DEPARTMENT OF HEALTH AND HUMAN SERVICES
NATIONAL INSTITUTES OF HEALTH
RECOMBINANT DNA ADVISORY COMMITTEE
MINUTES OF MEETING
September 2-3, 1999

The Recombinant DNA Advisory Committee (RAC) was convened for its 75th meeting at 9:00 a.m. on September 2, 1999, at the National Institutes of Health (NIH), Building 31, Conference Room 10, 9000 Rockville Pike, Bethesda, MD 20892. Dr. Claudia Mickelson (Chair) presided. In accordance with Public Law 92-463, the meeting was open to the public on September 2 from 9:00 a.m. until 5:00 p.m. and on September 3 from 8:30 a.m. until 12:30 p.m. The following individuals were present for all or part of the meeting:

Committee Members:

Dale G. Ando, Cell Genesys, Inc.
Theodore Friedmann, University of California, San Diego
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

***Ad Hoc* Consultants:**
Abbey S. Meyers, National Organization for Rare Disorders
Richard O. Snyder, Harvard Institutes of Medicine, Harvard Medical School
Doris T. Zallen, Virginia Polytechnic Institute and State University

Executive Secretary:

Debra W. Knorr, National Institutes of Health

Nonvoting Agency Representatives/Liaison Representatives:

Andra Miller, U.S. Food and Drug Administration
Philip Noguchi, U.S. Food and Drug Administration
Jeffrey M. Cohen, U.S. Office for Protection from Research Risks

National Institutes of Health Staff:

Joann Delenick, Office of the Director
Brenda Farmer, Office of the Director
Donald Fredrickson, National Library of Medicine
Christine Ireland, Office of the Director
Sandra Jones, Office of the Director
Richard Knazek, National Center for Research Resources
Becky Lawson, Office of the Director
Catherine McKeon, National Institute of Diabetes and Digestive and Kidney Diseases
Mike Miller, Office of the Director
Amy Patterson, Office of the Director
Cikena Reid, Office of the Director
Gene Rosenthal, Office of the Director
Thomas Shih, Office of the Director
Lana Skirboll, Office of the Director

Others:

Robert W. Anderson, U.S. Food and Drug Administration
W. French Anderson, University of Southern California

Anthony S. Andrasfay, Collateral Therapeutics
Ann Besignano, Capital Consulting Corporation
Christine Boisclair, Genzyme Corporation
Andrew G. Braun, Massachusetts General Hospital
Parris R. Burd, U.S. Food and Drug Administration
Jeff Carey, Genvec
Joy Cavagnaro, Consultant
Patrick Collins, National Hemophilia Foundation
Philip J. Cross, University of Pennsylvania Health System
Margaret Crowley, Eberlin Reporting Services
Thomas W. Dubensky, Jr., Chiron Corporation
Thomas L. Eggerman, U.S. Food and Drug Administration
Diane O. Fleming, Certified Biosafety Consultant
Dianne Flescher, George Washington University Medical Center
Donald Gay, Chiron Corporation
Angus J. Grant, GenCell
Thomas E. Hogan, The Blue Sheet
Joseph V. Hughes, University of Pennsylvania Health System
Deborah Hurst, Chiron Corporation
Beth Hutchins, Canji, Inc.
Bob Jambou, Cevric
Douglas J. Jolly, Chiron Corporation
James Kaisel, U.S. Food and Drug Administration
Jennifer Kostiuk, Capital Consulting Corporation
Steven A. Kradjian, Vical, Inc.
LaVonne L. Lang, Parke-Davis
Martha E.I. Leibrandt, Chiron Corporation
Robert Lieberman, The BDF Group
Jean MacDonald, Eastern Cooperative Oncology Group
Tanya M. Manor, Genzyme Corporation
J. Tyler Martin, SyStemix, Inc.
James F. Martin, Ethicon Endo-Surgery, Inc.
Alan McClelland, Avigen
Jerry R. Mendell, Ohio State University
Thomas Moon, Chiron Corporation
Lisa Needleman, Capital Consulting Corporation
Peter J. O'Dwyer, University of Pennsylvania Health System and Eastern Cooperative Oncology Group
Christine M. Pannunzio, Osiris Therapeutics, Inc.
Glenn F. Pierce, Selective Genetics Incorporated
Anne Pilaro, U.S. Food and Drug Administration
Barry Polenz, Targeted Genetics Corporation
Margaret Ragni, University of Pittsburgh
Cynthia Rask, U.S. Food and Drug Administration
Holger H. Roehl, Chiron Corporation
Brenda Ross, Johns Hopkins Hospital
Donna R. Savage, Intelligent Fingers
Tomiko Shimada, Ambience Awareness International, Inc.
David G. Shoemaker, Cato Research
Stephanie L. Simek, U.S. Food and Drug Administration
Barbara Singer, Capital Consulting Corporation

Cecil R. Smith, Ohio State University
Linda S. Sobolak, Valentis, Inc.
Lorna Speid, Valentis, Inc.
Rebecca S. Spieler, The Blue Sheet
Richard Strube, FDA Week
Marlies E.H.M. Van Hoef, TransOnc Consulting
Janet Vessotskie, Schering-Plough Research Institute
Nathalie Vincent, Genethol (France)
Margaret Wahl, Muscular Dystrophy Association, Inc.
James Wilson, University of Pennsylvania Medical Center
Nelson Wivel, University of Pennsylvania

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

Dr. Mickelson, the RAC Chair, called the meeting to order at 9:00 a.m. on September 2, 1999. The notice of this meeting under the *NIH Guidelines for Research Involving Recombinant DNA Molecules (NIH Guidelines)* was published in the *Federal Register* on August 11, 1999 (64 FR 43884). Issues to be discussed by the RAC at this meeting included a proposed amendment to the *NIH Guidelines* regarding the timing of institutional biosafety committee approval and initiation of gene transfer research in humans; a report from the Working Group on the Scope of the *NIH Guidelines for Research Involving Recombinant DNA Molecules*; a proposed amendment to the *NIH Guidelines* regarding prenatal gene transfer research; submission and reporting requirements for human gene transfer experiments, including a presentation by the U.S. Food and Drug Administration (FDA) on adverse event reporting and review; and RAC review of two human gene transfer protocols—(1) a phase I clinical trial utilizing gene therapy for limb-girdle muscular dystrophy using intramuscular instillations of adeno-associated virus vectors and (2) a phase I multicenter, single-treatment, dose-escalation study of human Factor VIII vector for treatment of severe hemophilia A.

Dr. Mickelson introduced *ad hoc* members Dr. Jeffrey Cohen, Office for Protection from Research Risks (OPRR) (standing in for Dr. Melody Lin); Ms. Abbey Meyers, National Organization for Rare Disorders; Dr. Richard Snyder, Division of Molecular Medicine at Children's Hospital, Harvard Medical School; and Dr. Doris Zallen, Center for Interdisciplinary Studies, Virginia Polytechnic Institute and State University.

Minutes of the June 14, 1999, Meeting/Dr. Ando and Ms. Levi-Pearl

Copies of the minutes were provided. Previously, the minutes were reviewed and approved by a subcommittee composed of Dr. Ando and Ms. Levi-Pearl. Dr. Ando stated that the scientific issues and technical discussions were portrayed accurately in the minutes. Ms. Levi-Pearl offered a few editing suggestions, all of which were requested by Dr. Mickelson to be passed on to Dr. Patterson for incorporation into the minutes.

Committee Motion 1

The RAC approved a motion made by Dr. Juengst and seconded by Dr. Greenblatt to accept the minutes of the June 14, 1999, RAC meeting (with the incorporation of minor editorial changes) by a vote of 11 in favor, 0 opposed, and 0 abstentions.

Proposed Action To Amend the *NIH Guidelines* Regarding the Timing of Institutional Biosafety Committee Approval and Initiation of Human Gene Transfer Experiments/Dr. Mickelson
Ad Hoc Consultants: Dr. Doris T. Zallen, Virginia Polytechnic Institute and State University and Ms.

Abbey S. Meyers, National Organization for Rare Disorders

Background

The NIH has continually refined its oversight of human gene transfer research as the field has developed. In December 1996, the RAC review process was modified to consist of a rapid initial analysis of each human gene transfer experiment to determine which protocols present significant novel scientific, safety, ethical, legal and/or social issues and therefore warrant further RAC review and public discussion. In October 1997, the *NIH Guidelines* were amended to eliminate the requirement for approval by the RAC of individual protocols. The objectives of both of these actions were to streamline the review process and ensure that the roles and responsibilities of the NIH complement, rather than duplicate, those of other Federal agencies while preserving public confidence in the field.

At present, human gene transfer protocols must be approved by the local Institutional Biosafety Committee (IBC) and the local Institutional Review Board (IRB) prior to submission to the NIH Office of Recombinant DNA Activities (ORDA) for RAC review. Within 15 days of receipt of the complete submission to NIH/ORDA, investigators are informed of the RAC's decision as to whether a given protocol is novel and therefore warrants further review and public discussion. To provide adequate time for additional analysis of the protocol and public notice of the upcoming RAC review and discussion, a protocol must be received by NIH/ORDA at least eight weeks prior to a RAC meeting. Over the past two years, approximately 10% of protocols were determined by the RAC to warrant further analysis and public discussion because they presented novel safety and/or ethical issues. Examples of novel characteristics included new disease indications, vulnerable patient populations, and new classes of viral vectors.

In an effort to optimize further and streamline this process, the NIH has proposed to modify further the requirements for protocol submission for RAC review. Specifically, clinical trial proposals may be submitted for RAC review before having been approved by the local IBC and IRB; however, clinical trial investigations may not be initiated until the RAC review process has been completed, IBC and IRB approvals have been obtained, and applicable regulatory authorization(s) have been obtained.

The above changes will allow investigators to receive RAC input at an earlier stage of protocol development and allow multiple levels of protocol review to occur simultaneously. The proposed actions are intended to reduce the delays in initiating clinical trials that may result from the multiple, sequential reviews currently conducted by the local institutional review bodies and federal government agencies. The NIH is interested in exploring strategies to expedite further the process of public discussion by the RAC of novel protocols.

Other changes to the *NIH Guidelines* are presented in these proposed actions in order to clarify the process and requirements for protocol submission, review, and reporting. These proposed actions will preserve RAC's critical role in the review and public discussion of novel human gene transfer experiments in advance of clinical application.

The proposed actions were published in the *Federal Register* of August 11, 1999 (64 FR 43884) for public comment. On August 24, 1999, an e-mail letter was received from Martin A. Turman, M.D., Ph.D., IBC Chair, Children's Hospital, Columbus, Ohio, stating that the Proposed Actions will be helpful for the investigators and that streamlining the RAC submission and review procedure will promote more investigators to try novel approaches. In a letter dated August 25, 1999, Ms. Jean MacDonald, Protocol Development Coordinator, Eastern Cooperative Oncology Group (ECOG), Brookline, Massachusetts, supported the Proposed Actions. She stated that the amended *NIH Guidelines* will allow ECOG to submit protocols to NIH/ORDA while they are still in development so that they may obtain RAC input at an earlier

stage. In a letter dated August 25, 1999, Alexander E.Kuta, Ph.D., and Christine Boisclair, Regulatory Affairs, Genzyme Corporation, Framingham, Massachusetts, supported the need to streamline the RAC review process while noting several concerns, e.g., delaying the initiation of protocols until RAC review is competed, unclear statement regarding "final approval(s) have been obtained from the IBCs at each clinical trial site" for multicenter trials, and the need to increase the frequency of RAC meetings to one every two months.

