

UNITED STATES FOOD AND DRUG ADMINISTRATION

PUBLIC WORKSHOP

SCIENTIFIC EVIDENCE IN DEVELOPMENT OF HCT/PS
SUBJECT TO PREMARKET APPROVAL

Silver Spring, Maryland

Thursday, September 8, 2016

1 PARTICIPANTS:

2 Welcome/Opening Remarks:

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4 Deputy Center Director of the Center for
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7 Session 1: Keynote and Regulatory Scheme

8 IRVING WEISSMAN, M.D.
9 Stem Cell Biology and Regenerative Medicine

10 STEVEN BAUER, PH.D.
11 FDA Perspectives on Scientific Evidence and
12 HCT/P Development

13 Session 2: Experiences in Product Development

14 JACQUES GALIPEAU, M.D.
15 How Mechanistic Studies on Mesenchymal Stromal
16 Cells Inform Design of Human Clinical Trials for
17 Autoimmune Ailments - The Fitness Paradigm

18 MICHAEL MATTHAY, M.D.
19 Mesenchymal Stem Cells for Treatment of ARDS
20 Patients: Challenges and Lessons Learned in
21 Pre-Clinical Testing, FDA Approval, and
22 Ongoing Clinical Trial

GREGORY RUSSOTTI, PH.D.
Drivers and Methodologies for Making Cell Therapy
Process Changes

DENNIS CLEGG, PH.D.
Development of ES-Derived Retinal Pigmented
Epithelium on a Scaffold for Age-Related Macular
Degeneration

CHRISTOPHER BREUER, M.D.
The Development and Translation of the Tissue
Engineered Vascular Graft: From the Bench to the
Bedside and Back Again

1 PARTICIPANTS (CONT'D):

2 Session 3: Views from Professional Societies

3 JONATHAN KIMMELMAN, PH.D.
4 Ethics, Evidence, and Regulatory Approval
For Cell-Based Interventions

5 MASSIMO DOMINICI, M.D.
6 Dissecting Unproven Cellular Therapies:
The International Society for Cellular
7 Therapy (ISCT) Position

8 PETER RUBIN, M.D.
Clinical Adipose-Based Therapies

9 Session 4: Views from Other Government Agencies

10 KRISTY POTTOL
11 Delivering Mission Ready Medical Solutions to
the Warfighter

12 MARTHA LUNDBERG, PH.D.
13 Enabling Development of Regenerative Medicine
Technologies and Therapies at the NHLBI

14 Session 5: Patient and Society Experience and
15 Expectations

16 JEFFREY KAHN, PH.D.
17 Societal Perspectives on Development and
Oversight of Novel Cell-Based Therapies

18 BRIAN MANSFIELD, PH.D.
19 Perspectives of Stem Cell Therapy for Orphan
Inherited Retinal Dystrophies

20 THOMAS ALBINI, M.D.
21 Severe Visual Loss After Intravitreal Injection
Of Autologous Adipose Tissue-Derived Stem Cells
For Age-Related Macular Degeneration

22

1 PARTICIPANTS (CONT'D):

2 MICHAEL MILLER, M.D., PH.D.
3 Glioproliferative Lesion of the Spinal Cord
4 Arising from Exogenous Stem Cells

5 Closing Remarks:

6 IRVING WEISSMAN, M.D.

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

2 (8:40 a.m.)

3 DR. WITTEN: Good morning. I think we
4 will get started. My name is Celia Witten. I'm
5 the Deputy Center Director of the Center for
6 Biologics Evaluation and Research here at FDA.
7 I'd like to welcome you to our public workshop on
8 Scientific Evidence in Development of Human Cells,
9 Tissues, and Cellular and Tissue-Based Products,
10 known as HCT/Ps, that are subject to premarket
11 approval.

12 The purpose of this workshop is to
13 identify and discuss scientific considerations and
14 challenges to help inform the development of
15 HCT/Ps regulated as biologic products and subject
16 to premarket approval, including stem cell-based
17 products.

18 As you may be aware, next Monday and
19 Tuesday, we are holding a Part 15 public hearing
20 on the draft guidances related to the regulation
21 of HCT/Ps. We have received some questions on how
22 the Part 15 hearing relates to this workshop.

1 The purpose of the public hearing is to
2 obtain comments on four draft guidance documents
3 that were issued to provide clarity about FDA's
4 existing regulatory framework for HCT/Ps. The
5 purpose of this workshop today is to discuss
6 scientific considerations in the development of
7 HCT/Ps that based on the regulatory framework are
8 regulated as biologic products and require an IND
9 or BLA.

