RECOMBINANT DNA ADVISORY COMMITTEE

Minutes of Meeting

September 17, 2003

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

CONTENTS

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

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

September 17-18, 2003

The Recombinant DNA Advisory Committee (RAC) was convened for its 92nd meeting at 10:30 a.m. on September 17, 2003, at the Bethesda Marriott Hotel, 5151 Pooks Hill Road, Bethesda, MD. Dr. Theodore Friedmann (Chair) presided. In accordance with Public Law 92-463, the meeting was open to the public from 10:30 a.m. until 4:30 p.m. on September 17. The second day of this meeting was postponed because of weather concerns related to Tropical Storm Isabel. The following individuals were present for all or part of the meeting on Day One.

Committee Members

W. Emmett Barkley, Howard Hughes Medical Institute
Martha C. Bohn, Northwestern University Medical School
James F. Childress, University of Virginia
Neal A. DeLuca, University of Pittsburgh
David DeMets, University of Wisconsin
Theodore Friedmann, University of California, San Diego
Thomas D. Gelehrter, University of Michigan Medical School
Linda R. Gooding, Emory University *(via teleconference and webcast)*
Larry G. Johnson, University of North Carolina, Chapel Hill
Philip R. Johnson, Jr., Columbus Children's Hospital
Terry Kwan, TK Associates
Bernard Lo, University of California, San Francisco
Madison Powers, Georgetown University
David Sidransky, Johns Hopkins University School of Medicine
Robert D. Simari, Mayo Clinic and Foundation
Diane W. Wara, University of California, San Francisco

RAC Executive Secretary

Stephen M. Rose, Office of the Director (OD), National Institutes of Health (NIH)

***Ad Hoc* Reviewers/Speakers**

Robert H. Carter, University of Alabama, Birmingham
Christopher H. Evans, Harvard Medical School

NIH Staff Members
Prakhakara Atreya, Center for Scientific Review
Sussan Eftekhari, OD
Robert Jambou, OD
Seong Jin Kim, National Cancer Institute (NCI)
Seung Hee Kim, NCI
Steven H. Krosnick, NCI
Laurie Lewallen, OD
Cheryl McDonald, OD
Maureen Montgomery, OD

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

Marina O'Reilly, OD
Alexander Rakowsky, OD
Gene Rosenthal, OD
Thomas Shih, OD
Charles Trimmer, OD
Gisele White, OD

Others

There were 66 attendees on Day One of this RAC meeting. A full list of RAC members, *ad hoc* reviewers/speakers, and nonvoting/agency liaison representatives is included as Attachment I. A list of public attendees is included as Attachment II.

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

Dr. Friedmann, RAC Chair, called the meeting to order at 10:30 a.m. on September 17, 2003. Notice of this meeting under the *NIH Guidelines for Research Involving Recombinant DNA Molecules* (*NIH Guidelines*) was published in the *Federal Register* on August 19, 2003 (68 FR 49783). The agenda for the first day of the meeting included in-depth review and discussion of two human gene transfer research protocols; presentation of the quarterly data management report; and update from the RAC Informed Consent Working Group.

Dr. Rose reminded RAC members of the rules of conduct governing Special Government Employees, the screening process they undergo before each meeting, and the need to be attentive to conflicts of interest that could arise during the course of the meeting.

II. Minutes of the June 18-19, 2003, RAC Meeting/Drs. Friedmann and DeMets

Drs. Friedmann and DeMets noted that no changes were required to the minutes of the June 2003 RAC meeting.

A. Committee Motion 1

It was moved by Dr. Lo and seconded by Dr. Bohn that the RAC approve the June 18-19, 2003, RAC meeting minutes. The vote was 15 in favor, 0 opposed, and 0 abstentions. (Dr. Gooding voted in favor via telephone.)

