection by investigators, institutions, and oversight agencies.

- Human subjects in gene transfer trials should be provided fully informed consent and should be provided with synoptic, up-to-date information regarding the potential benefits and risks of any gene transfer procedures or possible therapies.

- All risks, AEs, and outcomes in clinical gene transfer trials should be monitored, interpreted, and communicated in a timely fashion to current and prospective subjects, the public, investigators, IRBs, and research sponsors.

Protocol Submission

The current protocol submission process to the NIH can result in the RAC being bypassed entirely. Some protocols have begun before the RAC has had a chance to deliberate. As a result, deliberations at RAC meetings, although interesting and useful, may not inform the process as much as possible, and provision of advice may be diminished.

The ACD Working Group's proposed change in this process will ensure that no patients are treated in a protocol prior to completion of the RAC review process and that investigators inform the RAC regarding the final FDA-approved protocol, the final IRB-approved informed consent document, and responses to RAC recommendations.

The ACD Working Group's proposed model for NIH review of gene transfer protocols would ensure that no protocols requiring full RAC discussion begin prior to such discussion since few institutions would want to grant final approval to a protocol without RAC input. In addition, a mechanism for feedback to the RAC will be instituted. These changes will foster accountability without having to implement strict approval or disapproval.

SAE Reporting

Dr. Orkin outlined the ACD Working Group's goals for SAE reporting:

1. Allowing public discussion of SAEs as an important component of the oversight process

2. Maximizing subject protection and safety

3. Deriving maximum benefit from clinical experiments/trials

4. Making SAEs public and not considering them as trade secrets

5. Establishing streamlined, uniform reporting and analysis of SAEs as a goal, including:

    - Public disclosure
    - Protection of subject privacy
    - A single "home" for SAEs

- Harmonized rules for reporting (timing, criteria)
- Electronic reporting (into database of gene transfer trials)
- Critical analysis of trends that will inform various stakeholders such as the public, the RAC, and the NIH

Dr. Orkin also presented three minority views that were discussed within the ACD Working Group: (1) only the FDA should receive and analyze SAEs (a view supported by the FDA and industry representatives), (2) establishment of a national DSMB, and (3) presentation of SAEs as raw, unanalyzed data.

Consensus Views

Dr. Orkin presented the consensus views of the ACD Working Group as follows:

- Because the FDA is unable to disclose information, the NIH/OBA should continue to receive reports of SAEs.

- SAE data should be interpreted in context to be meaningful to the public and to inform decisions for the future.

- Reporting requirements should be harmonized between the NIH and the FDA. Until resolution of differences is accomplished, the NIH/OBA should receive reports identical to those sent to the FDA.

- A standing committee should be established to identify trends and recognize patterns, report to the NIH/OBA/RAC, and discuss issues in the public domain. The function of this standing committee would be to serve the RAC and the public. (Various options for the placement of such a standing committee were discussed by the ACD Working Group. The majority of the ACD Working Group members favored a committee that would report to the RAC but would not be a subcommittee of the RAC and that would be composed of some RAC members, officials of the FDA, basic scientists, clinicians, patient advocates, and ethicists.)

The ACD Working Group also discussed the fact that academic medical institutions have weak infrastructures for monitoring and educating investigators and problems arise from lack of training. The NIH should be encouraged to provide support for infrastructure and training/education at institutions.

No direct recommendations were offered by the ACD Working Group regarding conflicts of financial interest, but the group suggested that the NIH and others make a concerted effort to review this problem. Current policy allows the home institution's rules to apply, but institutions vary significantly as to what is allowed. A broad national consensus on this issue is needed.

