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UNITED STATES OF AMERICA
FOOD AND DRUG ADMINISTRATION
CENTER FOR BIOLOGICS EVALUATION AND RESEARCH

BIOLOGICAL RESPONSE MODIFIERS
ADVISORY COMMITTEE TELECONFERENCE

OPEN SESSION, Pages 1-46

National Institutes of Health
Conference Room 121, Building 29
8800 Rockville Pike
Bethesda, Maryland
Tuesday, May 6, 1997

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1 PROCEEDINGS

2 DR. FREAS: Seated at the table next
3 to me is Dr. Neal Goldman, who is Associate
4 Director for Research from Sandoz Biologics.

5 Across the table from me is Dr. Phil
6 Noguchi, who is Director of the Division of
7 Cellular and Gene Therapies.

8 Also seated at the table, as I
9 mentioned before, is Dr. French Anderson, the
10 Director of Gene Therapy, University of
11 Southern California School of Medicine.

12 And at the table are the two
13 individuals being reviewed from today's site
14 visit report. They are Dr. Gerald Marti, who
15 is Chief, Molecular Medical Genetics Staff, and
16 Dr. Raj Puri, Chief, Molecular Tumor Biology.

17 Also in the room, we have the
18 transcriber. And the reason I mention this is,
19 please, when you speak into the phone, state
20 your name, because all the comments will be
21 transcribed, and we would like to attribute
22 them to the appropriate speaker.

1 And Dr. Siegel is in the room. Of
2 course, you all are familiar with him. He is
3 the Director of the Office of Therapeutics
4 Research and Review.

5 And we also have in the back of the
6 room Curleen Muckleby, who you remember is the
7 Former Committee Management Specialist, and her
8 replacement, Rosanna Harvey, who will be taking
9 over.

10 For today's meeting, as detailed in
11 the conflict of interest statement, which I
12 will read momentarily, Dr. Richard Hong has
13 been designated the Acting Chair.

14 The reason for this is that I was
15 late in submitting the nomination packet for
16 the BRM Advisory Committee in order to extend
17 three former members and appoint two members to
18 the BRM Committee. While the packet has been
19 submitted, it has not been approved, so three
20 of you are serving as temporary voting members,
21 and as soon as that nomination packet has been
22 approved, we will return you to your previous

1 status as full BRM Advisory Committee members.

2 I apologize for that.

3 Today's teleconference will consist
4 of two sessions, an open session which is open
5 to the public, and they are invited to
6 participate, and a closed session.

7 The justification for closing the
8 latter part of the session will be to permit
9 the discussion of personal information
10 regarding individuals with the CBER's research
11 program.

12 At this time, I will read the
13 conflict of interest statement for this
14 meeting. This announcement is made part of the
15 meeting at the Biological Response Modifiers
16 Advisory Committee on May 6, 1997.

17 Pursuant to the authority granted
18 under the committee charter, the Director of
19 the Center of Biologics Evaluation and Research
20 has appointed the following individuals as
21 temporary voting members: Dr. French Anderson,
22 Dr. Virginia Broudy, Dr. Julie Vose. In

1 addition, Dr. Richard Hong will serve as the
2 Acting Chair for this meeting.

3 Based on the agenda made available,
4 it has been determined that all committee
5 discussions at this meeting for the review of
6 the intramural research program of the
7 Laboratory of Molecular Medical Genetics and
8 the research program of Dr. Raj Puri, Division
9 of Cellular and Gene Therapy, present no
10 potential for a conflict of interest.

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

18 With respect to all other meeting
19 participants, we ask, in the interest of
20 fairness, that they address any current or
21 previous financial involvement with any firm
22 whose product they may wish to comment upon.

1 So ends the reading of the conflict
2 of interest statement into the record.

3 Dr. Hong, I would like to turn the
4 meeting over to you.

5 DR. HONG: Fine. Is there any
6 response for the open public hearing today?

7 DR. FREAS: Dr. Hong, I'm sorry. I
8 was just checking. At this time, let me look
9 around the room.

10 To my knowledge, there is nobody here
11 who would like to make a comment during the
12 open public hearing. Is that correct?

13 Let me just explain for you, Dr.
14 Hong. The only people in the room at this time
15 are FDA employees, and we're ready to roll.

16 So, Dr. Hong --

17 DR. HONG: Do we close the public
18 hearing at this time or --

19 DR. FREAS: The public hearing is now
20 over, and we are on to the next item on the
21 agenda with your permission, Dr. Hong.