10 During today's workshop we are going to
11 hear from a number of distinguished speakers. In
12 Session 1, Dr. Irv Weissman will provide our
13 keynote address covering stem cell biology and
14 regenerative medicine.

15 Following his presentation, Dr. Steven
16 Bauer will provide an overview of the regulatory
17 framework for 351 HCT/Ps and FDA perspectives on
18 scientific evidence and HCT/P development.

19 During Session 2, speakers will provide
20 an overview of their experiences in product
21 development and describe challenges, scientific
22 questions, and lessons learned.

1 Following Session 2, the speakers will
2 engage in a panel discussion, and the audience
3 will have the opportunity to ask questions of the
4 panel members.

5 In Session 3, we will hear views from
6 professional societies. In Session 4, we will
7 hear from representatives of government agencies
8 on how their respective agencies advance product
9 development, and finally in Session 5, we will
10 hear from a bioethicist, a patient representative,
11 and two physicians about patient and public
12 expectations.

13 Following Session 5, there will be a
14 panel discussion with the speakers for Sessions 3,
15 4, and 5.

16 To end the day, Dr. Weissman will
17 provide some closing remarks.

18 Before I turn the floor over to Dr.
19 Weissman for his keynote address, there are a
20 couple of housekeeping items. Restrooms are
21 located in the hallway outside of this conference
22 room. Lunches, snacks, and beverages can be

1 purchased at the kiosk close to the registration
2 desk.

3 With that, I'd like to welcome Dr. Irv
4 Weissman. Just to provide a brief introduction,
5 Dr. Weissman is the Director of the Stanford
6 Institute for Stem Cell Biology and Regenerative
7 Medicine, and Director of the Stanford Ludwig
8 Center for Cancer and Stem Cell Research.

9 He is a member of the National Academy
10 of Sciences, the Institute of Medicine at the
11 National Academy, and the American Association of
12 Arts and Sciences.

13 He will give the keynote presentation
14 today. Thank you. *SESSION 1: KEYNOTE AND

15 DR. WEISSMAN: Thanks, Celia. Stem cell
16 biology is actually very simple. The difference
17 between a stem cell in the tissue and all other
18 cells in the tissue is that when a stem cell gives
19 rise to say on average two cells, one of the two
20 on average is a stem cell. Still, that is stem
21 cells are distinguished from any cell downstream
22 from the stem cell because they are the only ones

1 that self-renew, and in the whole blood forming
2 system, the hematopoietic stem cell is the one
3 that self-renews.

4 Years ago, we wanted to be able to
5 identify, isolate, and then transplant first in
6 mice and then in humans, the hematopoietic stem
7 cell. It turns out that is the only cell in the
8 bone marrow that regenerates the blood. If you
9 take away the stem cells and transplant everything
10 else, it lasts for about eight weeks.

11 So, if you want a permanent survival of
12 the cells and the biology and the medicine they
13 bring, stem cells are the important ones. For us,
14 the other cells are problematic in both autologous
15 transplants and allogeneic transplants.

16 Years and years ago, Mike McCune and I,
17 after we had isolated the mouse blood forming stem
18 cell by saving lethally irradiated mice with as
19 few as 100 of the cells versus 200,000 bone marrow
20 cells, we didn't get volunteer medical students to
21 say I want to be irradiated so you can find a stem
22 cell.

1 So, we put into immune deficient mice
2 human fetal bone, on the right, human fetal liver,
3 human fetal thymus, and found those organs in that
4 immune deficient mice would take, of course, and
5 then you irradiate those mice and put into them
6 the cell type that you think might be stem cells.

7 This is an old version. I'm sorry I put
8 in that gray background. If anybody wants the
9 slides afterwards, I'll get rid of the gray
10 background.

11 They lack markers of the B cell
12 myelomonocytic, T cell, and red cell lineage. You
13 can combine all the antibodies to those lineages,
14 make them green, with a green fluorescent protein
15 or fluorescein, and then positively select, and no
16 single marker on the surface will allow you to
17 isolate stem cells, no matter what people tell
18 you.

19 With a combination of markers, we could
20 isolate the cells. That was 1988. Then in the
21 humans, we found that very similar markers -- that
22 is mouse, that is human -- no B cell

1 myelomonocytic, T cell, red cell markers -- again,
2 very similar markers on the surface.