Dr. Mickelson explained that the proposed changes would include a request that the clinical trial not be initiated until RAC discussion had occurred. Within 3 weeks, the investigator would know whether the RAC considered this protocol novel enough to warrant public discussion and full RAC review. The RAC requires approximately 8 weeks to prepare for public discussion, including soliciting the opinions of *ad hoc* reviewers and allowing adequate time for the investigator to respond to RAC members' queries.

RAC Discussion

In response to Dr. Markert's questions, Dr. Patterson explained that the proposed wording indicates that an investigator can choose when to submit a protocol for IRB, IBC, and RAC reviews—the submission may be simultaneous but can also be sequential—but it is critical that the protocol being reviewed by all three bodies be the same document. Most investigators would likely submit protocols simultaneously to the local committees and the RAC, but flexibility in the timing may be important to some investigators. Flexibility in protocol submission is helpful to local review committees and to investigators; some IBCs and IRBs may want to see RAC review results before making their own decisions, whereas others may want to decide independently of public RAC review.

Under this Proposed Action, Dr. Friedmann was concerned that IRBs might not have time to fine-tune proposals before sending them to the ORDA. Dr. Mickelson responded that this issue was raised when the proposal was first made by Dr. Markert in the December 1997 RAC meeting; RAC discussion at that time focused on the fact that the most advantageous time for RAC review and public discussion to occur is prior to or at the same time frame of IRB and IBC review.

Dr. McIvor expressed concern about investigators submitting spurious or premature protocols that have not yet received IBC, IRB, or FDA approval, a situation that could force the review process through the ORDA and possibly trigger RAC review of a protocol that does not justify spending RAC and public review time. Dr. Noguchi countered that this new process would place a great deal of additional emphasis on the investigator to offer a more complete protocol, since it would be reviewed by several bodies. Investigators who are less familiar with the review process may need assistance. For investigators who are familiar with the process, this Proposed Action sets up the timing so that approvals occur at approximately the same time, rather than sequentially.

Ms. Meyers expressed concern about inaccurate or dishonest Informed Consent documents that would reach public RAC review before being refined by local review boards. Dr. Macklin explained that past consent forms that have reached the RAC, which had already been approved by an IRB, were not measurably improved beyond their initial content. Under the Proposed Action, consent forms would be reviewed in tandem by the IRB and the RAC, allowing the IRB to incorporate RAC suggestions at an earlier stage.

Ms. Meyers also expressed concern that the RAC's lack of voting power to table or defer a protocol means that the RAC cannot force investigators to comply with RAC recommendations. Dr. McIvor stated his interest in looking at protocol reviews conducted by the RAC during the past 2 years to determine whether RAC suggestions had been implemented by the investigators.

Dr. Cohen stated that, under the current system, IRBs are reviewing protocols before the RAC conducts its review—thus, without the benefit of RAC input. Under the proposed system, initial RAC review would be completed before IRB approval is finalized, so that the IRB would know that a problem arose or that the RAC considered the protocol to be novel.

Dr. Wolff stated that the RAC possesses scientific expertise that most IRBs and IBCs do not. Especially for the novel protocols, RAC review and subsequent input can be invaluable as IRBs review those protocols locally.

Dr. Markert indicated her concern about protocols that are flagged by the RAC as novel that cannot go forward for up to 5 months until there has been a full RAC review and public discussion. She referenced the letter from Genzyme Corporation that suggested that the RAC hold more frequent meetings, a phenomenon that is occurring locally among IRBs so as not to hold up the progression of protocols. She reiterated her preference for local control—IRBs and IBCs—and that approval should be obtained from them and the FDA and that RAC review and public discussion should not hold up the start of clinical trials. Dr. Mickelson reiterated that submission deadlines for RAC review are published on the ORDA Web site; Dr. McIvor stated that investigators who want to minimize the waiting time for RAC review can do so easily by checking a variety of information sources including the submission deadlines.

Dr. Noguchi brought forward the fundamental question of national vs. local oversight of a clinical trial, including the question concerning the Informed Consent document—whether national standards override local considerations or *vice versa*. Within the FDA, national review includes review of the Informed Consent document and suggested wording changes.

Dr. Macklin stated that her understanding of the requirement for and authority of local review is to implement a more informed understanding of local circumstances or conditions having to do with the subject population. Local IRBs are better equipped to know the specifics about a local subject population. In addition, she agreed with Ms. Meyers that considerations of science, safety, and benefits to subjects mean that protocols should not be rushed through review processes.

Dr. Juengst, Ms. Levi-Pearl, Dr. McIvor, and Dr. Mickelson agreed that protocol submission for review should not entail simply encouraging the investigator to submit the same document to IRBs, IBCs, and the ORDA; rather, the investigator should submit the same document at the same time or before the protocol is submitted to the local IRB. Dr. Juengst reminded the RAC that, of course, this order of protocol submission is voluntary.

Dr. Wolff expressed his concern that protocols proceed safely but that they also not be delayed unnecessarily. There is a sense of urgency from patients and their families, not just from the companies, to expedite clinical trials as quickly as possible.

Ms. Meyers queried whether the proposed changes included a provision that clinical trials should not be initiated until after the RAC's review of the protocol. If an investigator moves forward despite being told of pending RAC review, this would be considered noncompliance with the *NIH Guidelines*, a situation that puts NIH funding in jeopardy. Although there is no statute mandating this proscription, Dr. Harold Varmus, NIH Director, made clear in a speech at the American Society of Gene Therapy's June 1999 meeting that investigators must follow RAC recommendations.

Dr. Mickelson reiterated the value of the public discussions and the openness of access to information. The RAC has worked with various groups with an interest in gene therapy, to keep in contact with them

and to allow their viewpoints to be heard. The open discussions and RAC input are of value and represent one form of public trust. Public access to this kind of information represents the reason why so much progress has been made in the field of gene transfer research and numbers of clinical trials have occurred in the United States vs. other countries.

Public Comment: Dr. W. French Anderson, University of Southern California, suggested that the RAC consider a process of notifying IRB and IBC if a protocol is to be reviewed by the RAC. If theIRB is aware that RAC comments are imminent, theIRB can give provisional approval contingent on those comments. If the IRB is reasonably comfortable with the protocol, then theIRB chair can work with the investigator to implement the RAC recommendations, reducing significantly the delay in beginning the clinical trial.

Public Comment: Dr. Peter O'Dwyer, University of Pennsylvania Health System and ECOG, stated his support for increased flexibility of review by providing insight into how ECOG performs its studies, what constraints are involved, and how increased review flexibility would be helpful. Under the proposed changes for protocol review, protocols would be submitted simultaneously to the National Cancer Institute's (NCI) Cancer Therapy Evaluation Program (NCI-CTEP), where much internal review takes place, and to the RAC. After taking into account comments from the NCI and from the RAC, the protocol would be reformulated, resubmitted for NCI approval, and then transmitted to the appropriateIRBs for review.

Public Comment: Dr. Angus Grant, GenCell Division, Rhône-Poulenc, queried whether the above discussion was restricted to phase I protocols or to all phases. Ms.Knorr answered that the discussion and the Proposed Action would apply to all phases of trials. Dr. McIvor clarified that a phase II trial, which would change the focus fromsafety to efficacy even though it might be necessary to register the protocol with ORDA, would be highly unlikely to trigger a RAC review because it is not a novel recombinant issue. Dr. Grant countered that he wanted to make sure the RAC continues to protect the public trust while also to create an environment that takes useful products to a licensing phase as expeditiously as possible.

Dr. Noguchi explained that there is confusion in the gene therapy community about the process and the optimal timing of protocol submissions. During the past few years, the FDA has started a cross-notification system with the ORDA. He presented a draft of a letter that will be sent to all of FDA's current gene therapy sponsors and to societies such as the American Society of Gene Therapy. The letter supports the idea that the type of public review provided by the RAC is an important component of gene therapy oversight. For that reason, the FDA would support the notion of submission for public discussion andIRB review before the formal submission of an IND to the FDA. This process is not required by the FDA but is preferred; sponsors would be asked (not required) not to enter patients into a clinical trial, as a courtesy to the ORDA/RAC and to the public to ensure that issues are resolved appropriately.

Public Comment: Dr. Christine Boisclair, Genzyme Corporation, commented on the issue of waiting for RAC review. Genzyme is currently waiting to initiate a protocol involving gene therapy trials in severely ill cancer patients who have failed all existing therapy. Some of the oncologists within and outside of Genzyme have expressed concerns about waiting for RAC review before initiating a protocol that has already received FDA and IRB clearance. A potential 3-month delay, if the protocol is chosen for full RAC review, for some of these patients represents a long time, given their condition.

Dr. Mickelson stated that the time frame for RAC review is dependent on the RAC definition of "novel"; thus, before submitting a protocol, investigators should have a clear idea of whether it will be a quick process or whether their protocol will fall into the "novel" category, thus triggering RAC review and public discussion. She urged investigators to take advantage of the accessibility of theORDA staff, to discuss whether a protocol is likely to be considered novel.

Dr. Zallen questioned Dr. Noguchi about the FDA making decisions on protocols without public discussion and without the benefit of RAC public review. Dr. Noguchi responded that the FDA would like to receive protocols after RAC public review, if novel issues are present, and that the Proposed Action would allow that process to occur.

Public Comment: Dr. James Wilson, University of Pennsylvania Medical Center, reinforced the nature of the RAC's impact by referring to the discussion at the June 14, 1999, RAC meeting concerning inadvertent germ-cell gene transfer. He stated that that discussion was decisive and extremely helpful to the field, the FDA, and the investigators. He reiterated that the RAC can have a greater impact on the gene therapy community if the community is engaged at an earlier time, as the Proposed Action would allow. One parallel example cited by Dr. Wilson is the pre-IND meeting within the FDA, in which the FDA has significant impact on a protocol's direction. At present, there is no parallel process for the RAC, but the Proposed Action would create such a process.

Dr. Mickelson noted that the wording of the Proposed Action and the *NIH Guidelines* in general need to be examined for internal consistency of definitions, particularly the definitions for recombinant DNA and what constitutes gene transfer.

Public Comment: Dr. Margaret Wahl, Muscular Dystrophy Association (MDA), asked whether the RAC's scope might be expanded to include any drug that changes gene expression. Dr. Mickelson answered that this issue would be discussed later today in the context of a working group on the scope of the *NIH Guidelines*.

Dr. Markert suggested that the decision about whether to proceed to clinical trial should be made by the local committees (i.e., IRBs and IRCs) and the FDA, without waiting for RAC public review. Dr. Noguchi reiterated that Dr. Markert's suggestion actually supports the FDA's proposed letter, in that waiting to initiate a clinical trial is only requested (not required) and that the local IRB is empowered to make its own decision about whether the clinical trial should proceed. Ms. Meyers disagreed, saying that gene therapy should not move forward until such time as there are no public health concerns about recombinant viruses. Unique protocols should undergo RAC review before clinical trials are initiated; there would appear to be no way to stop poor and unsafe protocols from moving forward under the Proposed Action.

Dr. Macklin noted that most IRB members do not generally have expertise in the gene therapy field; the key to the RAC is the relevant scientific expertise on the RAC, especially for evaluating which protocols are novel and therefore should receive RAC public review. Ms. King added to Dr. Macklin's comments by stating that the RAC is not "holding up" protocols when novelty triggers RAC public review. The RAC has a role in the review process to engage in public discussion about novel gene therapy protocols.

Dr. Friedmann queried whether the RAC was satisfied that all the reviewing bodies—IRBs, IBCs, the RAC—are capable of identifying novelty. Novelty can be defined as technical scientific novelty or policy novelty, for instance. He suggested that language in the Proposed Action reflect that the RAC, the IRB, and/or the FDA could identify protocols as being novel and that each could call for a review by the RAC. Since the RAC has a working group on criteria of "novelty," Dr. Mickelson requested that Dr. Friedmann hold on to that thought for a later discussion of this topic.