III. Discussion of Human Gene Transfer Protocol #0307-594: A Phase I Study To Determine the Safety and Biological Activity of Cell-Mediated Gene Therapy Using TissueGene-C in Patients With Degenerative Joint Disease of the Knee Prior to Total Knee Arthroplasty

Principal Investigator:	Michael A. Mont, M.D., Sinai Hospital, Baltimore, MD
Additional Presenters:	Kwan Hee Lee, M.D., Ph.D., TissueGene, Inc.
Sponsor:	TissueGene, Inc.
RAC Reviewers:	Dr. DeLuca, Ms. Kwan, and Dr. Wara
Ad hoc Reviewer:	Robert H. Carter, M.D., University of Alabama, Birmingham

A. Protocol Summary

Degenerative arthritis (DA) is the most common orthopedic disease associated with cartilage damage, affecting one in seven people. Almost every joint in the body is susceptible to cartilage damage; the most commonly affected joints are the knee, hip, shoulder, and wrist. In degenerative arthritis the hyaline articular cartilage becomes deformed, fibrillated, and eventually destroyed during the course of the disease. Most current treatments for degenerative arthritis are aimed at reducing symptomatic pain.

Treatment involving cartilage replacement using autologous human chondrocytes has been developed but it entails two operations, excision of the soft tissues, and a lengthy recovery time. Autologous chondrocytes have been shown to have a limited capacity to regenerate hyaline cartilage.

TissueGene-C is a cell-mediated cytokine gene therapy approach for cartilage regeneration. TissueGene-C is a mixture (three to one) of non-transduced allogeneic human chondrocytes (hChon) and allogeneic human chondrocytes transfected with a retroviral vector encoding transforming growth factor-?1 (TGF-?1) (hChon?1). TGF-? is a multifunctional cytokine, playing a regulatory role in cell growth, differentiation, and extracellular matrix protein synthesis and has been reported to induce osteogenesis and chondrogenesis. Studies have suggested that TGF-? stimulates chondrocyte proteoglycan synthesis and the growth of articular chondrocyte cells. In addition to its stimulatory action on chondrocytes, TGF-? has been shown to possess anti-inflammatory and immune suppressive properties. TGF-?'s short half-life has limited its clinical usefulness.

In theory, cellular production of TGF-?1 could provide long term effects of TGF-?1 in stimulating hyaline cartilage generation. The non-transduced chondrocytes are used as supplementary cells for filling the defect site and as target cells for TGF-?1 expressed from transduced cells because TGF-?1 has both autocrine and paracrine modes of action. In preclinical studies, nude mice injected with TissueGene-C formed cartilage, but mice injected with non-transduced chondrocytes did not. In studies with rabbits or dogs, transduced human chondrocytes exhibited sustained TGF-?1 release and proliferation of regenerative cartilage with no overgrowth.

The protocol is intended to assess the safety of knee joint injections of TissueGene-C in patients who are scheduled for knee replacement surgery. TissueGene-C will be administered by local injection to the knee joint cavity 4 weeks prior to surgical replacement of the knee joint. In addition to safety information, data will be obtained about the dose-response of the hChon?1 cells in engrafting at the defect and any distribution outside of the injected site. At the time of total knee replacement, resected tissue will be evaluated microscopically for engraftment and subsequent cartilage production, and the joint analyzed for evidence of overgrowth or transformation of the engrafted product.

B. Reviews by RAC members and ad hoc reviewer

Eleven RAC members voted for in-depth review and public discussion of the protocol. RAC reviewers Dr. DeLuca, Ms. Kwan, and Dr. Wara and *ad hoc* reviewer Dr. Carter submitted written reviews, to which the investigators responded in writing and during this meeting.

Dr. DeLuca noted that the cells to be used in the study had not yet been generated, and he wondered what the criteria would be for selecting a given clone transduced with the retroviral vector, particularly in regard to the level of TGF-?1 expression. The planned preclinical studies to investigate cell overgrowth or transformation should be performed with the TissueGene-C product that will be used in the clinical trial. He asked how immune responses or toxicity due to TGF-?1 would be studied in preclinical models and suggested that the risk section of the informed consent document should discuss the issue of potential overgrowth.

Ms. Kwan noted that, in for the most part, the protocol and informed consent document were clearly and logically written and that the responses to Appendix M were thorough and responsive. She suggested the following changes to the informed consent document: simplify the purpose section; add a clear statement that, regardless of study outcome, the research participant will still need knee replacement surgery; include a compensation schedule; and clarify the exclusion of potential participants who currently take prescription or over-the-counter medications; add a statement about whether the investigators have a financial interest in the study; and clarify the meaning of placebo and randomization.

