

RECOMBINANT DNA ADVISORY COMMITTEE
NATIONAL INSTITUTES OF HEALTH
BLDG 31C/CONF ROOM 6, BETHESDA, MARYLAND

FINAL AGENDA¹

OCTOBER 7, 1991

- | | | | | | | | | | | | | | | | | | | | | | | | | | | |
|--------------|--|--------------|------------------|----------|----------------|------|---------------------|------------|---------------|------|---------------------|------------|------------------|------|--------------------|------------|---------------|------|------------------|------------|--|--|------------------|------------|--|--|
| I. | Call to Order and Opening Remarks from Chair..... | 9:00 a.m. | | | | | | | | | | | | | | | | | | | | | | | | |
| | Dr. McGarrity | | | | | | | | | | | | | | | | | | | | | | | | | |
| II. | Minutes of the May 30-31, 1991, meeting..... | 9:15 a.m. | | | | | | | | | | | | | | | | | | | | | | | | |
| | Tab 1464 May Minutes (Page 852) Ms. Buc | | | | | | | | | | | | | | | | | | | | | | | | | |
| III. | Proposed Amendment to Appendix D of the <i>NIH Guidelines</i> Regarding Human Gene Transfer Protocol entitled: "Gene Transfer for the Treatment of Cancer"/Dr. Freeman..... | 9:30 a.m. | | | | | | | | | | | | | | | | | | | | | | | | |
| | <table border="0" style="width: 100%;"> <tr> <td style="width: 15%;">Tabs 1453/I</td> <td style="width: 35%;">Federal Register</td> <td style="width: 15%;">(Page 4)</td> <td style="width: 35%;">Dr. Gellert</td> </tr> <tr> <td>1454</td> <td>Updated Protocol</td> <td>(Page 11)</td> <td>Dr. Kelley</td> </tr> <tr> <td>1455</td> <td>Comm. on July Prot.</td> <td>(Page 130)</td> <td>Dr. Geiduschek</td> </tr> <tr> <td>1462</td> <td>Freeman Add. Info.</td> <td>(Page 827)</td> <td>Mr. Brewer</td> </tr> <tr> <td>1467</td> <td>Gellert Comments</td> <td>(Page 939)</td> <td></td> </tr> <tr> <td></td> <td>Geiduschek Comm.</td> <td>(Page 940)</td> <td></td> </tr> </table> | Tabs 1453/I | Federal Register | (Page 4) | Dr. Gellert | 1454 | Updated Protocol | (Page 11) | Dr. Kelley | 1455 | Comm. on July Prot. | (Page 130) | Dr. Geiduschek | 1462 | Freeman Add. Info. | (Page 827) | Mr. Brewer | 1467 | Gellert Comments | (Page 939) | | | Geiduschek Comm. | (Page 940) | | |
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| 1462 | Freeman Add. Info. | (Page 827) | Mr. Brewer | | | | | | | | | | | | | | | | | | | | | | | |
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| | Geiduschek Comm. | (Page 940) | | | | | | | | | | | | | | | | | | | | | | | | |
| | (Coffee Break.....10:30-10:45) | | | | | | | | | | | | | | | | | | | | | | | | | |
| | Proposed Amendments to Appendix D of the <i>NIH Guidelines</i> Regarding Human Gene Therapy Protocols entitled: " <i>Immunization of Cancer Patients Using Autologous Cancer Cells Modified by Insertion of the Gene for Tumor Necrosis Factor,</i> " and <i>Immunization of Cancer Patients Using Autologous Cancer Cells Modified by Insertion of the Gene for Interleukin-2</i> " / Dr. Rosenberg..... | 11:30 a.m. | | | | | | | | | | | | | | | | | | | | | | | | |
| | <table border="0" style="width: 100%;"> <tr> <td style="width: 15%;">Tabs 1453/II</td> <td style="width: 35%;">Federal Register</td> <td style="width: 15%;">(Page 4)</td> <td style="width: 35%;">Dr. Leventhal</td> </tr> <tr> <td>1456</td> <td>July Prot. w/update</td> <td>(Page 147)</td> <td>Dr. Haselkorn</td> </tr> <tr> <td>1457</td> <td>Comm. on July Prot.</td> <td>(Page 501)</td> <td>Dr. Carmen</td> </tr> <tr> <td>1466</td> <td>Leventhal Comm.</td> <td>(Page 932)</td> <td>Mr. Barton</td> </tr> <tr> <td></td> <td>Barton Comm.</td> <td>(Page 933)</td> <td></td> </tr> <tr> <td></td> <td>Carmen Comm.</td> <td>(Page 935)</td> <td></td> </tr> </table> | Tabs 1453/II | Federal Register | (Page 4) | Dr. Leventhal | 1456 | July Prot. w/update | (Page 147) | Dr. Haselkorn | 1457 | Comm. on July Prot. | (Page 501) | Dr. Carmen | 1466 | Leventhal Comm. | (Page 932) | Mr. Barton | | Barton Comm. | (Page 933) | | | Carmen Comm. | (Page 935) | | |
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| 1456 | July Prot. w/update | (Page 147) | Dr. Haselkorn | | | | | | | | | | | | | | | | | | | | | | | |
| 1457 | Comm. on July Prot. | (Page 501) | Dr. Carmen | | | | | | | | | | | | | | | | | | | | | | | |
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| | Carmen Comm. | (Page 935) | | | | | | | | | | | | | | | | | | | | | | | | |
| | (Lunch.....12:30-1:30) | | | | | | | | | | | | | | | | | | | | | | | | | |
| V. | Proposed Amendment to Appendices B-I-B-1 and B-I-B-2 of the <i>NIH Guidelines</i> regarding the Bacterial Order, <i>Actinomycetales</i> / Dr. Fleming..... | 2:30 p.m. | | | | | | | | | | | | | | | | | | | | | | | | |
| | <table border="0" style="width: 100%;"> <tr> <td style="width: 15%;">Tab 1453/IV</td> <td style="width: 35%;">Federal Register</td> <td style="width: 15%;">(Page 7)</td> <td style="width: 35%;">Dr. Schaechter</td> </tr> <tr> <td>1463</td> <td>CDC Letter</td> <td>(Page 837)</td> <td>Dr. Krogstad</td> </tr> <tr> <td></td> <td>Lechevalier Ltr.</td> <td></td> <td>Dr. Brinckerhoff</td> </tr> <tr> <td>1468</td> <td>Brinckerhoff Comm.</td> <td>(Page 943)</td> <td>Dr. B. Murray</td> </tr> </table> | Tab 1453/IV | Federal Register | (Page 7) | Dr. Schaechter | 1463 | CDC Letter | (Page 837) | Dr. Krogstad | | Lechevalier Ltr. | | Dr. Brinckerhoff | 1468 | Brinckerhoff Comm. | (Page 943) | Dr. B. Murray | | | | | | | | | |
| Tab 1453/IV | Federal Register | (Page 7) | Dr. Schaechter | | | | | | | | | | | | | | | | | | | | | | | |
| 1463 | CDC Letter | (Page 837) | Dr. Krogstad | | | | | | | | | | | | | | | | | | | | | | | |
| | Lechevalier Ltr. | | Dr. Brinckerhoff | | | | | | | | | | | | | | | | | | | | | | | |
| 1468 | Brinckerhoff Comm. | (Page 943) | Dr. B. Murray | | | | | | | | | | | | | | | | | | | | | | | |
| | (Coffee Break.....3:15-3:30 p.m.) | | | | | | | | | | | | | | | | | | | | | | | | | |
| | End of Session..... | 5:00 p.m. | | | | | | | | | | | | | | | | | | | | | | | | |

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

OCTOBER 8, 1991

- VI. Proposed Amendment to Appendix D of the *NIH Guidelines Regarding a Gene Therapy Protocol* entitled: "Gene Therapy of Familial Hypercholesterolemia"/Dr. Wilson..... 9:00 a.m.
- | | | | |
|--------------|---------------------|------------|------------|
| Tab 1453/III | Federal Register | (Page 6) | Dr. McIvor |
| 1458 | Updated Protocol | (Page 515) | Dr. Doi |
| 1459 | Comm. on July Prot. | (Page 767) | Mr. Capron |
| 1465 | IBC Approval | (Page 917) | |
| | Meyers Comm. | (Page 924) | |
| | McIvor Comm. | (Page 927) | |
| | Doi Comm. | (Page 929) | |
- (Coffee Break.....10:15-10:30 a.m.)
- VII. Future Role of the Human Gene Therapy Subcommittee..... 11:15 a.m.
- | | | | |
|------------|------------------|------------|--------------|
| Tab 1453/V | Federal Register | (Page 8) | Dr. Post |
| 1460 | Anderson Article | (Page 821) | Dr. Atlas |
| | | | Dr. Bourquin |
| | | | Mr. Mannix |
| | | | Dr. Epps |
- VIII. Future Meeting Dates of the Recombinant DNA Advisory Committee..... 1:15 p.m.
- | | | | |
|----------|---------------|------------|---------------|
| Tab 1461 | List of Mtgs. | (Page 824) | Dr. McGarrity |
|----------|---------------|------------|---------------|
- IX. Adjournment..... 1:20 p.m.
- Dr. McGarrity

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NATIONAL INSTITUTES OF HEALTH

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BUILDING 31, CONFERENCE ROOM 6

OCTOBER 7-8, 1991

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Dr. Kelley

Mr. Capron

Dr. Post

Mr. Brewer

Mr. Mannix

Dr. Bourquin

Dr. Schaechter

Dr. McIvor

Dr. Epps

Dr. Leventhal

Dr. Carmen

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Dr. Geiduschek

Dr. Walters

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MATERIALS
FOR
MEETING

RAC. TABLE

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October 3, 1991

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FAX (302) 397-0034Dr. Nelson Wivel
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Dear Dr. Wivel,

I was asked to return to the experts for a list of pathogens in the Order Actinomycetales for the revision of Appendix B. I revised the list given to me by Dr. Schaechter to send to the three experts who had been consulted: Dr. Marie Lechevalier, Dr. Blaine Beeman and Dr. Jonathan Richmond.

Dr. Marie Lechevalier deferred to the CDC in matters of pathogenicity and provided clarification on taxonomy (See packet). Dr. Beeman provided verbal input to the CDC and indicated his agreement with a German assessment of risk. The CDC provided a detailed analysis of the organisms with references (See packet). Those which the CDC listed as proven to be human pathogens are:

Amycolata autotrophica
Dermatophilus congolensis
Nocardia asteroides
Nocardia brasiliensis
Nocardia otitidiscavarium
Nocardia transvalensis
Rhodococcus equi

The draft document sent by the CDC did not include Actinomadura madurae and Actinomadura palletieri as proven pathogens, and did not include normal host flora such as Actinomyces israelii and Actinomyces bovis which were on the original list submitted to the RAC for consideration.

I hereby submit the names of the seven proven human pathogens provided by the CDC as a revised list of bacterial agents of the Order Actinomycetales to be inserted in Appendix B-1-b-1. When Appendix B is amended in the future, points to consider in the risk assessment of etiologic agents which are proven or suspected to cause disease in healthy human adults and those which are opportunistic pathogens should also be developed.