Ms. Levi-Pearl reminded the RAC that she represents patients who have a fervent hope that gene therapies will be helpful to them, their families, and future generations. As a result, she and her constituents do not want to see anything occur that would discourage gene transfer research. With that background, Ms. Levi-Pearl stated that the RAC must be extraordinarily cautious about issues relevant to

safety. For the future of this entire field, public discussions about protocols are important to disease advocates and to patients themselves.

Sense of the Committee

Dr. Mickelson requested a sense of the RAC about retaining the suggested amended language in "Scope of the *NIH Guidelines*," Section I-A-1-a—specifically the sentence that reads "Experiments involving the deliberate transfer of recombinant DNA or DNA or RNA derived from recombinant DNA into human subjects (human gene transfer) cannot be initiated without submission to NIH/ORDA and completion of the RAC review process." The sense of the RAC members present was as follows:

- Seven RAC members indicated that protocols should not be initiated until the full review process is complete.
- Three RAC members indicated that the decision to proceed with clinical trials should be left to the IRB/IBC/FDA.
- One RAC member abstained.

Committee Motion 2

The RAC approved a motion made by Dr. Greenblatt and seconded by Ms. Levi-Pearl to accept the wording of the Proposed Action in Section III, Experiments Covered by the *NIH Guidelines*, first paragraph of the preamble, which describes six categories of experiments involving recombinant DNA, by a vote of 9 in favor, 1 opposed, and 1 abstention.

Sense of the Committee

Dr. Mickelson requested a sense of the RAC regarding the statement that a clinical trial can proceed at one site as soon as local approvals are obtained for that site (and after RAC review), regardless of the status of local approvals at other sites. Ten RAC members stated their support for this statement, 0 did no support it, and there was 1 abstention.

Committee Motion 3

The RAC approved a motion made by Dr. Juengst and seconded by Ms. King to accept the wording of the summary statement of the Proposed Action, which reads: "Specifically, clinical trial proposals may be submitted for RAC review before having been approved by the local IBC and IRB; however, clinical trial investigations may not be initiated until the RAC review process has been completed, IBC and IRB approvals have been obtained, and applicable regulatory authorization(s) have been obtained." The vote was 9 in favor, 0 against, and 1 abstention.

A working group was formed to look at the language in the Proposed Action in order to clarify the statement regarding IBC aproval(s) at each clinical trial site in a multicenter protocol. Members of the working group are Dr. Juengst and Ms. King. The working group returned later in the meeting to report tha they propose to add a sentence to the revised first paragraph of the preamble of Section III-*Experiments Covered by the NIH Guidelines* that reads, "*Throughout this section, it should be understood that each experiment involving recombinant DNA must be approved by the Institutional Biosafety Committee and, if needed, the Institutional Review Board at the institution where it will be carried out before it can be initiated at that institution*." This new paragraph is to read, **"**This section describes six categories of experiments involving recombinant DNA: (i) those that ... ,and (vi) those that are exempt from the *NIH Guidelines* (see Section III-F). *Throughout this section, it should be understood that each experiment*

involving recombinant DNA must be approved by the Institutional Biosafety Committee and, if needed, the Institutional Review Board at the institution where it will be carried out before it can be initiated at that institution."

Committee Motion 4

The RAC approved a motion made by Juengst and seconded by Dr. Markert to allow flexibility in timing for the investigators to submit their protocols to NIH/ORDA. The phrase "or will be" is to be added to the sentence regarding the cover letter of the proposed amendment to Appendix M-I-A, Submission Requirements. This sentence is to be amended to read, "The cover letter must acknowledge that the documentation submitted to NIH/ORDA complies with the requirements set forth in Appendix M-I of the *NIH Guidelines* and that an exact duplicate of this documentation has been *or will be* submitted to the IBC at the proposed clinical trial site(s)." The motion passed by a vote of 9 in favor, 0 opposed, and 1 abstention.

Committee Motion 5

At the conclusion of RAC discussion on the Proposed Action on the timing of IBC/IRB approvals and NIH/ORDA submission of human gene transfer experiments, the RAC approved a motion made by Dr. McIvor and seconded by Dr. Markert to accept the Proposed Action, by a vote of 9 in favor, 0 against, and 1 abstention. Friendly amendments for the purpose of clarification and minor editorial changes are to be made by ORDA.

Additional Proposed Action Language Change--Enrollment vs. Initiation/Dr. Mickelson

An issue regarding patient enrollment and trial initiation of clinical protocols came up during the discussion of Protocol #9902-284 on the second day of the meeting for which three subjects had already been enrolled in the clinical trial. The RAC also noted that patients were already *enrolled* in Protocol #9905-317 while waiting for RAC discussion at this meeting, although the trial was not technically *initiated* by administration of the vector to the patients. Dr. Patterson requested that the RAC comment on whether it is concerned about investigators enrolling patients or initiating the experiment. Responses from the RAC indicated that premature enrollment of patients onto a protocol pending RAC discussion was the issue.

Dr. Mickelson suggested that language in the Proposed Action be changed from "trial initiation" to "enrollment in the trial" to make it clear that investigators are requested not to enroll subjects in clinical trials until after public discussion at the designated RAC meeting.

Committee Motion 6

A motion was made by Dr. Juengst and seconded by Dr. Markert, to change the Proposed Action language from "trial initiation" to "enrollment in the trial." The intension of the Proposed Action is to require that investigators not to enroll subjects without completion of the RAC review process. The motion passed, with 9 in favor, 0 opposed, and 0 abstentions.

Announcement of Working Group on Criteria for "Novel" Protocols/Dr. McIvor

Dr. McIvor presented a history of how the review process evolved and how it works. The current review process for deciding on the novelty of protocols begins with materials that are sent to the ORDA, which are then summarized and e-mailed to RAC members. Within 15 days, RAC members must respond by

voting whether they believe the protocol is (1) novel and requires discussion by the RAC and public hearing, (2) is not novel and therefore can move forward, or (3) abstains due to a conflict of interest. This process was formulated at the December 9, 1996, RAC meeting. A minimum of three "novelty" votes by RAC members trigger RAC public review. At the June 1997 RAC meeting, Ms. Knorr synopsized the elements of a protocol that might trigger a "novelty" designation: new vector types, new vector production or transduction methods, new packaging lines, new helper viruses, new functional or marker genes, new delivery methods, new routes of administration (*in vivo* or *ex vivo*), new indications (disease or otherwise), new ethical issues, or new treatment groups.

The working group is composed of Drs. Ando, Breakefield, Macklin, and McIvor; Ms. King; the president-elect of the American Society of Gene Therapy; and public representation yet to be determined. The FDA and the OPRR will also be represented. The working group's charge includes:

- articulating and clarifying what designates a novel human gene transfer protocol;
- deciding whether only three RAC members' votes should trigger a full RAC review;
- determining whether local IBCs or IRBs or the FDA should be encouraged to bring protocols to the RAC for full public review;
- assessing how to include the possibility of bringing up an issue for discussion in advance of a fully developed protocol, perhaps necessitating a new category of experiments under Section-III-C of the *NIH Guidelines* (Section III-C-1 deals with fully developed protocols); and
- ascertaining whether the system that has evolved over the past 3 years is working effectively.

Dr. Macklin stated, and the other RAC members agreed, that it would be helpful for this working group to have a list of all protocols submitted to the RAC that have been designated as "novel" plus some indication about the reason for the novelty vote for each protocol.

Report From the Working Group on the Scope of the *NIH Guidelines for Research Involving Recombinant DNA Molecules/Dr. Mickelson*

Working Group: Drs. Mickelson (Chair), Aguilar-Cordova, Ando, McIvor,Juengst, and Wolff

The definition of recombinant DNA, which defines the scope of the NIH Guidelines, was developed in 1976. That definition, which is still in use at the present time, reads:

> *"Section I-B. Definition of Recombinant DNA Molecules*
>
> *"...recombinant DNA molecules are defined as either: (i) molecules that are constructed outside living cells by joining natural or synthetic DNA segments to DNA molecules that can replicate in a living cell, or (ii) molecules that result from the replication of those described in (i) above. ..."*

When Appendix M, was added to the NIH Guidelines in 1990 to address recombinant DNA research involving human subjects, human gene transfer research was further defined as:

> *"Section I-A-1-a. Experiments involving the deliberate transfer of recombinant DNA or DNA or RNA derived from recombinant DNA into human subjects (human gene transfer)... ."*

At the June 1999 RAC meeting the RAC noted that both of these two definitions may need to be revisited in light of emerging technologies and methodologies that have the potential for modifying the human genome. A working group was formed to develop a revised definition of recombinant DNA.

Dr. Mickelson presented the working group report, which consisted of the group's suggested wording changes to the scope of the NIH Guidelines. The definitions within the NIH Guidelines had not been reviewed since early 1976, although some changes occurred when Appendices M, P, and K were added. This report was submitted to the RAC so that the full committee could examine both the words and intent and come up with a Proposed Action that could be presented at the December 1999 RAC meeting. Ms. Knorr explained that the ORDA has been working with the FDA to be as consistent as possible in definitions—for instance, "human gene therapy."

Dr. Mickelson noted that none of the suggested wording changes would change Appendix M-VIII, Footnotes of Appendix M, of the NIH Guidelines, that exclude certain types of experiments being considered as gene transfer to human subjects, e.g., vaccines containing microbialimmunogens. Dr. Markert suggested adding a footnote to ensure that chemotherapy or radiation should not be subjects for RAC review, even though these agents do modify or alter genetic material. Dr. Macklin suggested adding the word "deliberate" to "administration of genetic material(s) ..." to clarify that point.

Public Comment: *Dr. Wahl (Muscular Dystrophy Association, Inc.) repeated her earlier query about whether it is the RAC's intention to include what may be a new generation of drugs that will not change the components of the genome but that may change its activity; for example, drugs that upregulate production of a protein from a gene or change the way the genome is read by the cell, even temporarily. Dr. Mickelson clarified that this point is up for discussion within the working group and subsequently by the full RAC.*

One global alteration was changing the term "human gene transfer" to "gene transfer in human subjects." Another change, suggested by Dr. Macklin, was to change the word "experiment" to "research" wherever it was found, as "research" is clearer and more inclusive. Dr. Mickelson read the working group's proposed overall definition of human gene transfer research, to be added to as the new 4th paragraph of Section I-B of the NIH Guidelines. The new definition reads as follows:

> *"For the purpose of the NIH Guidelines, gene transfer research in human subjects is defined as the administration of genetic material(s), including DNA, RNA, oligonucleotide molecules, chromosomes, mitochondria, and nuclei, in order to modify or manipulate the human genome, the expression of a gene(s), gene product(s) or to alter the biological properties of living cells. Cells may be modified ex vivo for subsequent administration or altered in vivo by gene transfer product(s) or material(s) given directly to the subject. Examples of such processes include, but are not limited to, the administration of sequence specific oligonucleotides to alter a DNA sequence, administration of artificial or natural chromosomes, and transfer of genome containing organelles such as mitochondria or nuclei."*

Ms. Knorr noted that Section III-C-1covers only gene transfer research in human subjects. Dr. Noguchi stated that, although the public review of gene transfer has been for human clinical trials, some preclinical studies are being conducted in animals. Because gene transfer research in animals is a potential source of public contamination, he preferred that theNIH Guidelines maintain some control over animal gene transfer research. Ms.Knorr noted that Section III-D-4 of theNIH Guidelines, covers experiments involving whole animals; this category of experiments require IBC approval before initiation.