3 CD34 alone is not sufficient to purify
4 blood forming stem cells. So, the idea for
5 transplants is to take the blood forming tissue,
6 which in the beginning was bone marrow, but now we
7 know you can mobilize peripheral blood, many ways
8 to do it, the clinicians taught the scientists
9 that this could work, post-chemotherapy cells are
10 mobilized. If you give Cytoxan by itself, now
11 there is a whole panoply of things you can give to
12 a healthy patient and you mobilize stem cells, and
13 not just stem cells but many cells in the bone
14 marrow into the blood. Also, marrow or mobilized
15 peripheral blood or umbilical cord blood.

16 The one thing you should know is that
17 hematopoietic stem cells make blood and only
18 blood, no matter what anybody tells you. Every
19 time we have tested with mouse or human,
20 hematopoietic stem cells make blood and only
21 blood. They don't make brain, they don't repair
22 heart. None of those other things that have been

1 claimed over the years. They don't
2 transdifferentiate under any circumstance to
3 become a brain forming or liver forming or gut
4 forming stem cell.

5 That means when you have a cancer
6 patient like somebody with metastatic breast
7 cancer, if you wanted to rescue them after high
8 dose chemotherapy, you don't give that mobilized
9 blood because over half the time you are giving
10 back the cancer after you have ablated their
11 immune system.

12 You want to get pure stem cells by a
13 cell sorting method. The current standard cell
14 sorter is a high speed cell sorter first developed
15 by the Herzenberg's, commercialized by
16 Becton-Dickinson, but there are a number of them
17 out there and of course, they have to be qualified
18 that they don't bring infections into the
19 operation, because you don't want LPS, infectious
20 agents and so on.

21 You can get pure hematopoietic stem
22 cells and they work in transplant, but they have

1 to be free of cancer if you are, for example, a
2 woman with metastatic breast cancer.

3 These are the results of the study.
4 These are either using single marker or CD34 or
5 two different commercial kinds of separators, and
6 the only thing that gives you 250,000-fold
7 depletion of breast cancer cells from the
8 mobilized blood is multiple marker, high speed
9 cell sorting, no solid device can get to that
10 purity because you get non-specific adherence of
11 the cells to part of the device, so it has to be
12 flow sorting at least so far.

13 What would you do if you had breast
14 cancer free or non-Hodgins lymphoma free or
15 myeloma free stem cells you try to transplant? I
16 formed a company called SyStemix, long gone, but
17 we isolated the blood forming stem cell, we
18 developed the sorters that were able to sort them,
19 and we did clinical trials in those three
20 diseases.

21 SyStemix was purchased by Sandoz and
22 that merged into Novartis, and eight years after

1 the initial purchase, they shut it all down in the
2 middle of a clinical trial.

3 Let me show you the results of at least
4 one of the clinical trials. This is the Stanford
5 clinical trial where we isolated cancer free
6 hematopoietic stem cells from women with
7 metastatic breast cancer, and they had to have
8 evidence of metastasis in bone or liver or lung,
9 the only exclusion was brain at the time this was
10 done, between 1996 and 1998.

11 There were 15 patients that we treated
12 in this way, and at that time, it was still
13 popular to give back mobilized peripheral blood
14 which by that time the bone marrow transplanters
15 erroneously called it stem cell transplant.

16 So, don't you believe anybody who says
17 they are doing a stem cell transplant unless they
18 are doing purified stem cells. They are doing
19 bone marrow or mobilized blood, and that
20 inaccuracy in the language accepted by the
21 journals, accepted by the bone marrow transplant
22 community, leads people astray who have memorized

1 their way to their field rather than being able to
2 understand the science and the questions that need
3 to be asked, hard questions, before you treat
4 patients.

5 So, it is now out 20 years for some, 18
6 for most. One-third of the women who were given
7 cancer free stem cells still today, I still follow
8 them, are cancer free. Mobilized peripheral blood
9 at 11 years, seven percent were cancer free.

10 Now, if that was a pill or a protein,
11 that would be a product, but the company that
12 bought us in 2000, roughly at this part of the
13 trial, made a business decision to move on to
14 other products to emphasize what they were doing.

15 That brings up a second point. What we
16 are trying to do is advance medicine for people.
17 The function of a company is to make a profit.
18 They are always going to be responsible to their
19 shareholders and their money first.

20 I personally believe after lots of
21 experience that we need a way to fund these kinds
22 of projects in competition at academic or

1 not-for-profit institutions until the end of a
2 phase 1 or phase 2 trial that tells you it is
3 safe, it is worth going forward, because the
4 amount of money isn't there, and the companies
5 have other reasons to exist.

