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FOOD AND DRUG ADMINISTRATION

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Jay B. Siegel, M.D.
Deborah Hursh, Ph.D.
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1 P R O C E E D I N G S

2 DR. SALOMON: Welcome this morning to the
3 Biological Response Modifiers Advisory Committee.
4 I have been complaining about the lack of titles
5 but at least they had numbers but ow they don't
6 even have a number here. Oh yes, we do, meeting
7 number 32. Eventually they will get the idea and
8 give me titles.

9 I am Dan Salomon. I have the pleasure of
10 chairing the committee today. What we are going to
11 do this morning is have about a one-hour open
12 session here that I guess merges into a closed
13 session at 8:45. Then, there will be a break at
14 9:00 and at 9:00 we will get into the main topic of
15 the morning. So, a lot of things like introducing
16 the members of the committee I will save for nine
17 o'clock if you guys will forgive the lack of pomp
18 and circumstance this early in the morning. I also
19 reserve the right to say something totally stupid
20 for the next hour since I am from California and it
21 is awfully early for me right now.

22 Without any further ado, we should get
23 going. It is Amy getting up there, Amy Rosenberg
24 from the Laboratory of Gene Regulation, to give us
25 an update on research programs, and that will be

1 followed by Ezio Bonvini, from the Laboratory of
2 Immunobiology.
3 Update Research Program
4 Laboratory of Gene Regulation
5 DR. ROSENBERG: I am actually the Director
6 of the Division of Therapeutic Proteins, and I am
7 here to speak for Ed Max and Serge Beaucage, who
8 are members of the Laboratory of Gene Regulation
9 who, unfortunately, could not be here today.
10 This is a follow-up to the site visit and
11 I will run through the follow-up for Dr. Max first.
12 Dr. Max works with three research scientists, as
13 you can see here. The non-research
14 responsibilities of a laboratory include primary
15 review responsibility for several cytokines and
16 thrombolytics and anticoagulants. They
17 additionally provide expert consultation on issues
18 of molecular biology, particularly quantitative PCR
19 assays and immunoglobulin genes. In addition, Dr.
20 Max performs a lot of administrative functions. He
21 is the associate director for research in OTRR and,
22 as well, he organizes semina series; he chairs the
23 research coordinating committee; and he manages the
24 CBER library.
25 The projects that are ongoing in his

1 laboratory, two were primarily dealt with in the
2 site visit, mechanisms of immunoglobulin isotype
3 switching and characterization of the human 3'
4 immunoglobulin heavy chain enhancer complex.
5 The mission relevance of the research is
6 listed here. Regarding gene regulation, FDA
7 regulates strategies to alter gene expression.
8 Basically, we have a lot of products being produced
9 by knock-in technology. Insulators are now
10 becoming increasingly important in transgenic
11 animals. Regarding isotype switching, there is a
12 little more activity, in fact. There are specific
13 strategies to have TH2 to TH1 switches. So,
14 increasing IgG, decreasing IgE to protect against
15 allergic type reactions. Additionally, our
16 division regulates several agents that are known to
17 directly affect isotype switching, cytokines IL4,
18 TGF-beta and CD40 ligand. As we all fervently
19 believe, good basic science enables appropriate
20 regulation.
21 Dealing with the first project, mechanisms
22 of immunoglobulin isotype switching, this is just
23 to remind you that isotype switching involves a
24 switch recombination event which juxtaposes VDJ
25 segments with downstream constant regions of

1 different isotype genes.
2 The first aspect of this project involves
3 a study of the Ku protein complex, how does this
4 participate in immunoglobulin gene recombination?
5 Ku protein has been found to be key in sealing
6 double-stranded DNA breaks, and it is found that
7 during isotype switching this protein increases in
8 B cells and that knockout mice that are deficient
9 for Ku seal DNA breaks inappropriately. Since the
10 site visit, this laboratory has cloned additional
11 breakpoints in tumors from Ku knockouts that they
12 are trying to characterize to clarify the role of
13 Ku in sealing these double-stranded breaks.
14 The second aspect of this project involves
15 characterization or identification of the role of
16 the ATM proteins in switch recombination. This is
17 a collaboration with Dr. Hodes at NCI. They found
18 that the ATM knockout mice show a defect in isotype
19 switch recombination intrinsic to B cells, and
20 since the site visit they have basically adapted
21 their assay to become really a quantitative assay
22 so that they can more accurately measure the degree
23 of switch recombination.
24 Regarding the second project, which is the
25 characterization of the human 3' IgH enhancer

1 complex, there are many aspects that they are
2 investigating, one, the genomic neighborhood. That
3 aspect has been completed. The human IgH 3'
4 enhancer complex in humans resulting from a
5 duplication event that causes large segments to be
6 duplicated so that downstream of C-alpha 1 and
7 C-alpha 2 constant regions the laboratory
8 characterized these nearly identical enhancer
9 complexes, each composed of a strong enhancer
10 designated HS12, which are flanked by two weaker
11 enhancers, HS3 and HS4. Both HS12 enhancers are
12 flanked by inverted repeats.
13 So, they went on to study the functional
14 motifs in HS12 and other 3' enhancers. The have
15 identified functional motifs in the enhancers by
16 sequence conservation between the human enhancers
17 and the murine homologs. They have performed in
18 vivo footprinting using LM-PCR, and they have
19 performed transient transfections with luciferase
20 reporter constructs that are driven by enhancers
21 mutated in putative functional motifs.
22 Regarding this aspect, since the site
23 visit the laboratory has used DNA swan protection
24 as an alternative technique for in vivo
25 footprinting. They have extended the footprinting

1 analysis outside the evolutionary conserved cores
2 of the HS12 and HS4 areas, and they have
3 constructed and tested additional reporter plasmid
4 containing DNA outside the core enhancers.
5 With regard to the response of this
6 enhancer complex to IL4 and CD40 ligand, it is
7 found that these are factors, which are TH2
8 stimuli, actually inhibited the action of the HS12
9 enhancer in the germinal center B cell lines.
10 Other enhancers, an endogenous one here, were
11 unaffected. Since the site visit they have
12 investigated candidate IL4 or CD40 responsive
13 elements in the HS12 enhancer by constructing
14 reporter plasmid driven by multimerized candidate
15 enhancer motifs.
16 Regarding the last project, looking at
17 locus control region function in chromatin, they
18 found that there is a CPG island within a cluster
19 of DNA swan hypersensitivity sites that showed the
20 activity of gene insulators. So, the level of
21 transcription in the normal situation is here. If
22 you have gene insulators it cuts down dramatically,
23 and these CPG islands as well cut down dramatically
24 on transcription. So, since the site visit they
25 have constructed additional plasmid to define the

1 active insulator element. They are also searching
2 for a possible homologous insulator downstream of
3 the murine enhancers.
4 Additional studies in progress involve
5 chromatin immunoprecipitation studies to identify
6 transcription factors found to be enhancers in
7 vivo, and they are using single cell assays for the
8 3' enhancer function using stable transfectants of
9 GFP constructs. That is the follow-up on the Max
10 lab.
11 DR. SALOMON: Thank you, Amy. I feel bad
12 for Alice since she is an attorney and she came in
13 a little late, she is going to have trouble with
14 the test questions on enhancer.
15 [Laughter]
16 We will try and help you through it. The
17 next is from the representing the laboratory of
18 immunobiology.
19 DR. ROSENBERG: No, I have to give
20 follow-up on Dr. Beaucage. I am sorry. So, the
21 laboratory of Dr. Beaucage, he works with five
22 postdoctoral fellows. His regulatory
23 responsibilities include primary review of
24 hematologic products, enzyme replacement therapies,
25 anti-cancer enzymes and thrombolytics. He provides

1 expert consultation on all of the nucleotide
2 diagnostic kits with the Center's Office of Blood.
3 He has large responsibility for helping to draft
4 the guidance for industry on submission of CMC
5 information for synthetic oligonucleotides. He has
6 also performed some inspections regarding
7 hematologic products and thrombolytics.
8 Overview of his program--as you know, he
9 is an oligonucleotide chemist, and he is
10 responsible in large part for development of the
11 phosphoramidite method so he has three major
12 efforts. The first is effects in development of
13 deoxyribonucleotide cyclic anacylphosphoramidetes
14 and stereo-controlled synthesis of oligonucleotide
15 phosphorofioates for potential therapeutic
16 applications.
17 Essentially, since the site visit the
18 group has optimized the coupling efficiency of
19 deoxynucleoside cyclic anacylphosphoramidites to
20 enable synthesis of nuclease-resistant P
21 stereo-defined oligonucleotides containing all four
22 nucleotides. They found that pryrrolidin and DBU
23 are the preferred bases for efficient coupling of
24 deoxyribonucleotide acylphosphoramidites
25 uncontrolled for GLAS, which is important for

1 potential applications for microarray. They
2 published a paper in the Journal of the American
3 Chemical Society, describing the development of a
4 simple NMR method to determine the absolute
5 configuration of deoxyribonucleotide
6 phosphoramidites at phosphorus, and the findings,
7 again, have appeared in the Journal. They are also
8 working to improve the resistance of CPG
9 oligonucleotides to nuclease activities by using
10 P-stereo defined oligos.
11 The second effort involves efforts towards
12 the discovery of phosphodiester protecting groups
13 for potential applications to large-scale
14 production of alphalation free therapeutic
15 oligonucleotides and to the synthesis of
16 oligonucleotides on microarrays. They found that
17 the 3-NN-dimethyl carboxymedopropryl group--this
18 group right here, is a novel phosphate
19 thiophosphate protecting group for solid phase
20 synthesis that has recently been developed. The
21 monomers which are required are easily prepared
22 from inexpensive raw materials. The protecting
23 group can be removed from the oligonucleotides
24 under the basic conditions that are used
25 standardly, and, thus, it is actually a very

1 convenient protecting group. But, most
2 importantly, the thermolytic properties of the
3 protecting group are particularly attractive to the
4 synthesis of DNA oligonucleotides on microarrays
5 because it minimizes exposure of the arrays to the
6 harsh nucleophilic conditions used for
7 oligonucleotide protection. So, these conditions
8 are actually quite mild and favorable.
9 The third effort is involved in the
10 development of thermophilic 5'hydoxyl protecting
11 groups for nucleoside or nucleotides for synthesis
12 of, again, DNA oligos on microarrays. The
13 thermolytic phosphate protecting groups described
14 in the site visit report have been applied to the
15 protecting group in the 5'hydroxyl of nucleosides
16 as carbonates, but this was found to be quite
17 impractical. Recently the laboratory has
18 discovered that the 5'O and methyl, 1 phenylmethyl
19 oxycarbinol protecting group can be thermolytically
20 cleaved from nucleosides in aqueous ethanol within
21 10 minutes at 90 degrees. Here is the loss of this
22 protecting group.
23 Interestingly enough, this forms a
24 fluorescent byproduct and it permits the accurate
25 determination of the D-protection deficiency. The

1 protecting group appears to be stable in organic
2 solvents at ambient temperature, which also again
3 makes it increasingly attractive to the synthesis
4 of oligonucleotides on microarrays. That is the
5 follow-up for the Beaucage lab.
6 DR. SALOMON: I think someone should get
7 the message back to them that you have represented
8 them really remarkably well. That was a beautiful
9 presentation of not your own laboratory efforts. I
10 think anybody who didn't know that would have had a
11 clue that this wasn't your own work.
12 DR. ROSENBERG: That is because they
13 didn't ask questions.
14 [Laughter]
15 Thank you very much, Dan, I do appreciate
16 it.
17 DR. SALOMON: It is also a representation
18 of the kind of quality work going on at the FDA.
19 My only regret is there aren't enough people in the
20 audience that should hear that kind of thing
21 because that is something that we should have saved
22 for the end of day when there are a lot of people
23 here. The next presentation is from Ezio Bonvini,
24 the Laboratory of Immunobiology, Division of
25 Monoclonal Antibodies.