Ms. Meyers' query about who is overseeing human cloning experiments was answered by Dr. Noguchi: Human cloning is not related to the germ line but is alteration of biological characteristics and uses nuclear transplantation. According to Dr. Noguchi, the FDA has taken the unusual position of saying that human cloning would be under FDA jurisdiction, that it is too dangerous to allow such experiments at this time, and that if any proposal for human cloning is submitted to the FDA it would be put on clinical hold and would be brought to a public forum.

Dr. Wolff assisted in changing the wording in the second paragraph of Section I-B, "Definition of Recombinant DNA Molecules," to exclude antisense oligonucleotides but to capture specific modification of the genome by oligonucletodes, to read: "Synthetic nucleic acid segments are considered as equivalent to their natural nucleic acidcounterpart. If the synthetic nucleic acid segment is not biologically active and is not intended to be expressed as a polypeptide, it is exempt from theNIH Guidelines."

Additional comments and rewording suggestions should be forwarded by RAC members to the ORDA, which will then submit them to the working group, to be incorporated for discussion at a future RAC meeting.

Human Gene Transfer Protocol #9905-317: Phase I Clinical Trial Utilizing Gene Therapy for Limb-Girdle Muscular Dystrophy (LGMD): α, β, γ, or Δ Sarcoglycan Gene Delivered With Intramuscular Instillations ofAdeno-Associated Virus Vectors/Dr. Mendel

Principal Investigator: Jerry Mendell, M.D., Ohio State University
Reviewers:Ms. King and Drs. McIvor and Wolff
Ad Hoc Consultants:Abbey Meyers, National Organization for Rare Disorders
Richard Snyder, Ph.D., Harvard Institutes of Medicine, Harvard Medical School
Doris Zallen, Ph.D., Virginia Polytechnic Institute and State University

Background

During its preliminary review of the proposal, the RAC determined that this human gene transfer protocol raises multiple issues that, when considered collectively, were deserving of further public deliberation. These collective issues included: (1) This protocol represents the first clinical gene transfer investigation proposed for muscular dystrophy. (2) The current proposal involves intramuscular injection of an adeno-associated viral vector. If expression of the gene is observed, yet transient, multiple injections into each muscle affected by the disease might be required. It is unknown at present whether the administration of this vector to humans will generate an immune response that would preclude the participation in future studies in which the identical vector would be administered. (3) Some RAC members raised concerns about the proposed subject population, i.e. minors 16 and 17 years of age.

During its September 2 discussion of the protocol, the RAC commended the investigators' ongoing research efforts and desire to foster the development of gene therapeutics for a relatively small population of patients with a genetic disease. Several committee members commented on the appropriateness and completeness of the supporting preclinical animal studies, as well as the overall quality of the clinical research design.

The RAC specifically highlighted investigators ' willingness to delay initiation of the proposed study pending public deliberation by the full committee. Investigators' compliance with this request highlights their continued commitment to uphold the basic principles embodied in this unique Federal oversight process: (1) facilitating public awareness and understanding of the meaning and significance of the proposed research, (2) upholding standards of excellence in research design and Informed Consent, (3) maintaining public confidence in the field of human gene transfer research, and (4) ensuring continued

progress in this promising area of biomedical research.

Ms. King and Drs. McIvor, Wolff, and Snyder had submitted written reviews to which the investigators responded in writing. Drs. James Wilson and Joseph Hughes, University of Pennsylvania Medical Center, provided oral responses to additional questions raised during the meeting.

Protocol Summary

Dr. Wilson provided a short summary of the protocol. He also introduced Mr. Philip Cross, University of Pennsylvania Health System, in charge of quality assurance; Dr. Joseph Hughes, University of Pennsylvania Health System, translational research program; and Dr. Nelson Wivel, University of Pennsylvania, regulatory affairs.

For this phase I trial, the investigators propose to evaluate the safety of direct muscle injection of genes using a recombinant, replication-deficient AAV delivery system. One of the four humansarcoglycan genes--α, β, γ, or Δ will be administered to relevant individuals with sarcoglycan-deficient limb-girdle muscular dystrophy (LGMD). LGMD is a heterogeneous group of autosomal-dominant and -recessive conditions characterized by progressive limb-girdle muscle weakness with variable age of onset. Four of the recessively inherited forms of LGMD arecaused by deficiencies in transmembrane proteins called sarcoglycans. Absent, deficient, or alteredsarcoglycans (α, β, γ, or Δ) have a profound effect on the dystrophin-glycoprotein complex, resulting in membrane instability.

Patients in this trial will have proven sarcoglycan-deficient LGMD; the primary objective of this trial is to determine a safe dose using gene transfer to deliver a normal gene product to a small muscle in the foot, the extensor digitorum brevis. Four types of LGMD will be targeted for this study-α, β, γ, or Δ sarcoglycan-deficient LGMD.

In prestudy tests, patients will be asked to provide blood for DNA testing and a muscle biopsy for analysis with specific antibodies to determine whether they have a sarcoglycan deficiency and which corresponding gene is required for the study (α, β, γ, or Δ). Once a specific sarcoglycan deficiency has been clearly identified, the patient will be enrolled in the protocol for treatment with a viral vector that contains the specific sarcoglycan gene. The vector to be used for delivery of the gene is anAAV, which apparently does not result in any known disease in humans. Eligibility criteria include all ethnic groups, males and females, and a lower age limit of 16 years and an upper age limit of 65 years.

The study will involve delivery of a recombinant AAV vector carrying one of the humansarcoglycan genes (α, β, γ, or Δ) via needle injection of the extensor digitorum brevis muscle. One foot muscle of the patient will receive the AAV sarcoglycan vector, and the same muscle in the other foot will receive saline as a negative control. A designated staff member will know the code for the vector or saline, but this will be unknown to the clinical team injecting the two samples. If successful gene transfer can be achieved in the absence of toxicity, this preliminary study would be critical to further studies of gene transfer therapy in LGMD.

Measures of safety and toxicity will be assessed throughout the study. Specifically, 43 days post-gene-therapy, a biopsy of the extensordigitorum brevis muscles will be taken and analyzed. This is a nonessential muscle in the foot, and only a portion of the muscle will be removed for analysis of gene transfer. This will be a dose-escalation study consisting of two groups of patients. A minimum of three patients will be enrolled in each group. Safety and toxicity will be assessed for each patient within each group. The primary objective of this trial is to determine a safe dose ofAAV vector delivered via needle injection to a muscle, to be used in subsequent trials of efficacy forLGMD patients with one of the

sarcoglycan deficiencies. The primary endpoint by which safety will be assessed is the development of any grade 3 or higher treatment-related toxicities.

RAC Review and Discussion

Ms. King's review focused on ethical issues within the Informed Consent document and process and the inclusion of minors in the subject population. She indicated that the responses from the investigators to her questions and concerns were complete. Her primary concern was that this is a study that does not promise any direct benefit to individual subjects, which should be made crystal clear in the Informed Consent document and process. No treatment-oriented language should be used in the Informed Consent document, since no direct benefits are ensured by this study. The investigators responded that they would add language to state that this study is for the benefit of future subjects and society and would not be individually beneficial to study subjects. Ms. King's other primary concern involved the inclusion of subjects younger than 18 because participation in this research does not provide direct benefit, a fairly burdensome situation for minors. The investigators reiterated the small potential subject population, the fact that "minors" would be 16 and 17 years old and presumably capable of understanding the issues involved, and the fact that the local IRBs involved have reviewed this protocol using the regulation category that applies to subjects younger than 18. Although it was suggested that subject age should be restricted to 18 years and older, the investigators stated that patients with LGMD—a rapidly progressing, early-onset disease—ideally should receive treatment as soon as possible. Patients selected will be those who are far along in the disease and who are not ambulatory.

Ms. King also stated that the Informed Consent document should not be slanted toward encouraging subjects to agree to participate in this study. Dr. Wilson explained that consent discussions begin with the subject's physician, who is not as invested in the science as are the researchers and who, therefore, is likely to provide the subject with a more balanced view of the potential benefits and disadvantages of research participation. The investigators are enrolling subjects from a network of clinical sites. Dr. Wilson acknowledged that this could be a problem if the researcher and the primary care provider are the same individual.

Dr. Wolff's review included technical questions that were addressed by the investigators. His main concern, which was partially addressed by the investigators, was making clear that this initial trial is looking only at safety. He wanted the PI to expand on the steps being taken to make it clear to subjects that this is only a safety protocol and not a therapeutic one, even though the protocol does have a good chance of leading to a therapeutic endpoint. Safety and toxicity issues should be articulated to all stakeholders. The PI stated that these issues will be communicated clearly. The protocol will generate good information, and as a result, it will be difficult for anyone to confuse results that occur in a small foot muscle with major improvements in health.

Dr. McIvor was impressed by (1) the creative vector approach in this protocol, a new approach to the way AAV is generated, (2) the breadth of the toxicity studies, which will benefit AAV studies in general, and (3) the thorough clinical design of this protocol. He had four questions that, for the most part, had already been answered by the investigators:

1. *Dr. McIvor wanted more detail regarding the genotypic analysis that would be carried out. In response, the PI provided a 2½-page manuscript on how the sarcoglycan genetic analysis will be conducted.*
2. *LGMD is a recessive disease by the absence of a polypeptide gene product that is made up of four different subunits, the absence of any one of which causes the disease. Because the patient population is limited, the trial is proposing to treat any one of these deficiencies. One should expect*

potentially different results from one vector vs. another one, and lumping the data together might be scientifically invalid in terms of safety and efficacy. The investigators' response provided an additional description that these four subunits are subunits of the same protein and that there have been encouraging results in animal models regarding the study design.

3. *Dr. McIvor was concerned that the investigators had chosen a small muscle for the initial testing, even though they will want to distribute the vector equally throughout the body. The investigators responded by providing a description about how they will attempt to distribute the vector along the injection track when it is being injected.*
4. *The ultimate target for gene transfer inLGMD is disseminated. Dr. McIvor stated that this was the main reason he wanted this protocol to be reviewed publicly by the RAC—the disseminated target is the challenge of treating these types of diseases by gene transfer. The investigators responded that, ultimately, new methodologies will need to be developed to produce a more disseminated distribution; plans are already under way to meet this challenge. Ultimately, Dr. Wilson stated, to cure a patient with MD is likely to involve using an intravascular route rather than an intramuscular one.*

Dr. Snyder's review concluded that this protocol has an elegant design. He had one additional question for discussion: In a previous protocol (#9901-279) dealing with AAV for hemophilia B, AAV was delivered into normal muscle tissue. In this protocol, it is being delivered into diseased muscle, but the question is whether the investigators have any data on the efficiencies of gene transfer into these two different types of tissue. Dr. Wilson responded that inserting a gene into muscles of rhesus monkeys or hamsters means targeting differentiated muscle fibers, not satellite cells, with a hope that the fiber will be stabilized. In humans, the closer to end stage the disease is, the fewer the targets and therefore the less efficient the gene transfer.

Dr. Mickelson expressed her concern about generating immunity to the vector in this patient population, which will likely be exposed to more than one round of AAV. The current animal studies look promising, but perhaps the clinical trial should wait until there are better developed methods to ensure more efficient dissemination of the vector in the muscle. The PI discussed the issue ofreadministration. Studies on the immunology of AAV and adenovirus indicate that, under some circumstances, patients develop antibodies to the vector capsid proteins that substantially diminish the ability to readminister the vector. Based on animal studies, including primates, and in the context of muscle, this problem is unlikely to occur; when the liver is targeted, however, the immune response may need to be blunted initially, requiring a more complex therapy. The investigators stated that they now have another serotype, AAV-1, that may transduce more efficiently in muscle than AAV-2.