6 By the way, it is statistically
7 significant both for progression free survival and
8 overall survival at all time points, and the only
9 place where this therapy now will be offered is at
10 Stanford. I gave away all the stock I had. I
11 negotiated on behalf of Stanford. We opened up
12 actually the day before yesterday a cell sorting
13 clinic, and we are beginning pure stem cell
14 transplants. I will talk about that more in a
15 minute.

16 Does the mouse predict the human in any
17 meaningful way? This is the time to get either
18 enough neutrophils or enough platelets to be safe
19 in a mouse for reconstitution. You get a dose
20 dependent survival, and at the dose that gives you
21 10 days to platelets or 10 days to neutrophils in
22 the mouse, it is about 10,000 hematopoietic stem

1 cells or on a weight basis, four times 10 to the
2 5th per kilogram.

3 Here is the breast cancer study. This
4 is the time to get to the 500 neutrophils per
5 microliter or 20,000 platelets per microliter, and
6 what you see is the break point is right about
7 here between 5 and 10 times 10 to the 5th.

8 I won a bottle of wine with our Chief
9 Medical Officer, Chris Yettner, who said mice do
10 not teach you about humans. In this case, it did.

11 Now, allotransplants bring another
12 issue, the T cells that are present contaminating
13 the mobilized blood or the bone marrow cause graft
14 versus host disease. The T cells have homing
15 receptors that take them to the lymphoid organs,
16 lymph nodes, spleen, and the activated cells go
17 back to the thymus, function we don't know yet,
18 but what means is the graft versus host disease
19 starts in the lymphoid organs. It destroys the
20 structure of the lymphoid organs. That is the
21 primary reason at least in animal models for the
22 immune deficiency that follows transplant, not

1 just the immunosuppression to get the transplant
2 in but the graft versus host disease.

3 You can put in, as Judy Shizuru did,
4 less than the number of T cells in a mouse model
5 of a matched unrelated donor that then would cause
6 systemic graft versus host disease, the one that
7 could be diagnosed, and of all doses of T cells,
8 the lowest dose she gave, there was a continuing
9 graft versus host disease reaction in the lymph
10 nodes and so on.

11 We wanted to get to pure stem cells to
12 get rid of graft versus host disease. We showed
13 in this mouse, no graft versus host disease with
14 pure hematopoietic stem cells, lots of T cells are
15 included. Mouse and pre-clinical for human, and
16 we are now set up to do the first clinical
17 transplants in human in allogeneic. It will be
18 severe combined immune deficient patients.

19 Now, God I hate this. This is terrible.
20 I put in gray so it would look good for you. So,
21 listen to what I say, and hopefully it will show
22 up on the graph.

1 We knew or we suspected that the genes
2 that cause autoimmune diseases like Type I
3 diabetes, multiple sclerosis, systemic Lupus, are
4 genes that are expressed in either the cells that
5 affect lymphocyte development, that is in the
6 blood forming system, or intrinsic defects in the
7 blood forming system, so that led to the idea that
8 if you could allotransplant stem cells from a
9 disease resistant donor, you might be able to
10 change the course of that disease.

11 Again, Judy Shizuru and I took mice that
12 had Type I diabetes, they get it four to five
13 months of age, we give them a lethal dose of
14 irradiation, we give them more antibodies to get
15 rid of the residual autoimmune T cells in their
16 bodies, then we transplant either whole bone
17 marrow from them, it buys a month, that is as far
18 as the transplant community has gone. That is the
19 Richard Burt protocol.

20 Pure stem cells from the NOD mouse, the
21 diabetic donor, buys another month, but stem cells
22 from a third party even a matched unrelated donor

1 prevents progression of the disease for life,
2 because stem cells self-renew.

3 Now they can deplete the T cells that
4 would cause the autoimmune attack on the insulin
5 producing islets because they have a system that
6 can do it. We even co-transplanted mice that had
7 been diabetic for six months with hematopoietic
8 stem cells and islets.

9 The reason behind that, and this is
10 probably the most important thing I can say, is
11 that hematopoietic stem cell transplant, when
12 successful, either as a partial chimera or a full
13 chimera, induces transplant tolerance of any other
14 organ, tissue, or tissue specific stem cell in
15 many, many animal trials.

16 It does so because the thymus depletes
17 autoreactive T cells, and it defines as
18 autoreactive those that will react against the
19 host, that is why you don't get GVH from the new T
20 cells coming up, and those that react against the
21 donor because the dendritic cells also deplete and
22 induce regulatory T cells that give you permanent

1 transplant tolerance.