1 Laboratory of Immunobiology
2 DR. BONVINI: Thank you very much. I
3 would like to thank Dr. Salomon and the members of
4 the advisory committee.
5 My duty today is to summarize the work
6 that we have done, and the focus of my laboratory
7 is on the regulation of phospholipase C-gamma
8 activation in immune cells. The laboratory is
9 operationally divided into two inter-related units,
10 one focusing on the coupling of C-gamma-1 to the
11 antigen receptor TMB cells. The second, which is
12 headed by Dr. Rellahan, looks at the control of
13 phospholipase C activation, and in particular the
14 control mediated by a complex molecule called
15 C-Cbl.
16 Recapitulating the functional division, we
17 have two interacting units, one that I coordinate
18 which is currently made up of a research assistant,
19 Karen DeBell, and a postdoctoral fellow, Carmen
20 Serrano. I would also like to acknowledge past
21 postdoctoral members of the laboratory that, in one
22 way or another, have contributed to this project,
23 and they have actually all left and found
24 employment elsewhere.
25 Dr. Rellahan has one permanent staff

1 member, Dr. Laurie Graham, a lab associate, and she
2 also enjoys the benefit of a number of students who
3 have actually contributed during the summer to her
4 project.
5 Now, we do what we do for a number of
6 reasons. The laboratory has the regulatory
7 responsibility for monoclonal antibodies and
8 protein directed against T-cells for the purpose of
9 immune suppression or immunomodulation. More and
10 more so, these antibodies interact with surface
11 receptors that interfere either in signalling
12 blockade or signalling manipulation with the
13 purpose of immunomodulation. Furthermore, signal
14 transvection targeting can be used as surrogate for
15 potency of biologics. A number of biologics and a
16 number of monoclonal antibodies, also trigger a
17 number of adverse events to undesired signaling.
18 Another fundamental reason is the familiarity with
19 the knowledge base and technology.
20 The focus on PLC-gamma, PLC-gamma
21 regulates calcium mobilization in a variety of
22 cells, including immune cells, and I don't think I
23 need to go any further for this audience but
24 calcium is a critical component in control for
25 transcriptional activation through a number of

1 elements, one of which is an important element,
2 calcineurin phosphatase as a target for a number of
3 drugs; the other path being calcium dependent
4 proteinases. The duration of the effects of the
5 flux of calcium controls a number of cellular
6 responses with a prolonged calcium flux being a
7 requirement for immunocompetence. As I said
8 earlier, a number of calcium-dependent pathways are
9 a target of immunosuppressive structures which
10 include cyclosporin A, among others.
11 Again, I don't think I can go through the
12 data in detail, but what I would like to give you
13 is a flavor for how complex PLC-gamma is. This is
14 the molecule which is a cytoplasmic molecule which
15 contains a number of separate domains. The
16 molecules need to be recruited to the surface where
17 the substrate where PTdinsP, a lipid, resides, and
18 needs to undergo presumably a confirmation or
19 modification to bridge together the X and Y domains
20 of the catalytic subdomain.
21 Our focus has been largely on the
22 cytochromology 2 domain, which are individual
23 domains which are known to interact with calcium
24 and phosphorolytic protein and the cytochromology 3
25 domains which are known to interact with the

1 protein rich region. When we started these
2 investigations, the mechanism of activation of
3 PLC-gamma was largely unknown or misinterpreted, I
4 should say, so we focused on this largely because
5 by their own nature we thought they were
6 responsible for targeting phospholipase C-gamma
7 with a number of regulatory proteins. So, we
8 pursued this by mutational analysis of the enzyme,
9 and recently we obviously focused on a number of
10 other domains but I will not go into any of this.
11 This enzyme is regulated by
12 phosphorylation, and there are at least four known
13 targets in phosphorylation, here in yellow, and
14 that is also another focus of our investigation but
15 we use studies of phosphorylation somewhat as a
16 surrogate marker for activation.
17 So, I will briefly summarize the results
18 of our studies, which have all been published, and
19 I will split them vertically into the different
20 domains. The cytochromology of amino-2 terminal
21 domain is the most critical domain in the
22 activation of PLC-gamma-1 in T and B cells. This
23 domain is required in sufficient phosphorylation.
24 It is required for membrane translocation and this
25 requirement, we think, is required for activation

1 because its activation correlates with the degree
2 of phosphorylation. What this domain does is bind
3 a number of adapters which were recently
4 discovered. One is Lat which we identified in
5 collaboration with Larry Samuelson. The other is
6 BLnk which we identified in collaboration with Tom
7 Korozaky, who actually cloned it. The
8 cytochromology to the C domain appeared to be
9 dispensable for phosphorylation of membrane
10 translocation, although it is required for
11 activation in vivo, and the function of this domain
12 is largely unknown, but since the site visit report
13 we have gained quite a number of insights and this
14 is a very critical domain to investigate as it
15 pertains to the ability of PLC-gamma to couple to a
16 number of different pathways, including
17 co-stimulatory pathways, and to a function of
18 PLC-gamma that is independent of this catalytic
19 activity.
20 The cytochromology 3 domain appears to be
21 dispensable phosphorylation, however, enhances
22 membrane translocation, and I will provide a
23 summary at the end of how it does that, and by
24 virtue of its announcement of membrane
25 translocation, enhanced activation of the enzyme in

1 vivo. Its function, we have identified binding to
2 the protocol gene C-Cbl and Art Wizer's group, one
3 of the leaders in the field, has shown that the
4 domain binds with Lp-76, another adaptive molecule.
5 Of course, I don't have the time to go
6 through all the details but I just want to
7 summarize again some of the milestones that we have
8 achieved since we started this project. With
9 respect to PLC coupling to the receptor, we
10 reported initially that PLC-gamma-1 SS-2 domain was
11 critical for coupling it to the T-cell receptor.
12 Then, we explored the role of cytochromology domain
13 of PLC-gamma coupling to the B cell receptor.
14 Recently we have focused on the ability of membrane
15 raft, which are a microdomain, to function at the
16 microdomain that segregates PLC-gamma and other
17 molecules for their regulators, and we have shown
18 that recompartmentalization of PLC-gamma to this
19 microdomain is, in itself, sufficient to lead to
20 PLC-gamma activation, activation of the cells and
21 IL-2 separation.
22 With respect to the negative regulation of
23 PLC-gamma, which is the focus of Dr. Rellahan's
24 research, we have shown that C-Cbl inhibits
25 TCR-induced 81 activation, a reporter gene whose

1 activation depends on raft and isoglycerol, and
2 isoglycerol is under the control of PLC-gamma.
3 PLC-gamma-1 binds C-Cbl in its HS-3 domain and
4 C-Cbl exerts inhibitory function, however, it
5 transforms a counterpart of C-Cbl-70Z-3 Cbl which
6 lacks the ability of C-Cbl molecule to ubiquinate
7 the target protein. This molecule, 76-C-Cbl,
8 activates PLC-gamma and does so through a
9 differential pathway, a pathway which is not shared
10 completely by the T cell receptors, suggesting the
11 possibility of regulation of PLC-gamma through an
12 alternate mechanism of activation.
13 Rather than going through data, I would
14 like to give you a model that will try to summarize
15 our findings with those of other laboratories and
16 put everything together.
17 This is a schematic TCR receptor. The TCR
18 receptor interacts with the antigen it encounters
19 of antigen presenting cells. Now, in the membrane
20 of many cells, including T cells, it is
21 homogeneous. Depicted here in red are rats which
22 contain a number of different molecules, including
23 the Lck which is brought together through the
24 T-cell receptor by the action of the antigen into
25 the raft. The rafts contain an adaptor molecule,

1 called raft, which we have shown to interact with
2 phospholipase C. This occurs subsequent to
3 phosphorylation of Lck of the CD3 molecules which
4 are associated with the alpha and beta chain of the
5 T cell receptor. Following phosphorylation, a
6 cytoplasmic kinase called Zap 70 is recruited, and
7 it is the Zap 70 that phosphorylates these other
8 transmembrane adapters into the rat.
9 This is the signal that tells PLC-gamma,
10 which is a cytoplasmic enzyme which is
11 constitutively bound to the Lck-76 through the
12 SSS-3 domain. That is the signal to recruit
13 PLC-gamma through the amino termini cytochromology
14 to this adaptor. This interaction is further
15 stabilized by the presence of Gads, a second
16 adaptor molecule, which interacts with Lck-76 and,
17 in turn, interacts with the cytochromology-2
18 domain. That explains the contribution of the
19 cytochromology-3 domain to stabilize the
20 interaction of PLC-gamma to the membrane.
21 PLC-gamma in the raft compartment can be
22 phosphorylated by a number of kinases which are
23 either present in the raft compartment, such as
24 RLK, or recruited to the raft compartment via the
25 action of another specialized phosphorylated lipid

1 PIP-3, such as ITK. These are a member of the TAK
2 family of kinase which are a member of the
3 subfamily of kinase, although their mechanism of
4 regulation is different. The contribution of Lck
5 and RLK in our hands shows that it leads to
6 phosphorylation of PLC-gamma-1 which presumably
7 induces a confirmation of modification of PLC-gamma
8 and the ability of PLC-gamma to activate and
9 mobilize calcium.
10 Our data showed that if we artificially
11 target PLC-gamma through the lipid raft we
12 basically bypass this entire initial phase,
13 although Lck and RLK are still required, presumably
14 because of their contribution to the
15 phosphorylation. Artificially targeted PLC-gamma
16 to the raft compartment is phosphorylated and is
17 active bypassing the receptor entirely. So, this
18 is a dominant, positive variant of the PLC-gamma.
19 What happened with the negative
20 regulation, initial phase is the same and PLC-gamma
21 is interacting with the Lck-76. C-Cbl binds to the
22 SU-3 domain of PLC-gamma very much in the manner
23 seen with Lck-76. So, there is probably
24 competition by a mechanism which we still don't
25 understand. C-Cbl is also phosphorylated in

1 response to activation of the T cell receptor and
2 that leads to inhibition of PLC-gamma presumably
3 via a mechanism of ubiquitilation. We are still
4 investigating this, however, data that confirm that
5 this may be the case is that the variant to 73-Z
6 C-Cbl, and we now have data with another variant
7 that is Ub-ligase deficient, which results in the
8 dephosphorylation of PLC-gamma by a mechanism that
9 we still do not know but that does not require
10 Lck-76, and that leads to the activation of
11 PLC-gamma by a mechanism that is independent of the
12 T-cell receptor. So, we believe that C-Cbl and
13 Lck-76 and the equilibrium between the two
14 coordinate the assembly of the complex that in one
15 case is activatory and in the other case is
16 inhibitory.
17 As far as our future plan, we will
18 continue to investigate the role of PLC-gamma-1 and
19 gamma-2 as a second isozyme present preferentially
20 in B-cells and in other hematopoietic cells where
21 gamma-1 is ubiquitously present in all cells. We
22 will focus further between these two enzymes and
23 other pathways in the co-stimulatory activation of
24 T cells.
25 I mentioned earlier the function that the

1 function of the SS2 domain is still unknown and we
2 have obtained quite a bit of new exciting results
3 on the function of this domain and its coupling to
4 a number of different molecules, but the bottom
5 line that I want to give you is that domain
6 regulates the intrinsic activity of PLC-gamma by
7 intermediate intermolecular interaction which
8 regulates its opening up and the availability of
9 the other subdomains. So, it is a fundamental
10 mechanism of regulation.
11 We will continue, of course, to
12 investigate the role and mechanism of
13 phosphorylation of PLC-gamma. What the enzymes are
14 that phosphorylate the PLC-gamma are largely
15 unknown. We have a candidates are, as I mentioned
16 earlier, but what the different candidates do in
17 terms of individual residues, and there are at
18 least four and mostly likely five residues, and
19 what is the role of the individual residue is still
20 quite unclear.
21 Because we have made a dominant positive,
22 we have now also developed a dominant negative
23 PLC-gamma, and we will certainly ask the question
24 of the role of PLC-gamma development by using
25 transgenic technology. Finally, and I am not going

1 to dwell on this, but we are using technology to
2 recompartmentelize PLC-gamma intracellularly by a
3 condition of mechanism.
4 With respect to the role of C-Cbl again,
5 C-Cbl is probably a threshold for activation, and
6 the impact of C-Cbl on the co-stimulatory signal is
7 the ability of the cell to behave as naive or
8 memory will be investigated. We are going to
9 generate some C-Cbl-deficient lines and we are
10 going to try to do that by a number of different
11 strategies. As I said, we have some new data on
12 the C-Cbl-mediated with the delineation of
13 PLC-gamma-1. I can tell you that it is
14 ubiquitilated. The role of C-Cbl in this remains
15 to be determined but we have evidence that by using
16 Ub-ligase to inhibit the C-Cbl negative cells is,
17 in fact, the case.
18 Finally, we will try, as I said earlier,
19 to generate some C-Cbl deficient cell line using
20 interferon RNA and that will help us in the study
21 of kinetics in mice for PLC-gamma activation.
22 I just want to leave you with the number
23 of individuals who have contributed in one way or
24 another with particular reagents and a number of
25 collaborators that we have worked with whom I would

1 like to acknowledge for their help in this. And, I
2 will be glad to take any questions.
3 DR. SALOMON: That was a very nice
4 presentation and good work, and also my same
5 comments, that I wish more people could see the
6 kind of quality work that is going on in the FDA,
7 oftentimes, with a lot less support not because of
8 your fault or the FDA support but just because of
9 the budget constraints than we are used to in
10 academia. It is excellent.
11 The part that is confusing me here,
12 besides the fact that I really am still asleep, is
13 that we now have to switch officially to a closed
14 session to vote on accepting the report. Gail will
15 make sure that the right people have to leave.
16 Anyway, we will see you again very shortly.
17 [Whereupon, the open session was recessed
18 to continue in closed session and reconvene in open
19 session at 9:15 a.m.]