RAC Questions and Comments

Regarding several questions about the proposed SAE analysis standing committee, Dr. Orkin stated that the ACD Working Group had not specified how often this standing committee would report to the RAC. The Working Group envisioned a quarterly or semiannual report to present the trends to the RAC so that it could then discern which areas needed attention and further discussion. The standing committee would have access to all SAEs reported to the OBA and would not be beholden to the FDA in any way, although it would not necessarily analyze SAEs on a real time basis as does the FDA. Dr. Orkin clarified that the function of the standing committee would be to serve the RAC and the public. In future, the RAC would look at protocols and trends, discuss scientific and ethical issues, and discuss (but not analyze) SAEs.

Dr. Aguilar-Cordova asked why the OHRP was left out of the discussion of who would receive reports of SAEs. Dr. Orkin responded that the Working Group had some difficulty figuring out where the OHRP would fit into this process. It was Dr. Orkin's sense that the Working Group wanted to keep this standing committee more allied with the NIH than with other agencies, in part because it was charged with examining NIH oversight. Dr. Cohen clarified that the OHRP's authority does not apply to all IRBs and does not apply at all to research at institutions that do not receive Federal funding; the OHRP's authority is limited to Federal funding and to institutions that voluntarily agree to accept 45 CFR 46. However, given the DHHS Secretary's announcement that the OHRP is to be a nexus and focal point of human subjects protection for funded and regulated research of the DHHS, Dr. Cohen believes it is critical that the OHRP be represented on the standing committee on SAEs.

Dr. Noguchi explained that the FDA's advisory committees generally provide advice about the licensing of a specific product. The transcripts of those committee meetings are publicly available in unedited versions on the FDA Web site. He added that the FDA is currently working on a rule to allow more public disclosure by the FDA of AEs and of the information the RAC normally receives. Although the FDA might have some concerns about SAEs being disclosed publicly before all of the information is in, it has always been supportive of public discussion of AEs and protocols because that discussion has moved the field forward. The FDA has worked with the RAC to disclose more information in gene transfer than in any other field it regulates.

Dr. Gordon expressed concern about a key issue that is not fully resolved by the ACD Working Group report—the standardization of the process of SAE reporting. Dr. Orkin agreed, stating that one of the first suggestions by Working Group members was that SAE reporting should be conducted electronically; this process should be a goal, as it is not yet available.

Dr. Aguilar-Cordova requested that the FDA refresh the RAC members' memories about the numbers and composition of the people at the FDA who review AEs as they come in, as well as how many AEs are reported in a given month. Dr. Weiss responded that her division comprises approximately 30 physicians with varying expertise, each of whom reviews applications related to their expertise. Each of those medical officers has under his or her purview approximately 100 different INDs including products beside gene transfer such as monoclonal antibodies. During an average month, Dr. Weiss stated that every medical officer sees a reasonably large number of AEs, including expedited reports, summaries, interim reports of aggregated data, annual reports, and protocols and their modifications. Dr. Aguilar-Cordova was concerned that the recommended standing committee would be duplicating FDA efforts. Dr. Orkin assured the RAC that the standing committee would be complementary, not redundant, to FDA efforts.

Dr. Woo presented the ASGT's response to the ACD Working Group report by responding to the consensus views. Continued public disclosure through the NIH is appropriate but should be revisited if the FDA makes changes to its guidelines to allow public disclosure of SAEs. Public discussion is very important. ASGT members do not mind that GTR is in the forefront regarding SAE reports, but they hope GTR will not be the only research in the public purview indefinitely; there is no inherent difference between GTR products and other experimental biologics, drugs, and devices. Harmonization is critical and will help investigators immeasurably. Toward that end, the ASGT hopes that the OHRP will buy into the AE reporting system as well, so that one report can be filed for all three agencies. Regarding the new standing committee, raw data are not helpful to the public; this committee should be analytical and not regulatory.