2 So, if you are planning to transplant
3 organs like livers, kidneys, lungs, hearts, this
4 will be the preferred way if you didn't have to go
5 through the chemotherapy or the radiation that
6 takes you next to death for a transplant of
7 purified hematopoietic stem cells to work.

8 We want to replace genetically defective
9 systems. We want to induce tolerance to organs.
10 We want to treat autoimmune diseases. We also
11 have success in the Lupus model. At any point, we
12 can stop the progression.

13 If you want to gene modify, those are
14 the cells that are most efficient to gene modify
15 and the only cells that self-renew and therefore
16 fixing a sickle cell gene, you would have to use
17 it.

18 Now, we hope very soon to have the
19 alternatives of either donors that don't have
20 sickle or gene corrected self stem cells where
21 there is no immunologic barrier. The chemotherapy
22 is the problem.

1 To try to address that, we began looking
2 at antibodies that might deplete hematopoietic
3 stem cells, Agnieszka Czechowicz, Deepta
4 Bhattacharya, and I.

5 If you take a mouse that is severe
6 combined immunodeficient and you transplant 5,000
7 stem cells -- there it is right there -- that is
8 50 times the dose you need. You get one percent
9 chimerism because those are the only open niches
10 for stem cells. I will just say that's the
11 problem.

12 If we give one dose of an antibody that
13 depletes c-Kit positive cells and all
14 hematopoietic stem cells are c- Kit positive, just
15 one dose of the antibody in mice, we are up to 15
16 percent, and if we give three doses, we code so we
17 know the first transplant is red genotype, second
18 green and third blue, we got 80 to 90 percent
19 chimerism.

20 Now, that is in a clinical trial for
21 patients who have severe combined immunodeficiency
22 at Stanford. Amgen has supplied the antibody, AMG

1 191, which depletes monkey stem cells that share
2 the same c-Kit, and in our mouse, the human
3 hematopoietic stem cells, and we will be testing
4 first in human, this month it has been discussed
5 with CBER, I know, not by me but by Judy Shizuru
6 and Maria Grottsi, and Ron Parell, the first test,
7 is this going to work.

8 It's not going to be exactly this
9 protocol, but will it work. It's an important
10 advance if we can get rid of radiation and chemo,
11 but when we tried to do this -- this is the
12 depletion of stem cells in immune deficient mice,
13 the same antibody, only dropped one or two logs
14 the number of stem cells in immune deficient mice.

15 Another part of my lab had been working
16 with a "don't eat me marker" called CD47. It says
17 "don't eat me" to macrophages, and we found that
18 the antibody to that would allow macrophages to
19 eat cancer cells, and that is now in clinical
20 trials, phase 1 trials at Stanford in the U.K.

21 The antibody blocks the "don't eat me"
22 signal and endogenous eat me signals, calreticulin

1 is the primary one, lets the macrophage deplete,
2 but we found also that we could give a very strong
3 eat me signal if we provided human IgG1, whether
4 it's Rituxan or Herceptin, or Trastuzumab or
5 Pinatuzumab, they synergize by blocking the don't
6 eat me signal and providing a strong eat me signal
7 for the high infinity FC receptor for human IgG1.

8 Students in the lab said well, couldn't
9 we apply that in the mouse model to our
10 conditioning. When we give the antibody condition
11 where we have antibody to stem cell, antibody to T
12 cells, because now they are immune sufficient,
13 we're going to do a matched unrelated donor, plus
14 anti-mouse CD47, and only that combination leads
15 to full chimerism for life, and we are testing
16 them for immunological tolerance now.

17 Antibodies exist that have been tested
18 in humans to human CD47, they are well past the
19 safety stage. They can be delivered safely.
20 Antibodies to T cells exist. The Amgen 191 sees
21 human hematopoietic stem cells and precursors, so
22 you will lose some of that tan you got, but the

1 point here is that we are moving toward all
2 antibody conditioning.

3 It will be a partnership with the
4 investigators here at the FDA to bring that
5 through safely because once you can treat patients
6 with antibodies, it is likely to be in an
7 outpatient setting eventually, you change whether
8 you would put anybody through the risk, a newborn
9 with sickle cell or Type I diabetes, to have the
10 treatment. So, target removal, no radiation or
11 chemotherapy, antibody conditioning.

12 Now, I want to just bring up the point,
13 the reason that we have all argued so hard with
14 the groups that don't want us to do embryonic or
15 fetal stem cell research, is that embryonic stem
16 cells, human, whether they are taken from
17 pre-implantation embryos, or reprogrammed from
18 adult cells, can make all tissue types in a dish,
19 can they make all tissue stem cells?