Dr. Zallen's review included concerns similar to those of Dr. McIvor and Ms. King. In addition, Dr. Zallenexpressed some concerns about the Informed Consent document and process. She wanted to see how the Informed Consent process would be implemented. The Ohio State University (OSU) consent form is problematic because of lack of clarity, poor general readability, and overly technical language. The assent form for parents to sign for their minor children must be separated from the adult consent form. A statement in the consent form says that the scientists manufactured the gene and that it replaces the defective gene, which Dr. Zallen believed should be corrected in the final document. The privacy of study participants might be compromised; it is important to let participants know to what extent theMDA will publicize this study and its results. Investigator responses to Dr.Zallen's queries about the consent form indicated that the OSU form is required by OSU IRB and cannot be changed. They have also written an assent form to accompany theOSU consent form.

Ms. Meyers queried whether thisAAV vector has been used in humans and, if so, what is known about its use. Dr. Wilson responded thatAAV seems to work well because it gets into the cells, is stable, and does

not elicit inflammation or immunity. It seems to work best in cells of the muscle, liver, brain, and retina. The first trials in which humans were tested with AAV were for cystic fibrosis in the lung, where it was discovered that it was not efficient. There has been one previous protocol of AAV in muscle for hemophilia B (#9901-279/Manno) in which she used AAV to express a Factor IX gene in the skeletal muscle. Although there have been just a small number of patients on AAV for a few weeks and most of the knowledge about it is based on animal studies, AAV is quite common in the human population as a common virus that does not cause a reaction in humans.

Ms. Meyers wondered whether, if this treatment works, there would be a way to distribute the four different types of vector to people with LGMD who want it. Dr. Wilson responded that his laboratory is not currently in the business of commercial-scale production, and he is not aware of any company that would be willing to produce and distribute this vector. Dr. Noguchi added that the current distribution system is not favorable for LGMD or any other rare disease and that the FDA's Office of Orphan Drug Development is attempting to expand the ability for these kinds of drugs to be distributed. The National Gene Vector Laboratories could be empowered to distribute the vectors once those treatments are proven effective. Dr. Noguchi also postulated that treatments for rare diseases may not be able to be delivered by the commercial sector, and a method of public sector involvement in distribution may need to be fashioned.

Dr. Mickelson summarized the items to be addressed in the letters to OSU and the University of Pennsylvania:

- *the OSU consent form, which suffers from lack of readability and clarity;*
- *the University of Pennsylvania consent form, which the RAC considered excellent and a model;*
- *excellent animal models, toxicity studies, and vector preparation;*
- *the high quality of the clinical protocol; and*
- *the importance of discussing, with this small patient population, the possibility of an immune response and that participation in this study may have some effect on their ability to participate in future trials.*

Dr. Noguchi stated that the FDA has asked Dr. Wilson to refrain from enrolling patients until after this RAC discussion; the investigators have complied. Six potential subjects have been prescreened for participation in this protocol, but gene transfer intervention has not occurred.

RAC Recommendations

The RAC recommended that the Ohio State University Informed Consent document should be modified as follows:

Unknown Risk Related to Future Participation in Similar Research

The proposed study is a phase I safety and toxicity trial involving Limb Girdle Muscular Dystrophy, a disease that affects only a small percentage of individuals. Patients enrolled on this study will receive intramuscular injection of an adeno-associated vector delivering the α, β, γ, or Δ-sarcoglycan gene. Although an immune response to this viral vector was not observed in preclinical animal studies, it is unknown at the present time whether the administration of this vector to humans will generate an immune response that would preclude their participation in future studies in which the identical vector would be administered.

The following language was recommended for inclusion in the Informed Consent document:

"An immune response has not been observed [to this viral vector] in preclinical animal studies, but it is not known if administration of this vector to humans will generate an [immune] response that would preclude participation in future studies (if the identical vector is to be administered)."

Unknown Risk to Privacy

During the course of its discussion the RAC was informed that the Muscular Dystrophy Association intends to publicize this first human gene transfer protocol involving muscular dystrophy. Wide-spread publicity could elicit significant media attention and possibly compromise the privacy of study participants. Therefore, the Informed Consent document should emphasize the fact that agreeing to participate in this study may have unintended consequences related to privacy.

Consent vs. Assent

The Informed Consent document contains numerous references such as, "I/my child", "am/is", "am/is not" that may significantly confuse potential research subjects and their parent or legal representative.

To ensure that potential study participants and their parent or legal representative have optimal understanding of the proposed study objectives, duration, experimental procedures, alternatives, risks, benefits, etc., the RAC recommends that two separate documents should be used rather than a single document that contains multiple-choice phrases: (i) an Assent document that is written in language can be easily understood by minors (the proposed study involves minors between 16 and 17 years of age who are capable of providing assent), and (ii) a Consent document that can be easily understood by subjects over 18 years of age. Although a representative of the University of Pennsylvania indicated that Ohio State University has a separate Assent form, this document was not submitted to NIH ORDA for RAC consideration.

Financial Responsibility for Research-Related Costs

Potential research subjects should be fully informed of financial responsibilities associated with their participation in this study; therefore, the RAC recommends that the Informed Consent document be modified to clarify whether the research subject and/or their parent or legal representative, Ohio State University, or a third-party payer is responsible for the following costs: (1) costs associated with participation in this study, e.g., costs associated with the genetic tests to determine whether a sacroglycan deficiency is the cause for the subject's muscular dystrophy; and (2) costs associated with medical treatment in the event of a research related injury related to their participation in this study.

Inaccuracies and Inconsistencies

- *Page 1, Paragraph 2, of the Informed Consent document currently reads: "Scientists are able to manufacture the normal gene for sacroglycan... ." This statement should be amended to read: "The investigators will administer an agent that is capable of producing the normal gene."*
- *Page 1, Paragraph 4, of the DNA Testing in Limb Girdle Muscular Dystrophy Consent document currently reads: "Gene therapy is an attempt to replace the abnormal gene with a normal one." While this statement is correct for some types of gene transfer interventions, this is not an accurate description of the objectives of the proposed study. For clarification, this statement should be amended to read: "The investigators are attempting to determine whether administration of this vector containing a sarcoglycan gene results in the synthesis of a protein that restores the loss of*

function associated with the abnormal gene."

- *The Informed Consent document contains inconsistent acronyms for the General Clinical Research Center, that may be confusing to potential study participants. While the acronym used on Page 1, Paragraph 5 reads: "GCRC"; the acronym used on Page 2, Paragraph 3 reads: "GRC". Consistent with NIH policy, the acronym, "GCRC" should be used to reference this facility through all documents.*

Committee Motion 7

A motion was made by Dr. Friedmann and seconded by Dr. McIvor that theRAC's concerns have been addressed and dealt with and that the RAC hopes that this phase I study will proceed. Dr. Mickelson stated that a letter will be sent toOSU articulating RAC members' concerns about the OSU consent form as well as communicating to participants the uncertainties about the impact on subsequent clinical trial participation. The motion passed by a vote of 11 in favor, 0 opposed, and 0 abstentions.

Day One Closing/Dr. Mickelson

Dr. Mickelson stated that one protocol (#9903-295) that was to have been reviewed on Day Two of this RAC meeting was withdrawn, because the investigators found the suggestions of the RAC reviewers interesting and pertinent enough to withdraw their protocol. She then adjourned the first day of the September 1999 RAC meeting at 5:00 p.m. on September 2.

Day Two Opening Remarks/Dr. Mickelson

Dr. Mickelson opened the second day of the September 1999 RAC meeting at 8:30 a.m. on September 3. She reviewed the day's agenda, which included a data management report, a proposed action to incorporate the RAC's statement on prenatal gene transfer research in theNIH Guidelines, a discussion on submission and reporting requirements for human gene transfer experiments, an FDA presentation on adverse event reporting and review, and a review of human gene transfer protocol #9902-284.

Data Management/Dr. Greenblatt

Dr. Greenblatt thanked Dr. Rosenthal for preparing data management charts and tables that were provided to the RAC.

To date, 331 human gene transfer protocols have been registered with theORDA, including 295 gene therapy protocols, 34 gene marking protocols, and 2nontherapeutic protocols. Of the 295 therapeutic protocols, 27 are for human immunodeficiency virus (HIV) infection, 41 for monogenic diseases, 206 for cancer, and 21 for other disorders.

Fourteen amendments and four updates to human gene transfer protocols have been received since the June 14, 1999, RAC meeting, most of which were minor (e.g., addition of a new test clinical site to the study, changes in patient eligibility, and minor dosage changes). Of note was an amendment to Protocol #9812-274, a phase I multicenter study of increasing single dose of NV1FGF administered by intramuscular injection in patients with severe peripheral artery occlusive disease. The inclusion requirement that restricted enrollment to only sterile patients has been modified to allow patients of childbearing potential. This new patient population must agree to use barrier contraception for 6 months after initiation of treatment. This change was made following the decision by the FDA's Center for Biologics and Evaluation to lift its ban on fertile patient enrollment in these types of studies.

Five safety reports of human gene transfer protocols were submitted during this reporting period, all of which reported complications not related to the gene therapy products.

The ORDA received 21 new protocols during this reporting period, 18 of which were exempt from public RAC review. Two protocols (#9905-317 and #9902-284) were reviewed at this meeting; one (#9903-295) was withdrawn from review at this meeting and was deferred until the December 1999 RAC meeting.

Proposed Action to the NIH Guidelines Regarding Prenatal Gene Transfer Research/Ms. Meyers and Dr. Zallen

On July 31, 1998, Drs. W. French Anderson, University of Southern California, Los Angeles, CA, and Esmail Zanjani, Veterans Hospital, Reno, NV, submitted the following two preliminary protocols for in utero gene transfer: (1) In Utero Gene Transfer for the Treatment of ADA-Deficient SCID and (2) In Utero Gene Transfer for the Treatment of a Thalassemia. These two "preprotocols" provided the catalyst for the RAC recommendation to the NIH Director, made at its September 1998 meeting, that a Gene Therapy Policy Conference (GTPC) be held on the topic of prenatal gene transfer. On January 7-8, 1999, the NIH convened a GTPC titled "Prenatal Gene Transfer: Scientific, Medical, and Ethical Issues." This meeting provided a public forum for the presentation and discussion of relevant scientific data and policy issues by members of the scientific, biomedical, ethical, and legal communities and the public. The anticipated outcome of the GTPC is twofold: (1) development of a policy paper to highlight the conclusions of the working groups and conference participants and (2) a comprehensive list of issues that should be discussed further by the RAC at subsequent meetings. To achieve this goal, RAC members and ad hoc experts were assigned to one or more of the following working groups on the basis of their individual areas of expertise: Working Group I—Preclinical Research Issues, Working Group II—Clinical Research Issues, and Working Group III—Ethical, Legal, and Societal Issues. At the March 11-12, 1999, RAC meeting, the RAC discussed the three working group reports and issued a consensus statement that reads: "The RAC continues to explore the issues raised by the potential of in utero gene transfer research. However, at present, the members unanimously agree that it is premature to undertake any human in utero gene transfer experiment."

