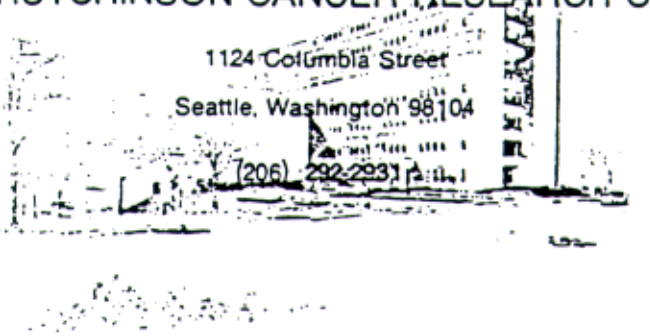
FRED HUTCHINSON CANCER RESEARCH CENTER



DATE: April 6, 1981

TO: Dr. Polissar and Dr. Ensinck

SUBJECT: Human Subjects Review Committee Meeting

RE: H814-180N

I am writing to ask if you would please serve as reviewer for the enclosed Protocol titled Prevention of Graft-Versus-Host Disease (GVHD) by Treatment in Vitro of Donor Bone Marrow with Anti-T cell Monoclonal Antibody (Oncology Protocol #126)

Your help as a reviewer is appreciated. Please do not hesitate to call if there is additional data you need. The Principle Investigator is J.A. Hansen, M.D. and can be reached at 292-6545

John Mills

#126
Rev. 3/81

UNIVERSITY OF WASHINGTON SCHOOL OF MEDICINE
DEPARTMENT OF MEDICINE, DIVISION OF ONCOLOGY
AND THE FRED HUTCHINSON CANCER RESEARCH CENTER

Consent Form for Pretreating Bone Marrow Cells In Vitro Prior to Marrow Transplantation In Order to Prevent or Modify Graft-Versus Host Disease

Investigators: Drs. J.A. Hansen, P.J. Martin, E.D. Thomas, and Members of the Division of Oncology. Emergency Phone (24 hours): 292-2892.

Investigators' Statement

PURPOSE AND BENEFITS

Risk of infection

Patients undergoing marrow transplantation are at risk to develop graft-versus-host disease (GVHD) (a reaction of the donor cells against recipient's tissues). This complication which effects approximately 50% of patients may vary from a mild skin rash to a severe form involving the skin, liver and/or gut and may be fatal. GVHD may represent a direct cause of death in 15-20% of patients transplanted, and in other patients it may contribute to an increased susceptibility to other potentially fatal complications such as interstitial pneumonia. GVHD can also occur in a relatively chronic form. Approximately 30% of patients surviving 150 days or more will develop chronic GVHD, a complication associated with considerable morbidity (requiring prolonged immunosuppressive therapy) and occasional mortality.

The immunological reaction that we identify as GVHD is caused by certain cells called T cells in the donor marrow that recognize the host as "foreign." This study is being carried out to determine whether treatment of bone marrow in vitro with recently developed murine monoclonal anti-T cell antibodies will prevent GVHD. This kind of treatment is now possible because of the high degree of specificity that monoclonal antibodies possess.

PROCEDURES

Before administering any bone marrow cells containing murine monoclonal antibodies, patients will be pretested for hypersensitivity (allergic reaction) to mouse proteins by intradermal skin testing. When this test is know to be negative, bone marrow will be removed from the donor and processed in the usual fashion. Purified monoclonal anti-T cell antibodies will be added to the bone marrow cells, the cells carefully mixed and then transferred according to the standard transplant procedure to transfusion bags for administration to the patient. The addition of monoclonal anti-T cell antibodies will cause no significant delay to the collection or processing of the donor marrow.

RISKS, STRESS OR DISCOMFORT

The use of monoclonal antibody in human patients is still investigational and with any such product there may be unanticipated adverse effects. There is a possibility of an allergic reaction even though the skin test reaction to mouse protein was found to be negative. The total amount of heterologous (foreign) protein administered (1 mg of antibody 9.6 and/~~or 1 mg of~~

antibody 10.2) is very small. Other possible effects are fever, chills, temporary difficulty in breathing, or drop in blood pressure. Your clinical situation will be monitored closely at all times.

To the best or our knowledge, treatment of marrow with monoclonal antibody does not damage the cells necessary for engraftment, but it is possible that engraftment will not occur following such treatment. To protect the patient should engraftment not occur, or be delayed, the patient will be maintained in a sterile environment within a laminar air flow (LAF) room. If engraftment fails, a second marrow transplant, without antibody treatment, will be necessary. Normally, evidence for engraftment of donor marrow cells should appear between 14-21 days after transplantation. If by day 21, the marrow biopsy does not demonstrate signs of engraftment, a second marrow transplant will be administered within 3-4 days. No additional treatment (cyclophosphamide or total body irradiation) of the patient will be required.