Sincerely yours,

Diane O. Fleming

Diane O. Fleming, Ph.D

944

October 4, 1991

A review of a protocol entitled:

"Gene Transfer for the Treatment of Cancer:
the treatment of Ovarian Cancer with a gene modified cancer vaccine."

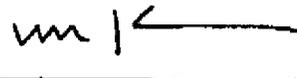
Freeman/Kelly
Comments

In response to the reviewer's comments at the Human Gene Therapy Subcommittee, the authors have provided additional information on the protocol which was reviewed by the Subcommittee on July 29, 1991.

1. The authors were asked to report on the construction of the STK vector.

The authors do describe in some detail the structure and sequence as well as the methodology for the insertion of the HSV-TK gene into the STK retroviral vector, which contains as its backbone, the pLNL6 vector. They also describe the development of a new vector, but this is not the vector proposed for the studies which will be considered by the Committee.

2. The authors were requested to test the cell lines to be used for the experiments. From the information provided, it would appear that the viral stock is negative for replication competent virus, and the cell line will be tested for potential pathogenesis including microplasma, bacteria, fungi, reverse transcriptase, hepatitis B, and replication competent retrovirus.
3. The investigators provided further information on the pretreatment tumor burden, analysis of the patient's immune status, and an updated preclinical data form. They also provided revisions in the consent form. I would recommend that the information be presented in some detail at the RAC.



W. N. Kelley, M.D.

RECOMBINANT DNA ADVISORY COMMITTEE
(October 7, 1991)

COMMENTS ON THE FREEMAN PROTOCOL:
"THE TREATMENT OF OVARIAN CANCER WITH A GENE-MODIFIED CANCER
VACCINE: A PHASE I STUDY"

I. Points-to-Consider

The patient selection criteria should be summarized in the Points To Consider document. The actual protocol may not be readily available. Incorporating by reference to the Protocol the patient selection criteria is not sufficient for the purposes of public disclosure and explanation that are to be served by the Points To Consider document itself.

II. Patient Selection Criteria: Are these specific enough to focus on patients for whom there is the best chance of therapeutic benefit consistent with the purposes of a Phase I Study (data on safety, dose-response, etc.)?

III. Informed Consent: Clarify the disclosure of risk due to complications from anesthesia in the laparoscopy-laparotomy procedure. Language such as:

"The patient is usually given anesthesia for this procedure. There is always a very low risk of harm, including death, from complications that can arise from the use of anesthesia."

IV. Informed Consent: Clarify the language concerning collection of clinical data after a patient withdraws consent to continue participation in the study. (See section on Voluntary Participation, p. 88.)

The patient should probably give specific consent at the time of withdrawal to participate in the collection of any clinical data that are not directly related to routine post-withdrawal medical surveillance and treatment necessary to guard against any complications arising from participation in the study itself.

V. Stopping Criteria: Is it possible to be more specific, more quantitative, in setting forth stopping criteria than the very general, qualitative language set forth in the Benefits paragraph of the Informed Consent form? (See p. 87.)


Michael F. Brewer
October 4, 1991

Brinckhoff

HGTS Subcom

Consolidating The RAC and The HGTS

I am a new member of the RAC and my comments may reflect a relative inexperience about the workings of the RAC and the HGTS. Nonetheless, it seems clear that the "real" work, the nitty-gritty of thrashing out the details of protocols and where questions about how to proceed in the future begin to bubble to the surface, is accomplished by the HGTS. When "final" protocols are presented to the RAC and final approval is given by the RAC, this represents the last step in what may have been a long continuum. Many of the presentations to the RAC by investigators have been made previously (in one form or another) to the HGTS and may be at least partly repetitious. Supposedly, these presentations have taken into account the comments of the subcommittee, and are improved. This may or may not be the case, depending, it seems, on the particular investigator.

The article in Science (253:624, 1991) clearly reveals the high level of frustration felt by the subcommittee members and by investigators asking for approval: "Even the 'lucky winners' would say that the approval process is unnecessarily time consuming and repetitious". Even my limited experience on the RAC would confirm this view, and I would like to advocate the consolidation of the two committees into one real working group that reviewed the protocols, critiqued them, and (eventually) approved or disapproved them. Concomitant with this, I would recommend a series of guidelines (that may already exist but that often may not be adhered to?) that both the investigator and the committee would follow. Is there a time limit for the presentation to the committee by the investigator? Are there guidelines for the structure of this presentation? It appears that sometimes the investigators are not well prepared and that the Committee does the investigator's work for him/her. Certainly, the RAC is more sympathetic and tolerant than the classical NIH study section, and seems to serve almost as an educational body to some investigators, rather than as an advisory one.

At the last RAC meeting, Bill Kelley suggested the format of a study section/council type relationship between HGTS and RAC. This is a possibility, and would eliminate some of the redundancy in the review/approval process. However, I would recommend that if such a model were adopted, that the "council" portion be composed of a small number of representative "study section" members who voted final approval. The potential problem here may be choosing people who are "representative" and thus present an accurate view of the full committee. However, from personal experience, I know that the reverse situation of bringing in new people to ultimately approve or disapprove a protocol (the current RAC mode) in the hope that they may bring a fresh approach is not very satisfying. Listening to a warmed over discussion of issues that have been thoroughly thrashed out previously in detail is disquieting, and one wonders what one has missed. Would more information help frame my judgement as a reviewer more accurately, or at least make me feel that it did? The real "experts" here - those who know what is going on - are those on the HGTS. It seems logical either to make that group the final decision making body or to restructure the RAC so that it has access to the process of the HGTS without the repetition currently involved.

Connie Brinckhoff

Wilson/Capron Comments

October 7, 1991

TO: Recombinant DNA Advisory Committee
FROM: Alexander M. Capron *AMC*
RE: Ex Vivo Gene Therapy for Familial Hypercholesterolemia

Most of the points raised in my July 22 memorandum to the Human Gene Therapy Subcommittee have been addressed. I continue to have several concerns, however.

1. At what point will the subjects first be informed about the study and decide to participate? If subjects are being drawn from "regional lipid centers" (p. 591), I gather they will come to the University of Michigan for the purpose of enrolling in the study. If the first full explanation of the study comes after they have arrived, isn't that rather after-the-fact? What other treatment would they receive by coming to Ann Arbor? Who pays their way? What actually happens if they do decline to participate in the study?
2. Dr. Wilson and his colleagues continue--albeit somewhat more mildly--to state that it is "critical" that subjects not withdraw after the liver is resected but before cells are reinfused. This insistence is (a) paternalistic (the reason given is the investigators' opinion that subjects would at that point have been exposed to risk yet have received no potential benefit); (b) inconsistent with the consent form (p. 575); and (c) self-serving, because the persons for whom subjects' withdrawal is "critical" are the investigators not the subject. I believe that we should insist that Dr. Wilson and his team agree to abide by the proposition that subjects may withdraw at anytime by: (1) removing this language; and (2) agreeing that they will not in any way pressure subjects not to withdraw.
3. I fail to see the justification for using minors in the first group of three subjects, since children cannot participate voluntarily and must be "consented" by their parents or guardians. If children are used, I trust that the "assent form" that Abbey Meyers and I were asked to develop, which was submitted to Dr. Wivel on September 27, will be used in place of the form on p. 584.
4. I have a number of small changes in the consent form to improve clarity. As these are primarily stylistic, I will discuss them directly with Dr. Wilson and his colleague. I continue to be concerned, however, that the form's overall tone is to treat the procedure as a new therapy for patients rather than as an experimental investigation with patient-subjects.

Wilson / Hasel Korn

October 7, 1991

TO: Recombinant DNA Advisory Committee
FROM: Dr. Robert Haselkorn 
SUBJECT: Review of Wilson Protocol

Regarding the Wilson proposal, I have the following concern: the patients to be selected for treatment appear to lack the LDL receptor protein entirely. Thus, they are not expected to be tolerant of this protein and may well mount an immune response to it when it is presented on the surface of (even) their own hepatocytes. The Watanabe rabbit does not answer this concern because the mutation in the rabbit is a small deletion in the receptor protein. Since most of the protein has been present since birth, the rabbit sees the transgene product as self and does not reject it.

The Wilson proposal should address this concern, possibly by inducing immune tolerance of the LDL receptor protein via thymus injection if the patients are young enough.

I also thought that more data from the baboon experiment could have been presented.

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National Institutes of Health
Bethesda, Maryland 20892

Office of Recombinant
DNA Activities
NIH, 31/4B11
Bethesda, MD 20892
Phone 301-496-9838
FAX 301-496-9839

September 30, 1991

Albert B. Deisseroth, M.D., Ph.D.
Chairman, Department of Hematology
MD Anderson Cancer Center
1515 Holcombe Boulevard
Houston, TX 77030

Dear Dr. Deisseroth:

This will acknowledge receipt of your letter of September 24.

I have forwarded copies of this letter to Drs. McGarrity and Walters and as soon as they have reached a determination concerning the proposed modifications in this protocol, I shall convey their response to you.

Sincerely,

Nelson A. Wivel
Nelson A. Wivel, M.D.
Director

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THE UNIVERSITY OF TEXAS
MD ANDERSON
CANCER CENTER

Albert B. Deisseroth, M.D., Ph.D.
Chairman, Department of Hematology
Anderson Professor
For Cancer Treatment and Research
(713) 792-8750

September 24, 1991

Dr. Nelson Wivel
Office of Recombinant DNA
NIH
Bldg. 32, Room 4B11
Bethesda, MD 20892

Dear Dr. Wivel:

I am writing you with a minor modification in the protocol which proposes marking of autologous marrow in CML patients, which has been previously approved by both the RAC committees. Please bring this minor modification to the attention of the Human Gene Therapy Subcommittee chairman, LeRoy Walters, and the Recombinant DNA Advisory Committee chairman, Gerard McGarrity. I would like their consideration of our protocol modification to determine if the proposed change is minor so it will not require full review by both committees.

My intention is to introduce a minor modification into the conditions in which the human autologous marrow is exposed to the LNL6 retrovirus as follows:

1.25 times the usual number of cells previously indicated (formally 2×10^8 /kg nucleated cells or 1.4×10^{10} nucleated cells for a 70 kg man) will be stored. The excess number of cells (0.35×10^{10} nucleated cells above 1.4×10^{10}) will be immediately applied to the development of autologous stromal monolayers, for use in the retroviral transduction procedure.

Before freezing, the cells will be subjected to monoclonal antibody purging as described in documents previously submitted in the attached protocol. Then, the purged marrow will be frozen in two aliquots: 70% of the total and 30% of the total.

When the monolayers are 60% confluent, the aliquot of the purged marrow that represents 30% of total will be thawed and applied to the stromal monolayer along with the LNL6 virus in a ratio of 10 CFU per nucleated cell. The cells also will be fed every 12 hours with a fresh aliquot of the virus. At the end of 72 hours, the cells will be rinsed, concentrated and frozen away. When the

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patient is eligible for autologous transplantation, both the 30% (virally transduced) and 70% aliquots of the marrow specimen will be thawed and infused according to protocol DM90-064.

We will also pre-screen the marrow cells of CML patients for the ability to be transduced by the LNL6 vector.

We have found that the minor change proposed in the transduction protocol (using autologous stroma) results in a significant increase in the efficiency of gene transfer. This increase in transduction efficiency will improve our ability to obtain the goals stated in the protocol by making the detection of marked cells (cancerous and normal) easier.