In response to Dr. Breakefield's query about the meaning of novelty, Dr. Orkin explained that the ACD Working Group concluded that the existing criteria for "novel" are not well articulated and need to be refined. Other definitions that also require refinement are "recombinant DNA" and "gene transfer," primarily because the field has changed. Providing appropriate specifications/definitions was deemed to

be within the purview of the RAC. In addition, the Working Group discussed the issue of how many RAC members should be required for a novelty vote to trigger public discussion; the general sentiment was that a larger fraction of the RAC than the current three votes would be more appropriate.

Noting that the package provided to the RAC members contained a letter from the Cystic Fibrosis Foundation, which has a DSMB that oversees CF studies, Dr. Greenblatt suggested that someone from the Foundation could provide a model for how such a committee could be constituted to oversee AEs.

Dr. Aguilar-Cordova commented that the issuance of the ACD Working Group's report approaches giving the RAC its most appropriate charge—to review trends and issues and then develop policy from those trends and issues. The RAC is not a regulatory body and should not be policing the application of its policies.

Dr. Friedmann asked about the international set of recommendations on harmonization. Dr. Weiss responded that the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) has been in existence for about a decade. It comprises regulatory bodies and pharmaceutical representatives from three major regions of the world: the United States, the European Union, and Japan. The ICH Steering Committee and its technical Expert Working Groups convene several times a year (most recently in Brussels on July 19-20, 2000), with the goal of harmonizing technical requirements for product quality, preclinical testing, and clinical testing. Among the outcomes of the ICH has been the development of published guidelines that are available on the ICH Web site (www.ifpma.org/ich1.html). The guidelines on AE definitions and reporting requirements, known as *ICH-E2A*, were developed and published in the early 1990s; these definitions and reporting requirements are harmonized throughout the regions of the world and have largely been adopted by the FDA. Dr. Patterson reminded those RAC members who were on the Serious Adverse Events Working Group that they were provided with a primer and notebook that contained the ICH document; other RAC members desiring a copy of this document can obtain one through the OBA.

Dr. Gordon commented that the RAC is a body that not only identifies trends but also serves as a public forum to reassure the public that information, whether positive or negative, is accessible.

Dr. Markert questioned whether the sponsors could report to the NIH, thus harmonizing reporting responsibilities with the FDA. Dr. Skirboll responded that the NIH has no authority over a sponsor, only over an investigator, whereas the FDA's responsibility is to interact with the sponsor, with no authority over the investigator. Dr. Mickelson pointed out, however, that the NIH can accept reports from a sponsor, but that the NIH would place the responsibility for ensuring reporting on the investigator.

Dr. Patterson asked Dr. Weiss to describe the reporting forms used by the FDA, with the goal of sponsors and investigators eventually needing to fill out only one form and submit it (on paper or electronically) to both the FDA and the NIH. Dr. Weiss explained that the FDA's standard "Medwatch" form is sometimes used by investigators to report serious adverse events even though it is actually designed for postmarket AE reporting. The NCI has a form for submitting AE information. For the majority of other applications, the FDA receives AE information in a narrative format. Although requiring a specific form is a major event in government, Dr. Patterson stated that a top priority should be for the involved agencies to work together to agree on the format and type of information required in an AE report. Dr. Weiss agreed that this goal should be undertaken, that an outline of the types of information and the format is achievable, and that achieving this goal would be helpful.

Dr. Markert asked about the effectiveness of IBCs as oversight bodies and suggested that a review of the role and effectiveness of IBCs might be warranted. Dr. Mickelson agreed that some sort of review of these issues should take place. Dr. Patterson noted that, in part through information gathered through the

not-for-cause site visits and meetings with IBC administrators, OBA is aware of the need for further interactions with and training programs for IBCs. Moreover, OBA is currently developing an enhanced outreach and oversight program for the IBC community and would welcome specific suggestions from RAC members, IBCs, and the public on strategies for enhancing IBC oversight.

Dr. Greenblatt said that he was pleased with the ACD Working Group's recommendation that protocols should not start without RAC review and that responses to RAC recommendations should be provided by investigators. He also agreed that education is needed among investigators about what should be reported to IBCs.