22 DR. HONG: Thank you.

1 DR. FREAS: Dr. Noguchi, if you're
2 ready, would you?

3 DR. NOGUCHI: Yes. I would like to
4 thank the committee again to allow us to
5 present some of our programs in the Division of
6 Cellular and Gene Therapies.

7 Just in brief, the Division itself
8 oversees a wide number and a widely diverse
9 area of biologics developments ranging all the
10 way from cellular extracts for cancer to the
11 latest gene therapies and some
12 xenotransplantation protocols.

13 The particular programs that some of
14 you have already reviewed in depth and all of
15 you have the materials on are the programs of
16 Dr. Raj Puri and Dr. Gerry Marti.

17 I won't go through their programs at
18 all except to update you on several items that
19 I think will be pertinent to today's
20 discussion.

21 Dr. Marti has continued several
22 collaborative studies with both the CDC and

1 Emory University in which they have been
2 examining some of the individuals who have been
3 located near toxic sites that have been
4 identified by CDC and the EPA. And some early
5 results of that do show that there are
6 phenotypic changes that can be detected by flow
7 cytometry which may be of interest in relation
8 to the potential of cytotoxic materials to
9 affect human genetic material as well.

10 For Dr. Puri, at the time of his
11 visit, he had been planning several things, one
12 of which was to be a co- investigator on an
13 investigation of a new drug application. That
14 particular application has been approved and is
15 ongoing, and, in fact, there were several press
16 releases soliciting patients for this
17 particular study at the John Wayne Cancer
18 Institute.

19 In addition, the first CRADA for FDA
20 which would involve active collaboration with a
21 company for commercialization of a product has
22 been passed throughout the Center and is now,

1 as I understand it, at the FDA CRADA Board.

2 This particular award, should it go through,

3 would provide something on the order of

4 \$500,000 over the next five years in terms of

5 helping to develop this particular

6 interleukin-4 immunotoxin that appears to have

7 extensive activity both in vitro and in vivo

8 models.

9 There is also widespread interest on

10 the NIH campus in Dr. Oldfield's lab for this

11 protocol.

12 DR. ANDERSON: I don't want to

13 interrupt you, but --

14 DR. NOGUCHI: Actually that's the end

15 of my opening remarks, French, so you're not

16 interrupting at all.

17 DR. ANDERSON: How much of that

18 project is involved with -- in terms of

19 proprietary rights, I notice you have some

20 patent applications in.

21 DR. PURI: I am Dr. Puri, and I will

22 respond to Dr. Anderson's question.

1 Several years ago, I discovered
2 receptors for interleuken-4 on epithemial tumor
3 cells when I was in Dr. Siegel's laboratory.
4 Since then, we have investigated many human
5 cancer cells and found that they express a
6 large number of receptors.

7 Interleuken-4, as you know, is a
8 peotropic immunocytokine, and a cytokine
9 receptor on tumor cells is still a very
10 perplexing and very accidental observation we
11 made. But we took that information and ran
12 with it and tried to collaborate with Dr -- and
13 met with him. He was reluctant at first, but
14 then he agreed to collaborate on this project.

15 And we made ioprotoxin. And now all
16 of us are very excited. So the discovery was
17 mine, and we had a patent together -- Dr.
18 Paston, Dr. Keitman, and Dr. Puri -- which had
19 been awarded.

20 DR. ANDERSON: And that's in terms of
21 FDA versus NIH? That's not a problem?

22 DR. GOLDMAN: This is Neal Goldman.

1 Joint patents as Government patents between
2 agencies is quite usual. And what happens with
3 something like this is, the Government can
4 award those who are holding the patent up to 50
5 percent of the share. It used to be 15; do you
6 remember that?

7 DR. ANDERSON: Yes, I remember.

8 DR. GOLDMAN: They have now moved the
9 markup. That's to encourage actually more
10 development, is what they refer to now as the
11 translational research. And that's been a very
12 large project that's ongoing since Dr. Bartus
13 came to the NIH.