As these modifications represent no additional risk to the patient and merely provide for an increase frequency of early progenitor marking, the modification may represent an improvement for the overall protocol. I will be happy to provide what other additional information the Drs. McGarrity and Dr. Walters, chairs of the RAC committees, require for this modification.

Sincerely,



Albert Deisseroth, M.D., Ph.D.
Anderson Chair for Cancer Treatment and Research
Chairman, Department of Hematology

AD:vg

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Close Encounters with Other Worlds

Venice, Jamaica, Southern India, the American Southwest and the Magic Kingdom, Sunday, Oct. 13, in the Fall Travel Issue of The Washington Post Magazine

Genetics

Cancer Vaccine Trial Gets Green Light at NIH

World's First Test of Genetically Engineered Vaccine

By Robin Herman
Washington Post Staff Writer

Researchers at the National Institutes of Health yesterday gained permission to inoculate patients with the world's first attempt at a genetically engineered vaccine for cancer.

Steven A. Rosenberg, chief of surgery at the National Cancer Institute, is prepared to inject cancer patients with a genetically altered version of their own live tumor cells. The goal is to provoke the body to mount a significant immune response against the cancer.

Permission for the experiment came from the NIH's Recombinant DNA Advisory Committee (RAC), charged with reviewing the science, efficacy and ethics of all human and animal experiments with altered DNA. Approval from the Food and Drug Administration for the clinical trial was granted last week.

Once the proposal is endorsed by NIH director Bernadine Healy, Rosenberg and his colleagues can start testing the experimental cancer vaccine in patients.

"I'm anxious to get started," said Rosenberg, the principal investigator. "Our challenge now is to use gene therapy to help people with cancer." In the experimental technique of gene therapy, scientists extract certain cells from the patient, alter the genetic structure of these cells in the laboratory and then reinject the altered cells into the patient.

Rosenberg's proposed anti-cancer vaccine is the first to use live malignant tumor cells that have been genetically altered on human patients.

Rosenberg has permission to treat an initial 30 patients who have advanced melanoma, kidney cell cancer or colon carcinoma that has failed all standard treatment. These patients are expected to live for six months or less.

Sections of the patients' tumors have been removed and cultured in the laboratory to insert either the gene for a hormone called tumor necrosis factor (TNF), a powerful anti-tumor toxin, or the gene for interleukin-2, a protein that encourages the body's tumor-fighting lymphocytes.

Laboratory studies with mice have shown that the immune system can be stimulated by genetically altered tumor cells. In these experiments, mouse immune systems more readily targeted tumors with these altered genes and attacked them.

The human body is capable of mounting an immune response to cancer on its own, but it is a weak one. Oncologists occasionally see what is called "spontaneous remission" when patients are able to fight off their own tumors. Researchers hope that the genetically altered tumor cells will heighten the body's immune response to the cancer.

Rosenberg's experiment is two-pronged.



Steven A. Rosenberg, chief of surgery at the National Cancer Institute, plans to inject 30 cancer patients with their own live tumor cells.

"Our challenge now is to use gene therapy to help people with cancer."

— Steven A. Rosenberg

First, he will inject the altered cells, carrying either the TNF gene or the IL-2 gene, into the thigh of a patient with the aim of stimulating an immune response. These cells would continually secrete either TNF or IL-2, presumably killing local tumor cells or helping tumor-killing lymphocytes from the immune system to grow in number.

Then, 21 days after the injection, Rosenberg would surgically remove the tumor cells from the local site and drain nearby lymph nodes. From this material he would cultivate an especially potent kind of anti-tumor cell. The newly cultivated anti-tumor cells would then be transfused in great numbers back into the patient.

Experiments in mice show that the altered tumor cells, when re injected, grow for a short time and then suddenly regress.

The RAC committee is requiring Rosenberg to closely monitor the injected tumor site for any unexpected growth. The amount of tumor injected is to be no more than one fiftieth of the amount of tumor the terminal patients already have in their bodies.

Rosenberg and colleague investigator W. French Anderson also are involved in the first trials of human gene therapy at the National Institutes of Health, in which four adult melanoma patients and two children with a rare immune deficiency disorder are being treated with genetically altered white blood cells.

HUMAN GENE TRANSFER AND HUMAN GENE THERAPY PROTOCOLS
SUBMITTED TO THE HUMAN GENE THERAPY SUBCOMMITTEE
OF THE NIH RECOMBINANT DNA ADVISORY COMMITTEE
1988-1991

Protocol for July 29, 1988, Meeting of the Subcommittee

#1. Tr. Addition to Clinical Research Project 86-C-183, a Project Entitled "The Treatment of Patients with Advanced Cancer Using Cyclophosphamide, Interleukin-2 and Tumor Infiltrating Lymphocytes," Steven A. Rosenberg, et al., National Cancer Institute

Protocol for December 9, 1988, Meeting

#1. Tr. Addition to Clinical Research Project 86-C-183, a Project Entitled "The Treatment of Patients with Advanced Cancer Using Cyclophosphamide, Interleukin-2 and Tumor Infiltrating Lymphocytes," Steven A. Rosenberg, et al., National Cancer Institute

Protocols for July 31, 1989, Meeting

None

Protocol for March 30, 1990, Meeting

#2. Th. "Treatment of Severe Combined Immune Deficiency (SCID) due to Adenosine Deaminase (ADA) Deficiency with Autologous Lymphocytes Transduced with a Human ADA Gene," R. Michael Blaese, et al., National Cancer Institute

Protocol for June 1, 1990, Meeting

#2. Th. "Treatment of Severe Combined Immune Deficiency (SCID) due to Adenosine Deaminase (ADA) Deficiency with Autologous Lymphocytes Transduced with a Human ADA Gene," R. Michael Blaese, et al., National Cancer Institute

Protocols for July 30, 1990, Meeting

#2. Th. "Treatment of Severe Combined Immune Deficiency (SCID) due to Adenosine Deaminase (ADA) Deficiency with Autologous Lymphocytes Transduced with a Human ADA Gene," R. Michael Blaese, et al., National Cancer Institute

#3. Th. "Gene Therapy of Patients with Advanced Cancer

Using Tumor Infiltrating Lymphocytes Transduced with the Gene Coding for Tumor Necrosis Factor," Steven A. Rosenberg, et al., National Cancer Institute

#4, #5, #6 (see below). Tr. "Use of Marker Genes to Investigate the Biology of Marrow Reconstitution and Relapse of Malignant Disease Following Autologous Bone Marrow Transplantation," Malcolm K. Brenner, et al., St. Jude Children's Research Hospital

Protocols for November 30, 1990, Meeting

#4. Tr. "Autologous Bone Marrow Transplant for Children with AML [Acute Myelogenous Leukemia] in First Complete Remission: Use of Marker Genes to Investigate the Biology of Marrow Reconstitution and the Mechanism of Relapse," Malcolm K. Brenner, et al., St. Jude Children's Research Hospital

#5. Tr. "A Phase I/II Trial of High-Dose Carboplatin and Etoposide with Autologous Marrow Support for Treatment of Stage D Neuroblastoma in First Remission: Use of Marker Genes to Investigate the Biology of Marrow Reconstitution and the Mechanism of Relapse," Malcolm K. Brenner, et al., St. Jude Children's Research Hospital

#6. Tr. "A Phase II Trial of High-Dose Carboplatin and Etoposide with Autologous Marrow Support for Treatment of Relapse/Refractor Neuroblastoma Without Apparent Bone Marrow Involvement," Malcolm K. Brenner, et al., St. Jude Children's Research Hospital

#7. Tr. "Retroviral-Mediated Gene Transfer of Bone Marrow Cells during Autologous Bone Marrow Transplantation for Acute Leukemia: Understanding Disease Recurrence," Kenneth Cornetta, et al., University of Wisconsin

#8. Tr. "The Administration of Interleukin-2, Interleukin-4, and Tumor Infiltrating Lymphocytes to Patients with Melanoma," Michael T. Lotze, et al., University of Pittsburgh

Protocols for April 5, 1991, Meeting

#5. Tr. "A Phase I/II Trial of High-Dose Carboplatin and Etoposide with Autologous Marrow Support for Treatment of Stage D Neuroblastoma in First Remission: Use of Marker Genes to Investigate the Biology of Marrow Reconstitution and the Mechanism of Relapse," Malcolm K. Brenner, et al., St. Jude Children's Research Hospital

#6. Tr. "A Phase II Trial of High-Dose Carboplatin and Etoposide with Autologous Marrow Support for Treatment of

Relapse/Refractor Neuroblastoma Without Apparent Bone Marrow Involvement," Malcolm K. Brenner, et al., St. Jude Children's Research Hospital

#8. Tr. "The Administration of Interleukin-2, Interleukin-4, and Tumor Infiltrating Lymphocytes to Patients with Melanoma," Michael T. Lotze, et al., University of Pittsburgh

#9. Tr. "Autologous Bone Marrow Transplantation for CML [Chronic Myelogenous Leukemia] in Which Retroviral Markers Are Used to Discriminate between Relapse Which Arises from Systemic Disease Remaining after Preparative Therapy Versus Relapse due to Residual Leukemic Cells in Autologous Marrow: A Pilot Trial," Albert B. Deisseroth, et al., M.D. Anderson Cancer Center

#10. Tr. "Hepatocellular Transplantation in Acute Hepatic Failure and Targeting Genetic Markers to Hepatic Cells," Fred D. Ledley and Savio L.C. Woo, et al., Baylor College of Medicine

Protocols for July 29, 1991, Meeting

#11. Th. "Ex Vivo Gene Therapy of Familial Hypercholesterolemia," James M. Wilson, et al., University of Michigan

#12. Th. "Immunotherapy of Malignancy by in Vivo Gene Transfer into Humans," Gary J. Nabel, et al., University of Michigan

#13. Th. "Gene Therapy in the Treatment of Cancer: The Treatment of Ovarian Cancer with a Gene Modified Cancer Vaccine," Scott M. Freeman, et al., University of Rochester

#14. Th. "Immunization of Cancer Patients Using Autologous Cancer Cells Modified by Insertion of the Gene for Tumor Necrosis Factor (TNF)," Steven A. Rosenberg, et al., National Cancer Institute

#15. Th. "Immunization of Cancer Patients Using Autologous Cancer Cells Modified by Insertion of the Gene for Interleukin-2 (IL-2)," Steven A. Rosenberg, et al., National Cancer Institute

Tr. = human gene transfer protocol

Th. = human gene therapy protocol

FUTURE ROLE OF THE HUMAN GENE THERAPY SUBCOMMITTEE
Recombinant DNA Advisory Committee Meeting - 10/08/91

Alexander M. Capron
Move that:

1. the RAC endorse the process established by the HGTS to reexamine the manner in which the committee and subcommittee handle various aspects of gene transfer experiments involving human subjects, and the RAC specifically looks forward to the result of the working groups on germ-line therapy (chaired by Dr. Robertson Parkman) and the working group to follow-up the protocols already approved (chaired by Dr. Brigid Leventhal);
2. the RAC assign to the Planning Subcommittee, chaired by Dr. R. Murray, the task of developing a set of principles to guide its operations and future formulation of guidelines;
3. barring major new developments, the RAC not further debate the issue of merging itself and the HGTS pending having taken action on the recommendation of the three working groups; and as an interim matter, the following procedures will be employed to facilitate effective and efficient review of protocols involving human subjects:
 - a. Immediately after the review of the protocol by the HGTS, the primary reviewer (working with the committee chair and Executive Secretary) will prepare a summary of the points needing further attention, which will be submitted to the principal investigator;
 - b. such statements will also be promptly circulated to members of the subcommittee, and any points that they identify as having been omitted from a summary will be added to the list and conveyed to the principal investigator;
 - c. as a standard routine matter, the principal investigator will be asked to provide a written summary and copies of any slides regarding material presented orally at a HGTS meeting that were not in prior written submissions to ORDA.
 - d. if a protocol is deferred, the summary of the prior discussion, along with minutes of the meeting, will be submitted to the HGTS prior to its next review of the protocol;
 - e. once a protocol has been fully or provisionally approved by the HGTS, it will be placed on the agenda of the next meeting of the RAC, whose members will be provided with any summary statements of the HGTS's consideration of the protocol, relevant minutes, and the written material submitted by the principal investigator to cover points presented orally.