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

2 Welcome and Administrative Remarks

3 DR. SALOMON: If we can get everybody to
4 sit down we will start the main show, I guess we
5 should say. For the larger group here now, this is
6 meeting number 32 of the Biological Response
7 Modifiers Advisory Committee. My name is Dan
8 Salomon. I have the pleasure to chair the meeting
9 this morning. What we usually do at the start, as
10 in many big committee meetings where a lot of us
11 don't know each other initially--we will certainly
12 get to know each other as the day goes on, is just
13 to go around the table and introduce yourself, and
14 make a couple of quick sentences about what your
15 interests are and your scientific expertise. We
16 can start at that end of the table. Dr. Casper?

17 DR. CASPER: Hi. I am Bob Casper, am a
18 professor of obstetrics and gynecology and
19 physiology at the University of Toronto, and I am
20 head of the Division of the Reproductive Sciences.
21 I have clinically been involved st in vitro
22 fertilization for several years, and our laboratory
23 at the present time has an interest in
24 mitochondrial research involving aging of human
25 oocytes. We have also been doing some work with

1 mitochondrial transfer experiments in mice.
2 DR. SALOMON: There is a button here that
3 you push and then you have to remember to turn it
4 off, otherwise there will be feedback.
5 DR. KNOWLES: Thank you. I am Lori
6 Knowles. I am from the Hastings Center. I have a
7 background in international law and policy, and I
8 am principal investigator right now of an
9 international project on reprogenetic regulation
10 and affects, and also do work in international stem
11 cell policy.
12 DR. NAVIAUX: I am Bob Naviaux, from the
13 Mitochondrial Metabolic Disease Center at the
14 University of California, San Diego. My basic work
15 is in mitochondrial DNA replication, and we also
16 have interest in inborn errors of metabolism and
17 adult and childhood mitochondrial disorders.
18 DR. SHOUBRIDGE: I am Eric Shoubridge. I
19 am a professor at McGill University in the
20 Departments of Human Genetics and Neurology and
21 Neurosurgery. I have a research lab at the
22 Montreal Neurological Institute and our laboratory
23 is interested in the basis of mitochondrial
24 disease, the molecular basis, and we are interested
25 in basic, fundamental aspects of mitochondrial

1 genetics.

2 DR. SCHON: My name is Eric Schon. I am a

3 professor of genetics and development in the

4 Department of Neurology at Columbia University, and

5 I do everything that Eric Shoubridge does.

6 [Laughter]

7 DR. VAN BLERKOM: Jon Van Blerkom. I am

8 from the University of Colorado, Molecular Biology

9 Department, and I am also in clinical practice in

10 in vitro fertilization, for about twenty years.

11 DR. MURRAY: I am Tom Murray. I am from

12 the Hastings Center these days, after fifteen years

13 of medical schools, most recently Case Western

14 Reserve University. My research has been broadly

15 in the field of ethics and medicine and the life

16 sciences, and I have done a lot of work on

17 reproductive technologies, genetics and parents and

18 children.

19 DR. RAO: My name is Mahendra Rao, and I

20 am a section chief in stem cell biology at the

21 National Institute of Aging, and I am a member of

22 this committee. My interests are in embryonic stem

23 cells and adult stem cells.

24 DR. MULLIGAN: I am Richard Mulligan. I

25 am from the Harvard Medical School, Children's

1 Hospital. I am a stem cell person and a gene
2 transfer person, and a member of BRMAC.
3 DR. SALOMON: I am Dan Salomon. I am from
4 the Scripps Research Institute and my lab is doing
5 cell transplantation, tissue engineering,
6 angiogenesis and therapeutic gene delivery.
7 MS. DAPOLITO: Gail Dapolito, Center for
8 Biologics, executive secretary.
9 DR. SAUSVILLE: Ed Sausville. I am the
10 associate director of NCI's Division of Cancer
11 Treatment and Diagnosis, with responsibility for
12 the development of our therapeutics program, and
13 our interest is in the preclinical studies leading
14 to the approval for INDs for drugs and biologics.
15 MS. WOLFSON: Alice Wolfson. I am the
16 consumer representative on the committee. I am an
17 attorney specializing in policy holder
18 representation, with particular emphasis on
19 disability policy holders and their struggles with
20 their insurance companies. I have a strong
21 interest in health. I am a founder of the National
22 Women's Health Network, and I am particularly
23 interested in the social effects of postponing
24 fertility as well as the social effects of not
25 postponing fertility and I think it may have, along

1 with the scientific elements in it, the beginnings
2 of a possibility of a resurgence of another wing of
3 the women's movement.
4 DR. ROSE: I am Stephen Rose. I am from
5 the National Institute of Health, Office of
6 Biotechnology Activities, deputy director for the
7 recombinant DNA program.
8 DR. MONROE: I am Scott Monroe. I am from
9 the Division of Reproductive and Neurologic Drug
10 Products at CDER. I am an
11 obstetrician/gynecologist and a reproductive
12 endocrinologist.
13 DR. SERABIAN: I am Mercedes Serabian. I
14 am an expert toxicologist with the Office of
15 Therapeutics in the Division of Clinical Trials,
16 and I will be part of the review team at CBER that
17 will be reviewing these INDs when they come in.
18 DR. MOOS: I am Malcolm Moos, from the
19 Division of Cellular Gene Therapy at the FDA. My
20 research interests are cell and tissue
21 specification and patterning, and I am also
22 concerned with review of cellular products,
23 primarily that have to do with that general
24 biological area.
25 DR. HURSH: I am Deborah Hursh. I am also

1 a cellular product reviewer in the Division of Cell
2 and Gene Therapy, and I have a research lab
3 studying developmental biology and signal
4 transduction.
5 DR. NOGUCHI: I am Phil Noguchi. I am the
6 director of the Division of Cell and Gene Therapy,
7 where we see these and other novel technologies and
8 continually struggle with doing the right thing.
9 [Laughter]
10 DR. SIEGEL: I am Jay Siegel. I direct
11 the Office of Therapeutics Research and Review at
12 the Center for Biologics, FDA.
13 DR. SALOMON: I welcome all of you. I
14 think one of the privileges of being on the
15 committee and certainly chairing it is the chance
16 to interact with experts at each of these sessions
17 that take me into areas that are often new to me,
18 and today is definitely one of those areas. It is
19 a fantastically important discussion that we are
20 going to have that has a lot of implications on
21 what is going to happen over the next several
22 years. So, I specifically feel a lot of
23 responsibility to this particular session and how
24 we go forward.
25 There will be some more comments later on

1 that, just simple administrative things. My job,
2 obviously, is to stay on time and also to get the
3 questions the FDA answered and keep everybody on
4 track. So, if you will forgive me sometimes
5 playing my administrative role which sometimes
6 includes being rude. I apologize in advance.
7 The button thing, we have all been through
8 it. It gets to be a real problem with feedback and
9 also with the transcriber. So, if I ever sort of
10 look at you and kind of point to the button, it is
11 just to let you know. I think that is the major
12 thing. I want to try and keep track of sort of
13 what we are going to do next so you will sort of
14 know where we are going.
15 What we will do now is a presentation of
16 the certificate of appreciation to Dr. Ed
17 Sausville, with some more comments to follow that.
18 Then Gail Dapolito has some official things to read
19 into the record and then we will start the full
20 session with Dr. Hursh.
21 Presentation of Certificate of Appreciation
22 DR. SIEGEL: It is indeed an honor, tinged
23 with regret at his departure but an honor to speak
24 of the many services that Dr. Sausville has
25 provided to us through his participation in BRMAC

1 in recent years, and to thank you for them. Those
2 of you on the committee, of course, are aware of
3 his many thoughtful contributions to the
4 deliberations to this committee. Some of you may
5 be somewhat less aware of his many contributions as
6 a representative of BRMAC to the Oncological Drugs
7 Advisory Committee and other FDA committees to
8 which we have taken products for consideration of
9 approval, as well as contributions to our lab
10 evaluation and site visiting program.
11 We ask a lot, as you know, of BRMAC
12 members. It ranges from discussion of the issues
13 regarding manufacturing a product, viral purity,
14 protein stability, immunogenicity, and so forth,
15 and how we should focus on safety. The issues of
16 clinical testing of a product; what is the
17 appropriate trial design to get the answers we need
18 and what to make of the answers when those trials
19 are done; and, of course, as you heard this morning
20 the issues of evaluating our research programs and
21 how to make sure that they are tied in intimately
22 to our mission and our goals and are of the highest
23 quality.
24 We choose experts in each and all of these
25 areas to help us in our functions, but it is rare

1 that we have an expert--rare both inside the agency
2 and outside but very much appreciated when we have
3 someone such as Dr. Sausville who really is the
4 regulatory expert triple threat, who integrates an
5 understanding of the clinical evaluation of the
6 basic science, of the research needed to support
7 that, and can participate in an integrated
8 assessment in any of those areas, understanding the
9 implications for the others. That is what you have
10 done for us for these several years and it is very
11 much appreciated. Thank you very much.
12 [Applause]
13 DR. GOODMAN: I know Dr. Zoon and I really
14 second that and appreciate the tremendous breadth
15 of expertise Dr. Sausville has brought. I was
16 going to stress the same thing. From what I have
17 understood and seen, this translational ability
18 between the laboratory and the clinical setting,
19 and an understanding of product development, those
20 things are just extremely important and we really
21 appreciate it. We look forward to continuing to
22 call on you and get your input and help. Thanks
23 very, very much. So, we have a nice certificate
24 and plaque.
25 [Applause]

1 DR. SALOMON: I can't not make my own
2 personal comments, having been together with Ed on
3 this committee for four years. I don't know how
4 many of you have seen the movie "The Scorpion
5 King." I guess is depends on how old your kids
6 are, but the actor in it is called "The Rock"
7 because I suppose he is a professional wrestler as
8 well. But I really think that he is competing with
9 the real "rock" who is Ed Sausville. On any
10 committee like this you have to have a rock. I
11 mean, you have to have the one guy who you can
12 always turn to, even though everything has gone to
13 shreds, and he just hits it right on the head. You
14 have to shut up and listen to him whenever he says
15 anything. Really, whenever there has been any kind
16 of issue here, he is one of the people that I come
17 to at the break and say, "you know, Ed, what the
18 heck do we do now?" And, he always has good
19 advice. This is not good at all, to have Ed
20 leaving and all I can do is say I will always be
21 dragging you back here, and he is really, really
22 going to be a loss to the committee. Thank you.
23 Gail?
24 MS. DAPOLITO: I would like to read the
25 meeting statement. This announcement is part of

1 the public record for the May 9, 2002 Biological
2 Response Modifiers Advisory Committee meeting.
3 Pursuant to the authority granted under
4 the Committee Charter, the director of FDA Center
5 for Biologies Evaluation and Research has appointed
6 Ms. Lori Knowles and Drs. Thomas Murray, Robert
7 Naviaux, Eric Schon, Eric Shoubridge, Daniel
8 Salomon and Jonathan Van Blerkom as temporary
9 voting members for the discussions on issues
10 related to ooplasm transfer in assistive
11 reproduction. In addition, Dr. Salomon serves as
12 the acting chair for this meeting.
13 To determine if any conflicts of interest
14 existed, the agency reviewed the submitted agenda
15 and all financial interests reported by the meeting
16 participants. In regards to FDA's invited guests,
17 the agency has determined that the services of
18 these guests are essential. The following
19 interests are being made public to allow meeting
20 participants to objectively evaluate any
21 presentation and/or comments made by the guests
22 related to the discussions and issues related to
23 ooplasm transfer in assisted reproduction.
24 Dr. Robert Casper is employed by the
25 University of Toronto in the Division of

1 Reproductive Science at Mt. Sinai Hospital in
2 Toronto. Dr. Jacques Cohen is employed by the St.
3 Barnabas Medical Center. Dr. Susan Lanzendorf is
4 employed by the Eastern Virginia Medical School at
5 the Jones Institute of Reproductive Medicine. Drs.
6 Amy Patterson, Marina O'Reilly and Stephen Rose are
7 employed by the Office of Biotechnology Activities,
8 NIH.
9 In the event that the discussions involve
10 other products or firms not already on the agenda
11 for which FDA participants have a financial
12 interest, the participants are aware of the need to
13 exclude themselves from such involvement and their
14 exclusion will be noted for the public record.
15 With respect to all other meeting
16 participants, we ask in the interest of fairness
17 that you state your name, affiliation, and address
18 any current or previous financial involvement with
19 any firm whose product you wish to comment upon.
20 Thank you.
21 DR. SALOMON: Thank you, Gail. Before we
22 officially get started, let me just make a couple
23 of quick comments. That is, the task we have here
24 is to begin now, through about four o'clock this
25 afternoon at which point we will have gone through