Ms. King noted that IRBs do not want the RAC to do their job but want the Committee to be available to provide guidance at appropriate points during the approval process. The RAC's place in the flowchart developed by the ACD Working Group will encourage communication between IRBs and IBCs and give IRBs an opportunity to state in their approval letter that approval is conditional on the RAC's action. To assist IRBs, letters sent by the RAC in response to the 90 percent of protocols that do not require public review should include a summary of RAC members' concerns.

X. Announcement: Farewell to Ms. Becky Lawson/Dr. Patterson

Dr. Patterson announced that Ms. Becky Lawson, OBA, will be leaving Government service shortly, after 25 years. Dr. Patterson presented Ms. Lawson with a dozen roses and heartfelt thanks for her work in support of the RAC.

XI. Report From the RAC Serious Adverse Events Working Group/Dr. Mickelson

Dr. Mickelson presented the report of the RAC SAE Working Group on behalf of its chair, Dr. Macklin, who was unable to attend this RAC meeting.

Dr. Mickelson summarized the timeline for the SAE Working Group. At its September 1999 meeting, the RAC recommended that protocols and SAEs should not be treated as confidential information and that the public should have access to information about SAEs. The RAC also agreed that patient privacy and confidentiality should be protected as should the confidentiality of proprietary/commercial confidential information, such as trade secrets. The RAC SAE Working Group that was formed at that meeting, with Dr. Macklin as chair, presented a discussion of the issues at the RAC's December 1999 meeting. In March 2000, Dr. Macklin presented the Working Group's recommendations on SAEs. Much discussion ensued, with a wide range of opinions among RAC members, about whether the scope and timeframe for reporting to NIH OBA should be harmonized with FDA's requirements.

Dr. Aguilar-Cordova proposed an addition to the *Points To Consider* to replace current wording in the *NIH Guidelines*:

> "To facilitate the acquisition and dissemination of data concerning adverse events related to gene therapy, the RAC maintains a public database. As an investigator, you are required to submit adverse events to the Office of Biotechnology Activities as described in the *NIH Guidelines*. As an alternative, you could authorize the Food and Drug Administration to forward to the Office of Biotechnology Activities all adverse events related to gene transfer associated with this protocol and derivatives of it. Do you authorize transfer of adverse events from the Food and Drug Administration?" (followed by a box to check YES or NO)

Dr. Aguilar-Cordova offered to reword and simplify his proposed addition as follows: "The OBA now requires you to report SAEs in the same manner and timetable as to the FDA."

RAC Questions and Discussion

RAC members discussed Dr. Aguilar-Cordova's suggested wording addition and the SAE Working Group report in the context of the recommendations made by the ACD Working Group, as previously discussed. The following comments were made:

- (Dr. Aguilar-Cordova) Does the OBA need real-time reporting? Such reporting will not provide information about trends, only what has happened to one research subject. If the OBA needs compiled and assessed data, annual reports might suffice.

- (Dr. Mickelson) The NIH/OBA has contact with and disseminates information to groups other than those of the FDA. SAEs reported to the OBA are sent out to institutional IRBs that are not contacted by the FDA. This communication loop is different from that of the FDA, and it needs to remain in place. In addition, SAE reports are used to trigger RAC conferences or symposiums such as the one held in December 1999 on adenovirus vectors.

- (Dr. Breakefield) Receiving SAEs informs the protocol review process.

- (Dr. Noguchi) Annual reports are valuable but vary greatly in content. These reports are summaries of AEs from the previous year and therefore may not capture enough useful information. Trend analyses would be difficult using only annual reports.

- (Dr. Mickelson) The process proposed by the ACD Working Group represents a stepping back from the desire of some RAC members that all SAEs be reported immediately; this proposed timeframe adopts the FDA timeframe.