14 DR. ANDERSON: Specifically the bulk
15 of the funding would go to FDA in this case,
16 though.

17 DR. GOLDMAN: And could that be used
18 for support of Dr. Puri's program?

19 DR. ANDERSON: Yes, it will be. In
20 fact, that's the intent. It would be directly
21 to support his program.

22 DR. SIEGEL: Are we talking now about

1 from the CRADA or from the patent, because the
2 CRADA is a separate item that would go --

3 DR. NOGUCHI: Yes.

4 DR. MEYERS: This is Abbey Meyers.

5 Can I ask a question?

6 DR. FREAS: Sure.

7 DR. HONG: Of course.

8 DR. MEYERS: Why is the Government
9 going to develop this? Is there no commercial
10 interest in the product?

11 DR. NOGUCHI: Oh, hi, Abbey. This is
12 Phil. In fact, there is commercial interest.
13 This will

14 Be a joint development project where
15 the discovery and some of the technical
16 development will be done here, but the actual
17 translation will be done by a company.

18 Perhaps Dr. Puri could -- I don't
19 know the company that's interested here.

20 DR. PURI: A company located in
21 Chicago called Neo-Pharm, Incorporated and a
22 company in San Diego that's called -- and both

1 of them are interested in two of my products.
2 One of them is ioprotoxin; another one is
3 iotradine toxin. Both of them have a
4 significant, remarkable anti-tumor activity in
5 the animal model in the laboratory for the
6 treatment of brain tumors for which there is no
7 treatment available.

8 DR. MEYERS: I'd like to just find
9 out, if I were a Congressman trying to --
10 worried more about the budget than anything
11 else, I would be asking why taxpayers' money
12 should go into developing a product where
13 there's already commercial interest. Why not
14 just turn it over to the companies and let them
15 develop them?

16 DR. SIEGEL: Yeah, actually -- this
17 is Jay Siegel, Abbey -- I think that it's
18 important to explain the nature and intent of a
19 CRADA.

20 A CRADA, which is a cooperate
21 research and development agreement, under this
22 CRADA what will happen is that the private

1 company's money will, if accrued, go into Dr.
2 Puri's lab for assistance in development of
3 this product. So that is not taxpayer money.

4 The philosophy, as noted by Dr.
5 Goldman, is that there is a desire that the
6 scientific expertise and research developed in
7 Government be efficiently translated into the
8 creation of jobs and the creation of health
9 care advances and that in many cases the most
10 efficient and appropriate way for that to be
11 done is by retaining the involvement of
12 Government scientists and expertise at more
13 advanced developmental levels.

14 So at least the intent and design of
15 the program are structured so that what we're
16 talking about here at this stage is not
17 taxpayer money, but private money supporting a
18 Government/private collaboration.

19 DR. MEYERS: Okay. I have another
20 difficult question. French Anderson will tell
21 you that I specialize in difficult questions.

22 DR. ANDERSON: That's true, Abbey.

1 DR. NOGUCHI: That's why you're on
2 the committee.

3 DR. MEYERS: Is there a conflict of
4 interest with FDA having involvement with the
5 development of a drug when, in fact, if the
6 drug ever reaches the MDA stage, FDA is
7 supposed to sit in judgement over this drug and
8 decide whether it should be approved or not
9 when it has a financial interest in approving
10 it?

11 DR. SIEGEL: No, that's a very
12 critical and important issue. In fact, it's
13 that very question which is why several months
14 ago we talked about the fact that there was a
15 proposed CRADA, and several months later we're
16 still talking about the fact that there's a
17 proposed CRADA.

18 We have in place a rather extensive
19 process of review at various levels, both
20 within the Center, across the agency, and so
21 forth, to explore the potential for these
22 agreements and to explore any concerns about

1 conflict of interest. Of course, at a very
2 simple level, this agreement, if pursued, would
3 require Dr. Puri and his group not be directly
4 involved with this product and some class of
5 related or competing products in their review.

6 But the exact totality of the nature
7 of safeguards and whether, in fact, a complete
8 set of safeguards that are sufficient to ensure
9 that there are not substantial concerns of
10 conflict of interest, whether that can be
11 developed and what it will look like under
12 substantial debate as we're trying to balance
13 the positive interests, as I mentioned, before,
14 against those concerns.

15 DR. BERMAN: This is Dr. Berman. I
16 have a question: Has there ever been precedent
17 for this before?

18 DR. GOLDMAN: This is Neil Goldman.
19 Yes, there has.

20 We currently at Foods have a complete
21 Center that, in fact, is being supported by the
22 food industry where they are supporting FDA

1 Foods people in research. So, in fact, this is
2 a trend that seems to be building, certainly as
3 FDA's dollars are retreating.

