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DR. FREAS: Seated at the table next to me is Dr. Neal Goldman, who is Associate Director for Research from Sandoz Biologics. Across the table from me is Dr. Phil Noguchi, who is Director of the Division of Cellular and Gene Therapies. Also seated at the table, as I mentioned before, is Dr. French Anderson, the Director of Gene Therapy, University of Southern California School of Medicine. And at the table are the two individuals being reviewed from today's site visit report. They are Dr. Gerald Marti, who is Chief, Molecular Medical Genetics Staff, and Dr. Raj Puri, Chief, Molecular Tumor Biology. Also in the room, we have the transcriber. And the reason I mention this is, please, when you speak into the phone, state your name, because all the comments will be transcribed, and we would like to attribute them to the appropriate speaker.
And Dr. Siegel is in the room. Of course, you all are familiar with him. He is the Director of the Office of Therapeutics Research and Review.

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

For today's meeting, as detailed in the conflict of interest statement, which I will read momentarily, Dr. Richard Hong has been designated the Acting Chair. The reason for this is that I was late in submitting the nomination packet for the BRM Advisory Committee in order to extend three former members and appoint two members to the BRM Committee. While the packet has been submitted, it has not been approved, so three of you are serving as temporary voting members, and as soon as that nomination packet has been approved, we will return you to your previous
status as full BRM Advisory Committee members.

I apologize for that.

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

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

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

Pursuant to the authority granted under the committee charter, the Director of the Center of Biologics Evaluation and Research has appointed the following individuals as temporary voting members: Dr. French Anderson, Dr. Virginia Broudy, Dr. Julie Vose. In
addition, Dr. Richard Hong will serve as the
Acting Chair for this meeting.

Based on the agenda made available,
it has been determined that all committee
discussions at this meeting for the review of
the intramural research program of the
Laboratory of Molecular Medical Genetics and
the research program of Dr. Raj Puri, Division
of Cellular and Gene Therapy, 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 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 product they may wish to comment upon.
So ends the reading of the conflict of interest statement into the record.

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

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

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

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

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

So, Dr. Hong --

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

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

DR. HONG: Thank you.
DR. FREAS: Dr. Noguchi, if you're ready, would you?

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

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

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

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

Dr. Marti has continued several collaborative studies with both the CDC and
Emory University in which they have been examining some of the individuals who have been located near toxic sites that have been identified by CDC and the EPA. And some early results of that do show that there are phenotypic changes that can be detected by flow cytometry which may be of interest in relation to the potential of cytotoxic materials to affect human genetic material as well.

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

In addition, the first CRADA for FDA which would involve active collaboration with a company for commercialization of a product has been passed throughout the Center and is now,
as I understand it, at the FDA CRADA Board.

This particular award, should it go through,

would provide something on the order of

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

helping to develop this particular

interleukin-4 immunotoxin that appears to have

extensive activity both in vitro and in vivo

models.

There is also widespread interest on

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

protocol.

DR. ANDERSON: I don't want to

interrupt you, but --

DR. NOGUCHI: Actually that's the end

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

interrupting at all.

DR. ANDERSON: How much of that

project is involved with -- in terms of

proprietary rights, I notice you have some

patent applications in.

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

respond to Dr. Anderson's question.
Several years ago, I discovered receptors for interleuken-4 on epithelial tumor cells when I was in Dr. Siegel's laboratory. Since then, we have investigated many human cancer cells and found that they express a large number of receptors. Interleuken-4, as you know, is a peotropic immunocytokine, and a cytokine receptor on tumor cells is still a very perplexing and very accidental observation we made. But we took that information and ran with it and tried to collaborate with Dr -- and met with him. He was reluctant at first, but then he agreed to collaborate on this project. And we made ioprotoxin. And now all of us are very excited. So the discovery was mine, and we had a patent together -- Dr. Paston, Dr. Keitman, and Dr. Puri -- which had been awarded. DR. ANDERSON: And that's in terms of FDA versus NIH? That's not a problem? DR. GOLDMAN: This is Neal Goldman.
Joint patents as Government patents between agencies is quite usual. And what happens with something like this is, the Government can award those who are holding the patent up to 50 percent of the share. It used to be 15; do you remember that?