1 a series of presentations on this issue of ooplasm
2 transfer that clearly touch on some absolutely
3 major areas, we encourage you to ask questions and
4 to set the stage for critical discussions which I
5 will try to keep on time, but also it is so
6 important that these critical discussions develop
7 that we will have to be a little flexible about how
8 that goes, leading up to a discussion at 4:00 of
9 specific questions that have been put together by
10 the FDA that will frame issues the FDA wants input
11 from us on regarding developing an IND process for
12 this field.
13 The only other comment I want to make to
14 all of you is get your thoughts out on the table.
15 There is no need to force an agreement on anybody.
16 You are more than welcome to articulate and defend
17 a minority opinion. I don't believe my job here is
18 to come up with some absolute consensus. My job is
19 to identify where consensus can be reached,
20 however, as well as to have you help us figure out
21 where there isn't consensus and perhaps other
22 additional efforts in those areas are coming.
23 We have to make sure that when we are
24 done--I feel very strongly--that we can say to the
25 public that this was an open, balanced discussion

1 of the issues. That is a major responsibility.
2 If, in the middle of discussions, somebody goes,
3 you know, we are really missing this piece and we
4 just don't have it here today, then that should go
5 into the record as well because I think that is
6 part of being fair to the whole field.
7 With respect to the audience, I feel you
8 are as much part of this discussion as we are. It
9 is a little harder to control you so you will have
10 to forgive that, but you are certainly not just
11 welcome but encouraged to step up at key points of
12 the discussion and bring your expertise and your
13 viewpoints to it. The rules are simply to keep it
14 brief and identify yourself, and realize that with
15 the competition to try to keep everything on time I
16 will also have to manage that. But very much,
17 please feel part of the discussion that will take
18 place today.
19 That is basically it and I am really
20 looking forward to any discussion that follows and
21 the diversity of expertise we have here. With that
22 introduction, Dr. Hursh?
23 Ooplasm Transfer in Assisted Reproduction
24 FDA Introduction
25 DR. HURSH: I would also like to welcome

1 the participants and the audience to this meeting
2 of the Biological Response Modifiers Advisory
3 Committee.
4 This is day one of a two-day meeting of
5 the Biological Response Modifiers Advisory
6 Committee. On this first day we will discuss
7 ooplasm transfer in the treatment of female
8 infertility. On the second day the topic will be
9 potential germline transmission during gene
10 therapy. We have chosen to link these two topics
11 as both of them deal with the transfer of genetic
12 material go gametes, sperm and eggs.
13 This has occurred in the case of ooplasm
14 transfer and is a potential inadvertent risk of
15 gene therapy. In both cases heritable genetic
16 modifications will be produced. While the FDA and
17 the Recombinant DNA Advisory Committee have
18 discussed some of these issues previously, FDA felt
19 it was timely to have further open public
20 discussion on the subject of gene transfer in
21 gametes in light of the evidence of new mechanisms,
22 such as the manipulation of oocytes by which germ
23 cells can be genetically modified.
24 Since today's discussion is focused on
25 ooplasm transfer, I will limit the rest of my

1 remarks to that topic. We will hear about this in
2 much greater detail from our first two speakers
3 but, in brief, in ooplasm transfer 5 percent to 15
4 percent of an unfertilized egg cytoplasm, which is
5 called ooplasm, is transferred from a donor into a
6 recipient, and is then fertilized in vitro.
7 Recipients are women who have been unable to
8 conceive through conventional in vitro
9 fertilization. The cytoplasm of an oocyte is
10 considered specialized and it contains proteins,
11 messenger RNAs, small molecules and organelles. It
12 is not clear which of these components is the
13 putative active component of ooplasm, but it is
14 with one of these organelles, the mitochondria,
15 that we will be primarily concerned with.
16 Most of you are probably aware that
17 mitochondria are the powerhouse of a cell, the site
18 where aerobic respiration, the production of energy
19 using oxygen occurs. But they have other
20 functions. They are involved in fatty acid
21 metabolism, intracellular ion balance and
22 programmed cell death.
23 As you can see on the schematic diagram
24 here, they are a very specialized subcellular
25 structure, membrane bound, and each cell has many,

1 many mitochondria to support the energy
2 requirements of that cell. I would like to draw
3 your attention to the little squiggle in the middle
4 because that is one of the issues about
5 mitochondria that concerns us here. Perhaps the
6 most important feature for our purposes is that,
7 due to their supposed evolution from primitive
8 bacteria, mitochondria contain their own genome.
9 The mitochondrial genome is very small.
10 It is only about 17,000 base pairs as opposed to
11 several billion for the human genome. However, it
12 has 37 distinct genes. Unrelated individuals have
13 distinct genotypes of mitochondria, so distinct
14 that they can be used by forensic biologists to
15 establish relatedness among human beings. The
16 mitochondrial DNA, while small, is very important
17 because mutations associated with mitochondrial DNA
18 result in human disease. While I realize you
19 cannot read what is in the balloons, the point of
20 the schematic diagram here is this is the circular
21 mitochondrial genome and each one of these balloons
22 represents positions of mapped mitochondrial
23 mutations that result in human disease.
24 Mitochondria obey unusual rules of
25 inheritance. In mammals, after fertilization, the

1 mitochondria contributed by the sperm are
2 apparently destroyed. Therefore, the only
3 population of mitochondria in a developing embryo
4 and in the resultant progeny come from the pool
5 existing in the oocyte prior to fertilization.
6 In general, oocytes therefore get all of
7 their mitochondria from the mother and that
8 mitochondria is a homogeneous pool of a single
9 genetic type. This is a condition that is called
10 homoplasmy. This is the more common situation in
11 human oocytes. Having two distinct genetic forms,
12 two distinct pools of mitochondria is less common
13 and this is referred to as heteroplasmy. While
14 heteroplasmy is unusual with wild type
15 mitochondria, it is actually seen in people who
16 have mitochondrial disease where you can have a
17 population of mutant and a population of wild type
18 mitochondria co-existing in the same cell.
19 In studies of heteroplasmy it has been
20 observed that mitochondrial genotypes can be
21 partitioned unequally among tissues, and I believe
22 we will hear a great deal more about this from one
23 of our speakers this morning, Dr. Eric Shoubridge.
24 So, what happens after ooplasm transfer?
25 If there are mitochondria transferred during

1 ooplasm transfer, what is the result? In March of
2 2001, a laboratory of Dr. Jacques Cohen reported
3 that two children born after the ooplasm transfer
4 protocol were heteroplasmic, which means the
5 genotypes of both the ooplasm donor and the mother
6 could be detected in their tissues. These children
7 were approximately one year old at the time of this
8 analysis, so this was a persistent heteroplasmy
9 that had been maintained.
10 At the time of Dr. Cohen's publication the
11 FDA was already considering action in the area of
12 ooplasm transfer. The report of heteroplasmy
13 raised our concerns, as did information in two
14 pregnancies occurring after ooplasm transfer
15 resulted in fetuses with Turner's syndrome, a
16 condition where there is only one X chromosome.
17 In addition, despite the fact that Dr.
18 Cohen refers to this as an experimental protocol
19 that should not be widely used, we felt that it was
20 beginning to spread rapidly into clinical practice
21 in the United States by 2001. There were at least
22 23 children born in the United States after using
23 ooplasm transfer. Three United States clinics had
24 published on this procedure and we, at FDA, were
25 able to find five additional clinics that were

1 advertising this procedure on the internet.
2 FDA had concerns about whether we
3 understood all the ramifications of this procedure
4 and whether we understood its safety in particular,
5 and reacted by sending letters to practitioners who
6 were identified by publications on ooplasm transfer
7 or by advertisements offering the procedure. We
8 advised practitioners that we would now require the
9 submission of an investigational new drug
10 application, or IND, to the agency and its
11 subsequent review to continue to treat new
12 patients. After the letter was issued we had
13 telephone conversations with several practitioners
14 who wanted to know more about the IND submissions
15 procedure.
16 After these conversations FDA felt this
17 topic would be well served by open public
18 transparent discussion of the ooplasm transfer
19 procedure and the data behind it, hence this
20 meeting. The major issue we, at FDA, are trying to
21 achieve consensus on at this advisory committee
22 meeting is are preclinical and clinical data
23 supporting the safety and efficacy of ooplasm
24 transfer sufficient to justify the risks of
25 clinical trials? If additional data are needed,

1 what types of data would be the most informative,
2 what model systems, what size studies?
3 FDA's tasks in regulating new therapies is
4 to weigh risks and benefits and to determine what
5 safeguards need to be in place to ensure the safety
6 of human subjects. That is what we will do with
7 ooplasm transfer. While the FDA welcomes
8 discussion with all interested parties, our topic
9 today is very limited. We will, therefore, limit
10 today's discussion to the science behind ooplasm
11 transfer and not extend that discussion to FDA's
12 jurisdiction in general, FDA's proposed rules for
13 the regulation of human cells and tissues and other
14 assisted reproductive technologies. Thank you very
15 much.
16 DR. SALOMON: Thank you, Deborah. Unless
17 there are any pressing questions, I think the
18 purpose of that was clearly just to set the stage
19 for what is to follow. What I would like to do is
20 invite Dr. Susan Lanzendorf to present cytoplasmic
21 transfer in the human oocyte. She is from the
22 Jones Institute of Reproductive Medicine.
23 Cytoplasmic Transfer in the Human
24 DR. LANZENDORF: I have come here today to
25 share some of the experiences that we have

1 encountered at the Jones Institute with the
2 procedure of cytoplasm transfer in the human.
3 Cytoplasmic transfer was first considered
4 at the Jones Institute back in 1990 when an
5 investigator, a clinical fellow, Flood et al.,
6 reported that the developmental potential of
7 oocytes to mature in vitro can be increased by
8 injecting with the cytoplasm of oocytes matured in
9 vivo. This was performed in the monkey model.
10 This study found that 13 percent of the
11 injected oocytes resulted in pregnancies while none
12 of the sham-injected or non-surgical controls
13 resulted in a pregnancy. The investigators felt
14 that this suggested that factors may be present
15 within the cytoplasm that control genetic,
16 maturational and/or developmental properties.
17 Then, in 1997, Cohen and coworkers
18 reported the first human pregnancy from the
19 transfer of cytoplasm from donor eggs. They
20 reported that the goal of the procedure was to
21 provide healthy cytoplasmic factors to the eggs of
22 the patients who repeatedly produce embryos of poor
23 quality.
24 We were very interested in this report.
25 We see a lot of patients who come through in vitro

1 fertilization who repeatedly fail to achieve a
2 pregnancy and many times we are at a loss on how to
3 continue treatment in these patients who just don't
4 seem to get pregnant. So, we approached our
5 institutional review board to see if we could
6 investigate this procedure.
7 We decided to look at two groups of
8 patients, in one of which the wife is 40 years of
9 age or older, or in couples who have had at least
10 two previous IVF attempts which resulted in only
11 poor quality embryos. In in vitro fertilization we
12 have found that when you transfer embryos that have
13 an ideal morphology they result in a higher
14 pregnancy rate than those who have less than an
15 ideal morphology. So, this was an attempt to try
16 to improve this and, hopefully, increase the
17 pregnancy rate.
18 Again, we put this to the institutional
19 review board and we requested permission to do this
20 with 15 consenting patients. We worked very hard
21 on our consent form, being that this was a
22 procedure where very, very little was known. So,
23 of course, we tried to emphasize to the patients
24 the risks that they might encounter, including that
25 the effect of the procedure on the couple's eggs or

1 their ability to establish a pregnancy totally
2 unknown. What is also unknown is if the procedure
3 would increase the risk of obstetric complications,
4 or if the thawed donor eggs would even survive. I
5 should point out here that we used frozen and
6 thawed donor eggs for our procedure. So, we
7 emphasized to the patient that if the thawed eggs
8 didn't survive the procedure would not be performed
9 and they may not get a transfer. In addition, the
10 patient's eggs may not survive the procedure or
11 they may fail to fertilize and develop normally and
12 they would not obtain a transfer.
13 We also emphasized the risk to the
14 offspring. It is not known if the procedure would
15 increase risk of obstetric complications or fetal
16 abnormalities. The eggs could be damaged in some
17 way that could affect the offspring. And, there
18 was the possibility that genetic material could be
19 transferred from the egg donor to the patient's
20 eggs and it is unknown if this could adversely
21 affect the offspring.
22 In our consent form we did break this out
23 into talking and making clear to the patient that
24 there are two types of genetic material, DNA from
25 the nucleus of the egg and the DNA from the