At the current meeting, a proposed addition to the Appendix M, "Points to Consider," preamble, was offered to appear after paragraph 3:

> *"The RAC continues to explore the issues raised by the potential of in utero gene transfer research. However, at present, the RAC concludes that it is premature to undertake any human in utero gene transfer experiment. Significant additional preclinical and clinical studies addressing vector transduction efficiency, biodistribution, and toxicity are required before a human in utero gene transfer protocol should proceed. In addition, a more thorough understanding of the ontogeny of human organ systems, such as the immune and nervous systems, is needed to better define the potential efficacy and risks of human in utero gene transfer. Prerequisites for considering any specific human in utero gene transfer procedure include an understanding of the pathophysiology of the candidate disease and a demonstrable advantage of the in utero approach. Once the above criteria are met, the RAC would be willing to consider well-rationalized in utero gene transfer protocols."*

The Proposed Actions to include the RAC consensus statement in Appendix M, Points to Consider, was published in Federal Register of August 11, 1999 (64 FR 43884) for public comment. No public comment was received in NIH/ORDA. At this meeting, the RAC discussed the Proposed Actions.

Ms. Meyers and Dr. Zallen reviewed the above wording and stated that it represents an accurate reflection of the determinations of all the working groups. Ms. Meyers expressed her opinion that gene transfer research holds great promise for serious diseases, that particular attention should be paid to the severity of the disease, and that the disease chosen should be one that is fatal in infancy or childhood.

Committee Motion 8

A motion was made by Dr. Juengst and seconded by Dr. Markert to accept the above Proposed Action to include the RAC consensus statement as a new paragraph 3 in the preamble of Appendix M, Points to Consider in the Design and Submission of Protocols for the Transfer of Recombinant DNA Molecules into One or More Human Subjects (Points to Consider), of the NIH Guidelines. The motion passed by a vote of 11 in favor, 0 opposed, and no abstentions.

Discussion Regarding Submission and Reporting Requirements for Human Gene Transfer Experiments/Dr. Mickelson

The discussion regarding submission and reporting requirements for human gene transfer experiments was based onissues that arose previously about what types of materials can be held confidential in a protocol submission.

First, although companies and investigators have the right to hold certain types of information as confidential because they have invested a lot of development time, Dr. Mickelson pointed out that the NIH Guidelines are clear that an entire protocol cannot be labeled as confidential. However, a few protocols marked "Entirely Confidential" have been submitted to the ORDA. When this occurs, the protocol can be seen by RAC members, but it cannot be discussed in public, which runs counter to the intent of the NIH Guidelines and the ORDA. Dr. Mickelson stated that the RAC has no desire to damage corporations by trying to force the revelation of information that could be patentable. However, most aspects of a protocol and the responses to Appendix M are within the RAC's purview, and information is expected to be provided that would allow public discussion of protocols. When protocols have been marked confidential in their entirety, the ORDA has contacted the PI and told the sponsoring institution that such designation is not in compliance with the NIH Guidelines; the ORDA then works with the PI and the institution to present the protocol in a way that does not breach confidentiality.

Second, Dr. Mickelson noted that, on several occasions, adverse events were not reported to IBCs or to the ORDA. In some cases this appeared to be a simple lack of awareness about which bodies should be informed about adverse events. In other cases, the adverse events were reported as confidential, which precluded them from public RAC discussion and from inclusion in the ORDA database. If the adverse event is related to the gene transfer protocol or to administration of the vector, then access to this information would be critical for other researchers.

Dr. Noguchi was asked to comment about the adverse event reporting and review definitions for the FDA, and Dr. Patterson was requested to review the issues faced by the ORDA.

Schering Corporation submitted a letter to the ORDA, dated August 25, 1999, stating that "We continue to be concerned that the information requested by NIH in connection with gene therapy protocols contains information that is confidential and proprietary." Dr. Markert asked for some opinions from industry representatives (Schering Corporation and others) about the confidentiality issue.

Dr. Patterson reiterated that the advances in gene transfer research in the United States are predicated on public trust and confidence that the research is being conducted in a safe and ethical fashion. Therefore,

the public sharing of information in forums such as the RAC is critical to the field.

Dr. Friedmann queried whether there is language in the NIH Guidelines that states that all adverse effects must be reported and that no confidentiality issues can be raised regarding the reporting of adverse events. He also warned that the RAC should be sensitive about the issue of perception—even if adverse effects are unrelated to the procedure, public or RAC perception could produce unwarranted damage to commercial interests simply through public discussion. Dr. Friedmann stated that the public good and public access to the information about adverse events should override the short-term financial interest to the corporations.

Ms. Knorr and Dr. Noguchi presented an example of one glioblastoma protocol using a vector expressing Herpes simplex thymidine kinase, in which an adverse event (patient death) occurred. A major newspaper called the ORDA and asked for comment by stating, "We have information that gene therapy is killing patients" and then cited the particular protocol. Working with the FDA, ORDA invited the investigators to present the adverse events to the RAC and the public was reassured that the adverse events were not directly related to gene transfer.

Dr. Noguchi discussed the question of possible financial harm as a result of public discussion, a fear expressed to the FDA by many companies. In his opinion, a large part of this fear is a mistrust by the pharmaceutical companies of what public reaction will be. However, Dr. Noguchi reiterated that reasonable people are willing to take reasonable risks in dreadful diseases. Dr. Macklin added that, if research subjects take risks, companies and investigators should also be willing to take risks by contributing to public discussion.

Ms. King suggested three ways to deal with the issue of confidentiality: (1) the language of a note in the preamble of Appendix M, Points to Consider, of the NIH Guidelines clearly states that "any application submitted to NIH/ORDA shall not be designated as 'confidential' in its entirely," and the ORDA should continue to remind investigators and institutions to pay close attention to these requirements; (2) the language in the note of AppendixM preamble regarding confidentiality of protocol submission could be expanded to include annual reporting, and adverse event reporting; and (3) current discussion on this issue reminds people that public RAC discussion of protocols will not ruin a company but rather shares useful information in a fruitful way.

Dr. Ando explained to the RAC that, from an industry perspective, adverse event reporting is complicated. There are different "grades" of adverse events, some of which for example, serious adverse event, have been defined by the FDA. Large corporations like Schering Corporation have fairly formalized way of assessing adverse events. More dialog with industrial sponsors would help the RAC obtain the information it wants from a sponsor.

Dr. Markert noted that adverse events possibly related to the therapy should be included in the Informed Consent document. Study participants need to know events that have occurred to make an informed decision about whether to participate in the study. Therefore, it would be difficult to keep such events secret. Dr. Ando stated that, for serious adverse events, there is a requirement to report back to the IRB; the IRB must then add this information to the Informed Consent document. Dr. Mickelson added that the NIH Guidelines state that serious adverse events are required to be reported to the IBCs as well. Dr. Patterson drew the RAC's attention to the appropriate section of the NIH Guidelines, i.e., Appendix M-VII-C, Adverse Event Reporting.

Dr. Noguchi explained that the definition of a trade secret was decided in the District Court about 15 years ago: A trade secret is not an idea or a concept but is an actual process that is used to manufacture a

product used in research. Whether public safety overrides financial implications (i.e., whether public discussion should receive higher priority than the possible financial concerns of making supposedly proprietary information public) has not been clearly addressed by the courts. The FDA has a designation titled "commercial confidential product" that is currently being tested in court.

Ms. Meyers pointed out that the FDA operates under different rules than the NIH. The NIH has a different set of responsibilities, and therefore, information that can not be released by the FDA may be able to be released by the RAC.

Dr. Mickelson listed parts of protocols that could and could not be kept confidential. Patentable items, intellectual property, production process, and financial information might be in the interest of the company to be held confidential. Informed Consent documents, protocol design, inclusion/exclusion criteria, sampling and testing regimens, and Appendix M answers are not appropriately held confidential.

Ms. King asked Dr. Cohen whether confidentiality regarding adverse events has been an issue with the OPRR. Dr. Cohen responded that the OPRR does not have a mandate for public discussion and that IRB meetings in some States are public meetings and in others are closed to the public.

Dr. Macklin stated that there is a sharp distinction between justifying nondisclosure of an adverse event vs. keeping secret all other aspects of a protocol. There appears to be no appropriate justification for confidentiality of adverse event reporting, even though companies might like to keep that information secret because of the possibility of adverse public perception.

Dr. Mickelson concluded this portion of the discussion by suggesting that, after Dr. Noguchi's presentation, the RAC might want to decide whether language changes or additions to the NIH Guidelines would clarify that the reporting of adverse events is not to be kept confidential. The appropriate working group would take such advice under consideration and would report back to the full RAC at its December meeting.

FDA Presentation on Adverse Event Reporting and Review/Dr. Noguchi

Dr. Noguchi presented some basic information on adverse event reporting, which he suggested should be termed "adverse experience" reporting, in relation to IND applications. "Adverse experience" for drug and biological product approved for marketing is defined in the latest US Code of Federal Regulations (21 CFR 600.80(a) for biologics and 21 CFR 310.305(b) for drugs) as:

> *"Any adverse event associated with the use of a biological product (drug) in humans, whether or not considered product (drug) related, including the following: An adverse event occurring in the course of the use of a biological product (drug) in professional practice; an adverse event occurring from overdose of the product (drug) whether accidental or intentional; an adverse event occurring from abuse of the product (drug); an adverse event occurring from withdrawal of the product (drug); and any failure of expected pharmacological action."*

IND safety reports for investigational biological products are defined in US Code of Federal Regulations, 21 CFR 312.32. A 'serious adverse event' is defined as any expected or unexpected adverse event, related or unrelated to the intervention, occurring at any dose that results in any of the following outcomes: death, a life-threatening event, in-patient hospitalization or prolongation of existing hospitalization, a persistent or significant disability/incapacity, or a congenital anomaly/birth defect. Important medical events that may not result in death, be life-threatening, or require hospitalization also may be considered

a serious adverse event when, based upon appropriate medical judgement, they may jeopardize the human gene transfer research subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

Adverse experiences may be related to dosage, thus the importance of preclinical studies; biology, especially unknown long-term consequences; route of administration, including method-of-entry concerns; other components such as excipients, biologics, drugs, or devices; and adventitious agents. The highest level of suspicion regarding adverse experiences occurs in the first 24 hours; however, for the agents with which the RAC is dealing, longer time courses are also important.

Dr. Noguchi stated that animal models do not necessarily prepare investigators and subjects for human experience with a drug. He offered one example, a study in which he was involved, of patients with lymphoma being given a monoclonal antibody (OKT3) directed against T cells, at a very low dose of 1 microgram. Although no effect was perceived on patients at a dose of 1 milligram, the effect at 1 microgram (a thousandfold lower) was to produce an adverse experience in the form of a cytokine cascade, in which the much lower dose triggered lymphocytes in the blood to secrete many types of lymphokines that have an extraordinarily toxic effect.