Dr. Wara asked about the multifunctional role of TGF-?1 and how it might affect efficacy. She also asked for more information about the possible effects of the differentiation, and overgrowth of the chondrocytes and the route and time of delivery of gene transfer at different stages of the disease process. Regarding

end point analysis, she asked which gene will be analyzed in tissue samples obtained at arthroscopy, what methods and samples would be used to study levels of transgene expression and vector DNA, and how the chondrocyte differentiation state (following *ex vivo* culture) will be evaluated. She requested additional information about the results of the dog study, mouse biodistribution study, and rabbit intra-articular injections. She suggested that informed consent document mention the remote risk of insertional mutagenesis following intra-articular (IA) injection of transduced cells using a retroviral vector.

Dr. Carter focused on the risks associated with the administered cells, the expression of TGF-?1, and disease specific issues. He asked to what extent the chondrocytes are altered, particularly chromosomally, by passage in culture. He suggested that delivery of chondrocytes into the defect would be difficult unless the procedure is performed under radiologic guidance. The investigators had responded that arthroscopic guidance may be used. Dr. Carter requested further discussion of this because he had concerns that this procedure may not necessarily result in improved delivery to the defect yet it could introduce risks which are greater than those of the simple needle injection procedure describe in the protocol. He asked whether joint fluid could be obtained at the time of surgery to assay TGF-? levels. While washing the cells prior to administration would decrease exposure to fetal bovine serum in the storage medium, this process could increase the risk of infection. He also expressed interest in learning the results of the biodistribution studies. Dr. Carter recommended that studies of the immune response include the testing of the activation/proliferation of peripheral blood mononuclear cells in response to irradiated chondrocytes or hChon?, from the same clones used for inoculation into the joint, with analysis of neutralizing anti-TGF-ß, if available.

C. RAC Discussion

During the meeting, the following additional questions and issues were raised.

? Dr. Carter asked whether human TGF-? is biologically active in rodents and rabbits and whether changes in the persistence of TGF-? might be seen because of the human immune response.

? Dr. L. Johnson asked whether the results of the preclinical experiments suggested that remodeling of the cartilage could be expected to occur in human recipients and whether, if overgrowth occurs, it might result in more normally appearing cartilage upon appropriate use of the joint.

? Dr. Gelehrter expressed concern about the effects of TGF-? expression on fibrosis in the joint and the extent of the role fibrosis plays in degenerative joint disease.

? Dr. Simari asked why the placebo arm was needed, what specific comparisons will be made, and how the results will be used in designing additional trials. He expressed concern about placebo participants undergoing arthroscopy.

? Dr. Wara suggested that investigators consider not requiring arthroscopy for the participants enrolled in the placebo group that would not be receiving modified chondrocytes.

? Dr. DeMets questioned the size of the study cohort (12 participants) and asked what the investigators hoped to learn from the results of the phase I investigation.

? Ms. Kwan noted the intervention is described as nonsurgical in the original protocol, so she asked whether that description would be accurate if, as currently proposed, arthroscopy was actually used.

? Dr. Gooding expressed concern about using human TGF-? in a rodent model. While cross-species activity does occur, it is possible that not all biological activity of the human TGF-? would be seen in the rodent model. She suggested, therefore, that preclinical studies use the TGF-? from the species being used in that particular animal model.

D. Investigator Response

Dr. Lee provided the following information in responses:

- Because it is not now generally possible to localize the joint site with MRI (although it may be possible in the future), arthroscopic guidance needs to be used. The investigators are considering performing the arthroscopy procedure in advance in order to minimize infection risks, and then injecting the cells only after the subject has complete recovered from the arthroscopy procedure. To address concerns regarding contamination during the manufacturing process, the investigators will attempt to develop a closed system for the preparation of the TissueGene-C product.

- Ms. Kwan's suggested changes to the informed consent document will be made. With regard to Ms. Kwan's question about whether the intervention should be described as nonsurgical if arthroscopy is performed, the investigators will be using diagnostic arthroscopy, but perhaps the arthroscopy procedure could be eliminated if a very good magnetic resonance imaging (MRI) image could be obtained.

- The effect of human TGF-? appears to be very similar in rabbits and rodents compared to humans and that the DNA sequences are about 80 percent homologous.

- Because the procedure aims to produce a limited level of TFG-? in a localized area, the risk that TFG-? will induce fibrosis is not significant. Also the transduced cells would become isolated as they become surrounded by fibronectin and matrix proteins, which will serve to further contain the TGF-?.