- (Dr. Gordon) Once the OBA receives an SAE report, that information is in the public domain, which means the RAC has direct access to it. The existence of the standing committee proposed by the ACD Working Group should not eliminate, for example, RAC review of an SAE that occurs 3 days before a RAC meeting.

- (Ms. King) The existence of this new committee does not change what the FDA does or the RAC's access to the SAE data.

- (Dr. Gordon) Having access to data does not necessarily mean doing something with it, and access to data should not be denied simply because something laudable cannot be done with the results of that access.

- (Dr. Noguchi) The ACD Working Group consensus view is a general set of operating procedures and principles that can enable the FDA, the NIH, and the RAC to function efficiently. Setting up a specific set of rules is necessary to address the formal needs, but much interaction occurs on a more informal level.

Dr. Patterson queried the RAC members as to whether the RAC would want to issue its own SAE report. To help answer that question, the OBA handed out the primer that had been given to RAC SAE Working Group members. This primer includes the initial proposed action from November 1999's *Federal Register*, a table summarizing all public comments, the original letters received, the ICH harmonization requirements, and a redrafted proposed action on SAEs. Dr. Patterson reminded the RAC that a new proposed action is needed if the *NIH Guidelines* are to be modified.

Dr. Mickelson requested that RAC members read the SAE and ACD Working Groups' reports and then forward specific comments to her by e-mail. She will compile all comments and forward them to RAC members before passing them on to the ACD Working Group.

Committee Motion 5

It was moved by Ms. King and seconded by Dr. Greenblatt that the RAC endorse the ACD Working Group recommendations, with wording that both adds an expression of the RAC's gratitude and advises the NIH Director that, if these recommendations are implemented, many of the issues the RAC has been struggling with will be resolved.

Dr. Mickelson expanded on the motion as follows: The RAC supports the ACD Working Group's proposed model for NIH review of gene transfer protocols, with the understanding that some specifics still need to be worked out. In addition, the RAC supports the consensus view on SAE reporting, with the understanding that it resolves many issues, including how to receive and how best to utilize SAEs.

The vote on this motion was 11 in favor, 0 opposed, and 0 abstentions.

XII. Discussion on Reassessing the Criteria and Process for Selecting Protocols for Public RAC Review and Discussion/Dr. Patterson

Dr. Patterson noted the recommendations of the ACD Working Group regarding the criteria in the *NIH Guidelines* for selecting protocols for public review as well as the concerns that have been expressed by some researchers, sponsors, and institutions that the criteria are vague.

Dr. Patterson reviewed the process for submission of protocols to the OBA, as set forth in Appendix M of the *NIH Guidelines*. Protocols are submitted to the OBA in accordance with Appendix M of the *NIH Guidelines* for RAC review and, within 15 working days, the RAC recommends to the NIH Director either full RAC review and public discussion or exemption of the protocol from any further RAC review, after which it is reviewed by the FDA only, if FDA review has not already occurred. The RAC determination is based on a summary of the protocol submission that is prepared by the OBA staff as well as other relevant information that RAC members often request. (As the OBA turns more to electronic retrieval of records, full protocols will be able to be provided to all RAC members.) Whether selected for further review or exempted from further review, all protocols are subject to the *NIH Guidelines*. Of the 230 protocols submitted to the RAC since 1997, 31 (13.5 percent) were selected for RAC public review.

Dr. Patterson also reviewed the current criteria for public RAC review which begin with a comparison of the protocol with previously reviewed protocols to determine whether there are any new and/or unresolved issues. Specific factors for comparison, as laid out in the *NIH Guidelines* and summarized in the preamble to Appendix M, include:

- Gene delivery vehicle
- Forms of the transgene, marker gene, and packaging cell
- Clinical indication of the particular disease, disorder, or condition being targeted
- Route of administration
- Patient selection criteria

Factors that may contribute to further review include:

- New vectors or gene delivery systems
- New diseases

- New applications
- Other issues considered by the RAC to require further public discussion

Public RAC review and discussion of a protocol at a RAC meeting can be initiated by the NIH Director or can be recommended to the NIH Director by three or more RAC members and/or members of other Federal agencies.