Other examples of adverse experience possibilities mentioned by Dr. Noguchi included:

- *Route of administration/method of entry. Oral administration may cause reversion to the wild-type virus because of the high degree of mutation and replication in the intestinal tract. Injection-site necrosis may occur, in which the drug works but, if injected several times in the same muscle site, tissue at that site may begin to die.*
- *Use of excipients. One example is allergic reactions to fetal bovine serum that may be left in the preparation.*
- *Adventitious agents that are not intended to be in the final product but are a component of it. One example is hepatitis virus; it is likely that millions of Americans who have hepatitis C, often asymptomatic, acquired the disease through contaminated blood products.*
- *Time course concerns. For agents with which the RAC is dealing, time courses other than the first 24 hours contain great potential hazard. One example is Guillain-Barré syndrome associated with swine flu vaccination in the 1970s. Another example is malignancy after immunosuppression; OKT3 was used as part of a regimen to induce tolerance for transplanted organs, but it also produced B-cell lymphoproliferative syndrome years after introduction, which was reversible by stopping OKT3.*

Public Comment. *Public comment was offered by two industry representatives. Dr. Angus Grant, GenCell Division, Rhône-Poulenc, offered an industry perspective on confidentiality issues. He began by stating that the United States is leading the way with gene therapy for two reasons: because of the public trust—and a great deal of the public trust has been established because of the FDA and RAC processes—and the investment opportunity. Some companies consider the entire gene therapy process as intellectual property. Products in late-phase development can be hurt by negative publicity.*

Public Comment. *Dr. J. Tyler Martin, SyStemix, stated that adverse events that are serious or unexpected (defined as not listed in the investigative brochure) are reported immediately (defined as within 7 to 15 days) to the FDA. He suggested adding "serious or unexpected" to language that defines adverse events; Ms. Knorr noted that the NIH Guidelines currently state "serious" but that adding "or unexpected" to that wording would be considered by the working group.*

Dr. Mickelson suggested that the RAC insert itself into the reporting loop for adverse experiences, using

the same definitions as the FDA, rather than generating a new—and therefore additional—reporting loop. Dr. Greenblatt agreed that a single reporting system, similar to the FDA's, would be beneficial and would be less cumbersome for industry. Dr. Ando explained that the FDA system includes an expedited system of reporting serious or unexpected adverse experiences coupled with an annual update for all grades of adverse experiences, with consent forms being rewritten by the IRB on an annual basis.

Dr. Friedmann expressed his concern about limiting reporting requirements on adverse experiences to those considered to be serious, which would limit the RAC's view and restrict the field's ability to update and provide adequate consent documents.

In response to Dr. Ando's concern that, contrary to the FDA's data management system, the ORDA does not have a database that could manage the expected volume of data for adverse experience reporting, Ms. Knorr stated that the ORDA has been working on the Human Gene Transfer Information System (HGTIS) that should be operational within the next 6 months. This system will have 400 data fields that will provide fully developed and extensive reports that will be available on the ORDA Web site.

Dr. Cohen stated that most of the adverse experience reports are being submitted to the appropriate IRBs. The problem, according to feedback from the IRBs, is that IRBs are receiving many adverse experience reports that they do not know how to handle. He also mentioned the issue of data safety monitoring boards, which many people in the field see as a possible solution to this problem—a knowledgeable committee would receive adverse experience reports and would process them using their expertise.

Dr. Mickelson suggested that a working group be formed to draft language for a Proposed Action that the RAC would examine at its December 1999 meeting. This group would examine the following issues: types of adverse experiences, suggested reporting system, appropriate language to capture the desired kinds of adverse experiences, and appropriate areas for confidentiality. She suggested that FDA and OPRR input into the proposed wording would be crucial. One of the purposes of bringing this Proposed Action to the RAC would be to assist the ORDA by removing some of the communication steps now necessary to release information marked confidential in answer to Appendix M and thus get proposals to the RAC in a more timely fashion.

Ms. King stated that the initial language developed by the NIH legal counsel and ORDA (included in the meeting material) was adequate with the exception of adding "or unexpected" after "serious" to the language in Appendix M-VII-C, Adverse Event Reporting. She suggested that adding "or unexpected" is a starting point and that the ORDA should circulate that text to the RAC members via e-mail to determine whether any other changes are necessary. Ms. King suggested the following statement be included in Appendix M-VII-C:

> *"Adverse event reports shall not be designated as 'confidential' either in whole or in part. Adverse event reports are essential to decision making by IBCs, IRBs, and potential subjects of gene transfer research in humans. The public disclosure of adverse events [in human gene transfer research] is also essential to public understanding and evaluation of gene transfer in humans. Adverse event reports should be made available for public discussion [by the RAC] without the inclusion of proprietary or trade information."*

Committee Motion 9

A motion was made by Ms. King and seconded by Dr. Juengst to form a working group to develop a proposed action to be published in the Federal Register for consideration by the RAC at its December

meeting regarding the issue of public access to protocol submissions and serious adverse or unexpected event reportings. The RAC endorsed the initial language developed by the NIH legal counsel and ORDA as a starting point for the development oftheproposed action. The motion passed by a vote of 10 in favor, 1 opposed, and 0 abstentions.

Sense of the Committee

Dr. McIvor requested a sense of the RAC to provide strong support for theORDA to pursue cases in which confidentiality is used to withhold disclosure of protocol submissions and adverse experiences. The vote to support ORDA efforts was 10 in favor, 0 opposed, and 1 abstention.

Human Gene Transfer Protocol #9902-284: Phase I Multicenter, Single-Treatment, Dose-Escalation Study of Human Factor VIII Vector [hFVIII(V)] for Treatment of Severe Hemophilia A/Dr.Ragni
Principal Investigator: Margaret Ragni, M.D., University of Pittsburgh (Sponsor: Chiron Corporation)
Reviewers:Drs. Chow, Macklin, and Markert
Ad Hoc Consultants:Abbey Meyers, National Organization for Rare Disorders
Doris Zallen, Ph.D., Virginia Polytechnic Institute and State University

Background

During its preliminary review of this human gene transfer protocol, the RAC concluded that systemic delivery of retroviral vector represents a novel gene delivery approach that raises important vector biodistribution and gene expression issues that warrant public deliberation by the full committee. In making this recommendation, the RAC carries out its responsibility to uphold the basic principles embodied in this unique Federal oversight process: (1) facilitating public awareness and understanding of the meaning and significance of the proposed research, (2) upholding standards of excellence in research design and Informed Consent, (3) maintaining public confidence in the field of human gene transfer research, and (4) ensuring continued progress in this promising area of biomedical research.

Protocol Summary

This protocol is sponsored by Chiron Corporation, which produces the vector. The gene being evaluated is a cDNA-encoding human Factor VIII (hFVIII) lacking a portion called "B domain." This gene is packed in a murine-leukemia-virus-derived retrovirus.

Hemophilia is a congenital X-linked disorder that affects 1 in 10,000 males. It is caused by a deficiency of hFVIII clotting factor, which results in bleeding into muscles and joints, hematomas, hemarthroses and, less frequently, central nervous system and retroperitoneal bleeding. Severe hemophilia A is a congenital bleeding disorder that results from the lack of a protein in the blood known ashFVIII, which is necessary for clotting. Affected individuals are born with a defective gene controlling hFVIII production. Because the hFVIII gene is located on the X chromosome, virtually all affected individuals are men. Conventional treatment of hemophilia A requires intravenous (IV) injection ofhFVIII to stop bleeding when it starts. An alternative treatment approach would be to provide a working copy of thehFVIII gene to the individual so that the body could produce hFVIII continuously at a level sufficient to prevent bleeding. This would protect the subject from developing progressive joint disease, pain, and disability—the usual complications of hemophilia treated in the conventional manner.

The study is a phase I multicenter, single-treatment, dose-escalation study. The objective of the study is to evaluate the safety and tolerability of human Factor VIII vector (hFVIII[V]) IV infusion at potentially therapeutic doses in adults with severe hemophilia A. Subjects must have severe hemophilia A (defined

as having less than 1 percent hFVIII), be at least 25 years old, be previously treated on at least 100 occasions with hFVIII concentrates, have no present or pasthFVIII inhibitor, and be sterile. Patients can be HIV-positive but cannot be on reverse transcriptase inhibitor and can be hepatitis C-positive but must not be in liver failure. Three patients have already been enrolled in this trial.

This phase I clinical study is designed primarily to evaluate whether administration is safe in humans at doses within the range shown to be safe in animals. (The vector has been shown to be well tolerated in rabbits, mice, and dogs.) Blood levels of hFVIII will be measured to evaluate whether hFVIII is produced at levels potentially protective against bleeding. The goal is to reach at least 7 percent of the normal blood level, sustained for at least 12 weeks. This level would be expected to prevent day-to-day bleeding that would otherwise commonly occur. Each participant will receive a single dose, administered intravenously into an arm or hand vein, in three equal parts on each of three successive days. After the highest dose is reached, all subjects will continue to be monitored closely for approximately 1 year and then less intensively in a lifelong surveillance registry to evaluate long-term safety.

Dr. Ragni indicated that hemophilia is an ideal disease for testing gene transfer therapy for two main reasons: (1) Current treatment is suboptimal and (2) neither precise regulation of thehFVIII level nor tissue specificity is required. This study's aim is to obtain a hFVIII level similar to that of mild disease and to prevent spontaneous bleeding, from which the major morbidity of hemophilia A is related. The potential benefits of gene transfer include providing prophylaxis—a continuous hFVIII level without peaks and troughs—that could prevent spontaneous hemorrhages, markedly decrease morbidity and mortality, increase the threshold for bleeding, reduce or prevent disabling joint arthritis, reduce costs and inconvenience and medical care, and improve patients' quality of life.

Safety studies were conducted for single-treatment and repeat/booster dose treatment. Single-treatment studies indicated that hFVIII(V) was well tolerated in rabbits, mice, and dogs, with no mortality. At doses 7.5 times the highest phase I dose, there wasanaphylactoid reaction in 2 of 10 rabbits; an association enhancement of preexisting neutrophil infiltration in pulmonary vessels was found, which was largely resolved by day 15. There were no similar findings on studies for up to 3 months or longer, and these findings were also noted in other studies of adenoviral vectors in rabbit models. In the repeat studies—booster dosing in animals that had no response, low response, or short-term response—no adverse events were noted on repeat administration in 12 rabbits, 1 normal dog, and 3 hemophilic dogs. Anaphylaxis was noted in one dog that had preexisting IgE antibody to fetal bovine serum and a previous similar reaction to canine plasma.

The pharmacologic studies included animal studies in which human hFVIII levels were measured in juvenile and adult rabbits that were treated with thehFVIII(V), which was comparable to potential therapeutic levels and with long-term expression up to 2 years. Dose response studies in rabbits found that the higher the dose the greater the proportion of animals responding, the shorter the time to response and the greater thehFVIII level. In terms of duration of response, the two hemophilia A dogs that were treated with thehFVIII(V) showed a shortening of the whole-blood clotting time for as long as 2 years. Biodistribution studies indicated that, in 77 rabbits and 4 dogs that received .07 x 10^8 to 60 x 10^8 colony forming unit (cfu) equivalents per kilogram, vector sequences by polymerase chain reaction (PCR) were localized primarily in the liver, spleen, and bone marrow, with intermittent threshold levels noted in other tissues, including lung, kidney, lymph node, and testes. In estimating the risk of inadvertent germ-line transmission, the researchers concluded that the semen samples were negative for vector in all studies and that the localization of the vector sequence in testes does not lead to presence in semen.

After FDA approval, the trial enrolled three subjects with severe hemophilia A, all of whom were enrolled at the time the RAC letter was received. The median subject age is 33 years. All three subjects are

hepatitis C virus positive, and two of them are HIV positive. With a median time on study thus far of 8 weeks and the longest being 12 weeks, there have been no serious adverse events; no change in blood counts, liver function tests, chemistries, viral load, hepatitis C virus (HCV), or HIV/RNA; no anti-FVIII inhibitors; and the semen have been negative for vector sequences byPCR.

RAC Review and Discussion

Drs. Chow, Macklin, and Markert submitted written reviews to which the investigators responded in writing. Drs. Ragni, Jolly, Roehl, Leibrandt, and Mr. Gay provided oral responses to additional questions raised during the meeting.