- All preclinical studies will be repeated using the exact agent to be used in the human trial.

E. Public Comment

Ms. Joann C. Delenick asked whether Dr. Lee believed that diagnostic MRI could be refined in the future to assist in localizing the injection to the defect. Dr. Lee stated his belief that it may be possible.

F. RAC Recommendations

Dr. Friedmann summarized the following RAC recommendations:

- A comprehensive review of the protocol was difficult because the supporting data were insufficient. As such and in light of other concerns, the clinical trial should not be undertaken until the recommended preclinical data is available, analyzed, and incorporated appropriately into the clinical trial design and informed consent document. Furthermore, because this application of gene transfer is novel and potentially precedent-setting, the strategies developed and the approach taken could have a significant impact on the field in general. The investigators were encouraged to present additional data at a future meeting of the RAC. The following additional issues should be resolved before the clinical study is initiated, including the following: 1) isolation and testing of the actual agent that would be administered to humans; 2) procurement of biodistribution data from long-term animal studies; and 3) selection of the mode of vector administration-intraarticular needle injection, a nonsurgical approach, or arthroscopically-guided intraarticular administration, which constitutes a change from the original protocol.

- Because some participants may choose to decline arthroplasty subsequent to the injection of the investigational agent, and there is at least a theoretical risk for bony or cartilage outgrowth in the joint, the animal studies should include long-term follow-up of animals that did not undergo arthroplasty.

- The animal data suggests that there was no immune response detected locally in the injected joints, but other evidence of immunization should be examined. Studying the activation/proliferation of

peripheral blood mononuclear cells to irradiated chondrocytes or hChon? should be considered. If they are available, the same clones used for inoculation into the joint should be used and neutralizing anti-TGF-ß should be analyzed.

? Aspects of the cell preparation process, such as washing cells prior to administration, need to be examined further to determine whether any aspect increases the risk of infections.

? While the dose escalation plan was not clearly explained in the first version of the protocol, the sponsor clarified that the escalation of doses would not occur until 14 days after the previous dose level has been shown to be safe. Additionally, the sponsor noted that the protocol will be revised to include a Data Safety Monitoring Board to evaluate the safety data, including histopathology, prior to dose escalation. The protocol should not set out a specific timeframe (e.g., 14 days) for evaluation of safety prior to dose escalation.

? A rationale for the choice of twelve participants as the planned enrollment, as well as a discussion of what could be learned from this phase I investigation would strengthen the protocol.

? The use of arthroscopy to localize the cartilage defect prior to injection of either the investigational agent or placebo was not discussed in the protocol as submitted. The sponsor's explanation at the RAC meeting did not address all the committee's questions. The use of arthroscopy needs to be re-evaluated. Alternative means of imaging, particularly non-invasive measures such as MRI should be considered. Additionally, if this trial is to be conducted as a "single blind" study, how participants will be randomized to the placebo and whether they will receive the pre-injection procedures needs to be clarified.

? The following changes should be made to the informed consent document: 1) Arthroplasty should not be listed as a benefit because the participants will undergo arthroplasty regardless whether they participate in this study; 2) concomitant medications that are allowed to be taken during the study should be listed; and 3) the randomization scheme should be clarified. Since only one of the four cohorts will be receiving the placebo, the process should not be described as "a flip of a coin."

G. Committee Motion 2

It was moved by Dr. DeLuca and seconded by Ms. Kwan that these recommendations expressed the comments and concerns of the RAC. The vote was 16 in favor, 0 opposed, 0 abstentions, and 0 recusals.

IV. Discussion of Human Gene Transfer Protocol #0307-588: A Phase I Dose-Escalation Study of Intra-Articular Administration of tgAAC94, a Recombinant Adeno-Associated Virus Containing the TNFR-Fc Fusion Gene in Rheumatoid Arthritis

Principal Investigator:	Philip J. Mease, M.D., Swedish Hospital, Seattle, WA
Other Investigators:	Allison E. Heald, M.D., M.H.S., and Barrie J. Carter, Ph.D., Targeted Genetics Corporation
Sponsor:	Targeted Genetics Corporation
RAC Reviewers:	Drs. Brody, Gelehrter, and Simari
Ad hoc Reviewer:	Robert H. Carter, M.D., University of Alabama, Birmingham, and Christopher H. Evans, D.Sc., Ph.D., Harvard Medical School

(Dr. P. Johnson recused himself from discussion of this protocol because of a conflict of interest.)

