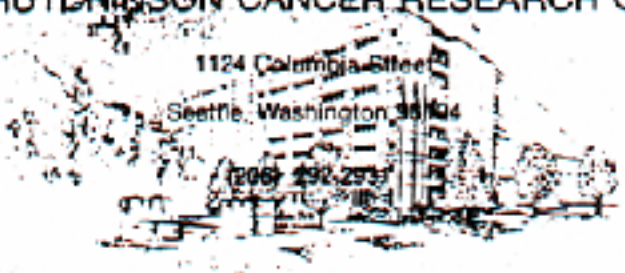
FRED HUTCHINSON CANCER RESEARCH CENTER



Dr. Henry G. Kaplan
Institutional Review Board Chairman
FHCRC Mailstop: I725

December 17, 1984

Dr. Robert W. Day, Director
Fred Hutchinson Cancer Research Center
1124 Columbia Street, M118
Seattle, WA 98104

Dear Bob:

Once again I approach you on behalf of the Institutional Review Board of Fred Hutchinson Cancer Research Center to voice concerns over the manner in which protocols involving the use of monoclonal antibodies are developed at this institution. We hope that our discussions and decisions of the November 13, 1984 IRB meeting might possibly be applied in a positive manner to what we view as a continuing problem.

Medical Oncology's Protocol 159, AUTOLOGOUS MARROW TRANSPLANTATION FOR TREATMENT OF MALIGNANT LYMPHOMA (Fred Appelbaum, M.D.) was up for IRB renewal of approval at the November meeting. This protocol recently went through review but was given approval only through its original expiration date so as to maintain the spread of the separate monoclonal antibody review processes over several months. The Board, once again, finds that it is being asked to authorize a study which we feel has not been thoroughly reviewed on scientific grounds. Although we do not feel adequately qualified to judge this protocol on scientific aspects, nor do we feel that that should be a function of this board, we do feel that there are obvious problems in design that must be resolved. In this protocol, for example, the design is such that the specific agents under investigation (i.e. monoclonal antibodies) are being used in what appears to be a completely uncontrolled fashion. The only possible favorable outcome of this research project, as far as we can see, would be the "successful" use of monoclonal antibodies in the treatment of malignant lymphoma, when in fact the only successful treatment employed may be the autologous bone marrow transplant itself. There is no comparative data being sought. Alternative therapy seems down played in importance. Concern has been expressed concerning the situation wherein the apparent successful use of these agents might establish them as "status quo" in the scientific community at which point careful testing and comparison of alternatives might never be attempted or allowed. In addition, the board is concerned about authorizing protocols in which the apparent successful use of an agent could be potentially beneficial financially to many of the investigators listed on the study.

On a larger plane, the Board would like to express some general thoughts about protocols in general being written and put into practice at the Fred Hutchinson Cancer Research Center. Because of the unique position of Fred Hutchinson Cancer Research Center in the research community, we feel an even larger responsibility to try to protect patients from unnecessary risks and treatments. In that sense, we feel that a more thorough, unbiased, third-party scientific review of all aspects of a new study should be undertaken.

In the current review mechanism at Fred Hutchinson, we feel there is an obvious weak spot. There does not appear to be an adequate amount of statistical forethought incorporated into the writing of these protocols. Many of the clinical protocols being reviewed do not clearly state the statistical details and goals of the proposed studies: thus, the Board is unable to glean a reasonable understanding of what the investigators really are attempting to learn from these protocols. Much concern has been expressed about the lack of a thorough statistical review prior to submission for our review process and eventual use on the wards. We feel this is a major problem in the process of protocol development.

The Board feels that its responsibility and energy should be centered on patient advocate issues and the actual ethics of treatment as viewed from a subject's point of view. Because of the composition of the Board, which includes laypersons and medical personnel, we can do no more than this. With that function in mind, it has become increasingly difficult to review and authorize protocols that have obvious design prejudices or problems. In review of all of these statements, the Board would like to propose some possible solutions to those problems detailed above. In quick retrospect, those problems are: a) the lack of a long-standing, permanent mechanism of recourse for unbiased, scientific review of all original protocols and for those protocols which are deemed in need of scientific review during the annual review; and b) documentation of the actual statistical review process in which careful evaluation of the controls to be used, the end-points to be sought, and the goals of the final analysis has been undertaken prior to submitting the protocol for IRB review.

The Board would like to propose the following as potential solutions to the problems:

1) In the case of Statistical Documentation - Ammend our current application and annual review forms to provide a section and signature line for the statistician that has reviewed the protocol for design validity. This section to be complete before submission to the Institutional Review Board for review.

2) In the case of Extramural Scientific Review - Set up a system similar to the one used for "manuscript review" whereby copies of the protocol are mailed out to perhaps three "experts" in the field throughout the country that have agreed in advance to be reviewers in these matters for our institute.

We would like to express our appreciation for the efforts made in the past to form a "Scientific Review Committee", but we feel that it was perhaps still too close to home to serve the kind of purpose that we had envisioned. At this time, we plan to authorize continuation of Dr. Appelbaum's protocol with a few minor modifications and much reserve, and with hope of establishing the proposed procedures within the next year. We look forward to receiving a reply from you on these proposals and concerns as soon as possible.

Sincerely,

Henry G. Kaplan, M.D.
Institutional Review Board Chairman

cc: File
E. Donnall Thomas, M.D.
Fred Appelbaum, M.D.
Members of the IRB