4 So, yes, there is precedent.

5 DR. ANDERSON: I interrupted you,
6 Phil.

7 DR. NOGUCHI: No, I'm sorry. My
8 presentation really is over. And the rest of
9 the time is -- well, I have nothing more to
10 add.

11 DR. FREAS: Dr. Hong, I know I make
12 it very tough on you since you're not here, but
13 this is the time when any Advisory Committee
14 member is more than welcome to either ask the
15 Division Director or the Office Director or the
16 Associate Director for Research and/or the two
17 people that are being reviewed any questions
18 that they may have in the background material
19 or in the site visit report related to this
20 meeting.

21 DR. HONG: Fine. Do I hear any
22 specific questions.

1 DR. ANDERSON: Well, I have one.

2 This is Dr. Anderson here in the room.

3 What is the present status --

4 actually Dr. Marti and I were talking about

5 this in the background of the so-called random

6 conversation -- what's the present status of

7 the attempt to set up the basically QC/QA

8 quantitation of stem cells?

9 DR. HONG: Of what kind of cells?

10 DR. ANDERSON: Well, CD34

11 specifically is the one that I was most

12 interested in and the one I think Dr. Marti is

13 most interested in. But he also has taking

14 leukocytes, lymphocytes, phenotyping also in

15 the system. But I think CD34 was the one you

16 specifically were trying to get quantitated.

17 DR. MARTI: I didn't anticipate this

18 question, but I recently prepared a paragraph

19 about quantitative flow. I just returned from

20 a regional flow cytometry meeting at the CDC,

21 and quantitative flow cytometry is now being

22 determined -- used to determine the level of

1 CD-38 expression on CD-8 cells in HIV
2 seropositive individuals.

3 At the risk of offending any members
4 in this room who are on the Advisory Committee,
5 I am concerned that the methods that are being
6 used to do quantitative flow at this particular
7 project arena are not exactly state-of-the-art.

8 I think that the need for a consensus
9 meeting, and particularly suggest that could
10 give some guidance in this area, would be very
11 timely.

12 Quantitative flow also has bearings
13 in the field of flow crossmatching for second
14 transplants in renal transplantation, and it
15 also is now being -- we are now being asked to
16 develop protocols for the determination of
17 intercytoplasmic cytokine levels.

18 Basically I'm very excited by this
19 development. Ten years ago when we proposed
20 quantitative flow cytometry, it was something
21 that was hardly talked about. But now I find
22 people not only aware of it, but wanting to

1 know how to do it.

2 And I think it would be good to have
3 a consensus meeting. In fact, I think it would
4 be timely for all of these various clinical
5 areas that it's needed in and also research
6 areas.

7 In terms of the funding of this
8 meeting, of such a consensus meeting, I've
9 thought about trying to involve the NIH and the
10 CDC and the FDA jointly, but my impression is
11 that although those institutions are all
12 willing to be involved, I think such a meeting
13 would have more power if it originated solely
14 from the FDA. We have an image of being
15 neutral in this matter in the community, and
16 from that standpoint, I think it would be best
17 if it happened just with sole FDA support.

18 I think what's happening in flow
19 cytometry is the same thing that happened with
20 automated blood cell counters. In other words,
21 the technician on Monday morning takes a vial
22 of blood out of the refrigerator and

1 standardizes the machine for the week. And the
2 same kind of standardization, linearity,
3 coefficient of response, sensitivity, what is
4 the range, the dynamic range is, that can all
5 be determined in 30 seconds or less.

6 That same approach now is not only
7 within grasp, but very close to being vanilla
8 or off-the-shelf. So I think this is right
9 where we are, and I would like to see this
10 through to completion, if at all possible.

11 DR. ANDERSON: Dr. Hong, the reason I
12 brought it up is I have to ask a question.

13 Have the two reviewees seen the site
14 report?

15 DR. HONG: No. In the closed
16 session, we'll discuss anything confidential.
17 But you may still ask questions that may
18 relate, as long as they're here.

19 DR. ANDERSON: Okay. In that case,
20 say that in the site visit report, there are
21 suggestions of various directions for the two
22 labs to go, and the question is how much of

1 that is appropriate for us to discuss.

2 DR. HONG: Well, that sounds like a
3 topic for the closed session.

4 DR. ANDERSON: Okay.

5 DR. HONG: Could I ask while we're on
6 the subject of trying to establish some sort of
7 standard, what occurred to me is: What is the
8 Government or who -- is there some sort of
9 ruling body that has the authority to set
10 standards for various types of cytometry that
11 you're interested in today?