20 Well, we have shown in fact that it can
21 be done. In the distant future, we will do that.
22 We needed to have - - yet another example, and I

1 want not to go over time.

2 I co-founded a company called StemCells,
3 Inc. with Fred Gage, David Anderson, Ann
4 Tsukamoto, and Nobuko Uchida. We isolated from
5 human fetal brains a cell subtype that has markers
6 I can tell you about, clears it away from all
7 cells in the fetal brain, they can be expanded at
8 least a million fold, they have been transplanted
9 into the brains of immune deficient mice. We
10 always want to go through a mouse model first to
11 see the biology of the cells.

12 This give rise to human cells, you see
13 the back one is mouse a year later, so you see
14 neurons, astrocytes, even neurons in the
15 cerebellum and the cerebral cortex when you do it
16 in newborn mice.

17 This is a picture of a mouse brain 47
18 weeks after transplant of pure human brain stem
19 cells. It is a ray gamma, that is a severe
20 combined immunodeficient mouse.

21 This is the subventricular zone where
22 stem cells reside. A year later, the human stem

1 cells are there, and like the mouse brain forming
2 stem cells, are dividing and self-renewing.

3 This is the olfactory bulb, which in the
4 mouse is critical for life, and those are human
5 cells migrating from this zone to the olfactory
6 bulb. That is an antibody to humans, and this is
7 the olfactory bulb showing the periglomerular
8 cells in human in exactly the right place.

9 We showed that human brain stem cells in
10 the context of a mouse brain in graft self-renew
11 in the appropriate place, migrate to the
12 appropriate places, and differentiate
13 appropriately. It is a whole science that is
14 going on there, and it led us to study lysosomal
15 storage disease in mice and then for humans,
16 Batten disease, and in Batten disease, they lose
17 their hippocampal structure, CA1, CA2, CA3, and
18 increasing doses of human cells into the mouse
19 model, neural protected, did not neural replace,
20 so the enzyme that was missing was made by the
21 human cells, secreted with six phospho-manos, and
22 retaken up into the disease cells, curing the

1 lysosomal storage disease.

2 It works in spinal cord injury, Aileen
3 Anderson, Brian Cummings, so long as you don't
4 severe the spinal cord, you have a contusion, you
5 can transplant above and below, all the brown dots
6 are human cells, transplanted 30 days after the
7 spinal cord injury. They were paralyzed. The
8 paralyzed mice, this is a large scale of their
9 walking behavior, stay paralyzed if you put in
10 mesenchymal stromal cells, which many people call
11 mesenchymal stem cells, but they can't
12 differentiate. Neural stem cells, they are
13 walking perfectly normal.

14 Human cells are exquisitely sensitive to
15 diphtheria toxin. Brian Cummings gave them
16 diphtheria toxin. They were immediately
17 paralyzed, and the re-myelinated axons in the area
18 of the injury, because the cells in an ischemic
19 injury like spinal cord injury, the cells that are
20 in the ischemic region that have their cell
21 bodies, not their cell processes, die.

22 They have naked axons going through the

1 region, the sensory neurons in the muscle, in the
2 leg, go through, and they are re-myelinated by the
3 human cells, but once you give diphtheria toxin,
4 they are gone. This is the mesenchymal stromal
5 cells or mesenchymal stem cells, they just sit in
6 a pocket. They don't become neurons.

7 I am told, but I don't study it myself,
8 they have anti-inflammatory properties. So, it is
9 a cell therapy and one that I know you probably
10 know more than I do, and that was done in clinical
11 trials, and for thoracic spinal cord injury, half
12 of the patients who has Asia A regained sensation.

13 However, this year, just a few months
14 ago, the company closed down when it ran out of
15 money in the middle of trials, and I'm willing to
16 talk about that but I am going to finish this very
17 briefly.

18 We know that a fertilized egg gives rise
19 to a pre-implantation blastocyst. In the middle
20 of that are the inner cell mass, and each of those
21 cells have the potential to give rise to all cell
22 types in the body, and all embryonic stem cell

1 research began by learning how to culture them,
2 but they go through tissue stem cells to make
3 liver, pancreas, brain, blood, and so on.

4 We published last month in Cell that we
5 can make from human embryonic stem cells or human
6 induced pluripotent stem cells, stem cells for the
7 liver, that was two years ago, bone cartilage stem
8 cells, verified, skeletal muscle stem cells, and
9 cardiomyogenic stem cells in five to seven days.