Several major issues/questions that have arisen in recent years were discussed by RAC members.

1. Questions from investigators about the transparency of review criteria—How can investigators predict whether their protocol will be selected for RAC review, and how consistent are those criteria?

    - (Dr. Cohen) Investigators become concerned when they are notified that their protocol has been selected for "review." They should be notified instead that their protocol has been selected "as a case study" to discuss a particular issue.

    - (Ms. King) RAC review is a review for the purpose of public discussion. Stating that a protocol is "significant" rather than "novel" might alleviate some investigator concerns. Most investigators understand that RAC review is intended to be helpful to the field.

    - (Ms. Levi-Pearl) RAC invitations to present protocols have not been frivolous, and RAC discussion is always helpful in enhancing the research.

    - (Dr. Gordon) The RAC is not a regulatory body and the threshold of requiring RAC review of a protocol should be high. The RAC should not try to advise investigators or sponsors as to what would trigger a RAC review.

    - (Dr. Patterson) Protocols are platforms for discussion. It should be possible in the review process to have a dual pathway whereby some protocols would warrant in-depth RAC review and smaller issues embedded in other protocols could be part of the RAC agenda for discussion (without triggering full review).

2. The number of votes needed to trigger public RAC review—Is three too few or too many?

    - (Dr. Aguilar-Cordova) The definition of the word "novel" needs to be expanded. Novel protocols contain some issue by which a policy can be discussed—such as a new vector, new disease, or new protocol design. The revised definition should encompass unresolved safety, ethical, and policy issues.

    - (Dr. Friedmann) The RAC is a diverse group whose technical knowledge of gene transfer research varies. There is a need to rely on small subgroups of the RAC for their varying and nonoverlapping expertise. Three votes make the RAC sensitive to this varying expertise and should not be changed.

    - Having three votes for review recognizes the importance of public-member representatives. Public slots on the RAC are limited.

3. Sharing of information among RAC members about their votes to review—Reversals of votes occur

via e-mail by stimulating informed consideration; is this desirable?

- (Dr. Friedmann) RAC members should not be prevented from conferring and discussing protocols with each other prior to a vote to review. To ask RAC members to vote blindly in areas in which they may be novices is unreasonable. Voting without conferring is a step backward.

- (Ms. King) Vigorous discussion via e-mail is helpful, especially to the nonscientists on the RAC.

- (Dr. Patterson) To enhance discussion and the learning process, improved access to the archives of the e-mail discussions is needed. The issues from e-mail discussions could be abstracted and put on the OBA Web site.

- (Dr. Mickelson) Some mechanism should be established to provide the results of RAC discussions of protocols that were not selected for public review; the OBA Web site might be an appropriate location for this mechanism. IBCs then can see the issues raised by the RAC. IBCs should receive the benefit of RAC members' time and effort spent reviewing protocols.

4. The fate of "minority" viewpoints—What if one RAC member expresses substantive concerns that ought to be shared with investigators or IRBs?

    - (Dr. Breakefield) Minority concerns should be communicated back to the IRB to assist the IRB in their oversight of the protocols.

    - (Dr. Noguchi) The minority view has importance, and that view should be transmitted by letter.

    - (Dr. Gordon) Sharing these minority views widely, e.g., posting at the OBA web site, might be helpful to IRBs.

Summary

Dr. Mickelson concluded from the discussion that the RAC believes that the current criteria and process for RAC review of protocols are satisfactory and should not change. Regardless of whether a protocol is held for full RAC review, comments on the protocol would still be forwarded to the IBC and the IRB.