1 mitochondria. So, we were careful to make them
2 understand that the two different possibilities of
3 genetic material could be transferred.
4 The consent form also stressed that
5 because the procedure is so new there is no way to
6 determine what the exact risks are, or at what rate
7 the risks occur. In our other consent forms we try
8 to say, you know, we have seen a 50 percent
9 survival rate, or we have seen a 60 percent
10 pregnancy rate but we couldn't even do this with
11 this procedure because it is so new so we
12 emphasized this to them.
13 It was also recommended that all of the
14 patients who achieve a pregnancy have an
15 amniocentesis regardless of their age. Then, of
16 course, the boiler plate other risks that cannot be
17 identified at that time.
18 This is just to show you quickly how we
19 perform the procedure. Again, we used
20 frozen-thawed donor eggs so the donor eggs that
21 contributed the cytoplasm were collected and
22 cryopreserved at a previous state. Then, when the
23 patient came through on the day of their aspiration
24 and cytoplasm transfer, the donor eggs were thawed.
25 So, before we get here what we will have

1 done is--this is the pipet here that we also use to
2 do the donation. This is the egg-holding pipet
3 which just holds the egg in place. This is the
4 egg. So, prior to getting here we would have got a
5 drop of sperm and picked up a sperm from the
6 patient's husband and loaded it in the pipet. We
7 then take this pipet with the sperm and insert it
8 into the donor egg. Then, once in the donor egg,
9 we draw up cytoplasm that will be transferred.
10 We then move to the recipient's egg, the
11 patient in this scenario, and then put that pipet
12 into the egg, inject that cytoplasm into the egg,
13 along with the husband's sperm. Actually, what
14 occurs is the cytoplasm transfer and the
15 utilization of the egg at the same time.
16 Our results, we had eight patients in
17 eight cycles who were 40 years of age or over, with
18 an average age of 44. The procedure did not appear
19 to have an effect on embryo quality. I say "did
20 not appear" because there are too few numbers of
21 actual embryos to compare with other embryos to
22 make a significant conclusion. No pregnancies were
23 established in any of these eight patients.
24 In the same 40 years or older group, 39
25 eggs were retrieved, with a mean of 3.2 eggs per

1 patient. This is low but is normal in patients in
2 this age group. We had a 54 percent fertilization
3 rate, and this would be with the cytoplasm transfer
4 occurring at the same time. To do these
5 procedures, we had to use cytoplasm from nine donor
6 eggs, and these donors ranged in age from 25 to 29.
7 Of the donor eggs, 62 percent survived the thaw
8 procedure and were used.
9 We had three patients who came through who
10 had a history of poor quality embryos. Actually,
11 this is the group of patients that we thought we
12 could really help with this procedure. We did not
13 go into it thinking that the older patients would
14 be the ones that would benefit mostly, and I think
15 the other investigators who performed this
16 procedure would probably agree that it is not
17 helping the older aged couples.
18 So, these were three patients who had
19 significant history of poor quality embryos in the
20 past. The age of these patients was 35, 35 and 38.
21 The procedure did appear to have an effect on
22 embryo quality. To us, the embryos looked much
23 better than those that we had seen from these same
24 patients previously. Of those three patients, one
25 achieved a pregnancy. It was a twin pregnancy that

1 was established. That particular patient had
2 undergone six previous IVF attempts with fresh
3 transfer and three attempts with cryotransfer and
4 never achieved a pregnancy.
5 In these three patients 42 eggs were
6 retrieved, a mean of 14.3 which, as you can see, is
7 much higher than in the older patients; 62 percent
8 fertilization rate with the cytoplasm transfer.
9 This is the information on the donors that provided
10 the eggs, and they had a 66 percent survival, those
11 three donors.
12 These are the twins. I have been told
13 that the medical director has spoken with the
14 couple about having their twins evaluated
15 genetically for all the questions that we are here
16 about today. The couple is not interested. They
17 feel their children, who are now three or four
18 years old, are very healthy and very normal and
19 they don't want anything else done with that.
20 We were also looking at other things when
21 we were doing these studies and before we received
22 our letter to stop doing them. One of the things
23 that we were interested in was the inadvertent
24 transfer of the nuclear material, the chromosomes
25 from the donor egg into the recipient egg. I

1 should point out here that would had actually met
2 with a mitochondrial geneticist at our institution
3 to find out--you know, we posed this problem of
4 transferred mitochondria, and ask him did he think
5 we would have a problem there; did he think that
6 these mitochondria that we transferred we be passed
7 on. He assured us no, it was too few mitochondria
8 and it couldn't happen. So, we really didn't go
9 into it thinking that that would be the problem.
10 We were more concerned with accidentally
11 transferring the nuclear material.
12 So, we looked at some of the eggs that we
13 had taken cytoplasm out of using staining. We can
14 actually see the spindle of the egg, and with this
15 stain we can see the chromosomes on the spindle.
16 So, we looked at these eggs that provided the
17 cytoplasm, and this was published just recently,
18 last year, and the oocytes that we evaluated
19 resulted from either clinical cases I just
20 described to you or research procedures which we
21 are doing.
22 In this case 12 oocytes were thawed but
23 were not used for the transfer. They weren't
24 needed to provide cytoplasm so we used those as
25 controls. We had 23 eggs that we thawed which

1 survived the donation procedure. These are the
2 ones that served as tests.
3 When we did the staining procedure on
4 these eggs, the control eggs all demonstrated
5 normal meiotic spindle but when we looked at the
6 test eggs we found that 2/23 eggs that provided
7 cytoplasm demonstrated total dispersion of the
8 chromosomes from the metaphase plate, and complete
9 disorganization of the spindles.
10 Of course, the numbers are very small but
11 there was no significant difference between the two
12 groups. So, we wondered if this was something to
13 do with the drawing out of the cytoplasm that
14 potentially disrupts the spindle. We wondered,
15 since it is a procedure that is very similar to
16 ICSI, if this would be the same rate of meiotic
17 spindle damage that you would see in ICSI oocytes.
18 Because we were worried about this we
19 looked at ways to see if there were some way we
20 could prevent this. So, we looked at a new
21 microscope that was on the market, the PolScope.
22 Having this attached to your microscope actually
23 lets you visualize, while you are doing a
24 procedure, the actual spindle so that you can see
25 the spindle and you can stay clear of it.

1 Here is the egg, just a small part of the
2 egg, the polar body and the spindle here. So,
3 while you are doing the procedure, you are sticking
4 something into the egg and you can see the spindle
5 and stay clear of it. This is equipment that is
6 currently used in many laboratories, including ours
7 now, in which clinical ICSI cases are performed, or
8 research involving enucleation where they want to
9 see where the spindle is so they can take out the
10 nuclear material.
11 We also did a little work with looking at
12 this from a research aspect. We had a clinical
13 fellow, Sam Brown, who wanted to see if the
14 original work of Flood in 1990, where we used
15 immature eggs, would have the same ft, cytoplasmic
16 transfer. The idea with it is the developmental
17 failure of human embryos derived from oocytes
18 matured in vitro may be due to the deficiency of
19 cytoplasmic factors. In in vitro fertilization we
20 have found that when patients get a lot of immature
21 eggs, eggs that need more time maturing before they
22 can be inseminated, these eggs do not do as well.
23 So, the idea was to see if human prophase I oocytes
24 became developmentally competent after
25 microinjecting them with the ooplasm of eggs

1 matured in vivo within the body.

2 Sam hypothesized that such an injection
3 would improve fertilization and blastocyst
4 development of these immature eggs. This was just
5 a research project. None of these eggs were
6 transferred back to patients. It was with the hope
7 of salvaging immature eggs. For example a patient
8 who gets all immature eggs after a retrieval could
9 have this procedure done and improve her chances of
10 achieving a pregnancy.

11 In the first part of the experiment looked
12 at the effect of cytoplasmic transfer from in vivo
13 matured eggs into PI eggs. So, we had three
14 groups, control eggs which were put on a stage of
15 the microscope but not actually injected. We found
16 that 74 percent of these matured to metaphase II
17 after continued culture. Sham eggs were eggs that
18 were injected with an equal amount of media only,
19 not cytoplasm, and we found that only 50 percent
20 matured to metaphase II. Cytoplasm transfer eggs
21 that actually had the procedure, 58 percent matured
22 to metaphase II. So, these findings suggested that
23 injecting a substance into an egg may have a
24 negative impact on maturation.

25 We also inseminated these eggs to see if

1 they could be fertilized, and in the control the 14
2 eggs that matured to metaphase II we had a 50
3 percent fertilization rate. Shame injected, we
4 only had 38 percent fertilization rate. With
5 plasmic transfer four of the eight fertilized,
6 which was 50 percent. The development after
7 culture was not remarkable between the three
8 groups. The numbers were very low and similar to
9 what we always see with immature eggs.
10 We also looked at the effect of
11 cytoplasmic transfer on eggs that matured in vitro.
12 They were first allowed to mature in vitro and then
13 they were given the cytoplasm of an egg that was
14 matured in vivo. There were 17 control eggs that
15 received no cytoplasmic transfer, and after
16 insemination 53 percent of these fertilized.
17 Cytoplasmic transfer, 47 percent of these
18 transferred. We did see a little bit higher rate,
19 since these were cytoplasmic transfers and the
20 injection of a single sperm having three prime
21 nuclei suggests that there was damage to the
22 spindle in these eggs.
23 In conclusion, we feel that cytoplasmic
24 transfer, if performed clinically, should move
25 forward cautiously and with the full consent of the

1 patients. Just to give you some of the feelings of
2 the patients, should this procedure be found to not
3 be harmful to the offspring and studies continue,
4 we do have many patients out there who are not
5 bothered by the fact that their offspring would
6 have the genetic material of another person because
7 for these patients the only other recourse is to
8 use donor eggs. So, in that case, their children
9 would have none of their genetic material. So,
10 having some of their genetic material appeals to
11 them, and a lot of patients would pick this
12 procedure over going to the donor egg. Thank you.
13 Question and Answer
14 DR. SALOMON: Thank you, Dr. Lanzendorf.
15 This initial presentation is open for questions and
16 discussion. There are so many different kinds of
17 questions here and you, of course, get the
18 privilege of being the fist one. One of the things
19 that is going to come up is if you go to an IND,
20 then in this whole area the big question is always
21 going to be preclinical work and models. So, let
22 me make the first question here a little bit about
23 these primate studies.
24 The primate studies were done in 1990, and
25 then the first clinical report you made was seven

1 years later, in 1997.
2 DR. LANZENDORF: Right.
3 DR. SALOMON: Maybe at some point you
4 could kind of explain to us in the seven years, but
5 specifically for the primate studies, can you make
6 me understand this a little bit better because it
7 will be important later in our discussions for is
8 this a good model because then one might focus on
9 such a model. To the extent it is not a good
10 model, one should be cautious.
11 DR. LANZENDORF: Right.
12 DR. SALOMON: So, the question I would
13 have specifically is what defines this model as a
14 model for infertility?
15 DR. LANZENDORF: The non-human primate as
16 a model?
17 DR. SALOMON: Yes. Essentially, you had
18 these oocytes. I am assuming, just guessing, that
19 you cultured them in vitro for a while and, the
20 longer they were in vitro, they became less and
21 less viable. So, when you implanted the
22 controls--I am not saying you did, I guess this
23 wasn't your study, but when they implanted the
24 oocytes and they didn't get a successful pregnancy
25 and they managed to salvage 13 percent with

1 cytoplasmic transfer from a fresh egg--is that
2 right?
3 DR. LANZENDORF: Right.
4 DR. SALOMON: So, it was the culture of
5 the oocytes for X number of days or weeks that
6 caused them to lose their viability?
7 DR. LANZENDORF: When you take immature
8 eggs from a primate, a monkey or a human, and they
9 haven't completed the maturational process within
10 the ovaries, they have to complete it in a dish and
11 that usually takes about 24 hours, sometimes 48
12 hours. These eggs historically are not as
13 developmentally competent as eggs that had
14 completed maturation in the body. Does that make
15 sense? Before we go in to remove an egg from a
16 patient we try to time it so that when we are
17 taking these eggs out they are already mature. So,
18 just the whole aspect of collecting immature eggs
19 for in vitro fertilization, monkey or human, has
20 always posed a problem when these eggs are not as
21 competent.
22 That early study that was published in
23 1990 was not looking at cytoplasmic transfer as a
24 way to cure this problem. It was trying to look at
25 what is the problem. What is it about immature