Dr. Markert's review included the following:

- *Concerns about evaluating investigators' responses: Because of the use of differing units of measure, equivalencies between animal studies and human doses were not immediately apparent.*
- *Concerns about allergic reactions: Two of 10 rabbits died after receiving a high dose of the vector, suffering a fatal anaphylactoid reaction. The RAC suggestions included testing other species (other than the 12 dogs already tested) for allergic reaction, plus possibly excluding patients with allergic tendencies. Dr. Ragni indicated that, of the three patients already enrolled in the trial, two had some flushing as a result of the injection; no allergic reactions have occurred.*
- *The consent form should be rewritten because of readability concerns—the type is small, and spacing makes reading difficult.*
- *The suggestion, echoed by other RAC members, that the trial include subjects beginning at age 18, rather than at age 25 as planned, was answered by Dr.Ragni, who indicated that that change could be made. She explained that the investigators had agreed originally on 25 years of age or older because of the initial concerns about germ-line transmission, but they have recently been discussing about lowering the age to 18.*

Dr. Macklin limited her review to the ethical considerations. She had asked questions about recruitment that were not stated in the protocol—Who would recruit subjects, and how would the recruitment proceed?—and the investigators answered those questions adequately by describing the individuals doing the recruitment and where it will take place. This is the first timehFVIII(V) will be administered to human subjects; potential benefits and risks are largely unknown. Possible benefits include reduced bleeding or prevention of bleeding, normalization of daily life, decreased pain and anxiety, preservation of normal joint function, decreased disability, and improved quality of life. Possible risks include acute toxic or hypersensitivity reactions, inhibition of clotting activity, exacerbation of existing chronic diseases, insertional mutagenesis or infection with replication-competent retrovirus, insertion into germ cells and inadvertent germ-line transmission, and inadvertent overdose of the experimental agent. Given the total absence of experience with this experimental agent in humans, Dr. Macklin concluded that there is no way to arrive at a realistic risk-benefit assessment. The ethical acceptability of this study must therefore rest on the adequacy of the protections provided for any harms that may develop. In response, DrRagni indicated that subjects will be followed for the rest of their lives. The half-life of the vector is minutes in the bloodstream, so there is little risk of horizontal transfer. The protocol appears to have identified safeguards for foreseeable risks and provided for immediate remedies as well as long-termfollowup; Dr. Macklin expressed her belief that Dr. Ragni's responses and the safeguard provisions were adequate.

Regarding Informed Consent document issues, Dr. Macklin stated that the form is complete and comprehensive but not comprehensible; some terms need explanation, and the language should be simplified. Since this study is confined to male subjects, the two sentences about possible pregnancy should be deleted. In response, Dr. Ragni noted that it is possible for hemophilia A to exist in a female, so

the language about pregnancy needs to remain in the Informed Consent document. However, Dr.Ragni indicated that investigators do not plan to enroll female hemophiliacs in this study.

Dr. Patterson requested that Dr.Ragni share with the RAC any clinical followup data in addition to the data already presented about the lack of serious adverse events of the three patients already treated. Dr. Ragni requested sharing efficacy information in a peer reviewed publication, and she reiterated that two of the three patients experienced a little flushing after they received the injection, one of whom has that reaction when injected with the standard hFVIII.

Dr. Zallen posed several questions. She commended the investigators for including in the protocol the registry for lifelong followup, but wondered what would happen to that followup if the sponsor terminated the study, which the protocol allows the sponsor to do at any time. Dr.Ragni responded that long-term followup is planned, whether the study is temporarily stopped or permanently terminated; Mr. Donald Gay, Chiron Corporation, added that all gene therapy programs require that patients who receive a gene therapy product be followed for life.

Dr. Zallen also was concerned about the vector being spread from person to person if the subject had a bleeding episode resulting from accident or injury, since the vector is in the bloodstream. Regarding the Informed Consent document, Dr.Zallen agreed with Dr. Macklin about the absurdity of including wording about the possibility of subjects becoming pregnant, adding that it is unacceptable to include inaccurate, absurd statements in an Informed Consent document because of the danger of rendering the entire form meaningless.

Ms. Meyers asked whether a representative from Chiron Corporation would respond to the question of why the clinical trial went forward despite the FDA's request to put it on hold until RAC public review; she indicated that this was the first instance of not in compliance with the rule in the last 10 years. Mr. Gay, Chiron Corporation, responded to Ms. Meyers' question. He summarized Chiron's process with the FDA and the ORDA, beginning in December 1998, which included presentation of information about the study at the March 1999 RAC meeting. Patients were enrolled only after FDA notification that it was in compliance with FDA requirements. Subsequently, Chiron received a notice from the ORDA asking that patients not be enrolled in this study until after public RAC discussion. According to Dr. Noguchi, the PI and Chiron received notification from the FDA that the IND was authorized and that the FDA requested (but did not require) that the clinical trial be postponed until after public presentation. As a point of clarification, Dr. Mickelson explained that in the past the RAC has reviewed several other protocols that had already enrolled patients and begun treatments. Dr.Ragni reiterated the need for changes in the timing of protocol submission, as discussed at yesterday's RAC session; this protocol was held up in the RAC review process while waiting for local IBC approval.

Dr. Markert asked for clarification with regard to the methods that were used to determine vector titers and doses for the human trial. Dr.Roehl clarified that vector titers in earlier preclinical studies were determined by G418 selection and expressed as colony forming units (CFUs). The vector proposed for the human trial does not have the neo^R gene and their titers were determined by a polymerase chain reaction (PCR) assay and expressed as transduction units (TUs) meaning vector copy numbers per cell genome equivalent; therefore, experimental results could not always be compared directly.

Both Dr. Greenblatt and Dr. McIvor queried the investigators about their rationale for using an IV route, the first such route of administration of a retroviral vector. Dr. Douglas Jolly, Chiron Corporation, explained the rationale for IV administration by stating that it appears to work in animal models and that it provides useful levels of hFVIII in the bloodstream. This route of administration was arrived at initially by intrahepatic injections in model animals but was changed to peripheral vein injection, primarily because

that seemed a more clinically less invasive way to deliver this vector. Dr. MarthaLeibrandt, Chiron Corporation, added that IV administration would be relatively noninvasive for this patient population and would be well tolerated. IV administration was found effective in both young and old animals.

Dr. Friedmann was interested in the data on survival of the injected vector—how stable it is in the circulation and how long it can be detected. Dr. Friedmann queried what target cells the vector will transduce and where exactly the hFVIII is produced. Dr. Leibrandt responded that it is not known exactly where the vector is being expressed. Data from the numerous animals treated to date show that the vecto localizes to the liver and spleen primarily; therefore, it is posited that cells in the liver and spleen are responsible for expression. She explained that, although the liver is associated with appropriate hFVIII expression, her understanding from the field is that there is no cell type that is determined to be inappropriate for making hFVIII, an important point in light of the investigators' chosen route of administration. Regarding the half life of the vector, Dr. Jolly stated that in chimpanzee (similar to human in complement inactivation of the virus) there is a biphasic half life where about 5% of the vector is left after 5 minutes after IV injection and the half life in the second phase is 20 minutes.

Dr. Wolff expressed a safety concern: Anaphylaxis in the rabbits was present. Dr. Wolff said that it is known that retroviruses produced in nonhuman cell lines can be inactivated by human complement. He requested some discussion or data on these retroviruses produced in human cell line in terms of inactivation by complement. Dr. Leibrandt responded that they have conducted in vitro experiments to show that this vector is not inactivated by human complement.

Additional Informed Consent document issues raised by the RAC written review included:

- *Wording changes were suggested. Reference to the experimental procedure as "treatment" should be replaced with "experimental procedure." This is a phase I study, never before conducted in humans, with unknown "treatment" potential. "Gene therapy" should be replaced with "gene transfer research."*
- *Because of vector being detected in some rabbit testes at 6 months and again at 17 months, the investigators should inform patients that they may need to use barrier contraception for a significant period of time to fulfillthe consent form requirement that barrier contraception last until three consecutive monthly semen samples test negative.*

Public Comment. *Public comment was received from Mr. Glenn Pierce, Selective Genetics Incorporated, who is past president of the National Hemophilia Foundation (NHF). The NHF, during the past 10 years, has enthusiastically embraced the idea of gene therapy as the next modality in the treatment of hemophilia, primarily because current treatment is not adequate and does not prevent the morbidity and occasional mortality associated with the disease. He stated that the NHF and hemophilia patients are acutely aware of the risk-benefit ratios evident in the previous treatments that patients have had to endure There is great excitement about gene therapy treatment as the next major step in treating hemophilia.*

Dr. Friedmann commented that this study is extremely attractive and important, is very likely to provide the field with useful information, and may prove to be therapeutically effective. Howeverphenomenologically powerful this study is, Dr. Friedmann was concerned that it is not supported by enough basic science, especially in areas of IV administration of a retrovirus. Further data are needed to understand the underlying mechanisms of which target cells are transduced and the source of hFVIII production, and behavior of the virus after systemic administration. Dr. Noguchi agreed with Dr.Friedmann's concerns but also cautioned that knowing the mechanism of the virus, even after approval, is a luxury at best. The basic questions should be, does it work in humans, and what are the

possible negative effects?

RAC Recommendations

Dr. Mickelson stated that a letter will be sent to the PI, with a copy to the local IRB/IBC, that will include RAC concerns about the format and content of the Informed Consent document.

In conclusion, the RAC's recommendations emanating from its September 3 discussion of the protocol were focused primarily on Informed Consent issues. The RAC commends the thoughtful attention that has been given to the Informed Consent process, i.e., maintaining an ongoing dialogue with potential study participants and their families through the entire decision-making process. However, the RAC raised several specific concerns about the adequacy of the Informed Consent document to serve as a reference in the absence of members of the research team. The RAC concluded that the document provided inaccurate information about the study population and insufficient explanation of potential risks to individuals participating in the study. In addition, the format and language of the document may be difficult for potential study participants to understand. To that end, the RAC made the following recommendations related to the informed consent process:

Study Population

The Informed Consent document should be amended to reflect accurately the study population. The current document includes information that specifically applies to females, i.e., pregnancy issues. However, the inclusion criteria for the proposed study is limited to male subjects because hemophilia is a disease that affects only males (with rare exceptions).

Potential Risk

Research subjects who participate in this study could potentially develop an immune response to the viral vector. Therefore, the Informed Consent document should be amended to include the following language:

> *"An immune response has not been observed to this viral vector in preclinical animal studies, but it is not known if administration of this vector to humans will generate an immune response that would preclude participation in future studies (if the identical vector is to be administered)."*

Format and Language

The Informed Consent document format is very difficult to read because of the small font, narrow margins, and close spacing. To enhance legibility of the document by potential study participants, the document should be revised using a standard font type and size, standard margins (minimum of 1 inch on sides, top and bottom), and standard spacing for sentences and paragraphs.

The RAC also noted that the Informed Consent document is written in language that may be difficult for some study participants to understand, and that much of the scientific and medical terminology is not defined in the document. While the RAC acknowledged that most of the study population will likely possess a significant level of understanding of the terminology related to their disease, every effort should be made to define terms in easily understandable language. The RAC emphasized that the language related to the gene transfer process should be more thoroughly described in lay terms, since most study participants will probably be unfamiliar with this aspect of the protocol.

Model Informed Consent documents/Dr. Mickelson

Dr. French Anderson, University of Southern California, suggested that the RAC (including Dr. Zallen, a past member) identify a few model Informed Consent documents that have been reviewed by the RAC; these model Informed Consent documents can be published in the journal Human Gene Therapy or posted at the web site of this journal or ORDA to help the investigators in their writing of Informed Consent documents.

Future Meeting Dates and Announcements/Dr. Mickelson

The next RAC meeting will be held December 9-10, 1999, at the National Institutes of Health, Building 31C, Conference Room 10.

Adjournment/Dr. Mickelson

Dr. Mickelson adjourned the meeting at 12:35 p.m. on September 3, 1999.

[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.]

Debra W. Knorr
Executive Secretary

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

Date: 9/3/99

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