Recommendation

Ms. King recommended that the RAC improve its connections with IRBs; the IRB chair's name and contact information, if not known, could be requested from the investigator. For example, informed consent document discussions and recommendations should be transmitted to the IRB. Dr. Mickelson agreed; particularly, if the RAC will be reviewing protocols at an earlier stage, results of RAC comments should be shared with IRBs as well as IBCs.

XIII. Miscellaneous Announcements

Dr. Mickelson asked about the letters from the review of protocols at the March 2000 RAC meeting. The RAC made recommendations to a number of protocols and asked for information and data. If replies had not been received from the investigators, Dr. Mickelson requested that the OBA send reminder letters. Dr. Patterson indicated that all replies had been received, with one exception; the OBA will follow up on this nonreply.

Dr. Aguilar-Cordova suggested that, as a result of the protocol discussed on Day One of this meeting, the wild-type virus issue may be appropriate for a future RAC symposium. He also suggested consent form

wording, offered at the outset of the form, that would read: "This is an experiment, the consequences of which are unknown and may present some risks for you."

Ms. King will prepare a background paper that examines language issues relative to point 6 (informed decision-making) of the Adenovirus Safety and Toxicity Working Group report. Boilerplate language does exist. This subject may be suitable for a Gene Transfer Policy Conference (GTPC).

XIV. Announcement of and Timetables for Other NIH Initiatives/Dr. Patterson

Regarding the scope of the *NIH Guidelines* and the definition of recombinant DNA, this issue will be discussed at the future meetings.

A future RAC meeting will feature a cardiovascular safety symposium. Preliminary dialog has begun with the National Heart, Lung, and Blood Institute. Three RAC members and FDA's representative volunteered to participate on the planning committee for this symposium: Drs. Breakefield, Friedmann, Greenblatt, and Noguchi (FDA).

The next GTPC date and topic have not been set. One suggestion was a good clinical practices conference, to include optimal informed consent policies. Other ideas should be forwarded to the OBA.

XV. Chair's Closing Remarks/Dr. Mickelson

Dr. Mickelson noted the RAC's appreciation of the support received from the ACD Working Group.

Comments about the SAE reporting proposal should be e-mailed to Dr. Mickelson; deadline for receipt of comments is July 14, 2000.

XVI. Future Meeting Dates/Dr. Mickelson

The next RAC meeting will be held on September 25 and 26, 2000.

XVII. Adjournment/Dr. Mickelson

Dr. Mickelson adjourned the meeting at 2:40 p.m. on June 29, 2000.

[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: September 25, 2000

Claudia A. Mickelson, Ph.D.
Chair
Recombinant DNA Advisory Committee
National Institutes of Health

Attachment I
Committee Roster

C. Estuardo Aguilar-Cordova, Harvard Gene Therapy Initiative
Dale G. Ando, Cell Genesys, Inc.
Xandra O. Breakefield, Massachusetts General Hospital
Louise T. Chow, University of Alabama, Birmingham
Theodore 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, Inc.
Ruth Macklin, Albert Einstein College of Medicine
M. Louise Markert, Duke University Medical Center
R. Scott McIvor, University of Minnesota
Claudia A. Mickelson, Massachusetts Institute of Technology
Jon A. Wolff, University of Wisconsin Medical School