A. Protocol Summary

Rheumatoid arthritis (RA) is a chronic autoimmune disease whose cause is not known. The immune system attacks healthy joint tissue leading to joint inflammation, pain and swelling and eventually joint

destruction and disability. RA is one of the most common chronic inflammatory diseases in the United States.

Patients with RA have benefited from a new class of medications, such as Enbrel?, Remicade?, and Humira?, which all block a protein called tumor necrosis factor-alpha (TNF-?). TNF-? plays a key role in the inflammation process of RA. These new therapies, which are injected under the skin or into the bloodstream, have led to remarkable improvement in the symptoms of RA of some patients. However, some RA patients have one or more joints that bother them despite these medications. Other patients with only one or two problematic joints may choose to not pursue the use of the new biologic treatment.

This protocol is designed to test whether such patients might benefit from direct injection into the joint of the gene coding for a protein the blocks TNF-?. The vector, tgAAC94, developed by Targeted Genetics Corporation expresses TNF receptor–immunoglobulin (IgG) Fc fusion gene (hTNFR:Fc). TgAAC94, is based on an adeno-associated virus serotype 2 (AAV) and produces the identical protein as Enbrel?. The long range goal of the company's study is to determine whether intra-articular delivery of the hTNFR:Fc gene results in protein expression in the joint space, production of therapeutic concentrations of soluble hTNFR:Fc, and minimal exposure.

B. Reviews by RAC members and ad hoc reviewer

Eight RAC members voted for in-depth review and public discussion of the protocol. RAC reviewers Drs. Brody, Gelehrter, and Simari and *ad hoc* reviewers Drs. Carter and Evans submitted written reviews, to which the investigators responded in writing and during this meeting.

Dr. Brody was not able to attend the meeting, but his review was presented by Dr. Lo on his behalf. Dr. Brody raised questions about several aspects of the study design, including the selection criteria, number of participants, the use of placebo controls, and the inclusion of the fourth cohort, whose purpose may be more appropriate to a Phase II study. He questioned why this phase of the study is not targeted to more seriously ill patients. He requested a clearer description of the role of the sponsor and possible conflicts of interest on the part of the investigators or the hospital. Dr. Brody suggested that all of these questions will also need to be addressed more fully in the informed consent document.

Dr. Gelehrter requested clarification of the rationale for patient recruitment. Specifically, he asked why untreated research participants would choose gene transfer over the established protein therapy, or why previously treated patients who had some persistent disease should expect gene transfer to prove more efficacious than protein therapy. In the event of toxicity, he asked whether it would be possible to turn off gene expression. He requested further information about the rat studies indicating that intra-articular injection can affect the contralateral joint. This suggests that there may be systemic effects from localized gene transfer.

Dr. Simari requested more information about the effects on distant, non-injected joints and circulating systemic concentration of transgene product; the effects of steroids on AAV maintenance and expression in animal models and the long-term care of research participants in terms of immunosuppressants. He asked for additional explanation of the exclusion of participants who have used TNF-modifying agents. He asked for clarification of the objective of the use of the placebo group. In addition, he requested that the informed consent document explain the duration of long-term follow-up.

Dr. Carter expressed concern about targeting patients with persistent disease in only one or more joints because this is not comparable to the inclusion criterion used in typical RA trials in which subjects must have intra-articular disease in at least six active joints. Selection of research participants with mono- or oligo-articular active disease might result in inclusion of subjects whose active arthritis is not RA (for example pseudogout can mimic the symptoms of RA). He also suggested that additional studies be conducted to determine whether the effect of intra-articular inoculation is local or systemic. He noted that in the rodent studies, DNA has been found in other organs, suggesting the systemic spread of AAV. Because the transgene product is immunogenic, he suggested that synovial fluid and serum be analyzed for the presence of antibodies to the fusion construct. Because efficacy has been linked to particular

allotypes of the FcR for some chimeric proteins, allotyping of FcR should also be considered. He suggested that the inclusion criteria be made more specific regarding the types of prior disease-modifying therapy subjects may have tried, and that subjects who have participated in a trial of methotrexate at full dose be added. Noting that the immunosuppressive properties of different DMARDs vary significantly, he questioned how this variability will be considered in the study.