12 It seems to me that is the group that
13 should be organizing the conference.

14 DR. SIEGEL: Let me address that.
15 This is Jay Siegel.

16 Equipment that's used in the clinical
17 lab and for clinical diagnostics is largely
18 regulated by the FDA Center for Devices and
19 Radiological Hazards Group with which Dr.
20 Marti works very closely in a consulting
21 capacity.

22 In the area, however, of quantitation

1 of stem cells, there is a tremendous regulatory
2 need within the Center for biologics.

3 As many of you are aware of, the
4 spectrum of products we regulate, including
5 products given to donors for margination, G and
6 GM, CSF; factors potentially used in vitro,
7 IL-3, IL-6, and stem cell factor; and a variety
8 of monoclonal antibodies or
9 monoclonal-antibody-based devices which purify
10 -- aim to purify stem cells and to a varying
11 extent to leave T cells or tumor cell
12 contaminants; and with the regulation of all
13 these products -- and I say "these products" to
14 distinguish them from the cells, which I will
15 address in just one moment -- but the
16 regulation of all these products in many or
17 most cases is -- appropriate regulation is
18 highly dependent upon meaningful and
19 reproducible measurements of a cell product, of
20 which while I think within this committee and
21 the outside community there is not perfect
22 consensus, or if anything there is consensus,

1 but there is no perfect marker for what are
2 stem cells.

3 There's also, I think, widespread
4 consensus that those cytometric
5 characterizations of the cells themselves is
6 one important characteristic in ensuring
7 quality and consistency. And what we are
8 hearing from our sponsors is that as they shift
9 from contract lab to contract lab, all of a
10 sudden the CD34 count may change by 50 percent.

11 And when your protocol design is to
12 do leukapheresis until you receive a certain
13 number of cells or give an agent to the patient
14 until they peak at a certain number of cells,
15 that sort of variability makes good science and
16 good clinical investigation very difficult to
17 do.

18 Recently perhaps all of you or many
19 or most of you are aware, the agency has taken
20 an aggressive relook at how we regulate tissue,
21 tissue-related products in self-based
22 therapies. And we've issued a proposed

1 regulatory approach. I think it was at the end
2 of February this year, or I guess the White
3 House issued it actually, I think.

4 But in any case, in that proposed
5 approach, which is open for comment, and I'm
6 sure the professional organizations you belong
7 to have not, if not you as individuals, have
8 commented, and hopefully you will all pay close
9 attention to that approach.

10 We have looked at the issue of
11 regulating stem cells themselves, an issue that
12 we discussed with the committee in a meeting a
13 little over a year ago, based on an earlier
14 proposal that received rather strongly-felt and
15 highly mixed reactions.

16 In the current proposal, some of the
17 stem cells we're talking about, notably those
18 that are on Toligas and some subset from
19 related donors, if not highly manipulated, will
20 have a rather minimal regulatory scheme with
21 controls to ensure adequate tracking and
22 freedom from infectious agents and so forth,

1 whereas others, notably a significant subset of
2 those that are allergenic or those that are
3 significantly expanded, genetically modified,
4 or otherwise altered in vitro, will be
5 regulated as products.

6 And specifically in the case of
7 allergenic stem cell therapies, we've proposed
8 a phase-in period, so as not to disrupt current
9 research, and we've indicated that it is our
10 goal, upon finding that such therapy or some
11 subset of such therapy is safe and effective,
12 to be able to make a broad class-wide
13 determination that a certain type of
14 allergenic cell, for example, processed a
15 certain way, meeting certain characteristics,
16 is effective. This would avoid each individual
17 investigator or each individual oncologist
18 having to separately show that he can produce
19 effective cells.

20 To do that would require us to
21 promulgate regulations that would set
22 standards, and then we could have a system that

1 anybody who certified that they met those
2 standards would be determined to be producing a
3 product that is effective if we can devise or
4 determine standards that will correlate with
5 efficacy.

6 That process is underway. We will be
7 consulting with you all a great deal about
8 that. I don't want to digress too much from
9 the point here except to say the obvious, that
10 there is a lot of discussion and controversy
11 about what those standards should be. As you
12 all know, there are some in the community of
13 transplanters who think that even viability of
14 the cells is not a good determinative of
15 whether it will transplant or not.