1 eggs that they don't do well? So, they said, well,
2 if we put some cytoplasm from one that was matured
3 in vitro into this egg, will it do better? And, it
4 did. So, that 1990 report was never, from what I
5 understand, a report to say let's go out there and
6 start doing cytoplasmic transfer. You know, I
7 don't think the Jones Institute looked at it as
8 though, oh, we can cure these immature eggs from
9 this problem and let's start doing this in
10 patients. So, that is why when you talk about the
11 seven years--you know, I don't think any of us even
12 considered doing it as a procedure to help
13 infertile couples.
14 DR. SALOMON: I appreciate that
15 clarification. Sort of the follow-up then is 13
16 percent were successful pregnancies with this
17 procedure.
18 DR. LANZENDORF: Right.
19 DR. SALOMON: Again, were there a whole
20 lot of miscarriages and other problems in the other
21 87 percent?
22 DR. LANZENDORF: I don't know, but having
23 done monkey IVS and worked with monkey IVS and used
24 it as a model, I can say that a lot of times doing
25 in vitro fertilization in fertile monkeys is a

1 hundred times harder than doing it in a group of
2 infertile human patients. You know, monkeys are
3 somewhat difficult to work with during in vitro
4 fertilization. There are sites around the United
5 States, primate centers and places like that, who
6 have got it down to a fine art and I do believe
7 that the non-human primate is the model that should
8 be looked at. But, again, it is a very difficult
9 procedure but there are places in the United States
10 that do it quite well and I believe could do these
11 experiments.
12 DR. SALOMON: Richard?
13 DR. MULLIGAN: Just to go back to the data
14 set, between the 1990 report and 1997, can you
15 characterize what is the complete data set? Or,
16 can some expert tell us? I assume there have been
17 other things that were done, repeats from the 1990
18 experiment?
19 DR. LANZENDORF: No, there was nothing
20 ever done.
21 DR. MULLIGAN: So, the wealth of
22 information about the potential of this comes from
23 that 1990 experiment?
24 DR. LANZENDORF: Right. Again, that was
25 not an experiment exploring cytoplasm transfer. It

1 was trying to look at is it the cytoplasm the
2 problem? Is it the nucleus that is the problem?
3 Is it the monkey's uterus that is the problem? So,
4 it was just a basic study trying to look at what is
5 the problem with immature eggs; it was never a
6 cytoplasmic transfer procedure. So, it was never
7 pursued as an experimental design to continue.
8 DR. MULLIGAN: Just for perspective, how
9 many actual eggs were in that group that resulted
10 in 13 percent pregnancy?
11 DR. LANZENDORF: I have no idea. I was
12 not there and I don't believe I brought the article
13 with me. I am sorry.
14 DR. SAUSVILLE: And when one speaks of a
15 sham procedure in this case, which comes up both in
16 the monkey experiments and in some of the more
17 recent data, does sham mean withdrawal from
18 something else--
19 DR. LANZENDORF: Right.
20 DR. SAUSVILLE: --in the donor egg and
21 manipulation of the recipient egg? Or is it
22 saline? Could you give us a little bit of
23 background about what the exact shams and controls
24 are?
25 DR. LANZENDORF: Well, in our lab a sham,

1 an actual control would be one that was just put on
2 the stage of the microscope, that would have seen
3 the effects of the change in temperatures and
4 moving around and being put into dishes. A sham
5 injection is one in which, at least in experiments
6 I was involved with, we would draw up culture media
7 and use that to inject into the egg. So, the egg
8 was actually seeing the movement of substance, the
9 puncture of the needle and things like that. You
10 know, in some of the experiments the sperm was
11 injected also, in some it wasn't. That wasn't part
12 of the design. But we tried to keep it exactly
13 like the actual procedure without the transfer of
14 the cytoplasm in a sham.
15 DR. SAUSVILLE: But a key point is that
16 the culture medium is what constituents the sham
17 injection. Isn't that correct?
18 DR. LANZENDORF: Yes.
19 DR. SAUSVILLE: And that, of course, has
20 145 millimolar of sodium chloride as opposed to
21 what is inside.
22 DR. LANZENDORF: Right.
23 DR. SAUSVILLE: So, a small amount
24 actually then could result in a market change--
25 DR. LANZENDORF: Right. We realize that

1 probably our shams should actually do worse than
2 cytoplasmic transfer because of these things being
3 dumped into them.
4 DR. SAUSVILLE: And they did, right?
5 DR. LANZENDORF: And they did.
6 DR. SALOMON: Dr. Monroe?
7 DR. MONROE: I have a question about the
8 relevance of the monkey experiment that we have
9 been addressing and the type of patient who might
10 be a recipient of this procedure. It seems to me
11 that in the monkey studies the question was the
12 issue of immature eggs.
13 DR. LANZENDORF: Right.
14 DR. MONROE: It wasn't a question of
15 people for whom that wasn't necessarily the problem
16 but just had poor embryo development. Is that the
17 correct interpretation? So, they are very
18 different questions that we would be addressing.
19 DR. LANZENDORF: Right. Those three
20 patients, the people that we think could be helped
21 from this procedure, we really don't know what is
22 wrong with their eggs but they are typically young
23 patients. They do well on retrieval. They stem
24 well. They get a large number of eggs. That is
25 what usually happens with this age group. They

1 fertilize find but then, after being in culture for
2 a couple of days, they usually would not even be
3 recognizable as an embryo--total fragmentation. We
4 use a grading scale of one to five, one being the
5 best and five the worst, and they were typically
6 all five. In the cases where we would see that
7 transfer would have been pointless but usually
8 patients like a transfer even if they are told that
9 it is probably pointless. So, there is something
10 inherent about those patients' eggs that is the
11 problem and whether it is a cytoplasmic thing we
12 don't know, but it is something we see over and
13 over again. The patient who achieved a pregnancy,
14 this happened to her in like six other stem
15 stimulations and there was nothing else that we
16 could offer her.
17 DR. RAO: Two sort of more scientific
18 questions, one was sort of an extension of what Dr.
19 Sausville asked, and that is, has there been any
20 comparison with cytoplasm from any other cell as a
21 control that has been used in these experiments?
22 DR. LANZENDORF: From another egg?
23 DR. RAO: Not just from another egg, from
24 any other cell as a control?
25 DR. LANZENDORF: No.

1 DR. RAO: I mean, do you really need
2 oocyte cytoplasm?
3 DR. LANZENDORF: We have always used
4 oocyte cytoplasm.
5 DR. RAO: And to your knowledge, there is
6 no data?
7 DR. LANZENDORF: Not that I know of.
8 DR. RAO: You showed data where you had
9 pronuclei, right?
10 DR. LANZENDORF: Right.
11 DR. RAO: So, there was maybe a high
12 probability of injury. Were those experiments done
13 with the spindle view imaging system?
14 DR. LANZENDORF: No. We got our PolScope
15 at the same time we got our letter.
16 DR. NAVIAUX: Just a question about the
17 optics that are being used. At any time, are the
18 oocytes exposed to ultraviolet light?
19 DR. LANZENDORF: No.
20 DR. NAVIAUX: And the imaging of the
21 PolScope, what are the physics of that?
22 DR. LANZENDORF: I am not sure, but it is
23 just a changing of the wavelength of the light that
24 allows you to see the spindle. It was initially
25 designed, I think, to look at the membrane around

1 it. We found that by using it we could also see
2 the spindle.
3 DR. NAVIAUX: Are dyes ever used to image
4 nucleic acid?
5 DR. LANZENDORF: No. The PolScope is used
6 by some labs pretty extensively for ICSI. So,
7 there are probably pretty good pregnancy results
8 for that. I hope I am not getting the PolScope
9 people in trouble. It is routinely used.
10 DR. SCHON: PolScope is polarizing optics.
11 It has been around for fifty years and it is just
12 like a microscope.
13 DR. NAVIAUX: The basis for that question
14 is that certain types of mitochondrial dysfunction
15 are responsive to ultraviolet lights and others are
16 less responsive. But that is not relevant.
17 DR. SALOMON: Dr. Casper?
18 DR. CASPER: Susan, do you know if any
19 monkeys were actually born from the cytoplasmic
20 transfer, from that 13 percent pregnancy rate? If
21 so, are there any records regarding their health,
22 life span or anything like that?
23 DR. LANZENDORF: I don't think there are
24 any records at all. I have the article here. It
25 just talks about pregnancy rate. It doesn't say

1 anything about live births that I can see.
2 DR. SALOMON: Dr. Rao?
3 DR. RAO: Another question, are the donor
4 oocytes tested in any fashion?
5 DR. LANZENDORF: Our donor oocytes are
6 eggs from our typical donor pool. We have an
7 active donor egg program. So, somebody coming into
8 the program to donate their eggs for a pregnancy in
9 another couple have extensive screening,
10 psychological as well as medical, and we do
11 genetics testing and things like that.
12 DR. RAO: Does that include mitochondria?
13 DR. LANZENDORF: No, it does not include
14 mitochondrial diseases, no. But they are tested.
15 DR. SALOMON: So, another question, you
16 know, in this perfect position to answer all these
17 questions at the beginning of the day, not all
18 necessarily that you have to defend, but you used
19 the term "embryo quality" a couple of times. If
20 you will excuse my ignorance, can you educate me a
21 little bit about what do you do objectively to
22 determine embryo quality?
23 DR. LANZENDORF: Embryo quality is just
24 basically all morphological. No one has devised
25 some kind of biochemical marker to say this embryo

1 is better than that embryo, but typically you start
2 out with the one cell; then you have two, then
3 four; and you see that beautiful clover leaf kind
4 of pattern going on there. When you start seeing
5 poor quality embryos you will see that the cleavage
6 divisions aren't equal. Some of the blastomeres
7 are very large, some are very small. There are
8 other things called cytoplasmic blebs and fragments
9 that start forming and these things can take over
10 the entire--all the blastomeres just start
11 fragmenting and people think this is some kind of
12 apoptosis that is going on.
13 Through the years we have seen that when
14 you transfer four perfect four grade cells with no
15 fragmentations, the implantation rate is
16 considerably high than if you were to transfer five
17 totally fragmented, very poor embryos. Very
18 rarely, if ever, would you see a pregnancy there.
19 So, we are even confident telling these patients
20 you don't want to undergo the transfer or pay for
21 the transfer; your chances of getting pregnant with
22 these three grade five embryos is zero. So, it is
23 an assessment. It is not always correct. A lot of
24 times we put three grade one embryos and a patient
25 doesn't get pregnant, or we put some very poor

1 quality embryos and the patient does get pregnant.
2 So, it is not 100 percent. But when you see a
3 patient come through six, seven times and every
4 single time they have very, very poor quality
5 embryos it becomes something about this patient.
6 You know, what can we do to improve this? Doctors
7 will try changing stimulation protocols and it
8 doesn't work. We have a certain class of patients
9 and this is their problem, and they are told to go
10 to donor egg.
11 DR. SALOMON: Just to summarize, if you
12 have a good relationship with your technologists
13 you have a sense of confidence in this subjective
14 reading--
15 DR. LANZENDORF: Oh, yes.
16 DR. SALOMON: --of good and bad embryos.
17 DR. LANZENDORF: Yes.
18 DR. SALOMON: I mean, just to show you
19 that you are not alone in that area, I am
20 interested in islet transplantation and we are
21 similarly clueless about an objective determination
22 of a quality islet preparation, and that is a major
23 area now focused for research in a program that I
24 am involved in.
25 DR. LANZENDORF: Right.

