U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES

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FOOD AND DRUG ADMINISTRATION

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CENTER FOR BIOLOGICS EVALUATION AND RESEARCH

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BIOLOGICAL RESPONSE MODIFIERS ADVISORY COMMITTEE

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WEDNESDAY,

SEPTEMBER 17, 1997

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The Advisory Committee met in Conference Room 121, Building 29 at the National Institutes of Health, Bethesda, Maryland, at 5:00 p.m., Dr. Ellin Berman, Acting Committee Chair, presiding.

PRESENT:

Ellin R. Berman, Chair

Hugh Auchincloss, Board Member

Richard Goldsby, Board Member

Pamela Hartigan, Board Member

Richard Hong, Board Member

Eugenie Kleinerman, Board Member

Abbey Meyers, Board Member

William O'Fallon, Board Member

Gail Dapolito, Executive Secretary

ALSO PRESENT:

Steven Bauer

Suzanne Epstein

William Freas

Neil Goldman

Steve Kozlowski

Philip D. Noguchi

Marjorie Shapiro

Jay Siegel

Kathryn E. Stein

A-G-E-N-D-A

P-R-O-C-E-E-D-I-N-G-S

(5:00 p.m.)

MS. DAPOLITO: I'd like to welcome you to today's committee meeting, BRM Advisory Committee. We're a couple of people short here. We're waiting for Doctor Siegel to join us. And we have another member, Doctor Bauer isn't here.

Does everybody have a couple of seconds we can wait for those folks to show up? I think we're tracking them down now.

In the meantime, I do want to let you know, we have a transcriber here so would everyone please identify themselves whenever they do speak. And in order to reduce the background noise -- it sounds pretty good right now, but it might be helpful if you have a mute button, and then just remember to release it when you want to speak.

Does everyone have the AT&T phone number and the ID number in case they get disconnected? Does anybody not have it? Okay.

PARTICIPANT: Can you give it to us again?

MS. DAPOLITO: I'd be glad to. It's 1-800-545-4387, and you'll need to give them the ID number which is R-64801.

Doctor Berman?

DOCTOR BERMAN: Yes.

MS. DAPOLITO: This is Gail. I shall turn it over to you for a roll call. Would you like to do that?

DOCTOR BERMAN: I don't have --

MS. DAPOLITO: Since we already went through?

What I'd like to do then is go around the table here --

DOCTOR BERMAN: Right. Why don't we go around formally now?

MS. DAPOLITO: Okay.

DOCTOR BERMAN: This is Doctor Ellin Berman. I'm at Sloan-Kettering in New York.

MS. DAPOLITO: Doctor Hong?

DOCTOR HONG: Dick Hong, University of Vermont.

MS. DAPOLITO: Doctor Auchincloss?

DOCTOR AUCHINCLOSS: This is Doctor Hugh Auchincloss, Boston Mass General Hospital.

MS. DAPOLITO: Doctor Kleinerman?

DOCTOR KLEINERMAN: Doctor Eugenie Kleinerman, MD Anderson -- Center.

MS. DAPOLITO: Doctor Hartigan?

DOCTOR HARTIGAN: Doctor Hartigan at the

VA in West Haven, Connecticut.

MS. DAPOLITO: Doctor O'Fallon?

DOCTOR O'FALLON: Doctor Michael O'Fallon, the Mayo Clinic.

MS. DAPOLITO: Ms. Meyers?

MS. MEYERS: Abbey Meyers, National Organization for Rare Disorders.

MS. DAPOLITO: And Doctor Goldsby?

DOCTOR GOLDSBY: Dick Goldsby, Department of Biology, Amherst College.

DOCTOR BERMAN: And this is Doctor Berman again speaking that I received a fax from Doctor Carol Miller, to tell me that she will be unable to participate in this afternoon's conference.

MS. DAPOLITO: Okay.

We'll go around the room now and identify ourselves here. We can start on my right.

DOCTOR EPSTEIN: Suzanne Epstein, Division of Cellular and Gene Therapies.

DOCTOR BAUER: Steve Bauer, Division of Cell and Gene Therapies.

MS. DAPOLITO: Dr. Siegel? Sorry.

DOCTOR SIEGEL: I just put a cookie in my mouth. I thought it was going the other direction.

Jay Siegel, Office of Therapeutics

Research and Review.

DOCTOR STEIN: Katy Stein, Division of Monoclonal Antibodies.

DOCTOR GOLDMAN: I'm Neil Goldman, the Associate Director for Research at CBER.

DOCTOR KOZLOWSKI: Steve Kozlowski, Division of Monoclonal Antibodies.

DOCTOR SHAPIRO: Margie Shapiro, Division of Monoclonal Antibodies.

MS. HARVEY: -- Harvey, Committee Management Specialist for the BRM Advisory Committee.

DOCTOR FREAS: Bill Freas from the Advisory Committee staff.

DOCTOR BERMAN: Okay, well, thank you very much.

I think next, Doctor Siegel, did you want to address us next?