Published in the Federal Register on September 3, 1991

[Billing Code 4140-01]

DEPARTMENT OF HEALTH AND HUMAN SERVICES

National Institutes of Health

Recombinant DNA Advisory Committee

Notice of Meeting

Pursuant to Public Law 92-463, notice is hereby given of a meeting of the Recombinant DNA Advisory Committee on October 7-8, 1991. The meeting will be held at the National Institutes of Health (NIH), Building 31C, Conference Room 6, 9000 Rockville Pike, Bethesda, Maryland 20892, starting at approximately 9 a.m. on October 7 to adjournment at approximately 5 p.m. on October 8. The meeting will be open to the public to discuss the following proposed actions under the *NIH Guidelines for Research Involving Recombinant DNA Molecules* (51 FR 16958):

Proposed Major Actions to the *NIH Guidelines*;

Four additions to Appendix D of the *NIH Guidelines* Regarding Human Gene Transfer Protocols;

Amend Appendices B-I-B-1 and B-I-B-2 of the *NIH Guidelines* to include only pathogenic genera and species of the bacterial order, Actinomycetales, in the current list of microorganisms.

Other Matters To Be Considered by the Committee.

Attendance by the public will be limited to space available. Members of the public wishing to speak at this meeting may be given such opportunity at the discretion of the Chair.

Dr. Nelson A. Wivel, Director, Office of Recombinant DNA Activities, National Institutes of Health, Building 31, Room 4B11, Bethesda, Maryland 20892, Phone (301) 496-9838, FAX (301) 496-9839, will provide materials to be discussed at this meeting, roster of committee members, and substantive program information. A summary of the meeting will be available at a later date.

OMB's "Mandatory Information Requirements for Federal Assistance Program Announcements" (45 FR 39592, June 11, 1980) requires a statement concerning the official government programs contained in the *Catalog of Federal Domestic Assistance*. Normally NIH lists in its announcements the number and title of affected individual programs for the guidance of the public. Because the guidance in this notice covers not only virtually every NIH program but also essentially every Federal research program in which DNA recombinant molecule techniques could be used, it has been determined not to be cost effective or in the public interest to attempt to list these programs. Such a list would likely

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require several additional pages. In addition, NIH could not be certain that every Federal program would be included as many Federal agencies, as well as private organizations, both national and international, have elected to follow the *NIH Guidelines*. In lieu of the individual program listing, NIH invites readers to direct questions to the information address above about whether individual programs listed in the *Catalog of Federal Domestic Assistance* are affected.

Dated: AUG 27 1991

Jeanne N. Ketley

Jeanne N. Ketley, Ph.D.
Acting Committee Management Officer, NIH

Published in the Federal Register on September 3, 1991

[Billing Code 4140-01]

DEPARTMENT OF HEALTH AND HUMAN SERVICES

National Institutes of Health

**Recombinant DNA Research: Proposed Actions Under the
Guidelines**

Agency:

National Institutes of Health, PHS, DHHS.

Action:

Notice of Proposed Actions Under the *NIH Guidelines for
Research Involving Recombinant DNA Molecules* (51 FR 16958).

SUMMARY:

This notice sets forth proposed actions to be taken under the *National Institutes of Health (NIH) Guidelines for Research Involving Recombinant DNA Molecules*. Interested parties are invited to submit comments concerning these proposals. These proposals will be considered by the Recombinant DNA Advisory Committee (RAC) at its meeting on October 7-8, 1991. After consideration of these proposals and comments by the RAC, the Director of the National Institutes of Health will issue decisions in accordance with the *NIH Guidelines*.

DATES:

Comments received by September 25, 1991, will be reproduced and distributed to the RAC for consideration at its October 7-8, 1991, meeting.

ADDRESS:

Written comments and recommendations should be submitted to Dr. Nelson A. Wivel, Director, Office of Recombinant DNA Activities, Building 31, Room 4B11, National Institutes of Health, Bethesda, Maryland 20892, or sent by fax to 301-496-9839.

All comments received in timely response to this notice will be considered and will be available for public inspection in the above office on weekdays between the hours of 8:30 a.m. and 5 p.m.

FOR FURTHER INFORMATION CONTACT:

Background documentation and additional information can be obtained from the Office of Recombinant DNA Activities, Building 31, Room 4B11, National Institutes of Health, Bethesda, Maryland 20892, (301) 496-9838.

SUPPLEMENTARY INFORMATION:

The NIH will consider the following actions under the *NIH Guidelines for Research Involving Recombinant DNA Molecules*:

**I. Addition to Appendix D of the "NIH Guidelines"
Regarding a Human Gene Therapy Protocol/Dr. Freeman**

In a letter dated May 10, 1990, Dr. Scott M. Freeman of the University of Rochester School of Medicine indicated his intention to submit a human gene therapy protocol to the Human Gene Therapy Subcommittee and the Recombinant DNA Advisory Committee for formal review and approval. The title of this protocol is:

"Gene Transfer for the Treatment of Cancer."

The protocol was reviewed during the Human Gene Therapy Subcommittee meeting on July 29-30, 1991. Provisional approval was given with the stipulation that the PA-1 ovarian cancer cell line be tested for potential pathogens as per FDA guidelines. Further, it was requested that there should be more preclinical studies on the MFG vector to assure that it does not contain replication competent retroviruses.

The Human Gene Therapy Subcommittee forwarded the protocol to the Recombinant DNA Advisory Committee for consideration during the October 7-8, 1991, meeting.

II. Additions to Appendix D of the "NIH Guidelines"

Regarding Human Gene Therapy Protocols/Dr. Rosenberg

In a letter dated June 6, 1991, Dr. Steven A. Rosenberg of the National Institutes of Health indicated his intention to submit two human gene therapy protocols to the Human Gene Therapy Subcommittee and the Recombinant DNA Advisory Committee for formal review and approval.

The first protocol is entitled: "Immunization of Cancer Patients Using Autologous Cancer Cells Modified by Insertion of the Gene for Tumor Necrosis Factor."

The second protocol is entitled: "Immunization of Cancer Patients Using Autologous Cancer Cells Modified by Insertion of the Gene for Interleukin-2."

The protocol was reviewed during the Human Gene Therapy Subcommittee (HGTS) meeting on July 29-30, 1991.

Provisional approval was granted with the following stipulations. Although the NIH Institutional Biosafety Committee had requested a preliminary experiment using tumor cells that were not gene-modified, the HGTS requested that only tumor cells transduced with the cytokine genes be used in these protocols. Further, the Principal Investigator was requested to report his results after the first five patients have been studied; he was asked to

measure the rate of cell growth at the injection site, and to do a polymerase chain reaction assay for cytokine DNA in the inguinal lymph nodes and in tumor biopsies at other sites in the body.

The HGTS forwarded the protocol to the Recombinant DNA Advisory Committee for consideration during the October 7-8, 1991, meeting.

**III. Addition to Appendix D of the "NIH Guidelines"
Regarding a Human Gene Therapy Protocol/Dr. Wilson**

In a letter dated June 7, 1991, Dr. James M. Wilson of the University of Michigan Medical Center indicated his intention to submit a human gene therapy protocol to the Human Gene Therapy Subcommittee and the Recombinant DNA Advisory Committee for formal review and approval. The title of this protocol is:

"Gene Therapy of Familial Hypercholesterolemia."

The protocol was reviewed during the Human Gene Therapy Subcommittee meeting on July 29-30, 1991. Provisional approval was granted with the following stipulations. It was requested that the Principal Investigator provide additional data about the quality control of the vector

system and the characteristics of the packaging cell line. In addition, the consent form is to be reviewed following several requested changes.

The Human Gene Therapy Subcommittee forwarded the protocol to the Recombinant DNA Advisory Committee for consideration during the October 7-8, 1991, meeting.

IV. Amend Appendices B-I-B-1 and B-I-B-2 of the "NIH Guidelines" regarding the Bacterial Order, "Actinomycetales."

In a written request dated April 15, 1991, Dr. Diane O. Fleming of Merck & Co., Inc., requested that only pathogenic genera and species of the bacterial order, *Actinomycetales*, be included in Appendix B-I-B-1 of the *NIH Guidelines*.

It was proposed that the following pathogens be included under Bacterial Agents in Appendix B-I-B-1 of the *NIH Guidelines* as follows:

Actinomadura madurae
Actinomadura pelletieri
Actinomyces bovis
Actinomyces israelii

Nocardia asteroides

Nocardia brasiliensis

In Appendix B-I-B-2, the entry under Actinomycetes would be deleted.

This request was reviewed at the Recombinant DNA Advisory Committee meeting on May 30-31, 1991. Following a discussion there was agreement that the Actinomyces should be reclassified as bacteria and removed from the list of fungi. However, there was disagreement about the number of species to be listed as pathogens. The number was thought to be considerably larger than the six species proposed for inclusion. Dr. Fleming was asked to consult with leading experts in the field and return with a revised list of pathogens, which will be reviewed at the Recombinant DNA Advisory Committee meeting on October 7-8, 1991.

V. Discussion of Future Role of Human Gene Therapy Subcommittee.

At its meeting on July 29-30, 1991, the Human Gene Therapy Subcommittee held a discussion about ways to shorten the review process for human gene therapy protocols. It was suggested by some members that consideration be given to merging the Human Gene Therapy Subcommittee and the

Recombinant DNA Advisory Committee with the idea that the present system creates an unnecessary double hurdle. The Recombinant DNA Advisory Committee will consider the issues raised at the most recent Human Gene Therapy Subcommittee meeting.

VI. Other Matters To Be Considered by the Committee.

Attendance by the public will be limited to space available. Members of the public wishing to speak at this meeting may be given such opportunity at the discretion of the Chair.

Dr. Nelson A. Wivel, Director, Office of Recombinant DNA Activities, National Institutes of Health, Building 31, Room 4B11, Bethesda, Maryland 20892, Phone (301) 496-9838, FAX (301) 496-9839, will provide materials to be discussed at this meeting, roster of committee members, and substantive program information. A summary of the meeting will be available at a later date.