DR. ANDERSON: Yes, I remember.

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

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

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

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

DR. SIEGEL: Are we talking now about
from the CRADA or from the patent, because the
CRADA is a separate item that would go --

DR. NOGUCHI: Yes.

DR. MEYERS: This is Abbey Meyers.

Can I ask a question?

DR. FREAS: Sure.

DR. HONG: Of course.

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

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

This will be a joint development project where the discovery and some of the technical development will be done here, but the actual translation will be done by a company.

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

DR. PURI: A company located in Chicago called Neo-Pharm, Incorporated and a company in San Diego that's called -- and both
of them are interested in two of my products.

One of them is ioprotexin; another one is iotradine toxin. Both of them have a significant, remarkable anti-tumor activity in the animal model in the laboratory for the treatment of brain tumors for which there is no treatment available.

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

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

A CRADA, which is a cooperate research and development agreement, under this CRADA what will happen is that the private
company's money will, if accrued, go into Dr. Puri's lab for assistance in development of this product. So that is not taxpayer money.

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

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

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

DR. ANDERSON: That's true, Abbey.
DR. NOGUCHI: That's why you're on the committee.

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

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

We have in place a rather extensive process of review at various levels, both within the Center, across the agency, and so forth, to explore the potential for these agreements and to explore any concerns about
conflict of interest. Of course, at a very
simple level, this agreement, if pursued, would
require Dr. Puri and his group not be directly
involved with this product and some class of
related or competing products in their review.

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

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

DR. GOLDMAN: This is Neil Goldman.

Yes, there has.

We currently at Foods have a complete
Center that, in fact, is being supported by the
food industry where they are supporting FDA
Foods people in research. So, in fact, this is a trend that seems to be building, certainly as FDA's dollars are retreating.

So, yes, there is precedent.

DR. ANDERSON: I interrupted you, Phil.

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

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

DR. HONG: Fine. Do I hear any specific questions.
DR. ANDERSON: Well, I have one.

This is Dr. Anderson here in the room.

What is the present status --

actually Dr. Marti and I were talking about this in the background of the so-called random conversation -- what's the present status of the attempt to set up the basically QC/QA quantitation of stem cells?

DR. HONG: Of what kind of cells?

DR. ANDERSON: Well, CD34 specifically is the one that I was most interested in and the one I think Dr. Marti is most interested in. But he also has taking leukocytes, lymphocytes, phenotyping also in the system. But I think CD34 was the one you specifically were trying to get quantitated.

DR. MARTI: I didn't anticipate this question, but I recently prepared a paragraph about quantitative flow. I just returned from a regional flow cytometry meeting at the CDC, and quantitative flow cytometry is now being determined -- used to determine the level of
CD-38 expression on CD-8 cells in HIV seropositive individuals.

At the risk of offending any members in this room who are on the Advisory Committee, I am concerned that the methods that are being used to do quantitative flow at this particular project arena are not exactly state-of-the-art. I think that the need for a consensus meeting, and particularly suggest that could give some guidance in this area, would be very timely.

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

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

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

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

I think what's happening in flow cytometry is the same thing that happened with automated blood cell counters. In other words, the technician on Monday morning takes a vial of blood out of the refrigerator and
standardizes the machine for the week. And the
same kind of standardization, linearity,
coefficient of response, sensitivity, what is
the range, the dynamic range is, that can all
be determined in 30 seconds or less.
That same approach now is not only
within grasp, but very close to being vanilla
or off-the-shelf. So I think this is right
where we are, and I would like to see this
through to completion, if at all possible.
DR. ANDERSON: Dr. Hong, the reason I
brought it up is I have to ask a question.
Have the two reviewees seen the site
report?
DR. HONG: No. In the closed
session, we'll discuss anything confidential.
But you may still ask questions that may
relate, as long as they're here.
DR. ANDERSON: Okay. In that case,
say that in the site visit report, there are
suggestions of various directions for the two
labs to go, and the question is how much of
that is appropriate for us to discuss.

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

DR. ANDERSON: Okay.

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

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

DR. SIEGEL: Let me address that.