Dr. Evans expressed concern about the limited correlation between transgene expression and efficacy in animal models. He asked whether expression from extra-articular sites, several of which contain vector DNA, contributed to the therapeutic effect to a significant degree and why the therapeutic effect of intramuscular delivery was equivalent to that of intra-articular administration in the animal models. He asked how the protocol could be designed to preclude the past or current use of TNF-? antagonists, as well as any prospective use for three months, in light of the American College of Rheumatology (ACR) recommendations that all patients with serious rheumatic disease be prescribed the new biologic medications when clinically appropriate.

C. RAC Discussion

The following additional questions and issues were raised during the RAC discussion:

? Dr. Lo suggested modifying the eligibility criteria to target only patients who are unlikely to benefit from standard therapies, who have refused those therapies, or who have failed more than one disease-remitting agent. This change might help participants understand that the protocol is not an alternative to current standard of therapy for RA.

? Dr. Lo suggested that investigators inform potential subjects, both orally and in the written consent document, that at any point during the trial, they have the option to begin taking one of the standard disease-remitting agents. Emphasizing this information might encourage potential subjects to think more critically about their participation. Dr. Lo also suggested that investigators administer a test of comprehension to make sure participants understand the options.

? Dr. DeMets suggested that the rationale for the protocol would be strengthened by additional calculations about what safety information a study of this size and design will provide.

? Dr. Friedmann asked for clarification about whether an inflamed joint is an appropriate tissue for generating immune responses.

? Dr. DeLuca asked whether intra-articular injection has advantages over intra-muscular injection.

D. Investigator Response

Dr. Mease provided the following responses to the RAC's questions and concerns:

The protocol sponsor will make every possible effort to develop a reliable assay to measure antibodies and investigators will conduct allotyping.

While patients taking a variety of medications may enter the study, it will be critical that the medications not be changed during the course of the trial. With regard to concerns about limiting the use of prednisone, Dr. Heald indicated that the intention is to enroll participants who are stable and are not expected to require medication changes during the three-months of the trial. If a participant should experience a flare up of RA, he/she will be treated with prednisone and all other appropriate medications.

The investigators do not regard the lack of evidence of transduction in some of the preclinical animals as a significant issue because transduction of all cells is not necessary given that TNF receptor-Fc (TNFR-Fc) is a secreted protein. In addition, lack of detection may be a function of the assay's sensitivity rather than an absolute lack of expression and other logistical and analytical issues that may also have

confounded detection in this in the animal model. Overall, efficacy measurements may be more sensitive than measuring RNA in joints.

Although it is possible that transgene protein could migrate systemically into non-injected joints, this was not seen in nonhuman primate studies in which a luciferase vector was administered through intra-articular injection. In addition, ribonucleic acid expression was not detectable in the animals' spleens or lymph nodes.

The purpose of the placebo control is to determine whether there is any reaction to the injection alone. Dr. Heald added that in preclinical rodent studies only a few of the animals (out of more than 100 tested) showed mild injection reactions.

Regarding recruitment, patients will only be offered gene transfer after they have been informed about and declined the protein-based biological treatments.

Dr. Mease agreed to consider involving a neutral third party in the recruitment and enrollment processes.

Intra-articular injection is considered safer than intra-muscular injection because there is a lower risk for systemic and persistence effects and less product is needed to achieve a therapeutic effect. Dr. Barry Carter added that investigators have seen therapeutic effects in animal models using extremely low levels of the fusion protein in the serum whereas intra-muscular injections resulted in much higher serum levels. The investigators believe that intra-articular administration is advantageous because the study is targeting specific joints and this route of administration allows the product to be delivered directly to the site.

E. Public Comment

No public comments were made.

F. RAC Recommendations

Dr. Friedmann summarized the following RAC recommendations:

- There is at least a theoretical risk that induced expression of the fusion construct in the inflamed joint could make the construct more immunogenic and induce the production of antibodies that would reduce the efficacy of etanercept in the future. Therefore, a careful analysis of antibodies to the TNFR:Fc protein in the synovial fluid, as well as in serum, would be important. Consideration should be given to developing a reliable assay to detect antibodies to the human TNFR:Fc and using it during this study.

