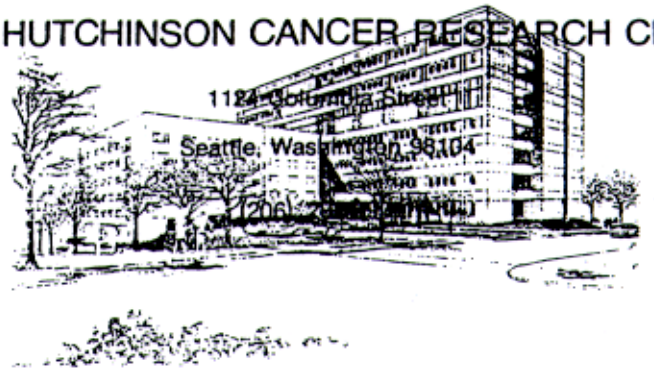
FRED HUTCHINSON CANCER RESEARCH CENTER



FRED HUTCHINSON CANCER RESEARCH CENTER

HUMAN SUBJECTS REVIEW COMMITTEE

MINUTES

MEETING HELD: Tuesday, January 20,1981 in the Hellstrom Library of the Fred Hutchinson Cancer Research Center.

MEMBERS PRESENT: Dr. Donald W. Tesh, Chairman
Dr. Kristine C. Doney
Dr. John W. Ensinck
Dr. Michael Kennedy
Rev. Richard Johnson
Ms. Janet Schwarz, R.N.
Dr. Meredith P. Smith
Mr. Val Tollefson

MEMBERS ABSENT: Mrs. Ethel Hopkins
Dr. Lincoln Polissar *
Dr. Vernon Riley

*Note: Although unable to attend, this member provided written recommendations prior to the meeting.

The meeting was called to order at 4:10 p.m. findings of the Fred Hutchinson Cancer Research Center's Human Subjects Review Committee were as follows:

H8012- 17R

H8012- 33R

though both
f approving
Chairman.

Both protoco

FRED HUTCHINSON CANCER RESEARCH CENTER
HUMAN SUBJECTS REVIEW COMMITTEE
MEETING HELD JANUARY 20, 1981

TRANSCRIPT OF:

H811-180N "Prevention of GVHD by Deletion in Vitro of Donor T Cells with Monoclonal Antibody and Complement. Oncology Protocol #126".
PRINCIPAL INVESTIGATOR: Dr. John Hansen

Committee Member Speaking

1 - O.K., 180N Prevention of Graft-versus-host Disease by Deletion in Vitro of Donor T cells with Monoclonal Antibody and Complement. Must be the inverse of the other study? (H811-182N M/O #128)

4 - Well, I guess the other person is not here?

9 - Right, he did submit some written comments however.

4 - Do you want to read that first?

2 - Preface your statement that this is what U.C.L.A. is in trouble for so be careful.

4 - Right. That's why I brought along copies of the articles in the Los Angeles Times. Have you seen these? I think they should be required reading for all the committee.

1 - Were they circulated to everybody?

9 - No, I did not, but will do so.

1 - I think you should do that before the next meeting. It certainly develops the role of the Human Subjects Review Committee.

9 - This member reports that "Concerning H811-180N, I see two problems. One, Section V. paragraph C of the application: Physician presence should be required. Point two: Is this procedure a radical departure from what they are doing now? I am concerned that the procedure has not really been peer-reviewed outside of FHCRC. I know that we are not constituted to review substantive research issues, but we should be sure that such a review has taken place."

2 - The attending physician is in attendance.

7 - I think he is concerned because the application says "and/or".

4 - I had some questions about it myself. First, to explain the background. These monoclonal antibodies, which most of you might have heard of, are generated using a fusion technique between cells that create antibodies and a spleen cell from a mouse which has been injected

with a particular antigen. Once the antibody producing cell has fused with the spleen cell you have the ability to generate antibody, supposedly of a monoclonal specific type, to just about anything. It's being used now for all sorts of diagnostic reagents and is starting to be used therapeutically as the techniques for making a specific antibody are honed to a finer degree.

The problem is that it is being used to prevent, in this situation GVHD, with the assumption, and he puts in references, that T cells, mature T cells in the marrow inoculum, are the ones contributing to the GVHD. The author cites one of the studies in the reference list which, in mice, show that you deplete mouse marrow using, non-monoclonal antbodies, but just anti-mouse T cell antiserum. In this way one can decrease the number of mice getting GVHD and increase survival.

The problem I have, is there any reason this study can not be done to demonstrate this effect in a larger animal first before moving straight to humans? Such as in dogs for instance which has been the precedent for most of the studies here. In other words, when the studies have been well carried out and the techniques perfected in dogs, then move on to humans. I think that, especially after reading the UCLA expose that this might be a major concern. The author may actually have data on dogs, but I am not aware of it. That is important.

Second, in terms of patient selection, I don't think the patients he is selecting for the pilot study are actually those who are at greatest risk for GVHD. I wonder why that is? They are taking patients with nonlymphocytic leukemia who are matched in remission. It does not say what age the patients are. I am not sure they are actually looking at a patient group that is at a very high risk.