16 That having been said, certainly flow
17 cytometric or other evaluations of cell surface
18 antigens, whether CD34 or others yet to be
19 developed, are likely candidates for important
20 product controls that potentially would allow a
21 regulatory scheme that would in some sense both
22 provide good controls and avoid unnecessary

1 intrusiveness through the establishment of
2 standards which ensure safety and efficacy.

3 So aside from the fact that the
4 machines and maybe even the reagents would
5 likely be regulated in the Center for Devices,
6 with whom we're working very closely on this
7 and other issues, we see -- I can tell you a
8 similar story about HIV therapies and other
9 therapies -- but we see particularly in this
10 area an important potential role for
11 reproducible, standardized, and quantitative
12 flow cytometric measures in clinical trial
13 design and in analysis and in the drug
14 regulation and standard-setting.

15 DR. HONG: Well, that's the short
16 answer.

17 DR. SIEGEL: I'm sorry. I have
18 trouble being concise.

19 DR. HONG: It seems to be the only
20 player in setting up regulations today, that
21 there's no other competing agency. It seems to
22 me you have to know who the standard-setter is,

1 and that standard-setter has to have a certain
2 legal backing and also have the acceptance of
3 the scientific community. And what I've heard
4 is that I think the FDA is the only player.

5 DR. SIEGEL: We're not the only
6 player in that we intend to work very closely
7 and have already worked very closely with
8 private groups in collaboratively developing
9 standards. But in terms of a Government agency
10 that can, with the force of law, promulgate and
11 enforce such standards, I think this is where
12 it is. This is where we think it ought to be
13 as well.

14 DR. GOLDMAN: That's right. When I
15 gave the presentation at, I guess, the February
16 site visit, I included that standards and
17 methods development, especially for biological
18 products for the therapies from biological
19 products, are an important area of what we
20 refer to as mission-related research. Not only
21 do we then do the research, but we take the
22 responsibility for it, and we do have the

1 backing of the law as an authority to see to it
2 that these things such as holding these
3 standards up and having these set standards is,
4 in fact, the FDA's responsibility.

5 DR. SIEGEL: I forgot to mention
6 that, of course - - well maybe not -- but we
7 have, in fact, continued to work very closely
8 with the Heart, Lung, and Blood Institute in
9 determining together what sorts of research
10 will be helpful in terms of addressing the
11 types of issues, as I said, but obviously it
12 falls in our court and not theirs to actually,
13 at least under current design, to actually set
14 such standards and promulgate such regulations.

15 DR. HONG: Are there comments or
16 questions for either Dr. Marti or Dr. Puri?

17 DR. ANDERSON: Yes. This is Dr.
18 Anderson again. I guess I'm trying to sort of
19 formulate what I'm
20 really trying to ask, and so I'll
21 just do it. And so I'll just do it, and that
22 is: Because of the potential of reduced

1 research funding, it is clearly important for
2 the FDA to determine what each of its labs
3 works on.

4 And therefore I'd like to ask the two
5 investigators if they could summarize the
6 priorities of the various projects we've talked
7 about. If funding for research is cut, what
8 are you most keen on working on and what things
9 have lesser priority?

10 And I guess I sort of gave my own
11 bias away by that first question I asked Dr.
12 Marti. But if that's appropriate, Dr. Hong,
13 just to have the two investigators say here are
14 the things they're most interested in doing and
15 here are the things without adequate funding
16 they would like to do.

17 DR. HONG: Well, my sense is that's
18 appropriate for the closed session, unless
19 there's a compelling reason it needs to be
20 discussed in the open. I think anything
21 relating to the progress, their present plans,
22 future plans, those kind of items really all

1 fit in together.

2 So unless there's a valid reason for
3 having any of this in the open session, I would
4 like to defer it to the closed, so we can just
5 do it all at once.

6 DR. ANDERSON: What's the difference
7 between the open and the closed?

8 But I wanted them to say what they
9 want to do. So it has to be in the open
10 session. And then in the closed session, we
11 can talk about it together with their input as
12 to what their particular interests are.

13 DR. FREAS: Would that be okay with
14 you, Dr. Hong, if we just had their input
15 before we went into the closed session?

16 DR. HONG: Well, I don't think it's
17 going to make any difference. It's probably
18 not worth the time to make the distinction. So
19 I'm happy to go ahead and have them respond.

20 DR. ANDERSON: But they're not here
21 in the closed session, so it has to be in the
22 open session, right?

1 DR. FREAS: I think he said yes.

2 DR. PURI: This is Raj Puri. I'll

3 take a first shot at it.