- Fc receptors (FcR) are increasingly being recognized as playing an important role in the *in vivo* functioning of chimeric proteins with an Fc domain. For some chimeric proteins, efficacy has been linked to particular allotypes of the FcR, which alter affinity. Because Fc receptors may also control side effects as much as efficacy, considerations should be given to allotyping the FcR of the study participants. Such information might allow a more informed interpretation of any side effects seen in the participants.

- The roles of the treating physician for the patient and the investigator of the study should be clearly separated. This would help ensure that the patient's decision to forgo systemic therapy for persistence of disease in a single joint precedes or is separate from the decision to enroll in the study. When a researcher is also the personal physician of the patient, an independent third party should discuss the details of the study with the patient and carry out the consent and enrollment processes with the potential research participant. These stipulations and the role of the third party should be clearly delineated in the protocol.

- Consideration should be given to developing a test to assess how well potential research participants understand certain aspects of the study. Such a test could help determine whether a potential

participant understands that the study's goal is to evaluate the safety of the study agent and that direct benefits are not expected; standard medications are available that may be effective for the treatment of the disease; and the study agent cannot be considered superior to currently available standard medications.

G. Committee Motion 3

It was moved by Dr. Simari and seconded by Dr. DeMets that these recommendations expressed the comments and concerns of the RAC. The vote was 14 in favor, 0 opposed, 1 abstention, and 1 recusal. (Dr. Gooding abstained because she missed part of the discussion due to technical difficulties. Dr. P. Johnson had recused himself from discussion of and voting on this protocol.)

V. Data Management Report/Drs. Brody, Gooding, L. Johnson, Simari, and Wara

A. Adverse Events

Dr. Simari reported that 16 protocols had been submitted since the prior reporting period (June 2003). Protocol #589 was deferred for discussion until the December 2003 RAC meeting because the principal investigator (PI) could not attend the September 2003 RAC meeting. All of the 11 trials not selected for public discussion were cancer studies.

During the period May 7 to August 7, 2003, 109 AEs were reported, 100 of which were considered serious adverse events (SAE). A total of 15 were classified as possibly related to the gene transfer product (so called type A events), 9 of which were initial reports. Dr. Simari discussed two of the reported type A events, the first from Protocol #457 which involves the use of an adenoviral vector expressing tumor necrosis factor cDNA for soft tissue sarcoma of the extremities, and the other from Protocol #453, involving adenoviral interferon-beta gene transfer in the treatment of recurrent or progressive glioblastoma multiforme.

In Protocol #457, the SAE was described as follows. A participant with malignant fibrous histiocytoma of the upper limb without known metastases received the first dose of $4x10^{11}$ biologic plaque-forming units in August 2002. Tumor resection in November 2002 was followed by recurrent wound problems and wound debridement in January 2003. The debrided skin and subcutaneous tissue showed gangrenous necrosis. In February 2003, the participant's right leg was amputated due to a chronic wound infection and gangrenous changes. The medial groin area wound was marked by areas of necrosis that extended down and into the leg. The pathologic examination of the resected limb showed rare malignant cells consistent with residual irradiated malignant fibrous histiocytoma, calcific atherosclerosis, necrotic skin and underlying soft tissue with acute inflammation. The investigator suggested that the event was possibly related to the study agent and/or procedures involved in the study. Several other examples of AEs involving cellulitis have been reported on this protocol, but none of this magnitude has been reported to date.

In Protocol #453, a participant developed mental status changes subsequent to tumor resection of a left temporal glioblastoma and delivery of adenoviral vector expressing the interferon beta gene followed by complex partial status epilepticus and general encephalopathy in the absence of frank meningeal encephalitis. The investigators believed that these effects could be caused by any of the following: adenovirus, intraparenchymal interferon beta, triple anticonvulsant therapy, or the large tumor excision. The SAE was classified by the investigator as possibly related to the gene transfer product. To date, nine participants have received the agent, and this was the first type A SAE reported.

B. Annual Updates and Amendments

Dr. Wara reported that 56 annual updates and 19 amendments had been filed in during the prior reporting period. She briefly discussed amendments reported from three protocols: #453, #337, a protocol involving the retroviral vector transduction of CD34+ cells from children with Adenosine Deaminase (ADA)-Deficient Severe Combined Immunodeficiency (SCID); and #419, using an adenoviral vector

encoding a Factor VII immunoconjugate to induce a cytolytic immune response against melanoma tumors.