OMB's "Mandatory Information Requirements for Federal Assistance Program Announcements" (45 FR 39592, June 11, 1980) requires a statement concerning the official

government programs contained in the *Catalog of Federal Domestic Assistance*. Normally NIH lists in its announcements the number and title of affected individual programs for the guidance of the public. Because the guidance in this notice covers not only virtually every NIH program but also essentially every Federal research program in which DNA recombinant molecule techniques could be used, it has been determined not to be cost effective or in the public interest to attempt to list these programs. Such a list would likely require several additional pages. In addition, NIH could not be certain that every Federal program would be included as many Federal agencies, as well as private organizations, both national and international, have elected to follow the *NIH Guidelines*. In lieu of the individual program listing, NIH invites readers to direct questions to the information address above about whether individual programs listed in the *Catalog of Federal Domestic Assistance* are affected.

Dated: AUG 29 1991



Jay Moskowitz, Ph.D.
Associate Director for Science Policy
and Legislation, NIH

Wilson/Capron Comments

October 7, 1991

TO: Recombinant DNA Advisory Committee
FROM: Alexander M. Capron *AMC*
RE: Ex Vivo Gene Therapy for Familial Hypercholesterolemia

Most of the points raised in my July 22 memorandum to the Human Gene Therapy Subcommittee have been addressed. I continue to have several concerns, however.

1. At what point will the subjects first be informed about the study and decide to participate? If subjects are being drawn from "regional lipid centers" (p. 591), I gather they will come to the University of Michigan for the purpose of enrolling in the study. If the first full explanation of the study comes after they have arrived, isn't that rather after-the-fact? What other treatment would they receive by coming to Ann Arbor? Who pays their way? What actually happens if they do decline to participate in the study?
2. Dr. Wilson and his colleagues continue--albeit somewhat more mildly--to state that it is "critical" that subjects not withdraw after the liver is resected but before cells are reinfused. This insistence is (a) paternalistic (the reason given is the investigators' opinion that subjects would at that point have been exposed to risk yet have received no potential benefit); (b) inconsistent with the consent form (p. 575); and (c) self-serving, because the persons for whom subjects' withdrawal is "critical" are the investigators not the subject. I believe that we should insist that Dr. Wilson and his team agree to abide by the proposition that subjects may withdraw at anytime by: (1) removing this language; and (2) agreeing that they will not in any way pressure subjects not to withdraw.
3. I fail to see the justification for using minors in the first group of three subjects, since children cannot participate voluntarily and must be "consented" by their parents or guardians. If children are used, I trust that the "assent form" that Abbey Meyers and I were asked to develop, which was submitted to Dr. Wivel on September 27, will be used in place of the form on p. 584.
4. I have a number of small changes in the consent form to improve clarity. As these are primarily stylistic, I will discuss them directly with Dr. Wilson and his colleague. I continue to be concerned, however, that the form's overall tone is to treat the procedure as a new therapy for patients rather than as an experimental investigation with patient-subjects.

Move that:

1. the RAC endorses the process established by the HGTS to reexamine the manner in which the committee and subcommittee handle various aspects of gene transfer experiments involving human subjects, and the RAC specifically looks forward to the result of the working groups on germ-line therapy (chair by Dr. Robertson Parkman) and the working group to follow-up the gene transfer protocols already approved (chaired by Dr. Brigid Leventhal);
2. the RAC establish a working group to develop a set of principles to guide its operations and future formulation of guidelines;
3. barring major new developments, the RAC not further debate the issue of merging itself and the HGTS during the coming year, pending taking actions based on the recommendation of the three working groups; and as an interim matter, the following procedures will be employed to facilitate effective and efficient review of protocols involving human subjects:
 - a. Immediately after the review of the protocol by the HGTS, the primary reviewer (working with the committee chair and Executive Secretary) will prepare a summary of the points needing further attention, which will be submitted to the principal investigator;
 - b. such statements will also be promptly circulated to members of the subcommittee, and any points that they identify as having been omitted from a summary will be added to the list and conveyed to the principal investigator;
 - c. as a standard routine matter, the principal investigator will be asked to provide a written summary and copies of any slides regarding material presented orally at a HGTS meeting that was not in prior written submissions to ORDA.
 - d. if a protocol is deferred, the summary of the prior discussion, along with minutes of the meeting, will be submitted to the HGTS prior to its next review of the protocol;
 - e. once a protocol has been fully or provisionally approved by the HGTS, it will be placed on the agenda of the next meeting of the RAC, whose members will be provided with any summary statements of the HGTS's consideration of the protocol, relevant minutes, and the written material submitted by the principal investigator to cover points presented orally.

Wilson / IBC Approval
Meyers Comments
McIVOR Comments
Doi Comments

TAB 1465

THE UNIVERSITY OF MICHIGAN

Biological Research Review committee

4080 Fleming

ANN ARBOR, MICHIGAN 48109-1340

Wilson
IBC Approval

October 1, 1991

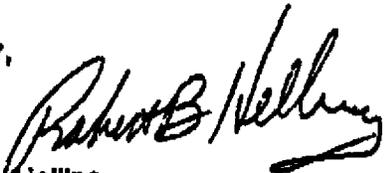
Dr. Nelson A. Wivel
Director, Office of Recombinant DNA Activities
Office of Science Policy and Legislation
National Institutes of Health
Building 31, Room 4B11
Bethesda, Maryland 20892

SUBJECT: Proposal of James Wilson: "Ex Vivo Gene Therapy of Familial
Hypercholesterolemia"
Containment Level BL2
Status: Approved

Dear Dr. Wivel:

At its meeting this morning, Tuesday, October 1, 1991, this committee approved initiation of gene therapy for familial hypercholesterolemia. Proposal, facilities and procedures meet the requirements of the National Guidelines for Research Involving Recombinant DNA Molecules, and of the University of Michigan. We consider this an excellent proposal, and likely to be a model for other work in gene therapy. The comments of the primary reviewers are attached. Dr. Wilson will use 0.22 micron filters as recommended. Other comments were discussed with Dr. Wilson and are dealt with satisfactorily in the proposal or through oversight by FDA. The laboratory was inspected and facilities and procedures were found to be satisfactory. Final inspection of the Human Applications Laboratory will be made following completion of its renovation, and prior to use.

Sincerely,



Robert B. Helling
Chair, Biological Research Review Committee
(Institutional Biosafety Committee)

JBH/jl

Enclosures: 2 primary reviews
Review form

cc: J. Wilson
Office of the Vice President for Research

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GENE THERAPY PROPOSAL REVIEW (Provisional Version)

Biological Research Review Committee
(Institutional Biosafety Committee)

4080 Fleming 1940

Telephone 938-3834

FAX 788-0088

Date Sent _____

Reviewer

Title

Date Completed

Office Address

Telephone

Proposal

Please review the proposal to see if it conforms to the National Guidelines for Research Involving Recombinant DNA Molecules and if the proposed containment levels are appropriate. The Institutional Review Board will separately review gene therapy proposals relative to human patient care and ethical concerns. If possible review this proposal within one week. After the review is complete, or if you have questions or difficulty completing the review, please call Janet Linear at the Office of the Vice President for Research, telephone 938-3834.

The structures and properties of the vectors may need especially careful examination. If you wish to confer with the principal investigator about details, you may do so, but it may be advisable to contact the BIRRC Chair first (R. Helling, 784-1455 office, 788-8006 home, or through OVPR 938-3834).

Laboratory inspections will be arranged following the proposal review if BL2 or BLS level containment is required.

Please respond in each section:

1. Nature and source of DNA
Is the description adequate?
Is the containment level proposed appropriate to the cloned DNA?
Are there any problems?

1. The description of the nature and sources of the DNA to be used in these studies is complete and adequate. Although not explicitly stated, I assume that these experiments will be carried out under BL2 containment.

2. The description of the recombinant retrovirus is adequate and complete. Indeed, Dr. Wilson is having the virus sequenced. Dr. Wilson is using state of the art propagation techniques to assure that the viral stocks are free of replication-competent helper viruses. Thus, once the recombinant virus (which is not competent for replication) has infected the hepatocytes, there should be no further release of infectious virus. See (1) above regarding containment.

I have only one small concern: although the virus-infected hepatocytes are washed extensively prior to infusion into the patient, what steps are taken to ensure that no free virus particles are carried along with the cells? If they were, they presumably could be carried through the bloodstream to non-target organs in the patient. Are any tests to be run on the hepatocytes post-infection but pre-infusion to test for free virus? Is such non-targeted infection possible, is this cause for concern?

3. The description of cell lines is adequate and complete, and Dr. Wilson has covered the possible problems.

4. N/A

5. This is a thoughtful and well documented proposal. In my opinion, the potential benefits far outweigh the risks of this procedure. Indeed, the risks associated with surgery, etc. appear to be higher than those due to the use of recombinant agents. Assuming that the probability of the scenario raised in (2) is low and, in all likelihood, not a serious concern, I recommend approval of this protocol.

GENE THERAPY PROPOSAL REVIEW (Provisional Version)

**Biological Research Review Committee
(Institutional Biosafety Committee)**

4080 Fleming 1340

Telephone 936-3934

FAX 763-0085

Date Sent _____

Reviewer _____ Title _____ Date Completed _____

Office Address _____ Telephone _____

Proposal _____

Please review the proposal to see if it conforms to the National Guidelines for Research Involving Recombinant DNA Molecules and if the proposed containment levels are appropriate. The Institutional Review Board will separately review gene therapy proposals relative to human patient care and ethical concerns. If possible review this proposal within one week. After the review is complete, or if you have questions or difficulty completing the review, please call Janet Linear at the Office of the Vice President for Research, telephone 936-3934.

The structures and properties of the vectors may need especially careful examination. If you wish to confer with the principal investigator about details, you may do so, but it may be advisable to contact the BRRC Chair first (R. Helling, 754-1455 office, 789-2006 home, or through OVPR 936-3934).

Laboratory inspections will be arranged following the proposal review if BL2 or BL3 level containment is required.

Please respond in each section:

1. Nature and source of DNA
 - Is the description adequate?
 - Is the containment level proposed appropriate to the cloned DNA?
 - Are there any problems?

The source and nature of DNA are explicitly stated with no margin of error. The containment facilities, although adequate, should be clearly defined vis-a-vis the processing of the cloned DNA.

"Ex vivo Gene Therapy of Familial Hypercholesterolemia"

2. The investigators have furnished a detailed description of the methodology used to achieve the purpose of the project. The molecular techniques, the analysis and follow-up did furnish adequate safeguards through: 1) the use of an appropriate virus vector; 2) its method of propagation and harvesting; and 3) its inoculation into hepatocytes which provided the margin of safety for the recipient.
3. In the in vitro cultivation of cells, minor concerns are raised: 1) the use of 0.22 μ filter is preferable to the use of 0.45 μ filter; 2) the source, purity and concentration of the dissociating enzymes (Trypsin, collagenase) should be listed; 3) the source, quality and safety of the lot(s) of fetal bovine serum used; and 4) testing for possible sensitivity of the patients to the antibiotic penicillin.
4. Not relevant.
5. The approval of the protocol is recommended. The project offers, through molecular medicine, an avenue not only in identifying a risk factor of a disease process but also in using state-of-the-art techniques for intervention to the benefit of patients in control and possible prevention of diseases.

