SUMMARY: FRED HUTCHINSON CANCER RESEARCH CENTER (FHCRC)

KM [12-8-93]

April 1993

Background:

In April 93, Dr. John Pesando of Seattle, WA, raised concerns regarding human subject protections in several studies at FHCRC that were supported by the DHHS, namely, 2P01 CA18029-07, CA29548, CA18221, CA15704, CA09515 and CA30924 awarded by the National Cancer Institute; Career award to Dr. E. D. Thomas AI02424.

Dr. Pesando also raised the following specific questions about the level of competence, and degree of authority, etc., of the FHCRC-IRB:

A. When IRB members apparently raised questions regarding protocols 159 and 126, and informed the responsible institutional official of their concerns, why were these studies allowed to continue: - without following the advise of IRB for external review and approval; - without providing requested information to IRB about production procedures, quality control and selection criteria for products used in the studies; and - without resolving the significant financial conflict of interest issues of the investigators involved, as identified by the IRB.

B. When IRB wrote to the responsible institutional official about on-going concerns with regard to protocol development at FHCRC, what was done to address these concerns.

August 17, 1993

OPRR wrote to FHCRC asking for a written report from the FHCRC addressing the above concerns by September 18, 1993.

September 14, 1993

FHCRC asked for an extension till 10-18-93 to respond, which was approved. Documents came in October.

November 1993

OPRR meeting (11-24-93) Preliminary Analysis:

Question: Were the rights, safety and welfare of human subjects compromised in monoclonal antibody studies Under M-1008?

MAIN CONCERNS:

1. **MOAB USED WITHOUT PRIOR TESTING AND STANDARDIZATION:** Monoclonal antibodies were produced by Paul J. Martin, M.D., at FHCRC (Appendix 8). Investigators participated in studies involving use of these antibodies for in vitro treatment of bone marrow prior to its infusion into human subjects for treatment. **Antibodies were used in patients to determine safety and efficacy without prior testing in animals or evaluation under any set of rules.** IRB stated that antibodies were being used in what appeared to be "a completely uncontrolled fashion" (appendix 9). IRB stated "we feel even larger responsibility to try to protect patients from unnecessary risks and treatments" (appendix 9).

These antibodies were not standardized in any manner such as is required by the FDA for use as Investigational New Drugs (INDs). They were used without the benefit of IND checks and balances (Appendix 21); no safety and efficacy was determined.

2. **MOAB LICENSED TO GENETIC SYSTEMS:** Dr. Day stated that while all antibodies used in protocols 126 and 159 were produced at FHCRC (possibly involving use of NIH Grant support!), most of the antibodies were licensed to Genetic Systems (Day letter, page 18, paragraph 1). One antibody, Bi-1F5, used in protocols 126 and 159 at FHCRC, was produced by Oncogen in a joint venture with Genetic Systems.

3. **CONFLICT OF INTEREST:** Dr. Day indicated that **Dr. John Hansen and Dr. E. D. Thomas had substantial holdings in founders stock of Genetic Systems and Dr. Paul Martin also held Genetic System's founder stock.** Dr. Hansen also served as Medical Director, and Dr. Thomas as advisory committee member, for Genetic Systems (appendix 7). They were also participants in the protocols involving the above testing.

Dr. Day indicated that both **Drs. Hansen and Thomas were listed on protocol 126 and Dr. Hansen was the principal investigator** on this protocol **in 1982.** Dr. Paul Martin became the principal investigator on this protocol in **1983.** Minutes of the Advisory Group meeting of February 23, **1984** (Appendix 7) indicate that Dr. Hansen was currently Medical Director of Genetic Systems, and Dr. Thomas continued to serve on the advisory committee of the company and both continued to hold substantial founder stock in the company.

reluctant to, and in fact did, require changes in protocols in order to obtain IRB approval. Similarly, the IRB's stipulation that it would not review and approve research which had not been signed by a statistician and approved by a committee designated to review the scientific merit, is indicative of the IRB's exercise of appropriate authority. And FHCRC's acceptance of this recommendation and ultimate implementation of it, to the satisfaction of the IRB, is indicative of support of the authority of the IRB and not an obstruction. The fact that the IRB accepted the establishment of an FHCRC review body (the Monoclonal Antibody Advisory Committee) in lieu of a non-FHCRC review body, will not be second-guessed by OPRR.

With regard to the alleged conduct of a study involving high mortality rates being carried out in patients for whom the outcome was known to be better outside of the activity and for which reporting of adverse outcomes came only indirectly to the IRB: The evidence presented leads to the conclusion that the protocol criticized was never carried out in the absence of IRB approval. OPRR will not attempt to establish, retrospectively, whether the risks of this research were reasonable in light of anticipated benefits. That is the function of the IRB, and the IRB approved this research. Further, there is no allegation that the IRB withdrew an approval or halted any project based upon information about adverse outcomes which had been previously withheld from it, or had not been intended to be provided to it, but came to the IRB circuitously. Nevertheless, it is not acceptable that the IRB be responsible for obtaining information about research outcomes which might influence its continued approval of ongoing research. Researchers and their institutions, in this case FHCRC, are responsible for communicating this information to the IRB. The regulations require that institutions ensure prompt reporting to IRBs of "...any unanticipated problems involving risks to subjects or others..." (45 CFR §46.103(b)(5)(i)). Mechanisms such as discussing these problems at a meeting to which an IRB administrator and one or more members of the IRB are invited do not meet this reporting requirement.