With regard to Protocol #453, an inclusion/exclusion amendment to this protocol allowing enrollment of research participants whose tumors are in close proximity to the ventricles was discussed at the March 2003 meeting. The RAC expressed concern that increased inflammation intraventricularly might occur with injections so close to and/or in the ventricle. NIH OBA notified the sponsor of RAC's concerns in a letter sent in August 2003. Members reiterated their concerns about the risks associated with enrolling participants with tumors so close to a ventricle and their recommendation that the institutional biosafety committee and possibly the data and safety monitoring board (DSMB) review the amendment. Dr. Rakowsky noted that the sponsor responded to the letter and reported that the issue will be brought to the attention of the DSMB.

The amendments to Protocol #337, the ADA SCID study, have also been submitted to the FDA with a request that the protocol's clinical hold be lifted. The amendments to the protocol were as follows: modification of the inclusion criteria so as to enroll children with late onset ADA-deficient SCID; all participants stop receiving pegylated-ADA prior to enrollment; new stopping rules for participants not taking pegylated ADA; and addition of a monitoring scheme for both monoclonality and insertional mutagenesis after gene transfer.

In Protocol #419, several broad amendments are proposed, the most significant of which seeks to expand the study beyond melanomas. The PI volunteered to discuss the proposed amendments with the RAC. [The discussion, which was scheduled for Day Two of the RAC meeting, has been rescheduled for the December 2003 RAC meeting.]

VI. Informed Consent Working Group Draft Guidance Update/Dr. Rose

Dr. Rose reported that the working group had taken into account comments made during the March 2003 RAC meeting and that the updated version of the document had been distributed to RAC members. Several RAC members noted that the final document will be an excellent contribution to the field and expressed their gratitude to the working group members. The following additional suggestions about the document were made.

- Dr. Childress suggested clarifying how the guidance will fit with other kinds of guidances already available. Dr. Childress and Dr. Simari expressed concern that the document could be viewed as an amendment of Appendix M. Dr. Rose explained that it is intended as a supplement of Appendix M and that this will be clarified in the final version.

- Ms. Kwan recommended that the guidance suggest that first-person voice be avoided in informed consent documents.

- Workshops should be organized to assist investigators in using the document.

- Dr. Lo suggested that the guidance clarify that informed consent documents should make clear that the intention of phase I trials is not to produce benefit and that participants should not expect any benefit from their participation in such studies.

VII. Day One Adjournment/Dr. Friedmann

Dr. Friedmann adjourned the first day of the September 2003 RAC meeting at 4:30 p.m. on September 17, 2003.

VIII. Day Two

Due to the closure of all Federal Government offices in the Washington, D.C., area on Thursday, September 18, 2003, because of the impending arrival of Tropical Storm Isabel, the second day of the September 2003 RAC meeting was postponed. [Date subsequently set: October 17, 2003.]

[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.]

_____
Stephen M. Rose, Ph.D.
Executive Secretary

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

Date:

_____
Theodore Friedmann, M.D.
Chair

Attachment I

Recombinant DNA Advisory Committee

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Attachment II
Public Attendees

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Sunil Chada, Introgen Therapeutics, Inc.
Cheauyun Chen, FDA
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Youngsuk Yi, TissueGene, Inc.
Yongjie Zhou, FDA

Attachment III
Abbreviations and Acronyms

AAV	adeno-associated virus
ADA	adenosine deaminase
AE	adverse event
DA	degenerative arthritis
DMARD	disease-modifying antirheumatic drug
DNA	deoxyribonucleic acid
DSMB	data and safety monitoring board
IA	intra-articular
IM	intramuscular
MRI	magnetic resonance imaging
NCI	National Cancer Institute
NIH	National Institutes of Health
NIH Guidelines	*NIH Guidelines for Research Involving Recombinant DNA Molecules*
OD	Office of the Director, NIH
PI	principal investigator
RA	rheumatoid arthritis
RAC	Recombinant DNA Advisory Committee
SAE	serious adverse event
SCID	severe combined immunodeficiency disease
TGF-?1	transforming growth factor beta-1
TNF-?	tumor necrosis factor alpha
TNFR	TNF receptor
TNFR-Fc	TNF receptor secreted protein