GENE THERAPY PROPOSAL REVIEW (Provisional Version)

Biological Research Review Committee (Institutional Biosafety Committee)

4080 Fleming 1340

Telephone 936-3934

FAX 763-0055

Date Sent _____

Reviewer _____ Title _____ Date Completed _____

Office Address _____ Telephone _____

Proposal _____

Please review the proposal to see if it conforms to the National Guidelines for Research Involving Recombinant DNA Molecules and if the proposed containment levels are appropriate. The Institutional Review Board will separately review gene therapy proposals relative to human patient care and ethical concerns. If possible review this proposal within one week. After the review is complete, or if you have questions or difficulty completing the review, please call Janet Lincer at the Office of the Vice President for Research, telephone 936-3934.

The structures and properties of the vectors may need especially careful examination. If you wish to confer with the principal investigator about details, you may do so, but it may be advisable to contact the BRRC Chair first (R. Helling, 764-1455 office, 769-2008 home, or through OVPR 936-3934).

Laboratory inspections will be arranged following the proposal review if BL2 or BL3 level containment is required.

Please respond in each section:

1. Nature and source of DNA
 - Is the description adequate?
 - Is the containment level proposed appropriate to the cloned DNA?
 - Are there any problems?

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2. **Vectors**

Is the description adequate?

Are any unanticipated hazards associated with the vector?

Is the containment level proposed adequate for work with the vector including any helper nucleic acids or viruses?

Are there any problems?

3. **Bacteria, yeast, and cell lines**

Is the description adequate?

Are any unanticipated hazards associated with the use of these organisms?

Are there any problems?

4. **Other organisms**

Are there any unanticipated hazards?

Are there any problems?

5. **Recommendation**

National Organization for Rare Disorders, Inc.

NORD • P.O. Box 8923, 100 Rt. 37 • New Fairfield, CT 06812-1783 • (203) 746-6518



President:
Jesse Thoms, M.D.

Executive Director:
Abbey S. Meyers

Organizations:
 Neuroma Association
 of Genetic Support Groups
 Alan Norelcoy Association
 American Porphyria Foundation
 American Syringomyelia Alliance Project
 Amyotrophic Lateral Sclerosis
 Association
 Aplastic Anemia Foundation of America
 Association for Brain Tumor Research
 Association for Glycogen
 Storage Disease
 Batten Disease Support &
 Research Association
 Benign Essential Sphincterospasm
 Research Foundation, Inc.
 Charcot-Marie-Tooth Association
 Chromosome 18 Registry and
 Research Society
 Cornelia de Lange Syndrome
 Foundation, Inc.
 Cystinosis Foundation, Inc.
 Dysautonomia Foundation, Inc.
 Dystonia Medical Research Foundation
 Dystrophic Epidermolysis Bullosa
 Research Assoc. (D.E.B.R.A.)
 Ehlers-Danlos National Foundation
 Epilepsy Foundation of America
 Families of Spinal Muscular Atrophy
 Fraxoni Anemia Research Fund
 Foundation for Ichthyosis &
 Related Skin Types (F.I.R.S.T.)
 Guillain-Barre Syndrome
 Foundation International
 Hemochromatosis Research
 Foundation, Inc.
 Hereditary Disease Foundation
 Histocytosis Association of America
 Huntington's Disease Society
 of America, Inc.
 Immune Deficiency Foundation
 International Fibrodysplasia Ossificans
 Progressiva (FOP)
 International Joseph Diseases
 Foundation
 International Rett Syndrome
 Association, Inc.
 Interstitial Cystitis Association
 of America, Inc.
 J's Syndrome Association
 and Hyperthermia Association
 in the United States
 J's Network (EAR Foundation)
 Lapsy Network
 National Addison's Disease Foundation
 National Alopecia Areata Foundation
 National Association for
 Sickle Cell Disease, Inc.
 National Ataxia Foundation
 National Foundation for
 Ectodermal Dysplasias
 National Gaucher Foundation, Inc.
 National Marfan Foundation
 National Mucoopolysaccharidosis
 Society, Inc.
 National Multiple Sclerosis Society
 National Neurofibromatosis Foundation
 National PKU News
 National Sjogren's Syndrome Association
 National Tubercous Sclerosis
 Association, Inc.
 National Vitigo Foundation, Inc.
 Neurofibromatosis, Inc.
 Obsessive Compulsive Foundation
 Oculogenesis Impairata Foundation
 Oculosis & Hyperbasuria Foundation
 Paget's Disease Foundation, Inc.
 Parents of Galectosemic Children
 Parkinson's Disease Foundation, Inc.
 Polycystic Kidney Research Foundation
 Prader-Willi Syndrome Association
 Reflex Sympathetic Dystrophy
 Syndrome Association
 Retinite Pigmentosa Foundation
 Fighting Blindness
 Scleroderma Federation, Inc.
 Scleroderma Info Exchange, Inc.
 Sjogren's Syndrome Foundation, Inc.
 Tourette Syndrome Association, Inc.
 United Leukodystrophy Foundation, Inc.
 United Parkinson Foundation
 Vestibular Disorders Association
 Wegener's Granulomatosis Support
 Group
 Williams Syndrome Association
 Wilson's Disease Association

September 27, 1991

Wilson/Meyers Comments

Nelson A. Wivel, M.D.
 Director, Office of Recombinant DNA Activities
 Human Gene Therapy Subcommittee
 NIH, Bldg. 4B11, Room 903B
 Bethesda, MD 20892

Dear Dr. Wivel:

Attached you will find a revised children's consent form for the familial hypercholesterolemia study at the University of Michigan. Alexander Capron and I have agreed to these changes, which should make the form more understandable to children.

Please send a copy of the revised form to the investigators at the University of Michigan since I do not have their names and addresses.

Very truly yours,

Abbey S. Meyers

Abbey S. Meyers
 Executive Director

ASM:aa

Attachment

cc: Alexander Capron

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About Face/CANADA
 Alzheim Syndrome Newsletter
 Alabama Society for Sleep Disorders
 American Behcet's Association, Inc.
 American Pediatric Gastroesophageal
 Reflux Association, Inc.
 American Self-Help Clearinghouse/N.J.
 American Research Group
 Association for Children with
 Russell-Silver Syndrome, Inc.

Brain Impaired Adult Resource Center
 Center for Research in Sleep Disorders
 Charcot-Marie-Tooth International
 Children's Leukemia Foundation MI
 Chronic Granulomatous Disease
 Association
 Congenital Adrenal Hyperplasia
 Assoc., Inc. (CAHSA)
 Deveraux Foundation

Family Survival Project for
 Brain-Damaged Adults
 Foundation for Nager & Miller
 Syndromes
 Freeman-Sheldon Parent Support
 Group
 Kippel-Trenaunay Support Group
 Lethbridge Society for Rare
 Disorders/Canada
 Lyme Borreliosis Foundation

Ataxias
 Myeloproliferative Disease
 Research Center
 National Chronic Fatigue Syndrome
 Association
 National Coalition for Research in
 Neurological & Communicative
 Disorders
 National Cushing's Association
 New England Retinoblastoma
 Support Group

North American Pediatric
 Pseudo-Obstruction Society
 Organic Acidemia Association, Inc.
 Parent To Parent of GA, Inc.
 Parent To Parent of New Zealand
 Research Trust for Metabolic
 Diseases in Children
 Sickle Cell Association of the
 Texas Gulf Coast
 Society for Progressive Supranuclear
 Palsy

Soto's Syndrome Support Group
 Sturge-Weber Foundation
 Tourette Syndrome Assoc. of MD
 Tourette Syndrome Assoc. of
 Nova Scotia
 Tourette Syndrome Assoc. of OH
 Treacher-Collins Foundation
 Tubercous Sclerosis Assoc. of IL
 *Associations are joining
 continuously. For newest listing
 contact the NORD office.

Dedicated to Helping People with Orphan Diseases

CHILD'S ASSENT FOR THE PERFORMANCE OF GENE TRANSFER
THERAPY FOR FAMILIAL HYPERCHOLESTEROLEMIA

You are being asked to take part in a medical experiment that we hope will help people with familial hypercholesterolemia. Because you have this illness, certain fats (called lipids) are not cleaned out of your blood because your liver does not work properly. Too many lipids in the blood can cause heart disease, poor circulation and other serious illnesses.

Your doctor wants to fix your liver by making it able to produce a protein that is presently missing. To do this he must first remove part of your liver after a doctor has put you to sleep so you won't feel any pain. Then the doctors will place a gene in the liver cells that will manufacture the missing protein. Finally, the doctors will inject the liver cells back into your body.

The reason we think the experiment will work in people with familial hypercholesterolemia is because we have been able to replace the protein in the livers of animals using the same procedure, and they have been cured of familial hypercholesterolemia. However, there is no guarantee that the experiment will also be successful in humans.

This is a very serious study and involves many risks to you. You will have an operation to remove part of your liver and will have to be in the hospital for at least three weeks. After you are discharged from

the hospital, you will have to come back to the doctor's office very often for at least four months after the surgery. You will suffer pain and discomfort from the surgery for at least several weeks, and there is even a small risk that this study will hurt your liver or even kill you. You can, however, decide to quit and stop this study at any time and it will not affect how the doctors take care of you. If you are hurt in any way because of this experiment, your doctors and this hospital will continue to take care of you.

It is important that you let us know that you understand all of the things we have told you. Please ask us any questions you have. If you have any second thoughts about taking part in this study, please tell us and we will let you stop the study. If you decide to participate in this study, we will want to keep track of your progress for many years.

Your signature on this paper tells us that you have been told all these possible benefits and problems, you have had all your questions answered, and you are willing to take part in the study.

Participant

Date

Witness

Date

926

Twin Cities Campus

Institute of Human Genetics
Medical School
Health SciencesBox 206 UMHC
Harvard Street at East River Road
Minneapolis, MN 55455
612-624-3110
Fax: 612-626-7031

September 30, 1991

Dr. Nelson Wivel
Office of Recombinant DNA
National Institutes of Health
Bethesda, MD 20892RE: Review of protocol: "Ex Vivo Gene Therapy of Familial Hypercholesterolemia",
submitted by Dr. Wilson.

Dear Nelson:

I originally reviewed this protocol for the July 29/30, 1991 meeting of the Human Gene Therapy Subcommittee (Tab 1459). The pertinent issues which were identified have been addressed as follows;

A. Safety; transduction of LDL-receptor expressing retroviruses into human hepatocytes. As outlined, the only safety issue over and above the standard consideration that viral stocks be helper-free is the possibility of an immune response to the LDL-receptor in individuals not normally expressing this protein. However, such an immune response has not been observed in studies using the WHHL rabbit, and the investigator indicates that patients will be monitored closely for such an immune response. Dr. Erickson also raised a question about the risk of eliciting liver tumors by culturing hepatocytes *ex vivo* and reinfusing into the patient, but this concern was apparently allayed in considering that the transduced liver cells are a quite differentiated cell type. There are other safety concerns of a more surgical nature, having to do with infusion of hepatocytes into the portal vein, but these risks are not associated with the genetic manipulation of the cells.

B. LDL-receptor retroviral vectors; Gene transfer and expression in human hepatocytes. All of the questions raised concerning which virus would be used and at what titers/multiplicities were essentially addressed in Dr. Wilson's response (pg. 786-793). Concerns about scale-up were also discussed at the Subcommittee meeting, where the investigator stated that the proposed number of cells to be targeted for gene transfer during a human trial have indeed been handled in his laboratory previously.