4 Since the discovery of IL-4
5 receptors, we set out to ask whether this novel
6 antigen is present on human tumor cells. And
7 then we discovered, lo and behold, many solid
8 human cancer cells express these receptors.

9 At the same time, in collaborative
10 study with Dr. Bill Hall and Dr. Warren
11 Leonard, a study led by Dr. Warren Leonard, we
12 discovered an aisle to the receptor chain is a
13 component of aisle proteceptors in a paper
14 published in Signs.

15 Subsequent to that, it was imperative
16 to study with a gamma chain, which is also a
17 component of aisle proteceptors on tumor cells.
18 And this study was important to understand the
19 biology of the receptors, of the tumor cells,
20 and we found that the interleukin-4 proteceptor
21 gamma chain, which is an Aisle 2 receptor, was
22 not present on the tumor cell, and, in fact, we

1 were the first to identify a novel protein
2 which we call it now Aisle 13 receptor alpha
3 chain, which is shared with an aisle protein
4 receptor.

5 So we demonstrated for the first time
6 that the receptors had expressed on the tumor
7 cells, that its structure is different from the
8 new cells. The gamma chain is presented on the
9 T cells, D cells, and monocytes, but it is not
10 presented on the tumor cells.

11 Next we wanted to ask how the
12 receptor signals within the tumor cells and
13 within human cells, and we found that in the
14 new cells, as other labs have demonstrated that
15 involve -- kinases and STAT and in Aisle 4
16 causes the possibilities of JAC-1 and JAC-3 in
17 the immune cells on which Aisle 4 has got
18 promoting effects, but on tumor cells Aisle 4
19 had got an inhibitory effect.

20 We investigated whether there is any
21 impact on -- and we found that in contrast to
22 the human cells, Aisle 4 did not contribute to

1 JAC-3, because tumor cells did not have it.

2 They did not have gamma chains.

3 So we demonstrated not only the

4 structure is different, the -- toxin is

5 different.

6 And then we went to further explore

7 -- this information is very important, by the

8 way, in the inflammatory disease, autoimmune

9 disease, oncological diseases -- where do you

10 want to destruct. By signaling for an Aisle

11 13, one can merely suck up STAT-6; you can

12 knock down the computer for IO-4 toxin on Aisle

13 13.

14 After this demonstration, we

15 obviously wanted to know whether the receptors

16 are functional and can be targeted by IO-4

17 toxin on Aisle 13 toxin. We discovered these

18 two receptors, and we find that these two

19 molecules appear to be very, very cytotoxic on

20 the cancer cells in vitro, in vivo, and note

21 that in the interests of public health, I think

22 this is a very important observation and can

1 translate to the clinic for the treatment of
2 diseases for which there is no treatment
3 available. And the animal data so far suggests
4 that the study is very feasible, and the Phase
5 I trial has begun.

6 So at this point, I think the signal
7 toxin aspect has completed. The structure
8 aspect is still open to question and the aspect
9 why has nature provided a receptor for --
10 cytokine, Aisle 4 on the tumor cells, because
11 the IO-4 receptor could be an oncogene or
12 associated to an oncogene, and unraveling the
13 structure of the interleukin-4 receptor and
14 finding out the significance on the tumor cell
15 may unravel another oncogene such as -- or any
16 of the oncogenes you have.

17 And I think continued development in
18 targeting these drugs has given another way
19 where they can use these targets for the gene
20 therapy where we can take -- vectors, and we
21 can express the gene for interleukin-4 in the
22 envelope of the retroviruses or adenoviruses

1 and use it to target L-vector, which is an
2 injectable vector, which is a true -- gene
3 therapy where it can have a specificity to
4 target to the tumor site where it is hard to
5 reach with the current technology. And I think
6 I will continue in this aspect, and the
7 research is ongoing, to double up those --
8 vectors targeting those receptors.

9 DR. MARTI: Gerry Marti. I'm going
10 to rephrase your question just to be sure that
11 I understand it correctly.

12 You want us to prioritize our
13 research, our research plan. Basically for me
14 -- and I'll just do one or two; there's no need
15 to do more than that.

16 With regards to quantitative flow
17 cytometry, I or we have been asked to prepare a
18 definition of an international worldwide
19 standard for CD34 salinumeration, and I will
20 attempt to do that to the best of my ability,
21 not because I know anything about CD34 or the
22 wonderful and exciting subsets. I always tell

1 people that if a CD-4 4- plus hypercellular
2 acute leukemia was in my backyard, I probably
3 wouldn't know it.