With regard to alleged resistance to the IRB's request for external scientific review of studies involving MAb and marrow infusion: As reflected in the OPRR determination above, the IRB sought to require this review and accepted FHCRC's decision to appoint the Monoclonal Antibody Advisory Committee in lieu of a non-FHCRC review body. There is no indication in the record that the IRB was in anyway inappropriately influenced in deciding that this was an acceptable alternative. It must be remembered that the IRB had the ultimate authority to approve or withhold approval of the study criticized. OPRR will not conclude that FHCRC should not have put forward an alternative mechanism to an outside review body, nor will it conclude that the IRB should not have found that alternative acceptable. Such negotiations are, as far as the record at hand indicates, acceptable.

With regard to alleged lacking on the part of the IRB of authority, guidelines, and regulatory experience to carry out its responsibilities: The record demonstrates that the IRB was then and continues to be properly qualified, adequately provided with guidance, and vested with the appropriate authority.

February 15, 1994 OPRR received response.

I. Latest version of protocol 126:

The latest version of protocol 126 is numbered 766. It uses immunomagnetic separation and removal of specific T cell subsets. No patients have been entered in this protocol.

On 9/23/92, 766.0 was approved with questions by Committee 03(B).

On 3/24/93, it was approved with questions by Committee 03 and renumbered 766.1.

On 7/14/93, it was reviewed by Committee 02 (Committee A).

On 12/21/93, an expedited review was done by Committee 03 (B).

In Dec 93, Committee 02 reviewed and approved.

On 1/12/94, final approval was given by Committee 02 (A).

II. IRB Roster:

IRB roster shows that Ms. Karen Hansen, B.A., a non-voting member, is named alternate voting member if needed to satisfy quorum requirements. Wendy K. Tyer, B.S., is named alternate for Ms. Hansen. Both are identified as administrators.

III. Minutes:

Minutes record no discussion or basis for approval.

OPRR asked for correction of inconsistancies in committee number on Page 1 of minutes versus on IRB roster, and for corrections regarding asterisks on the IRB roster. FHCRC faxed back the corrected pages.

FRED HUTCHINSON CANCER RESEARCH CENTER (FHCRC)

Kamal K. Mittal's SUMMARY

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Proving that these antibodies were clinically useful, would have financially benefitted Genetic Systems, and subsequently its stock holders, including the three investigators named above. This possibility of financial gain as a result of the clinical success of these antibodies, and conversely of loss if the

antibodies fail, poses the problem of conflict of interest for the three investigators in their role as participants in clinical studies involving these antibodies.

Drs. Hansen and Thomas appear to have had conflict of interest based on the FHCRC policy, dated June 9, 1983, as given in Exhibit E (Appendix 23), and according to FHCRC's own Guidelines, dated June 9, 1983, given in Exhibit F (Appendix 23).

There is the issue of developing and testing products with HHS funds, and allowing a commercial company and oneself to financially profit from it.

4. **NON-ANSWER ABOUT PRE-CLINICAL SCREENING:** When IRB asked Dr. E. D. Thomas about any preclinical screening to assure that antibodies were ready for clinical use, a non-answer was provided by Dr. Thomas (Thomas's letter of October 14, 1993, page 3, top).

5. **IRB CONCERNS:** IRB identified protocols having a lack of adequate statistical forethought and design prejudices and problems. IRB felt uncomfortable in approving protocols for clinical evaluation of these antibodies. It asked for outside scientific review of the protocols (appendix 6). No such outside review was made available.

IRB had first raised concerns to Dr. E. D. Thomas on September 28, 1983 (appendix 4). On November 30, 1983, IRB raised concerns with Director (Appendix 6). On December 17, 1984, IRB again raised concerns with Director (Appendix 9). In May 1985, IRB again wrote to FHCRC director about continued concerns: (i) protocols must be reviewed for statistical merit; (ii) must be reviewed for scientific merit by outside review process. This was necessary because monoclonals had no checks and balances (appendix 21) such as those for INDs, and there were no institutional guidelines regarding safety and efficacy; and adequacy of trial design.

INSTITUTION WAS NOT ADEQUATELY RESPONSIVE TO IRB CONCERNS.

6. **INSTITUTIONAL COMMITTEE NOT ACCORDING TO IRB'S REQUEST:** The Scientific Review Committee (appendix 7) set up by FHCRC consisted of FHCRC staff and was "too close to home to serve the purpose suggested by IRB" (appendix 9, last para)

Conclusions of the above meeting:

1. IRB should have required more information about local MAbs before approving their use in patients.

2. IRB should have questioned continued use after finding high mortality.

3. Conflict of interest is not OPRR issue.

December 1993

12-8-93 Visited Barbara Nishkin's office; requested copies of selected documents.

February 4, 1994

Issues to resolve:

1. Did the IRB feel compromised, as alleged by the Complainant?

2. In the judgement of the IRB, was the risk/benefit ratio in favor of the subjects in the protocols at the time of their approval by the IRB?

3. Were patients fully and correctly informed regarding the use of locally manufactured monoclonal antibodies during the period in question? (Were they expected to be informed about this technical step of in vitro treatment of bone marrow with Moab?)

4. After FHCRC established the policy to the contrary, did Dr. J. Hansen continued to be named on the protocol 126, in spite of holding financial interest in Genetic Systems which held patents on Moabs? Answer appears to be yes! (See File 2, Tab 23, FHCRC Conflict of Interest Policy dated 6-9-83).

To get answers to these questions, it may be necessary to arrange a site visit to speak with various individuals including the members of the IRB at the time period in question.

To establish appropriateness of current IRB procedures and independence of IRB in conducting the reviews, it may be useful to speak with the current IRB members.

February 7, 1993

OPRR has asked Ms. Karen Hansen to provide: a. latest IC document for protocol 126; b. IRB roster of latest protocol 126; and, c. IRB procedures.