C. Infusion of transduced hepatocytes and repopulation of the liver. Questions concerning the proportion of infused cells which contribute to repopulating the liver and the proportion of cells in the liver derived from the infused population post-infusion were addressed in Dr. Wilson's response (pg. 786-793). The feasibility of infusing large numbers of hepatocytes into humans has since been further addressed by conducting the proposed resection, gene transfer, and reinfusion process in a baboon (see pg. 535-539). This experiment went well in terms of the surgical procedure and gene transfer frequency (30%). Long-term gene transfer and expression results from this experiment and others like it will be of great interest.

D. Molecular and metabolic evaluation post-infusion. It is stated in the response (pg. 535-539) that analyses to be performed will depend on the amount of material available.

E. Anticipated efficacy of the proposed procedure. Variability in the observed level of LDL-receptor expression among different retroviral integrants was presented in Dr. Wilson's response (p. 793). The metabolic capacity of hepatocytes expressing high levels of LDL-receptor to metabolize cholesterol is a question that is difficult to assess.

In conclusion, all of the questions raised in my review for the Human Gene Therapy Subcommittee have been addressed. The preclinical workup of this protocol using a relevant animal model as well as in human hepatocytes and now in a non-human primate has been extremely thorough, lending confidence that the procedure will be successful in humans. I would be in favor of approving this protocol once it has been discussed at the upcoming meeting of the RAC.

Sincerely,



R. Scott McIvor, Ph.D.
Assistant Professor
Institute of Human Genetics
Department of Laboratory Medicine and Pathology

Wilson / Doi

October 2, 1991

PI: James M. Wilson

Reviewer: Roy H. Doi

Title of Proposal: Ex vivo gene therapy of familial hypercholesterolemia (FH)

This is an important proposal to use gene therapy to relieve the effects of FH which is an autosomal dominant disorder caused by a deficiency in the receptor that clears low density lipoprotein (LDL) from the serum. Patients with one abnormal LDL receptor allele (heterozygotes) suffer premature coronary heart disease, while patients with two abnormal LDL receptor genes (homozygotes) have severe hypercholesterolemia and life threatening coronary artery disease in childhood usually dying at about 12 years old.

The strategy proposed by the PI and his colleagues is to isolate a functional human LDL receptor gene and transfer the gene by retrovirus mediated techniques to a large proportion of human hepatocytes. Preliminary evidence indicates that such transduced hepatocytes are capable of expressing functional LDL receptor protein at a level that exceeds normal endogenous levels.

Strengths of the proposal are as follows:

1. The preclinical results with an animal model, the WHHL rabbit model, have been very promising. A functional rabbit LDL receptor gene was transduced into a high proportion of hepatocytes using recombinant retroviruses and the genetically corrected cells were transplanted into the animal from which they were derived. The recombinant autologous hepatocytes was associated with a 30-40% decrease in serum cholesterol that persisted for 4 months, LDL receptor RNA was detected for 6 months, and no immune response was noted for the recombinant LDL receptor. Thus there appeared to be a therapeutic effect with this treatment in rabbits.

2. Control experiments with the retrovirus indicated that any retrovirus contaminants that may have accompanied the transplanted hepatocytes did not replicate.

3. The constitutive expression of the LDL receptor gene to a level 4-fold higher over normal levels did not have an adverse effect on cell viability or morphology for 72 hours - the time course of the experiment.

4. The allogeneic experiments worked well when hepatocytes from the test rabbit was used for retrovirus treatment and transplanted back into the same rabbit. A substantial decline in serum cholesterol was noted with the test cells over that of the control cells treated with mock infected hepatocytes and the decline persisted for 122 days or the duration of the

experiment). Thus there is relatively little or no rejection of infected allogeneic hepatocytes. Long term function can be achieved in the absence of immunosuppressive therapy.

5. Preliminary work with recombinant retroviruses, isolation and efficient infection of human hepatocytes, and assays by RNA blot analysis of gene expression have worked well.

6. Experimental design for human gene therapy have been worked out with a baboon. The technical aspects of partial hepatectomy and catheter placement apparently worked well with no postoperative difficulties.

7. The details for studies on three patients with homozygous FH have been presented in great detail and the evaluation and treatment of patients have been thought out with great care.

8. Attention has been paid to patient evaluation and selection with the exclusion of certain patients with poor histories.

9. A thorough evaluation of the patient prior to, during and after treatment has been proposed.

10. Informed consent form describes the operations in layperson's terms. The potential benefits, risks, and discomforts are defined. No cost to the patient. Voluntary nature of consent.

11. Personnel with much experience. They are aware of the difficulties that may be encountered in terms of technical immunological, physiological, and genetic aspects.

Recommendation:

This is a well thought out proposal based on solid preclinical data and the probability of success seems high. I would recommend approval of this proposal.

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Rosenberg / Leventhal Comments
Barton Comments
Gorman Comments

TAB 1466

Rosenberg / Laverthal Comments

Steven Rosenberg, R.I.

IMMUNIZATION OF CANCER PATIENTS USING AUTOLOGOUS CANCER CELLS MODIFIED BY INSERTION OF THE GENE FOR TUMOR NECROSIS FACTOR

Reviewer: Brigid G. Laverthal, M.D.

in these experiments Dr. Rosenberg plans to take tumor from patients, attempt to start them growing in long term tissue culture and, if this is successful to transfect the lines with a gene coding for tumor necrosis factor. If the patient should relapse or progress, they will then have the transfected cells injected subcutaneously into the thigh and 21 day later the draining lymph nodes will be harvested. Lymphocytes from these draining lymph nodes will be expanded and then reinfused into the patients along with IL-2.

The rationale for these experiments is that 'TNF transfected cells are more immunogenic than untransfected cells.' The cells do appear, in the models to grow less well than the unmodified cells, but the immunologic basis for this growth failure is not completely proven. In addition, Dr. Rosenberg's previous study with neo modified TIL showing that they home to tumor in 3/5 patients may not be relevant since he is not planning to use TIL here but rather all cells from a draining lymph node. Early studies relative to the trafficking of TIL cells cannot really be used to predict what the pattern will be for TNF modified lymph node lymphocytes and this is critical to his hypothesis since he hopes to use these cells to increase the local (i.e. in the tumor) rather than the systemic concentration of TNF.

There are a number of concerns about this protocol. First, will the tumor cells grow in the patient after they are modified. If they do grow will they endanger the patient in terms of being "seeded" with cells that make TNF constantly and render the patient symptomatic? If they do not grow, will they be capable of stimulating the draining lymph node lymphocytes? If the cells are reinfused with IL-2, how will it be possible to tell whether they have any intrinsic toxicity?

Because of these concerns the HGTS elected to approve the initial treatment of 5 patients with the caveat that the local reaction be observed closely and that measurements and descriptions (?photographs) of the injection sites be submitted. (A local lesion with high TNF production might be quite painful and necrotic). The draining lymph nodes and other tumor sites should be studied by PCR for signs of spread of transfected (i.e. tumor) cells to study the trafficking pattern. In addition we request that a description of the cells harvested from the lymph nodes be provided, i.e. are they TIL cells? a mixture of cell types? are they cytotoxic to tumor cells lines? and that a toxicity reporting scale be developed that provide us with more detail than what is shown in Table 8. Toxicity should be reported with grades per course and per patient.

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JOHN H. BARTON
GEORGE E. OSBORNE PROFESSOR OF LAW
September 29, 1991

Rosenberg/Barton Connects

FROM: John Barton
TO: NIHRAC/ORDA
SUBJ: Rosenberg Protocols

1. If I understand correctly, the protocol will involve the simultaneous administration of tumor cells, modified to produce IL-2 or TNF, and then, should TIL be available from the area of tumor cell administration, of cultured TIL derived from that area and of IL-2. We are assured that, for these patients, risks deriving from the introduction of the tumor cells themselves are acceptable; there appears to be a basis for concern that the quantity of IL-2 or TNF produced by the introduced cells might give rise to unacceptable risk. Previous experiments have shown that TNF and IL-2 alone in mice encourages tumor regression and that IL-2 or the combination does in humans, but that TNF alone in humans would be effective only at levels too high to be tolerated. (Packet at 155 and 169). TIL with the TNF gene are currently being tested.

If this understanding is correct, I have two questions. First, would it be possible to obtain the same experimental information by introducing a combination of IL-2 or TNF, unmodified tumor cells, and TIL produced as described in the protocol? If this is the direction implied by the NIH IBC in the proviso to its June 19, 1991 letter, why was the proviso not accepted? Second, what are the implications of the difference between IL-2 and TNF with respect to relative levels of tolerance? Are the risks of introducing tumor cells modified to produce TNF different from those for cells producing IL-2?

2. Considering the difficulties of this experiment, the number of patients seems very high. Any approval should be conditioned on regular reporting and an earlier stop point should there be problems. And information deriving from the ongoing studies of introducing non-transduced tumor cells and of the TILs transduced with TNF should be tracked as well for stop indications for this experiment.

3. How are the costs handled (or is this outside our jurisdiction)?

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4. The consent form (version starting at page 176) appears very well done. My only concern is the opposite of the usual -- neither of the first two summary paragraphs explains the potential positive benefits of the TIL, and yet a large portion of the procedure (from the patient's perspective) involves the TIL. These two paragraphs might be better organized to (1) warn that the procedure is highly experimental, (2) explain more of the research goals, including the TIL role as well as the TNF (or IL-2) role, and (3) outline the procedures themselves.

26 September 1991

Rosenberg/Carmen Comments

To: ORDA and RAC Colleagues

From: Ira H. Carmen

IHC

Subject: Review of Rosenberg Protocols

The two research studies herein assessed--the first, a procedure designed to immunize cancer patients employing autologous cancer cells modified by insertion of the gene for TNF, and the second, a procedure designed to immunize cancer patients employing autologous cancer cells modified by insertion of the gene for IL-2--constitute the third set of experiments which Dr. Steven Rosenberg has presented to our committee. I make this point because I think the current agenda items can best be evaluated when seen as part of the larger context of research activity which has driven Dr. Rosenberg's work over the past several years. In 1988, this committee approved the Anderson-Blaese-Rosenberg protocols, thus authorizing the first-ever transfer of exogenous DNA into humans. More specifically, the investigators transduced tumor-infiltrating lymphocytes with the bacterial NEO gene in order to scrutinize closely the activity and effects of the TIL. I am aware of no deleterious consequences arising from this study, though I am not certain what significant theoretical knowledge the research has as yet provided. Certainly we can say that the retroviral vector there employed--and employed since in other protocols sanctioned by the RAC--is eminently safe given the condition of the recipients for whom it has been intended. In 1990, this committee approved a Rosenberg therapeutic regimen in which TIL was used to transmit the TNF gene into human subjects suffering from advanced cancer. These experiments are now underway, but evidently it is too early to evaluate their consequences.

