THE FRED HUTCHINSON CANCER RESEARCH CENTER

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Henry Kaplan, M.D.
IRB Chairman

Dear Dr. Kaplan:

Thank you for your letter of September 28th. I can understand the concerns of the Committee about the use of monoclonal antibodies and will attempt to address some of these questions. On June 21, 1983, Drs. Martin, Hansen and I appeared before the Committee to give a one hour presentation about monoclonal antibodies and to answer questions raised by the Committee. I understand that the personnel of the Committee has changed and thus these questions arise again.

The ability to produce monoclonal antibodies, first described by Koeler and Milstein in 1975, undoubtedly constitutes the greatest "breakthrough" of the last decade. These antibodies are under intensive investigation in most of the major medical centers of the world and will certainly be applied with increasing frequency to a wide spectrum of diseases. It is now possible to make such a wide variety of monoclonal antibodies as to be almost impossible to comprehend. These antibodies, each differing from the other, constitute true "magic bullets" because of the remarkable specificity of their action. The ability to bind these antibodies to toxin or drugs so that highly specific target cells can be damaged is under rapid development.

In our Institution, we are particularly involved with monoclonal antibodies that react with human T-cells, (Drs. Hansen and Martin), for prevention or treatment of graft-versus-host disease and for treatment of T-cell malignancies, with antibodies against myeloid cells, (Drs. Bernstein and Pesando), for treatment of myeloid leukemias and for monoclonal antibodies that react against B cells and other epitopes on the surface of lymphoma cells (Dr. Appelbaum). We fully understand that the Committee members have had, and will continue to have, great difficulty in keeping up with the multitude of technical details involved. We are willing to spend a great deal of time in assisting the Committee members in these problems, particularly the ethical considerations involved. We would be happy to provide the IRB Committee members with more detailed technical information and, to this end, we have included with this letter the Appendix, consisting of (A) production protocols, (B) selected reprints and (C) a bibliography. We could, in the future, be available when new protocols are being considered by the IRB for discussion and questions. We feel that these proceedings should be well documented and available for review by future Committee members. However, I would have to object to arbitrary restrictions on our research activities, for example the 60 day extension

mentioned in your letter, because I think the Committee members have not only an obligation to review the ethical aspects of this work, but also an obligation to assist us and not impede our research, which is directed toward solving some of those problems that are killing the children and young adults who come to us with fatal disease.

The following is an attempt to answer the numbered paragraphs in your letter.

1. "Define the decision-making process by which you and your staff decide which monoclonal antibody is suitable for clinical application".

   The studies currently under consideration have been in planning and development for 3 to 4 years. The basic concepts and some of the more specific proposals discussed above have been incorporated into our major clinical grant applications (ALC, Aplastic Anemia, Autologous grant), presented at site visits and have thereby undergone extensive external scientific review. In the laboratory, this process begins with a fusion of cells which results in thousands of potential antibody producing hybridomas. An extensive screening process of these antibodies with both normal and malignant cells leads to the identification of antibodies that appear to be of interest. In general, this implies high reactivity against the target cell and negligible reactivity against other normal tissues. The cells producing these antibodies are then cloned and the antibodies are produced in larger quantities for further extensive in vitro testing. Antibodies that "survive" this process are then considered for clinical application. The results of the laboratory tests are discussed extensively among the investigators, discussed at one or more of our conferences, including the immunology conference at noon on Mondays, the staff conference at 5:00 p.m. on Tuesdays and the graft-versus-host disease conference at 9:00 a.m. on Wednesdays. Eventually, two or three of the staff members write a rough draft of the proposed protocol, which is then submitted to all faculty members and eventually discussed and approved by all of the faculty at the Tuesday Faculty Meeting. The protocol is then completed and submitted to the IRB.

2. "What are the Division's established controls for monoclonal antibody production?"

   The production and preparation of monoclonal antibodies are essentially the same as those now used in many major medical centers. Appendix A describes this process in detail and gives appropriate references. Also provided in Appendix B is a preprint of a manuscript (by Remlinger et al., Human Immunology, in press) that describes in detail (see methods) the production, biological specificity and quality control of murine monoclonal anti-T cell antibodies.

   "Members would like to review standards for toxicity, both chemical and microbiological".

   This information is provided in Appendix A. It should be noted that these antibodies have now been widely used in humans and are remarkable for their lack of toxicity.

"What preclinical (e.g. animal) screening is carried out to assure that final monoclonal antibody preparations are ready for clinical use?"

As we explained to the Committee in our previous meeting, these antibodies are species specific and therefore cannot be tested in animal systems. Some of the antibodies do react with the cells of higher primates, such as chimpanzees, but these animals are not available. We do conduct experiments in lower primates, when applicable, but other than for the evaluation of "acute toxicity" these studies are of limited value. The results of these experiments are indicated, when applicable, in the background/scientific section of our protocol applications.

3. "Division guidelines for screening monoclonal activity in terms of biological activity".

This question addresses a fundamental premise of ours that we agree warrants thorough emphasis and explanation. The clinical protocol proposals brought to the IRB members represent the product of a long rigorous investigative process (see comments above, questions 1 and 2). Individual monoclonal antibodies brought forward for clinical trials have been extensively studied. Most of these represent the products of experiments initiated as early as 1978. The properties of these antibodies, the antigens or molecules that they recognize and their tissue distribution are thoroughly described in multiple scientific publications. We have made a determined effort to bring forward proposals for clinical trials that incorporate concepts and specific reagents (monoclonal antibodies, assay systems, etc.) for which we have, through our laboratory work, developed a strong data base and knowledge (this is documented by scientific publications). Specific protocols and the antibodies employed represent an objective and logical plan for addressing major clinical problems.

4. "What checks and balances are utilized to deal with potential conflicts of interest between academic and financial considerations of the staff".

This question is rhetorical since there are no such conflicts.

It is worth noting that both the University of Washington and the Fred Hutchinson Cancer Research Center have a long history of working with various companies on a variety of developmental products such as antibiotics, anti-cancer drugs and other agents. In many instances, the company does provide financial support for these activities. The University of Washington and the Fred Hutchinson Cancer Research Center have drawn up guidelines (quite similar to each other) relating to matters of conflict of interest, involvement with outside centers, patents and inventions and consultations. We intend to abide by these guidelines in the future as we have in the past.

Appendix C is a list of references that refer either directly or indirectly to some of the questions raised by the IRB. I would suggest that the Committee members carefully read these references, keeping in mind that this field is evolving so rapidly that much of the material is still in

press or comes directly from frequent communications with other scientists within the field.

I do not believe that it would be practical to write a new set of guidelines and a new protocol for each of the monoclonal antibodies that are now being studied or that may soon be studied. We would be glad to provide a summary sheet for each of these antibodies which details the preparation, the specificities and all relevant information for each antibody.

Finally, Dr. Hansen, Dr. Martin, Dr. Appelbaum and I would be happy to meet again with the Committee to discuss these problems.

Sincerely,

E. Donnall Thomas, M.D.
Professor of Medicine, UW
Associate Director for Clinical Research FHCRC

EDT:jc

cc: Dr. Hansen
Dr. Martin
Dr. Appelbaum