DOCTOR SIEGEL: Well, just for a moment to offer a particular expression of appreciation and thanks. We've discussed this before. You all know how important these assessments are to us and I can assure you that in the recent site visits you've done, very careful attention has been paid to the recommendations in terms of providing resources and planning directions for the research programs that

have been looked at. We anticipate the same here.

I know that this was extremely difficult to schedule, and I'm particularly appreciative of the fact that at least for those of you in the East, this is heading toward the end of the day and I appreciate your giving your time for this very much.

MS. DAPOLITO: Doctor Berman, this is Gail.

DOCTOR BERMAN: Right.

MS. DAPOLITO: With your permission, I'd like to read the Conflict of Interest Statement.

DOCTOR BERMAN: All right.

MS. DAPOLITO: Okay. "This announcement is made a part of the record at this meeting of the Biological Response Modifiers Advisory Committee on September 17, 1997.

Based on the agenda made available, it has been determined that all committee discussions related to the review of the intramural research program for the Laboratory of Molecular and Developmental Immunology, Division of Monoclonal Antibodies; and the individual research program of Doctor Bauer in the Laboratory of Molecular Immunology, Division of Cellular and Gene Therapies, present no potential for a conflict of interest.

In the event that the discussions involve specific products or firms not on the agenda for which FDA's participants have a financial interest, the participants are aware of the need to exclude themselves from such involvement and their exclusion will be noted for the public record.

With respect to all other meeting participants, we ask in the interest of fairness that they address any current or previous financial involvement with any firm whose products they wish to comment upon."

And Doctor Berman, I just would like to ask if there's anyone present who would like to comment during the Open Public Hearing, and I'll ask Doctor Freas to check in the hallway.

DOCTOR FREAS: There's nobody here.

MS. DAPOLITO: Did you hear that?

We have no public comment at this time, and I shall turn it over to you, Doctor Berman.

DOCTOR BERMAN: Thank you very much.

What I would like to do is first ask those who are directly involved in this site visit review to leave the room, if you would. I believe we'll be discussing you individually.

I believe, Doctor Stein, that was the name

I heard clearest. I think since we'll be reviewing you first, would you mind if you left for a few minutes?

DOCTOR STEIN: I don't mind at all.

MS. DAPOLITO: Doctor Berman?

DOCTOR BERMAN: Yes.

MS. DAPOLITO: We have on the agenda, a short overview of the program.

DOCTOR BERMAN: Oh, fine. Right, I see it right here.

Doctor Stein, we need you back.

DOCTOR STEIN: I thought I could get out of this one. Good try. I tried to get out the door.

Well, I think there's a good deal of detail in the book itself on the research program. The Laboratory of Molecular and Developmental Immunology is one of three laboratories in the Division of Monoclonal Antibodies. The research is conducted by four investigators in the areas of the immune response to thymus independent and thymus dependent forms of polysaccharide and B cell signal transduction in response to thymus independent stimuli, and that's in the Stein lab; characterization of B cell surface markers and regulation of antibody gene expression in the Shapiro lab; pathogenesis of

autoimmunity in the Miller lab; and the role of co-stimulation molecules in T cell activation in the Kozlowski lab.

The area of expertise of the investigators relates to the work that they do in terms of the review program. The Laboratory of Molecular and Developmental Immunology has primary regulatory responsibility for the review of applications dealing with antibodies to stem cells and other lineage markers, immunoglobulins, adhesion molecules, some cytokines and infectious agents.

In addition, the staff provide a major consultative role in the review of the monoclonal antibodies conjugated to drugs, used in conjunction with devices and in gene therapy protocols. Some of the staff provide clinical reviews for antibodies used in autoimmune disease and oncology settings, and they provide a major policy input into the regulation of monoclonal antibodies in the area of genetically engineered antibodies and antibodies used as drugs and devices.

The IND workload is shown in a figure that's in your book and I won't go into that. It's a rather heavy workload. The monoclonal area has really matured in the last few years after a number of early,

shall we say, false starts. Many protocols have now matured to Phase III status and to license application. Indeed, we expect a number of new applications to come in this year. We have several underway and a number of the investigators in the laboratory will be major product reviewers and BLA chairs during this year.

I think that's all I'm going to say. I think that we try to have an integrated program, again, where the expertise in the laboratory is used in our review and policy programs. I think we have an ongoing effort to try to keep those integrated as both research projects as well as just providing scientific expertise.

Thank you.

DOCTOR BERMAN: Thank you, Doctor Stein.

Doctor Epstein, are you there?

DOCTOR EPSTEIN: Yes?

DOCTOR BERMAN: Would you give us an overview of the research program of Doctor Steven Bauer who is in the Laboratory of Molecular Immunology.

DOCTOR EPSTEIN: Yes, and I may ask a clarification first. I had prepared remarks that were a bit more detailed, about seven minutes. Do you

prefer I omit discussion of the actual research program, or is that okay?