This is Jay Siegel.

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

In the area, however, of quantitation
of stem cells, there is a tremendous regulatory
need within the Center for biologics.

As many of you are aware of, the
spectrum of products we regulate, including
products given to donors for margination, G and
GM, CSF; factors potentially used in vitro,
IL-3, IL-6, and stem cell factor; and a variety
of monoclonal antibodies or
monoclonal-antibody-based devices which purify
-- aim to purify stem cells and to a varying
extent to leave T cells or tumor cell
contaminants; and with the regulation of all
these products -- and I say "these products" to
distinguish them from the cells, which I will
address in just one moment -- but the
regulation of all these products in many or
most cases is -- appropriate regulation is
highly dependent upon meaningful and
reproducible measurements of a cell product, of
which while I think within this committee and
the outside community there is not perfect
consensus, or if anything there is consensus,
but there is no perfect marker for what are stem cells.

There's also, I think, widespread consensus that those cytometric characterizations of the cells themselves is one important characteristic in ensuring quality and consistency. And what we are hearing from our sponsors is that as they shift from contract lab to contract lab, all of a sudden the CD34 count may change by 50 percent. And when your protocol design is to do leukopheresis until you receive a certain number of cells or give an agent to the patient until they peak at a certain number of cells, that sort of variability makes good science and good clinical investigation very difficult to do.

Recently perhaps all of you or many or most of you are aware, the agency has taken an aggressive relook at how we regulate tissue, tissue-related products in self-based therapies. And we've issued a proposed
regulatory approach. I think it was at the end
of February this year, or I guess the White
House issued it actually, I think.

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

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

In the current proposal, some of the
stem cells we're talking about, notably those
that are on Toligas and some subset from
related donors, if not highly manipulated, will
have a rather minimal regulatory scheme with
controls to ensure adequate tracking and
freedom from infectious agents and so forth,
whereas others, notably a significant subset of
those that are allergeneic or those that are
significantly expanded, genetically modified,
or otherwise altered in vitro, will be
regulated as products.

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

To do that would require us to
promulgate regulations that would set
standards, and then we could have a system that
anybody who certified that they met those standards would be determined to be producing a product that is effective if we can devise or determine standards that will correlate with efficacy.

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

That having been said, certainly flow cytometric or other evaluations of cell surface antigens, whether CD34 or others yet to be developed, are likely candidates for important product controls that potentially would allow a regulatory scheme that would in some sense both provide good controls and avoid unnecessary
intrusiveness through the establishment of standards which ensure safety and efficacy.

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

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

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

DR. HONG: It seems to be the only player in setting up regulations today, that there's no other competing agency. It seems to me you have to know who the standard-setter is,
and that standard-setter has to have a certain legal backing and also have the acceptance of the scientific community. And what I've heard is that I think the FDA is the only player.

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

DR. GOLDMAN: That's right. When I gave the presentation at, I guess, the February site visit, I included that standards and methods development, especially for biological products for the therapies from biological products, are an important area of what we refer to as mission-related research. Not only do we then do the research, but we take the responsibility for it, and we do have the
backing of the law as an authority to see to it
that these things such as holding these
standards up and having these set standards is,
in fact, the FDA's responsibility.

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

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

DR. ANDERSON: Yes. This is Dr.
Anderson again. I guess I'm trying to sort of
formulate what I'm
really trying to ask, and so I'll
just do it. And so I'll just do it, and that
is: Because of the potential of reduced
research funding, it is clearly important for
the FDA to determine what each of its labs
works on.

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

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

DR. HONG: Well, my sense is that's
appropriate for the closed session, unless
there's a compelling reason it needs to be
discussed in the open. I think anything
relating to the progress, their present plans,
future plans, those kind of items really all
Dr. Anderson: What's the difference between the open and the closed?

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

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

Dr. Anderson: But they're not here in the closed session, so it has to be in the open session, right?
Since the discovery of IL-4 receptors, we set out to ask whether this novel antigen is present on human tumor cells. And then we discovered, lo and behold, many solid human cancer cells express these receptors.