10 You can massively expand the human ESCs,
11 so cell number isn't a problem, cell sorting and
12 cell differentiation becomes the issue. You don't
13 want any of the pluripotent cells left behind
14 because they cause teratomas.

15 This is a mouse that received the bone
16 cell, and there is bone that comes from it.

17 So, what I have told you is that there
18 are tissue specific stem cells. Every tissue we
19 have looked for it, we found it. You can purify
20 them from other cells. The purified cells are the
21 only cells with the life-long regenerative
22 potential. If you can combine hematopoietic stem

1 cells and one of these other tissue stem cells,
2 say bone and cartilage or cardiomyogenic or
3 skeletal muscle, the hematopoietic stem cell can
4 induce tolerance from the same donor tissue.

5 Instead of waiting for somebody to die
6 for a liver transplant, in the future, not now, in
7 the future, we expect to be able to get liver stem
8 cells and hematopoietic stem cells from the same
9 donor, in this case, an embryonic or induced
10 pluripotent stem cell line.

11 We expect to condition the patients with
12 antibodies, not chemotherapy and radiotherapy, so
13 we don't have a primary anti-cancer reason for
14 putting people through a bone marrow or a
15 mobilized blood transplant, we don't have graft
16 versus host disease, so what I hope I have shown
17 you is that the science of the past and the
18 science that is going on now should change the
19 future.

20 The future of not having to hospitalize
21 everybody who gets a bone marrow transplant to
22 treat their graft versus host disease, to keep

1 them away from infections, to give them life-long
2 immunosuppression, should make the cost of
3 medicine cheaper, so long as those who
4 commercialize it try to remember that although
5 their function is to make a profit, the most
6 important thing we can do is to change medicine
7 for people.

8 Thank you. (Applause)

9 DR. BAUER: Thank you, Irv. We have a
10 few minutes for some questions if anybody has some
11 for Irv. (No response) No questions. Thank you,
12 Irv. That was very nice. We will move ahead.

13 My name is Steve Bauer. We just heard
14 some very, very eloquent science, starting off
15 with a perfect illustration of how important that
16 can be in thinking of how to develop products,
17 establishing proof of concept in animal studies,
18 and helping facilitating bringing the important
19 next generation medicines into the clinic.

20 I am part of the FDA Office that
21 regulates a large number of the kinds of products
22 that we will be concentrating on today, so I'm in

1 the Center for Biologics Evaluation and Research,
2 and the Office of Cellular, Tissue, and Gene
3 Therapies. I am going to be talking about FDA
4 perspectives on scientific evidence and
5 development of these HCT/P products.

6 I think in order to understand how
7 important science really is in this endeavor, you
8 need to understand a bit about the regulatory
9 framework that is established through laws,
10 regulations, and guidance, and how that important
11 aspect of science interacts with the regulatory
12 framework, and talk about regulatory science, so
13 the second part of my talk will be that. I'll
14 summarize with a few highlights, and at the end,
15 leave a few slides up with some resources and
16 contact information for people who want further
17 information.

18 As I sort of just alluded to, in the
19 U.S., we have a three-tiered system that is based
20 on statutes or laws, and these are acts of
21 Congress and they are signed by the President, so
22 those are the underpinning legal authorities under

1 which the FDA acts, and two important ones are the
2 Food, Drug, and Cosmetic Act and the Public Health
3 Service Act.

4 Based on those, we have regulations that
5 are actually written by the FDA but approved by
6 the Executive Branch, and we see those in the CFR,
7 and you will hear me quote from the CFR, Code of
8 Federal Regulations, as we go through a little bit
9 today. I'll try not to do that too much, but I do
10 think it is important that people understand where
11 these things come from.

12 Then there is guidance, and this is
13 FDA's interpretation of the regulations, and those
14 are written and approved within FDA. They are
15 intended to facilitate product development and
16 understanding by people who want to bring things
17 before the FDA, and it's advice that is non-
18 binding on the FDA or the sponsor.

19 HCT/Ps are biologics. I put up the USC
20 Code that gives the definition. I won't go
21 through that. Since the topic today is HCT/Ps, I
22 put that up there. That is from 21 CFR Section

1 1271. That is the sort of scope of today's
2 meeting. We are talking about products that
3 include human cells, tissues, and cellular and
4 tissue based products. You will hear this term
5 "HCT/Ps."

6 These are articles containing or
7 consisting of human cells or tissues intended for
8 implantation, transplantation, infusion, or
9 transfer into a human recipient.