4 But we can clearly see that
5 quantitative flow cytometry will provide the
6 level of QC and QA that seems to be in need,
7 and I think now, because there are so many
8 points arriving, coming together, that we could
9 show some kind of leadership in this area.

10 The other area of interest is really
11 a genetic one in terms of genetic disease
12 testing. And more than 20 years ago, Robert
13 Kile at the Mayo Clinic discovered something
14 that was subsequently named a monoclonal
15 gamopathy of unknown significance.

16 I am happy to say that we have
17 discovered and defined, described, a B-cell
18 monoclonal metacytosis. We don't know that the
19 incidence of the general occurrence of this in
20 the population at large, but we suspect that it
21 is as high as the 9-monoclonal gamopathy. We
22 are suspicious that it is a preclinical

1 condition for common B-cell CLL.

2 We are very suspicious that in the
3 setting of familial B-cell CLL, where we
4 recently had two siblings, one that underwent
5 Richter's transformation, the second sibling
6 whose disease is advancing quite rapidly, we
7 were asked to see in consultation a third
8 sibling.

9 You can rest assured that we looked
10 very carefully at that blood count and saw
11 several abnormal subpopulations of lymphocytes
12 in the setting of a normal white count in the
13 normal lymphocyte differential.

14 This person had a very easily
15 detectable clone circulating in the peripheral
16 blood. When we first started these studies, we
17 were told that this would be impossible to do.
18 In retrospect, it's easier than determining
19 CD34 stem cells.

20 If I had to choose between our
21 interest and expertise in familial B-cell CLL
22 and the use of quantitative flow cytometry for

1 CD34 enumeration, I would probably choose the
2 CD34 stem cell enumeration at this point in
3 time, because I think that that is something
4 very timely that would be beneficial to the
5 community. There are 8 or 10 organizations
6 that are trying to develop class-wide standards
7 for both autologous and allogeneic peripheral
8 blood stem cells.

9 And in the suggested parameters that
10 need to be standardized for this, one of them
11 is called functionality, and it's a foregone
12 conclusion that flow cytometry, at least on a
13 24-hour basis or 4-hour basis is and will
14 remain for some time to be the method of
15 choice. The sooner that that can be
16 implemented, the sooner that field, I think,
17 will be able to move on.

18 Familial CLL will be around for some
19 time to come.

20 DR. ANDERSON: What about SKY?

21 DR. MARTI: Oh, SKY. That gives me
22 chest pain. SKY. I have a rather developed

1 part in the briefing documents outlining how to
2 do the pilot project. One of the reasons I
3 selected SKY was somewhat like stem cells. We
4 have no research interest in stem cells per se.
5 SKY is spectral karyotyping. This is
6 one of the most incredible physical detection
7 methods to be developed. It hedges right on
8 the level of single fluorescent molecule
9 detection, and it is only fitting that it
10 should have been determined microscopically.
11 But within months of it being determined
12 microscopically, it was determined in flow.
13 You can just determine single molecules. This
14 work is being done primarily at Los Alamos and
15 Lawrence Livermore in spectral karyotyping.
16 It's a very complex technology, and I
17 don't mean that it's a complex technology
18 because it involves the sorting of chromosomes.
19 That's the least of it. It's the proper
20 preparation. It's the PCR application. It's
21 the labeling; it's the painting. And even the
22 incredible software analysis that's required to

1 make the final picture, if you will. It
2 represents, I think, one of the most complex
3 approaches to genetic testing, but it's been
4 growing for 20 years, and I'll be very
5 surprised if it doesn't become a standard.

6 I thought it would be as usual from
7 my approach, I learned flow cytometry the
8 old-fashioned way by just grappling with the
9 data on a daily basis. And I don't think I
10 could learn spectro-karyotyping. I can read
11 about it, but I think it would be better to set
12 it up and grapple with it, and work our way
13 through it, then I think we could probably
14 regulate it or contribute to a meaningful
15 regulation if we had some hands-on experience.

16 DR. HONG: Any further questions?

17 DR. FREAS: There are no further
18 questions on this end, Dr. Hong. If we can
19 have a two-minute recess to clear the room
20 before we go into closed session, I would
21 appreciate it. Is that okay with you?

22 DR. HONG: Fine.

1 DR. FREAS: Okay. In two minutes,

2 we'll be right back with you.

3 (Recess)

4 (End of Open Session)

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