Attachment II
Attendees

Bruce Agnew
Ann Besignano, Capital Consulting Corporation
Bridget Binko, Alza
John Bishop, U.S. Food and Drug Administration
Philippe C. Bishop, U.S. Food and Drug Administration
Adwoa Boahene, U.S. Senate and House of Representatives
Samar Burney, Juvenile Diabetes Foundation International
Jeffrey W. Carey, GenVec
Margaret Charette, Genzyme
Shirley M. Clift, Cell Genesys
Laura Coleman, Eli Lily
Cheryl Corsaro, Congressional Research Service
Margaret Crowley, Eberlin Reporting Services
David L. Cureton, cancerpage.com
Joann C. Delenick
Michael Dowd, ImClone Systems
Steve Eckert, Dateline NBC
Traci Eng, Capital Consulting Corporation
Jeffrey Fox, Capital Consulting Corporation
Deirdre Y. Gillespie, Vical
G. Yancey Gillespie, University of Alabama, Birmingham
Angus J. Grant, Aventis
Lauren Hafner, U.S. Senate and House of Representatives
Nancy L. Herring, Transgene
Brian Horsburgh, NeuroVir Therapeutics
Beth Hutchins, Canji
Dorothy Jessop
Bhanu Kannan, U.S. Food and Drug Administration
Lisa Kaplan, Capital Consulting Corporation
Connie J. Kohne, Genstar
Steven A. Kradjian, Vical
Didier Lamy, Transgene
LaVonne L. Lang, Parke-Davis
William T. Lee, Cato Research
Jeffrey B. Levine, Healtheon/WebMD
Deborah B. Lynch, ImClone Systems
J. Tyler Martin, Systemix
Maritza McIntyre, U.S. Food and Drug Administration
Tina Moulton, U.S. Food and Drug Administration
Joseph T. Newsome, University of Pittsburgh
Stuart L. Nightingale, U.S. Department of Health and Human Services
Mi-Sun Park, Korea Food and Drug Administration
Phil Pendergast, Ohio State University
Kim Penland, *FDA Week*
Joanna Peterkin, NeuroVir Therapeutics
Glenn F. Pierce, SelectiveGenetics
Barry Polenz, Targeted Genetics

Andrew Quon, Association of American Medical Colleges
Abdur Razzaque, U.S. Food and Drug Administration
Isabelle Rivière, Memorial Sloan-Kettering Cancer Center
Laura Lyman Rodriguez, Federation of American Societies for Experimental Biology
Bernard Roizman, Marjorie B. Kovler Viral Oncology Laboratories, University of Chicago
Mary Frances Ryan, SmithKline Beecham Pharmaceuticals
Donna Savage, Capital Consulting Corporation
Mayumi Shikano, U.S. Food and Drug Administration
T. Shimada, Ambience Awareness International
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Richard Sublett, Introgen Therapeutics
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Frank Tufaro, NeuroVir Therapeutics
Steve Usdin, BioCentury
Janet Vessotskie, Schering-Plough Research Institute
Rick Weiss, *The Washington Post*
Richard J. Whitley, University of Alabama, Birmingham
Carolyn Wilson, U.S. Food and Drug Administration
Doris T. Zallen, Virginia Polytechnic Institute and State University
Julie Zawisza, U.S. Food and Drug Administration

Attachment III
Abbreviations and Acronyms

ACD--Advisory Committee to the Director (NIH)
AE--adverse event
ASGT--American Society of Gene Therapy
CF--cystic fibrosis
DHHS--U.S. Department of Health and Human Services
DSM--data and safety monitoring
DSMB--Data and Safety Monitoring Board
FDA--U.S. Food and Drug Administration
GCP--good clinical practice
GTPC--Gene Transfer Policy Conference
GTR--gene transfer research
HIV--human immunodeficiency virus
HSV-1--herpes simplex virus type 1
IBC--institutional biosafety committee
ICH--International Conference on Harmonization
IND--investigational new drug application
IRB--institutional review board
NCI--National Cancer Institute
NIH--National Institutes of Health
(NIH Guidelines)--NIH Guidelines for Research Involving Recombinant DNA Molecules
OBA--Office of Biotechnology Activities (formerly ORDA, Office of Recombinant DNA Activities)
OER--Office of Extramural Research
OHRP--Office for Human Research Protections (formerly OPRR)
OPRR--Office for Protection from Research Risks (now OHRP)
PCR--polymerase chain reaction
PHS--U.S. Public Health Service
PI--principal investigator
QA/QC--quality assurance/quality control
RAC--Recombinant DNA Advisory Committee
SAE--serious adverse event
UR--University of Rochester