1 DR. SALOMON: So, it is not unusual.
2 DR. SCHON: These patients who have gone
3 through six or seven times and have always had
4 these poor quality embryos, are they consistently
5 poor quality from day one to fertilization onward,
6 or is it sort of an abrupt change, let's say, on
7 day two or three?
8 DR. LANZENDORF: It is usually the first
9 cleavage division.
10 DR. SCHON: So, at the first cell division
11 you start seeing these abnormalities, but these
12 multiple patients that were selected for
13 cytoplasmic transfer and had had consistently poor
14 embryo quality up to that point on multiple
15 attempts, was there any attempt to see whether or
16 not the embryos could be put back earlier, let's
17 stay at the one cell stage or at the two cell stage
18 before this fragmentation occurred to divorce the
19 notion that there was an embryo problem versus the
20 ability of that particular patient's embryo to
21 survive in culture?
22 DR. LANZENDORF: The patient who got
23 pregnant, I believe but I can't say for certain she
24 had a ZIFT procedure. I mean, this patient was
25 hell-bent on getting pregnant and eery time she

1 came she was going to do something different to try
2 to improve her chances. So, we are talking about
3 three patients and I know I could look this up for
4 you in their records, but I feel pretty confident
5 that even those procedures would not have helped
6 them, and I believe that one had tried other
7 procedures.
8 DR. SALOMON: Dr. Murray and then Dr.
9 Mulligan.
10 DR. MURRAY: Thank you. Dr. Lanzendorf,
11 in your presentation the last point you made was a
12 kind of empirical claim with a moral punch line.
13 You said that most patients having to choose
14 between a donor egg and cytoplasmic transfer would
15 not be bothered with the fact that the child may
16 have genetic material from the mitochondria of the
17 egg donor. In ethics we are as intensely focused
18 on the text as scientists are focused on data. So,
19 it would be very helpful to know, if not now and
20 you could submit later, exactly what question the
21 patients were responding to and what information
22 they had been given about the significance and
23 risks of getting heteroplasmy for example.
24 DR. LANZENDORF: Well, before the two
25 pregnancies from Jacques Cohen's lab, we would talk

1 to the patients about what it would mean to have
2 mitochondria from somebody else, and that there
3 mitochondrial diseases and things like that.
4 Again, at that point we were more concerned about
5 transfer of nuclear material after being reassured
6 by a mitochondria person that mitochondria would
7 not be transferred, but we did always have it in
8 the consent form. Then after those pregnancies
9 became evident, we immediately amended our consent
10 form to talk about the two children who had been
11 born. I don't believe that we did any patients
12 after that because that was soon after we received
13 the letter.
14 DR. MURRAY: Did your mitochondrial expert
15 not inform you about the possibility of
16 heteroplasmy?
17 DR. LANZENDORF: No, he didn't. Well,
18 that is what we went to ask him about because one
19 of the things we were interested in was looking at
20 transferring mitochondria from one egg to the
21 other. We actually had a patient who came to us
22 also with a mitochondrial disease and wanted us to
23 do nuclear transfer for her so that her nucleus
24 could be put into an egg with normal cytoplasm.
25 So, we also explored with her being able to take

1 just a small amount of cytoplasm from a normal
2 donor egg, and we were assured from our person we
3 talked to that that much transfer of cytoplasm
4 would not affect the egg. It would not be passed
5 on to the progeny, and things like that.
6 DR. MURRAY: They were wrong.
7 DR. LANZENDORF: We initially approached
8 this as wanting it to be the mitochondria that
9 provided the benefit.
10 DR. MURRAY: So, you got incorrect--
11 DR. LANZENDORF: Oh, yes.
12 DR. MURRAY: I don't know what the
13 protocol is. This is my first meeting with the
14 committee, but I would appreciate it if you could
15 give us at some point the actual question asked on
16 which you based this particular conclusion.
17 DR. LANZENDORF: Well, it was just sitting
18 down, talking to patients, consenting patients and,
19 you know, we do a weekly lecture, an egg class
20 where embryologists just sit around the table and
21 we present slides, similar to these, and show them
22 the kind of thing and, you know, patients
23 immediately jump up and, "oh, I don't have to go to
24 a donor egg. I can possibly have my genetic
25 material in my child." Then you say, "well, but

1 there is the chance of mitochondrial transfer." "I
2 don't care about that." "Well, it may change the
3 way the baby looks." You know, those are the
4 things that an infertile couple are thinking about.
5 DR. MURRAY: You have a mitochondrial
6 genome and a nuclear genome that comes into balance
7 in some way that we don't understand. So, really
8 part of the issue is not simply having somebody
9 else's mitochondria. The issue is whether that
10 mitochondrial DNA, in its interactions with that
11 woman's nuclear DNA, is going to draw you into a
12 new aspect of being that you would otherwise not
13 have had the possibility of encountering. So, I
14 think there is a complexity there.
15 DR. LANZENDORF: Right, and at that time
16 we did not understand the complexity so we would
17 most definitely change the way we talk to the
18 patient, get more information, explain to them more
19 about the role of mitochondria and things like
20 that. But I still believe that should this
21 procedure receive an IND, there are going to be
22 patients who will be lining up for it. We get
23 calls weekly from all over the world wanting the
24 procedure.
25 DR. SALOMON: Along the same line as the

1 ethics aspect of it, what does it mean that when
2 you went back to the couple that had the twins that
3 they just said, forget it; we don't want to know
4 anything. Again, I am not in your field but that
5 kind of concerns me that either they weren't really
6 prepared for the experimental nature of the
7 procedure or they don't really appreciate how
8 important it would be to test their children.
9 DR. LANZENDORF: Right.
10 DR. SALOMON: Or, is this really such an
11 emotional issue and, of course, we know it is such
12 an emotional issue that this is going to be a very
13 difficult problem going forward in these studies,
14 that the parents really are not going to want you
15 to come near their kids.
16 DR. LANZENDORF: This is information that
17 I obtained from a medical director, and I can go
18 back to the medical director, or maybe you can go
19 back to the medical director and explain why you
20 think it is important, that these things occur and
21 maybe the couple can be brought back in and talked
22 to again. But when the letter went out and, of
23 course, when I found out about this meeting I asked
24 would she consider having her children evaluated.
25 He said, no, I just saw them last week and

1 mentioned it and they had no interest in it; they
2 couldn't care less if their kids have mitochondria
3 from somebody else. They are perfectly normal and
4 they are happy and, no, they don't want to be
5 bothered. So, whether it is the medical director or
6 not, making it a big enough issue--I don't know.
7 DR. SALOMON: What I think this tells us
8 is it is just as an insight that as we go forward
9 in this area, part of what happens is educating the
10 whole process and how you do clinical trials in
11 cutting edge technologies.
12 DR. LANZENDORF: Right.
13 DR. SALOMON: In a gene therapy trial, for
14 example, we couldn't expect any of our patients
15 afterwards to be surprised that we have come
16 forward to them and want to see whether or not--I
17 mean, even though these are not minor issues, as
18 Jay is hand waving to me, in any clinical trial it
19 is really important of course, and I think it does
20 reflect part of what is going to happen to this
21 whole area as we get more used to thinking of it in
22 these terms.
23 DR. LANZENDORF: Right.
24 DR. SALOMON: Dr. Sausville?
25 DR. SAUSVILLE: Actually, before my

1 question I just have a comment. I would simply
2 state that people have wildly different takes on
3 what their view of reasonability is in terms of
4 going after this. It is well documented in my own
5 field that in cancer susceptibility testing that
6 some people just don't want to know.
7 DR. LANZENDORF: Right.
8 DR. SAUSVILLE: And one has to respect
9 that. Actually, the reason I was pushing down the
10 button is that I wanted to actually return a little
11 bit to the data that was in your presentation,
12 specifically the more recent experiments of Dr.
13 Brown.
14 DR. LANZENDORF: That was a small amount
15 of work that a clinical fellow did before he
16 departed. It has not been published. We thought
17 the numbers were too low to even publish. So, it
18 was just an effort of going through my files,
19 trying to find information that I thought--
20 DR. SAUSVILLE: And I appreciate your
21 candor in showing us the preliminary nature of the
22 data, but I did want to try and go back to I guess
23 the three slides that talk about the difference
24 between controls and shams. So, I guess,
25 recognizing the numbers are small in terms of

1 statistics, the slides that have the fertilization
2 results, lead me through the clear evidence that
3 there is even a suggestion of an effect of the
4 cytoplasmic transfer as opposed to the sham
5 procedure. I am showing my ignorance in the field.
6 DR. LANZENDORF: Evidence that it helped?
7 DR. SAUSVILLE: Right.
8 DR. LANZENDORF: There was no evidence.
9 DR. SAUSVILLE: Right, so one has to be
10 concerned, therefore--and maybe we will hear from
11 other speakers--that the underpinnings either
12 historically or currently are somewhat
13 questionable.
14 DR. LANZENDORF: Right, I agree.
15 DR. SAUSVILLE: I wanted to make sure I
16 wasn't missing anything.
17 DR. SALOMON: I guess I get to be blunt.
18 Why would you do this? I don't get it.
19 DR. LANZENDORF: Why would we do the
20 procedure?
21 DR. SALOMON: Yes, I mean I don't see any
22 data, and it is very early in the day and this is
23 not my field, but so far from what you presented, I
24 wouldn't imagine doing this.
25 DR. LANZENDORF: That small study that I

1 presented at the end, again, was trying to
2 reproduce that first study with immature eggs.
3 When we are doing this procedure for patients, for
4 the patients that we did it wasn't an immature egg
5 issue. Again, when I said it didn't help, it was
6 not helping immature eggs. To me, there is no data
7 out there yet that shows that it does or does not
8 help mature eggs.
9 DR. SALOMON: What is the data that it
10 helps? I mean, you showed us data from the older
11 mothers. Right?
12 DR. LANZENDORF: Right.
13 DR. SALOMON: And that, you said, didn't
14 show any difference. Right? Then the second thing
15 you showed us was the data from three women who had
16 had a history of non-successful implantation and
17 pregnancy. Right? I hope I am using the right
18 terms. One of those gave birth to the twins.
19 DR. LANZENDORF: Right.
20 DR. SALOMON: Was that just a statistical
21 blip? Or, that one set of three, is that the data?
22 DR. LANZENDORF: That is why we need more
23 data. I mean, was it just her time? If it had
24 been a regular IVF she could have got pregnant.
25 So, it may have just been her time. I am not

1 saying that any of this supports that the procedure
2 actually does something.
3 DR. SCHON: One of the peculiarities of
4 the IVF field is that it is largely patient driven,
5 and if somebody put on the internet, for example,
6 that extracts of dentine were found to improve
7 pregnancy rates, I would venture to say that people
8 from all over the world would be calling and asking
9 for that procedure to be done. That is the history
10 of this field. Many things are done without any
11 evidence-based medicine traditionally used in other
12 studies or without any validation and that is why
13 we are here today. That is part of the nature of
14 this field from day one.
15 DR. VAN BLERKOM: Your comment about some
16 patients may go through nine cycles before being
17 successful. You described a particular pattern of
18 severe dysmorphology in embryonic development in
19 patients that you thought this might help. Is it
20 possible that patients who show significant
21 consistent dysmorphology in embryonic development
22 nonetheless become pregnant after six, seven,
23 eight, nine cycles?
24 DR. LANZENDORF: No, I would have to pull
25 out the stats.

1 DR. VAN BLERKOM: We just don't know the
2 answer?
3 DR. LANZENDORF: No. We can maybe find
4 out. There are programs out there with thousands
5 and thousands of patients and, you know, it might
6 be interesting to look. Of those patients who
7 finally got pregnant after their ninth attempt, did
8 they have a history of poor morphology.
9 DR. SCHON: I can answer that from my
10 experience. We had a patient from Israel who had
11 18 attempts at IVF in Israel and all failed. I
12 think this was about six years ago. Her 19th
13 attempt in our program and she had twins.
14 DR. LANZENDORF: It could have been the
15 program.
16 DR. SCHON: It could have been the program
17 or it could have been something else. That is the
18 point. When you have consistent failures, the
19 question is are the failures consistent with your
20 program or are they from other programs. So, are
21 the objective criteria that you use and someone
22 else uses the same?
23 DR. LANZENDORF: Right.
24 DR. SCHON: That is really the problem
25 because if you are evaluating performance of

1 embryos in vitro from different programs, there is
2 no standard objective criteria. It is empirical.
3 So, what looks bad to you may not look so bad to
4 somebody else; and what looks terrible to you may
5 not look terrible to somebody else. And, that is
6 part of the problem in this field. It is
7 empirically driven.
8 DR. LANZENDORF: Right, but it could have
9 been the method of transfer that finally got her
10 pregnant, if the way they were transferring changed
11 over time or something like that.
12 DR. RAO: Maybe this will sound naive, but
13 in your opinion then what kinds of cases would you
14 actually look at for cytoplasm transfer?
15 DR. LANZENDORF: Cases where there is
16 documented poor morphology over repeated IVF
17 attempts, where the patient was younger than 40
18 years of age is what I think should be looked at.
19 One of the reasons we included the 40 and over in
20 the study is because many of the patients who are
21 trying to achieve a pregnancy are of that age
22 group, and you could not convince them that you
23 didn't think it would work for them. We have done
24 this in eight patients. Still we have patients who
25 want to do it even though we have shown that, but I

1 think we need to stop focusing on that age group.
2 DR. RAO: Let me extend that, poor
3 morphology in a young age group, where you mature
4 the eggs in culture?
5 DR. LANZENDORF: No, in vivo.
6 DR. RAO: In vivo, and you will then
7 select those eggs and look at those which have poor
8 morphology.
9 DR. LANZENDORF: You do the cytoplasm
10 procedure on all of the eggs at the time of
11 fertilization.
12 DR. RAO: You just do it on all and then
13 just pick the best.
14 DR. LANZENDORF: Yes, and on the day of
15 transfer, what we typically do with any patient is
16 we decide how many will be transferred, and then
17 transfer the ones with the best morphology.
18 DR. MULLIGAN: I actually have a different
19 question but just in response to his point, I am
20 still missing the line of reasoning for the context
21 in which you say that this might be the most
22 useful. I mean, you said that basically there is
23 really no data out there, yet when you are asked,
24 well, what specific context would you think this
25 would be most useful in, is that completely

1 independent of the fact that there is no data?
2 DR. LANZENDORF: That is my hypothesis.
3 DR. MULLIGAN: And the hypothesis is that
4 ooplasm could be useful but you would agree that
5 there is no data?
6 DR. LANZENDORF: I agree.
7 DR. MULLIGAN: Just scientifically, I find
8 it a little odd that that 1990 study just kind of
9 disappeared. Does anyone know what happened to the
10 people who did this? That is, did they do this and
11 then have a train wreck or something?
12 DR. LANZENDORF: Dr. Flood is practicing
13 IVF in Virginia Beach, down the street from us. I
14 could try to talk to her. Three of the other
15 people are not in this country. Gary Hodgins is
16 retired for medical reasons.
17 DR. MULLIGAN: You know, scientifically,
18 usually when something like this does happen there
19 is a paper and you could look at something and say
20 that is very interesting. If you see no report in
21 the next four or five years, certainly in my field,
22 it means something. So, I am just curious. It
23 would probably be very useful to try to track these
24 people and see. Can you do literature searches?
25 Did they eve publish anything on this?