This type of treatment is of unproven value. It is not known whether the risk of GVHD will be decreased or whether treatment of the marrow with monoclonal T-cell antibodies will be associated with a greater risk than "conventional" marrow transplantation. At this time, however, there is no alternative method or established procedure for preventing GVHD.

OTHER INFORMATION

The antibody will have been prepared in mice. If you are aware of any allergies to these animals, you should let your physician know of this. Participation in this form of therapy is voluntary and you may withdraw at any time without prejudice.

Personal identity and records are confidential. Access will be restricted to responsible hospital personnel.

The patient and/or his insurance carrier is responsible for all costs accrued during this therapy except for extraordinary or unusual costs unrelated to therapy but related solely to experimental aspects. These extraordinary costs will be assumed by the Division of Oncology. No compensation is available for loss of wages as a result of this treatment.

Signature of Investigator _____ Date _____

Subject's Statement

The study described above has been explained to me and I voluntarily consent to participate in this research program. I have been made aware of alternative courses of action in my case. I understand that my clinical condition will be closely watched at all times. I have had an adequate opportunity to discuss with the faculty of the Division of Oncology all the purposes and hazards related to this experimental treatment and I am satisfied with this discussion.

I give permission for my medical records to be available to physicians and data collection personnel at the University of Washington and Fred Hutchinson Cancer Research Center. I understand that my identity and records will be

treated as confidential and only key personnel will have access to them. The Federal Food and Drug Administration may review studies such as this. Medical records, including identifying material may be released to this agency.

I am aware that I and/or my insurance carrier is responsible for the costs incurred in the therapy provided. I acknowledge receipt of a signed copy of this consent form.

Witness	Adult Patient
Mother	Minor Patient
Father	Date

#126 - 3/81
Copies to: Patient
Medical records
Research file

- Level of presentation was scientist to scientist.
- No negative aspects about this particular study. The longer a person is without white cells the more there chance of dying.
- What about second engraftment? Well we have have supportive care so that's not a problem.
- No credence that this is a risky procedure even though these people need risky procedures to survive.

- This meeting was not a scientific review of Dr Hansen's study. Furthermore there is no evidence the study has been review outside the Center by a peer group. Is it humane? Is it good for people? This committee really has no way to judge

- What are the risks and are they adequately explained in the Consent form, What if engraftment is ruined, what are the chances; what if engraftment failing

- Riley + Tollefsen / These people are concerned Our task is to be certain the consent forms need current standards

- What was not said that some of the Boston studies Monoclonal anti. body stove Nuetro and patients did dont engraft. There point is there is negative data coming out.

Can enough marrow be made

IRB file on 126.
6 inches thick.

Application Dec. 16, 1980 Hansen martin Thomas
To disprove, see transcript of discussion in meeting minutes
Investigator notified 1/26/81 s/tesch

Copy of article in journal, "fighting cancer w cancer, the promise of hybridomas" in cancer center, published by public affairs, memorial sloan kettering

3 pages of notes on yellow paper:
tenor of presentation was scientist to scientist
no negative aspects about this particular study
the longer a person is without white cells the more their chance of dying
Q: what about 2nd engraftment? A: Well we have supportive care so that's not a problem.
No credence that this is a risky procedure even tho these people need risky procedures to survive.
This meeting was not a scientific review of dr. hansen's study. Furthermore there is no evidence the study has been reviewed outside the center by peer groups. Is it humane? Is it good for people? This committee really has no way to judge. But what are the risks? Are they adequately explained in the consent forms? What if engraftment is ruined? What are the chances of a 2nd engraftment ~~(illegible)~~? Failing?
Riabik and tollefson. These people are … certain the consent forms meet current standards.
Did they go through purification steps? Yes to the extent the monoclonal is much more purified …. Further purification… more pure through ATG.
In my estimation the final analysis has to be in whether or not the consent form adequately describes the risk to the patient. The investigator should be able to give ballpark figures of - risk of dying of GHD - risk of dying becaused of a failed 2nd transplant. if these are in the consent then the patient can make an educated consent."

- the weakness is that previous ATG protocol had never treated marrow outside the body. Always before the patients had been treated once they developed GVHD.
- what was said that some of the boston studies mcab's patients don't engraft? The point is there is negative data coming out.q can enough marrow be made?