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

Subsequent to that, it was imperative to study with a gamma chain, which is also a component of aisle proteceptors on tumor cells. And this study was important to understand the biology of the receptors, of the tumor cells, and we found that the interleukin-4 proteceptor gamma chain, which is an Aisle 2 receptor, was not present on the tumor cell, and, in fact, we
were the first to identify a novel protein
which we call it now Aisle 13 receptor alpha
chain, which is shared with an aisle protein
receptor.

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

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

We investigated whether there is any
impact on -- and we found that in contrast to
the human cells, Aisle 4 did not contribute to
JAC-3, because tumor cells did not have it.

They did not have gamma chains.

So we demonstrated not only the structure is different, the -- toxin is different.

And then we went to further explore -- this information is very important, by the way, in the inflammatory disease, autoimmune disease, oncological diseases -- where do you want to destruct. By signaling for an Aisle 13, one can merely suck up STAT-6; you can knock down the computer for IO-4 toxin on Aisle 13.

After this demonstration, we obviously wanted to know whether the receptors are functional and can be targeted by IO-4 toxin on Aisle 13 toxin. We discovered these two receptors, and we find that these two molecules appear to be very, very cytotoxic on the cancer cells in vitro, in vivo, and note that in the interests of public health, I think this is a very important observation and can
translate to the clinic for the treatment of
diseases for which there is no treatment
available. And the animal data so far suggests
that the study is very feasible, and the Phase
I trial has begun.

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

And I think continued development in
targeting these drugs has given another way
where they can use these targets for the gene
therapy where we can take -- vectors, and we
can express the gene for interleukin-4 in the
envelope of the retroviruses or adenoviruses
and use it to target L-vector, which is an
injectable vector, which is a true -- gene
therapy where it can have a specificity to
target to the tumor site where it is hard to
reach with the current technology. And I think
I will continue in this aspect, and the
research is ongoing, to double up those --
vectors targeting those receptors.

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

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

With regards to quantitative flow
cytometry, I or we have been asked to prepare a
definition of an international worldwide
standard for CD34 salinumeration, and I will
attempt to do that to the best of my ability,
not because I know anything about CD34 or the
wonderful and exciting subsets. I always tell
people that if a CD-4 4- plus hypercellular
acute leukemia was in my backyard, I probably
wouldn't know it.

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

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

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

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

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

This person had a very easily detectable clone circulating in the peripheral blood. When we first started these studies, we were told that this would be impossible to do.

In retrospect, it's easier than determining CD34 stem cells.

If I had to choose between our interest and expertise in familial B-cell CLL and the use of quantitative flow cytometry for
CD34 enumeration, I would probably choose the
CD34 stem cell enumeration at this point in
time, because I think that that is something
very timely that would be beneficial to the
community. There are 8 or 10 organizations
that are trying to develop class-wide standards
for both autologous and allogeneic peripheral
blood stem cells.

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

Familial CLL will be around for some
time to come.

DR. ANDERSON: What about SKY?

DR. MARTI: Oh, SKY. That gives me
chest pain. SKY. I have a rather developed
part in the briefing documents outlining how to
do the pilot project. One of the reasons I
selected SKY was somewhat like stem cells. We
have no research interest in stem cells per se.

SKY is spectral kereotyping. This is
one of the most incredible physical detection
methods to be developed. It hedges right on
the level of single flourescent molecule
detection, and it is only fitting that it
should have been determined microscopically.

But within months of it being determined
microscopically, it was determined in flow.
You can just determine single molecules. This
work is being done primarily at Los Alamos and
Lawrence Livermore in spectral kereotyping.

It's a very complex technology, and I
don't mean that it's a complex technology
because it involves the sorting of chromosomes.
That's the least of it. It's the proper
preparation. It's the PCR application. It's
the labeling; it's the painting. And even the
incredible software analysis that's required to
make the final picture, if you will. It represents, I think, one of the most complex approaches to genetic testing, but it's been growing for 20 years, and I'll be very surprised if it doesn't become a standard.

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

DR. HONG: Any further questions?

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

DR. HONG: Fine.
DR. FREAS: Okay. In two minutes,
we'll be right back with you.

(Recess)

(End of Open Session)

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