1 DR. LANZENDORF: No, I know they didn't.
2 I was doing my post doc somewhere else so I had
3 very little information.
4 DR. VAN BLERKOM: These were probably
5 clinical fellows doing a paper for clinical
6 fellowship.
7 DR. LANZENDORF: Right.
8 DR. VAN BLERKOM: But it was preceded in
9 the '80s and '70s by work in mice and other
10 species, by the way, and it was really designed in
11 the mouse to look at cell cycle regulation, cell
12 cycle checks which led to the discovery of factors
13 involved in the maturation of their egg and their
14 timing. So, these guys just looked at it in the
15 monkey, again looking for whether or not
16 cytoplasmic factors from one stage would induce
17 maturation or assist maturation in other eggs.
18 That is all. There is a precedent for this type of
19 work in mouse and lots of other invertebrates.
20 DR. MULLIGAN: At that point, was there
21 impact upon the work?
22 DR. VAN BLERKOM: No.
23 DR. MULLIGAN: No one really read the
24 paper or thought it was interesting?
25 DR. VAN BLERKOM: No, there was no point

1 to it. I mean, it was just a confirmation that as
2 in the mouse, as in starfish, as in sea urchins
3 there are factors in the cytoplasm that are
4 spatially and temporally distinct and are involved
5 in miotic maturation of the egg, period.
6 DR. SALOMON: I was told by Gail that
7 there is someone in the audience that wanted to
8 make a comment. If so, I didn't want to exclude
9 them. If you could please identify yourself?
10 DR. WILLADSEN: I am Steen Willadsen. I
11 work as a consultant at St. Barnabas, the Institute
12 of Reproductive Medicine and Science. It was
13 actually something else I wanted to comment on.
14 It was the statement from, I think,
15 Jonathan Van Blerkom that the IVF work is patient
16 driven. I don't basically disagree with that. So
17 is cancer treatment. But he then went on to say
18 that all sorts of things were being offered that
19 had no scientific background, or at least suggested
20 that. I would disagree with that. I would
21 disagree that all sorts of things are being
22 offered. I don't think there are that many things
23 that are being offered.
24 Since I have the microphone, I think I
25 should say also that the people on the committee

1 are very much concerned about how clinical trials
2 should be conducted. Therefore, you focus on
3 whether all the things are in place for that when
4 you hear about research. Therefore, it sounds
5 strange and looks like a big jump, here we go from
6 experiments with monkeys and then nine years later,
7 or whenever it is, suddenly it happens in humans
8 and looks to you as if the duck hasn't been moving,
9 so to speak, but in fact there has been a lot of
10 paddling going on. The first mammalian cloning
11 experiments were successful were in 1984 or 1985
12 and, yet, Dolly was in 1996 and in between it
13 looked like it had kind of gone dead. Not at all.
14 There was plenty of work going on, but that doesn't
15 mean that it would be worth publishing. It might
16 be for you because you are interested in the whole
17 process of how this is controlled; what steps
18 should be taken from the administrative level. But
19 that is not how research is done in basic
20 embryology. Thank you.
21 DR. SALOMON: Thank you. Well, you have
22 to understand we look forward and we ask our
23 questions to discover what has been going on that
24 has not been published, as well as what has been
25 published. The question, if you remember, that was

1 asked was what happened between 1990 and 1997 and
2 if there were things going on that weren't
3 published that were pertinent, that is the time to
4 hear about them. We certainly understand the fact
5 that much goes on that doesn't come to the public.
6 But now when you want to step up and start doing
7 clinical trials, it is time to think about those
8 things.
9 I want to thank Dr. Lanzendorf. You have
10 shouldered a bigger responsibility--
11 DR. LANZENDORF: Thank you.
12 DR. SALOMON: Oh, I am sorry, there is
13 someone else from the audience.
14 DR. MADSEN: I Pamela Madsen. I am the
15 executive director of the American Infertility
16 Association and I do represent the patients, and I
17 am a former patient and a former infertile person.
18 It is an echo but I decided the echo
19 should come from the patient organization in
20 response to the gentleman from St. Barnabas. Yes,
21 it is patient driven. I was going to use the exact
22 same model of the cancer patient who doesn't have
23 hope. These patients, you have to be clear, are
24 looking for certain technologies. There isn't
25 anything else being offered to them and you really

1 need to be clear about that. These patient groups
2 are looking for these technologies. IVF is not
3 working for them and their only other hope, if they
4 want to experience a pregnancy, is donor egg. That
5 is all they have and you need to be clear about
6 that.
7 You also really need to be clear that when
8 you are looking at small data sets, and I am not a
9 clinician, not a doctor or a scientist so forgive
10 me, these are very small data sets because you have
11 stopped the research and, as patients, we want to
12 see the research. We want there to be bigger data
13 sets, and there are lots of patients who are very
14 eager to have a chance at this research. We need
15 to continue and I thought you should hear that
16 again from a patient as well as the clinicians.
17 Thank you.
18 DR. SALOMON: I appreciate that.
19 Certainly, one of the things I want to reiterate
20 here is that anyone who is here today, part of your
21 responsibility is to make sure that we are being
22 appropriately sensitive to all the public
23 stakeholders in this area as we venture into this
24 conversation, both to have a sense of how it is
25 practiced in the clinical field--you know, I said

1 in your experience do you feel comfortable and your
2 answer was, yes, you do. That is the kind of thing
3 that we need to hear and be reassured on, and the
4 same thing from patient advocacy groups and
5 research advocacy groups. If you feel like we have
6 veered off a line that is sensitive to the state of
7 this field, then it is very appropriate to get up
8 and remind us.
9 Again, thank you very much, Dr.
10 Lanzendorf. That was excellent; a good start. We
11 will take now a ten-minute break and start again.
12 [Brief recess]
13 DR. SALOMON: We can get started. Before
14 we go on with the regular scheduled presentations,
15 it is a special pleasure to introduce Kathy Zoon,
16 who is--I know I will blow this--the director of
17 CBER. My only concern was not to promote her high
18 enough!
19 DR. ZOON: Dan, thank you and the
20 committee very much for giving me an opportunity to
21 come here today. I apologize that I couldn't be
22 here this morning to speak to you but we were
23 working on some budget issues at FDA. I know you
24 can understand that.
25 I would like, in a few minutes, to give

1 the committee and the interested parties in the
2 audience an update on CBER's proposal for a new
3 office at the Center for Biologics. This new
4 office has the proposed title of the Office of
5 Cell, Tissue and Gene Therapy Products, something
6 very close to the heart of this committee. One
7 might ask why is CBER doing this. CBER is doing
8 this because there are many issues regarding
9 tissues and the evolution of cell and cell
10 therapies and gene therapies that we see as an
11 increasing and expanding growth area for our
12 Center. Rather than reacting when it gets ahead of
13 us, CBER has always taken the position of being
14 proactive, trying to establish an organizational
15 structure and framework so that we can be ready to
16 deal with tissue-engineered products, regular
17 cellular products, banked human tissues, repro
18 tissues and, of course, the topic of today,
19 assisted reproductive tissues.
20 We have gotten the go-ahead from Deputy
21 Commissioner Crawford and Secretary Thompson to
22 proceed on this office, and we are very much
23 engaging in the communities of all affected people,
24 especially our committee who has had to deal with
25 so many issues to get your feedback and advice

1 because we want to do this right. We want to make
2 sure that we have as much input when we go in to
3 finalizing the structure and functions of this
4 office to do the very best job we can. We
5 recognize that this will be an evolution for all of
6 us because we are still evolving with our tissue
7 regulations as rules, as well as the sciences
8 surrounding cellular therapies and tissue
9 engineering, and we very much understand that but
10 we believe it is time to be prepared and move
11 forward and get ready for this area.
12 So, my plea at this point is, please,
13 provide the advice; certainly, those in the
14 audience as well that have an interest in this
15 area. We are very much interested in hearing from
16 you. There are two e-mail addresses for those who
17 might wish to do it through e-mail. It is
18 zoon@CBER.FDA.gov. Then, Sherry Lard who is the
19 associate for quality assurance and ombudsman at
20 FDA is also taking comments in case people prefer
21 to remain anonymous because that is important. Her
22 e-mail address is lard@CBER.FDA.gov. If you prefer
23 not to e-mail and you prefer to call, the numbers
24 are on the HHS directory off the web site, if you
25 want to find any of us.

1 We are very happy and very pleased that
2 this committee would deliberate and think about
3 this, and I will be looking forward. The time line
4 for this new office, we hope to have as many
5 comments as possible by the end of May. We would
6 like to finalize the structure and functional
7 statements probably in June, and then work on the
8 issues that are administrative to moving the office
9 forward, and are looking forward to an
10 implementation date of October 1, which is the
11 beginning of the fiscal year. So, just to give you
12 a sense of the dynamics and the organization. It
13 is a goal. We are hoping that we can achieve this
14 goal and that is where we are focused on.
15 So, I am very happy to have the
16 opportunity today to be here and present this
17 proposal to you, as well as receive your feedback.
18 Thank you.
19 DR. SALOMON: Thank you very much, Dr.
20 Zoon. Tomorrow when we have some time because I
21 see today as being very busy, we will try and find
22 some time as a group to discuss this just as an
23 initial thing, because I am interested in some
24 thoughts that everyone has. That is not to mean
25 that anything else can't go on informally or

1 formally otherwise.
2 Just one question, it is a pretty big
3 deal, how often do you guys make new offices like
4 this?
5 DR. ZOON: We sometimes create new
6 offices. In fact, over the past probably three
7 years we have elevated the Division of
8 Biostatistics and Epidemiology, which is
9 responsible for our statistical reviews at the
10 Center as well as for overseeing adverse events, we
11 have elevated that office, led by Dr. Susan
12 Ellenberg, to an office level. Most recently, we
13 broke out our information technology group, which
14 was an office under an office, as a separate
15 office. This one is more complicated because it
16 takes the experiences in both the Office of
17 Therapeutics that is relevant and the Office of
18 Blood that had a lot of the tissue programs and
19 tissue activities, and moving people together as
20 appropriate. So, this is a much bigger
21 reorganization, more complex. The last big one we
22 did was in 1993.
23 DR. SALOMON: That is more what I was
24 thinking. I mean, my initial response is that this
25 is a remarkable recognition of where this field has

1 gone in the last five to ten years. We are talking
2 now about such a myriad of studies going from
3 neural stem cells to xenotransplantation to islet
4 transplantation to gene therapy of various sorts,
5 all of which have been major touchstones for public
6 comment and regulatory concerns. So, I think this
7 is a really big deal and we appreciate the
8 opportunity to hear about it and also to give you
9 some input constructively while it is being
10 developed. Thank you, Dr. Zoon.
11 It is my pleasure to introduce Dr. Jacques
12 Cohen, from the Institute for Reproductive Medicine
13 and Science of St. Barnabas, and to get back to
14 today's topic of ooplasm transfer. Dr. Cohen?
15 Ooplasm Transfer
16 DR. COHEN: Good morning. Thank you, Mr.
17 Chairman. Thank you for your kind invitation.
18 For my presentation I will follow or try
19 to follow the guidelines for questions that the
20 BRMAC has asked in this document that I found in my
21 folder. But I will deviate from it now and then.
22 First of all, I would like to acknowledge
23 three individuals, two of them are here, that have
24 been crucial for this work, Steen Willadsen who,
25 about twelve years ago or so, suggested that there