The research designs currently under review carry forward the central thrust of the 1988 and 1990 investigations; however, they contain several new features which should be noted:

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1) the gene for IL-2 will be introduced into human subjects, the third gene to be so transmitted for therapeutic purposes

2) the exogenous DNA (TNF and IL-2) are to be inserted subcutaneously and intradermally

3) the cells to be transduced are tumor cells themselves, not lymphocyte cells; according to the terms of the original protocol presented before our subcommittee, they would be injected concurrently with unmodified tumor cells

4) the recipients are afflicted with many different forms of malignancy such as renal carcinoma and colorectal cancer, whereas the terminally-ill in previous submissions included only patients with melanoma

There is evidence that subcutaneous insertions will be more effective than visceral insertions, and there is evidence that the coinjection of modified and unmodified tumor cells can lead to the inhibition of growth for both cell lines. There is also evidence that IL-2 has much in common with TNF: both are known cancer-fighters and both can precipitate serious, but eminently treatable, side effects. The reintroduction of tumor, transduced or not, could cause tumor growth; again, however, appropriate countermeasures are available and the patients have failed all other possible avenues of treatment.

My observations and reservations are as follows:

1) By what criteria does Dr. Rosenberg determine which patients will receive the gene for TNF and which patients will receive the gene for IL-2?

2) The NIH IBC recommended a pilot study which would test only the subcutaneous insertion of autologous tumor, leaving for another day the recombinant DNA phase of the protocol. The HGT Subcommittee considered such postponement unwarranted (wisely, I think) but substituted its own safety measure, vetoing the insertion of unmodified tumor cell lines. Insisting that only cells transduced with cytokine genes be employed in these experiments seems a drastic revision. Though Dr. Rosenberg has apparently acquiesced in the name of compromise, this committee need not acquiesce, and I would like to hear a discussion of the pros and cons.

3) The RAC has recently adopted an amendment to its Points To Consider requiring human gene therapists to provide pretests using the "most appropriate animal models." The question is: what animal model is "most appropriate" in this circumstance? Dr. Parkman believes that only tests measuring the impact of modified tumor cells in animals with established tumors will meet that requirement. Dr. Neiman, however, thinks there may not be an experimental model adequate to this task short of the protocol itself. The issue becomes even murkier when one reads the Colombo-Parmiani correspondence (p. 509), which treats the relevant animal tests thus far reported as a very mixed bag indeed and which urges, therefore, considerable caution in human cytokine gene therapy. I would like to hear Dr. Rosenberg's operational definition in this research context of the term "most appropriate."

All in all, I think these investigations taken as a whole have great promise, and I hope they can proceed with all deliberate speed, unimpeded by reservations based on speculative risk.

Freeman / Geller Comments
Geidushek Comments

TAB 1467

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M. Gellert
September 30, 1991

Review of protocol entitled: "Gene Transfer for the Treatment of Cancer: the Treatment of Ovarian Cancer with a Gene Modified Cancer Vaccine".

by S. Freeman et al.

This protocol is designed to treat ovarian cancer by infusion of radiation-killed tumor cells that have been gene-modified to express the herpes thymidine kinase (TK) gene. These cells are sensitive to the drug Ganciclovir, and there is some evidence that they also render neighboring tumor cells sensitive. Treatment will consist of three infusions with increasing numbers of the killed TK⁺ cells, followed on each occasion by a dose of Ganciclovir.

While this is an interesting proposal, I believe there are serious problems that need attention before it can be approved.

1) The preliminary animal experiments are not a good model for the planned therapy. They consist of injecting mice with a suspension of tumor cells, followed shortly by the TK⁺ cells and Ganciclovir. This has little similarity to treating ovarian cancer, where solid tumor masses must be eliminated. The experiments must be extended to mice bearing established ovarian tumors, before studies on human subjects are begun.

2) The rationale of the therapy is not entirely clear. Two kinds of experiments are described. In the mouse experiments described above, killing of tumor cells seems to depend entirely on an immune mechanism (no killing in nude or pre-irradiated mice). In a second experimental design, the two types of cells are mixed in vitro and treated with Ganciclovir; the TK⁺ cells are killed in the presence of TK⁺ cells. But here no immunological effects are possible, so the relevance to studies in whole animals is dubious. Yet both mechanisms are cited in support of the planned therapy.

3) Unless the question of what patients are to be treated (raised in Dr. Kelley's review of July 25, 1991) was answered at the HGTS meeting, it needs to be raised again. As written, the protocol implies that patients with stage I, II, or III cancer, with good to fair chances of survival, will be given this experimental therapy in place of well-established treatment that could be curative. The plan has to be clarified.

4) Information previously requested on the structure of the MFG vector and the possible contamination of the PA-1 cell line has still not been supplied. If these items are not available for the RAC meeting, consideration of the protocol should be postponed.

Comments on the Protocol "The Treatment of Ovarian Cancer with a Gene-Modified Cancer Vaccine: A Phase I Study" submitted by Dr. S.M. Freeman and collaborators
REVISED

Summary

This protocol involves the following sequence: 1) introduction of the HSV TK gene into cells of a human ovarian cancer cell line; 2) intraperitoneal injection of these TK-expressing cells into patients suffering from ovarian cancer; 3) treatment of these patients with ganciclovir. The therapeutic concept underlying the above sequence is that ganciclovir treatment specifically kills the peritoneal TK⁺ cells, which confer ganciclovir lethality to the otherwise drug-resistant ovarian tumor by one of two routes. One route apparently involves uptake of particulate material derived from the TK⁺ cells by cells of the nearby ovarian tumor. The other route involves elicitation by the killed TK⁺ cells of an immune response directed against the ovarian tumor.

This proposal is for a phase I study, primarily designed to obtain information on safety and appropriate cell dosage rather than effectiveness, although clinical parameters will be followed and evidence regarding disease remission will obviously be looked for. The stated objectives are:

- 1) to evaluate the safety and side effects of treatment with a gene-modified ovarian cancer "vaccine", which is administered intraperitoneally and activated by ganciclovir;
- 2) to determine a maximum cell dose of vaccine that can safely be administered intraperitoneally;
- 3) to evaluate the immunologic response to this vaccine treatment;
- 4) to note clinical effects on the residual ovarian cancer.

A protocol on this subject was reviewed by the Human Gene Therapy Subcommittee on July 29, 1991. The protocol that I have examined was submitted on September 6, 1991 and contains revisions reflecting the critique of the Human Gene Therapy Subcommittee. I have also had the opportunity to examine "Progress Report 1", transmitted on September 23, 1991.

In what follows, I list concerns about various aspects of this protocol. Unless these concerns are substantially answered by discussion at the meeting, I am prepared to recommend against approval of the protocol at this time.

Specific concerns

- 1) The murine (animal) model.

The relevance of this model to the therapeutic scheme was questioned in reviews submitted to the Human Subjects Subcommittee, and I am impressed by these arguments. One reviewer stated that "the preliminary animal experiments do not adequately support the contention that this treatment might have some utility in human patients . . ." As I understand it, the problem of the proposal is that the *in vivo* experimental work has been done with concurrently or almost concurrently injected TK⁺ "vaccine" cells and TK⁻ tumor "target" cells. Thus, the action of the intraperitoneally injected TK⁺ cells has not been tested against a tumor model consisting of tumor masses resembling the ovarian tumor.

The second objection has been that cell dosages in the model experiments have mostly been very different from those projected for the phase I human study. The "Progress Report I" document presents a new experiment on this subject, in which tumor model "target" cells are injected subcutaneously and comparable doses of "vaccine" TK⁺ cells are injected intraperitoneally one day later. While this recent experiment comes closer to meeting certain objections raised against aspects of the animal model, it surely is not adequate to settle matters (with three data points and eighteen mice).

2) The choice of the PA-1 human ovarian cancer cell line from the American type culture collection for transfer of the HSV TK gene.

The choice of this cell line has been criticized on two counts. First, the safety of the cell line is not yet assured (Progress Report I, pages 2 and 3). If I understand it correctly, approval of the protocol in advance of such information would be without precedent. Secondly, to the extent that the immune response to the patients' ovarian tumors is an important contribution to the functioning of the "vaccine", the use of heterologous cells has been questioned. By opting for the technical advantage of using the established cell line, the project appears to risk entirely uninformative outcomes of the phase I study.

3) The postulated therapeutic mechanism.

This impresses me as being still quite unclear. For example, the Figure 5 experiment of Progress Report I follows upon the submission of the human therapy protocol, instead of having preceded it and having been accompanied by attempts to answer the questions that this new experiment raises.

4) Informed consent.

I suggest that this document be made more direct and forthright on the following points:

a) The term "cancer vaccine".

There is nothing absolutely wrong with calling the proposed treatment a "cancer vaccine" *except* when addressing the lay public. To the layman, vaccines are part of the known world, and vaccination works. Whether it is prudent to describe this leap into the mechanistic void as a vaccine when addressing patients is a question that should be reconsidered.

b) Statements on benefits and risks.

The paragraph on benefits starts with "it is not possible to predict whether any personal benefit . . .". At the very least with regard to patients 1-8 in the current protocol, (page 26 of the application and page 71 in the RAC numbering), the investigators must be capable of making a prediction, because they propose to treat patients with dosages of TK⁺ cells that are small compared to the number of cells in a 2cm tumor. These patients should be informed that they are participating in a procedure that is predicted to fail as therapy, but is being followed for the sake of the information that it will yield.

The paragraph on risks and discomforts fails to list the extra days that participating patients will have to spend in the hospital as one of the discomforts.

c) Compensation.

Should not the patients be more forthrightly assured that under no circumstance will they accrue additional costs as a consequence of their participation in this study?

Fleming/Brinckerhoff Comments

TAB 1468

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Fleming/Brinckerhoff Committee

To: Nelson Wivel, M.D.

October 2, 1991

From: Constance E. Brinckerhoff, Ph.D. *Connel*

Re: RAC Meeting, Oct 7-8, 1991; Bacterial Order, "Actinomycetales"

Background. At its meeting on May 30-31, 1991, the RAC agreed that the Actinomyces should be reclassified as bacteria and removed from the list of fungi. At that time, Dr. Die ~~is~~ Fleming from Merck proposed that 6 species be listed as pathogens:

Actinomyces madurae
Actinomyces pelletieri
Actinomyces bovis
Actinomyces israelii
Nocardia asteroides
Nocardia brasiliensis

Discussion of this proposal resulted in the conclusion that the number of pathogens might well be considerably larger than 6, and that the list should not be so limited. Dr. Fleming was asked to submit a revised list which would be more inclusive.

Critique. The material that the committee received for this meeting is presented in a confusing manner. First, a letter from Professor Mary Lechevalier, a taxonomist from Rutgers, gives two lists of organisms, with the initials "DE" marked by some to indicate "duplicate entry". However, what is not clear is how Dr. Fleming's list matches up with or corresponds to Dr. Lechevalier's. Thus, just what organisms we are supposed to consider, and what their names are is not clear.

Second, Drs. McNeil, Brown and Knudsen from the CDC submitted 4 pages, listing various organisms, the diseases they cause, and whether they are proven or suspected pathogens. While this is useful and important raw data, they have made no attempt to make any conclusions from this information. What, then, do they want us to approve specifically? While the general principle of assigning organisms to categories is laudable, it would be helpful for those individuals who want this list to construct it, at least in an initial way, rather than simply presenting us with all this material.

Recommendation As it stands now, the proposal to reclassify certain Actinomycetales is diffuse and unorganized. Those individuals who are directly interested in reclassifying certain of these organisms should do so, based on the information available and they should present this proposed reclassification to the Committee for discussion and approval. Their proposal should have a concise and up-to-date listing of the organisms, the category into which they will fall, and appropriate references.

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