Third point was that, there does not seem to be FDA regulations for using monoclonal antibodies, at least in this situation. I wonder, is the same true for using commercial rabbit complement? I just don't really know how we can get around using these things when the FDA is so stringent about other forms of treatment. I just don't really know the answer to that.

Those were three points regarding the protocol. In terms of the consent form, I think if the purpose of the Human Subjects Review Committee is to actually make sure the patient is fully informed, it should include in the consent the risk of GVHD in the patients. You can give them those percentages roughly from the other protocols. Transplant #93 protocol estimates that between 20 and 40 percent overall develop GVHD then include what chance of dying if you do get the disease and that's about 20-40 percent. This fact should be balanced against the chance of marrow graft failing after treatment coupled with an attempt at a second marrow transplant and its failing. What is the chance of death? Which, as much as I am familiar, is pretty significant although, the consent form makes it sound like if the first engraftment fails, then another one will be done without difficulty. You have to realize that the time period after total body irradiation is critical. At two or three weeks

out, a new graft at that time is certainly much more difficult than the first time. I think those are significant risks. If they were in the consent form, I think as a patient, I would be very hesitant at this point to sign the consent.

2 - Unfortunately, these protocols are a hot potato in terms of what is happening at UCLA. It would behoove the investigators to have a meeting with this committee to answer some of the questions raised. So if there are any questions from the public in the future, we will have looked into the matter regardless of the monoclonal antibody stuff.

You know in-house drugs have no requirements with regard to FDA. So it's really the rules that we decide upon.

4 - That's what we need.

2 - The Medical Oncology Staff have gone around on this the last couple of days. They have been discussing the monoclonal antibodies in terms of what the people making monoclonal antibodies have regarding the relative toxicity.

I am really surprised this has come up for review without any dog studies.

4 - That's what also surprised me. Just because they are citing these mouse studies does not give me that much confidence that they can move right ahead and get into the huge volumes that they are going to need to work with. Then there is the problem of treating marrow with just complement and then trying to reinfuse it. Whether that would decrease chances for a graft is of serious consideration. These are patients who are in remission and not at real high risk for GVHD much less of dying from the disease. With these factors in balance, it would be difficult to approve the protocol the way it is written.

1 - Is it desirable to try to eliminate GVHD?

4 - Well that's another question.

1 - This could be a paradox when considered with the next protocol (H811-182N M/O #128) because there they are trying to increase the risk of GVHD.

4 - That's another point. The other thing is that, and it's not in here, but when they talk about what other treatment is available, they sort of say that there is not much in the way of other treatment.

Oh, here it is! "Alternate procedures will be the standard marrow infusion with prophylactic methotrexate." For instance, they do say that is used to prevent GVHD. Then there are other experimental protocols for preventing the disease not mentioned.

Under "F Nature and the Amount of Risk". I think that the delay of engrafting or failure of graft is because of inability to provide

a second graft before overwhelming infection sets in needs to be elaborated upon.

I don't know chances of long-term survival after transplanting. Under protocol #93 an ANL in first remission is 65 percent balanced against a 25 to 40 percent chance of getting GVHD and 20 percent of those dying from GVHD. You are looking at, to me anyway, you are looking at a fairly small percentage of probability of dying and I would want to know what is the risk of not getting a graft and dying to balance this decision.

8 - So under the circumstances, instead of saying we just have these concerns, maybe it would be appropriate to move to disapprove this protocol and pass on to the investigator at least a summary, if not a transcription, of the concerns expressed. If they want to resubmit the protocol we would appreciate having these concerns addressed.

1 - Or, they would come in person to discuss these issues. There are too many concerns here to consider tentative approval.

8 - I so move.

7 - (3) What is your reaction to this?

3 - My reaction is that I would have liked to have seen some data in lower species of animals. The jump from mouse to man is too great without dosage information. I was just thumbing through this protocol again. There is no references at all to anything that has been done outside of the mouse and the rat.

2 - There is no data that I know of using monoclonal antibodies in this setting. There is some recent human data from Germany using allogeneic ATG. They treated the marrow in vitro with ATG and got the marrow to graft. The public reports of that indicate a limited number of patients who were grafted and did not get GVHD. However, only the investigator presenting the paper said the patients did not get GVHD. The people taking care of the patients said the patients did get GVHD.

4 - But is that published?

2 - It is published somewhere, but it is not with a monoclonal antibody.

4 - The references cited were not monoclonal antibodies either and the investigator probably would have cited that as supporting evidence if it were known.

2 - In defense of Section V., paragraph C., you could delete the "or" because there always are physicians in attendance at the initial conference.

9 - O.K.

4 - There is one other concern regarding stem cells on the very last page under "F". "The monoclonal antibody will be used in vitro to

remove stem cells from the donor marrow before infusion". Well I hope they are not going to do that.

1 - Is there a motion for disapproval?

(A motion was duly made and seconded)

1 - Is there any further discussion?

(Motion carried to disapprove)

1 - A letter will be drafted to the principal investigator outlining the reasons for disapproval. A request will be made for further information and for a personal presentation if at all possible.

(Discussion ended regarding the subject protocol.)

Respectfully submitted,

John E. Mills, IRB
Secretary

JEM:lr