DOCTOR BERMAN: Just that, or in a way, yes, I think that's fine. I think that most of us who actually weren't at the site visit, since I was the only one there, don't have a real feeling for Doctor Bauer's work. So, if you could condense it or read it, that's fine.

DOCTOR EPSTEIN: Okay, I'll try and condense it.

The Molecular Immunology Laboratory was originally established in 1986 in the former Division of Biochemistry and Biophysics, but has since transferred to Cell and Gene Therapy. The staff have participated in review of numerous IND applications for gene therapies mediated by adenovirus, retrovirus and plasmid vectors, cellular therapies and biological devices. In addition, they've made contributions to policy development in the areas of gene therapy and use of transgenic animals, leading the development of two Points to Consider documents in these areas. There are currently only two research programs due to staff transfers. Besides Doctor Bauer's research, the other program focuses on immune responses to viral infections and to viral and plasmid vectors, and

that's my laboratory.

Doctor Bauer's research has centered on molecular mechanisms in normal B cell development and neoplastic transformation. Before coming to CBER, he was a Scientific Member at the Base Institute of Immunology. And he there developed transgenic animals over expressing the myc oncogene. The studies identified four distinct pre-B tumor phenotypes.

Since coming to the FDA, he's continued to use myc oncogene transgenic mice to study B cell development and tumorigenesis. Molecular and cell surface studies of pre-B cell tumors revealed a correlation between expression of the surrogate immunoglobulin complex and down-regulation of RAG gene expression, suggesting an explanation for allelic exclusion.

He has also studied the role of oncogene collaboration in B-lineage tumors in these mice. Studies of p53 revealed that 30 percent of myc-induced B-lineage tumors had either mutations or loss of p53 expression. And he has established an RT-PCR assay capable of quantifying expression of 20 different oncogenes for further studies of the multi-step process of tumorigenesis and collaboration. This is essential to our assessment of many cancer gene

therapies.

Doctor Bauer's recent work is focused in two areas. First, his discovery of the role of the dlk protein in governing cell-cell contact in B cell development. This protein, a member of the EGF-like homeotic gene family was already known to influence differentiation of one bone marrow cell type, pre-adipocytes. Pre-B cells normally require both stromal cell contact and IL-7 to proliferate in vitro. His new finding is that down-regulation of stromal cell surface dlk expression results in the growth of pre-B cells in the absence of IL-7, thus identifying dlk as a key molecule governing signaling between pre-B cells and stromal cells. This project was done with Doctor Jorge Laborda in the Division of Monoclonal Antibodies, and serves as a model for collaboration between divisions within CBER. This work is the beginning of a crucial understanding of stromal cell-stem cell interactions, given the growing interest in and importance of in-vitro propagation of cells and tissues. These are parts of gene therapy, tissue engineering, and xenotransplantation, all areas that CBER deals with.

The second area of investigation is the basis of genetically determined susceptibility or

resistance to retrovirus-induced tumorigenesis. Using retroviruses carrying abl+myc or raf+myc, Doctor Bauer has shown that B lineage cells from mice resistant to tumorigenesis, mainly DBA/2, can be infected and transformed in vitro. And others have reported that the IL-7/JAK-STAT signal transduction pathway is constitutively activated by the abl kinase. Doctor Bauer's work has shown this pathway is also activated by the abl-myc virus. However, in contrast, his work has shown that the raf-myc retroviral infection abrogates IL-7 dependence by a different pathway. Advances in understanding of signal transduction have led to proposals of therapies targeting these pathways. His studies show that treatments at disruption of one particular signaling pathway could be ineffective since multiple pathways appear to cause similar tumors.

These two projects open significant areas of new investigation that Doctor Bauer's lab is pursuing.

Since coming in 1992, Doctor Bauer has reviewed 22 IND original submissions, 114 amendments, 10 Master Files, 11 device applications, and has post-market oversight for a licensed product. Many of these submissions raised novel and complex issues,

such as the first adenoviral gene therapy IND with contamination with replication competent adenovirus as an issue. The dissemination of vectors to the tissues, including gonadal dissemination which has the potential for germline alteration, where his PCR expertise has been critical. He has also confronted novel issues in assessing device applications. This allowed him to pioneer CBER's finding of substantial equivalence between immunoassay-based HLA typing kits and PCR-based kits.

Doctor Bauer has demonstrated a talent for cooperation and leadership in policy development, working with Doctor Joy Cavagnaro on the transgenic animal points to consider, and with members from the Centers for Veterinary Medicine, Drugs and Biologics, Center for Devices and Department of Agriculture. His expertise in molecular biology and use of transgenic animals were critical for the scientific framework of that document. He has also participated in the development of guidelines on xenotransplantation.

Because of his important contributions to CBER's research and regulatory mission, the Division of Cellular and Gene Therapies has recommended continued support for his laboratory and his conversion to a permanent FDA position. This

recommendation was presented to the May 9th site visit committee in asking them to evaluate him for conversion to permanent status.

Thank you.

DOCTOR BERMAN: Thank you, Doctor Epstein.

(Whereupon, the proceedings went immediately into Closed Session.)