10 Within the U.S., we have this paradigm
11 for medical product regulation based on
12 centralized authority, that is the FDA. We look
13 at the entire life cycle, which I'll explain in a
14 little more detail in a few minutes, from the
15 investigational product stage to actually
16 marketing and then post-marketing surveillance and
17 study of products.

18 We look at it from the first clinical
19 trials, and even beforehand, to post-marketing.
20 This is all done within applicable laws, and FDA
21 does have enforcement provisions, and these apply
22 to clinical investigations and marketing

1 authorization.

2 The documents, the policies and
3 guidelines are freely available to the public, and
4 you can find them in the Federal Register or FDA
5 guidance documents, and we intend there is as much
6 transparency, and there are fora for public
7 discussion. These include FDA advisory
8 committees, public workshops, such as this one,
9 and sometimes interactions with the NIH RAC.

10 The regulatory approach for HCT/PS is a
11 tiered and risk based framework, so tissues and
12 cells that are highly processed and used for other
13 than their normal function and sometimes combined
14 with non-tissue components or used for metabolic
15 purposes are considered to be higher risk, so they
16 are regulated with more oversight, and they
17 require demonstration of clinical safety and
18 effectiveness, pre-market review, and the
19 pertinent regulations are written down there. I
20 won't read that.

21 More conventional tissue grafts that
22 undergo little processing used for their normal

1 function, these are perceived as lower risk and
2 can be regulated solely under Section 361 of the
3 Public Health Service Act, and are meant to help
4 prevent communicable disease transmission.

5 361 HCT/Ps, products can be regulated
6 providing they meet all of these following
7 criteria, not more than minimally manipulated,
8 intended for homologous use only, and not combined
9 with another article, and not have a systemic
10 effect, and not dependent upon the metabolic
11 activity of living cells, or have systemic effect
12 or is dependent upon the metabolic activity of
13 cells for its primary function, and is for
14 autologous use, allogeneic use, and first degree
15 or second degree blood relatives or reproductive
16 use.

17 So, that is the world of 361 HCT/Ps. We
18 are focusing on the ones -- I've given you a few
19 examples of the 351 HCT/Ps that are in that higher
20 risk category and regulated in the pathways that
21 I'll be going through in a few seconds in my talk.

22 Examples include allogeneic unrelated

1 cord blood, allogeneic unrelated pancreatic
2 islets, and these are just examples, autologous
3 tumor vaccines, CAR-T cells, neuronal stem cells,
4 and multipotent stromal cells. As Irv pointed
5 out, some people call these mesenchymal stem
6 cells.

7 In order to get those kinds of products
8 from the idea in the lab and to the bedside, we're
9 going to be talking about the premarket approval
10 pathway a little bit, and discuss how science
11 interacts with the different stages of that. I'm
12 going to be putting in a little talk on some of
13 the research that is actually done at FDA that is
14 meant to facilitate development of these kinds of
15 products.

16 We are doing this in real time, and I
17 think you might have gotten a sense from Irv's
18 talk and certainly just following the literature,
19 we have to do this in real time with what is
20 available now. We have to work within the
21 constraints of these regulations, which I just
22 pointed out. It is a complex system or set of

1 kinds of products that we are regulating, but it
2 really is dependent on sound science. Again,
3 available technology.

4 In our work, we try to identify
5 knowledge gaps and help point those out, help
6 people in the field, and sometimes address with
7 our own research some of those gaps and come up
8 with possible solutions.

9 That is our sort of focus for today. We
10 are going to hear from a lot of people about some
11 of the challenges in this arena, and some of the
12 possible approaches to moving the field forward.

13 I do need to point out that our
14 objective in review, the primary objective is all
15 about safety in all phases of clinical
16 investigation. We apply scientific principles to
17 the study of the products, the pre-clinical
18 knowledge, clinical outcomes early and late, to
19 assure the safety and rights of subjects.

20 As we advance the products to later
21 phases, we increasingly emphasize the importance
22 of scientific evaluation to permit an evaluation

1 of drugs' effectiveness and safety.

2 There are lots of different mechanisms
3 and resources available in translational
4 development. There are FDA regulations, and there
5 are ICH documents, FDA guidance documents, and
6 standards that are being developed through a
7 variety of standard setting organizations. Those
8 interact with and help guide people who are
9 interested in translational development as they do
10 their basic research and discovery, product
11 development, proof of concept studies, tox
12 studies, and study things like cell fate and
13 biodistribution.

14 There are opportunities to interact with
15 FDA at multiple times during product development
16 to discuss the scientific issues and to help you
17 understand how they fit into the regulatory
18 paradigm, and those can begin with pre- IND
19 discussions that mostly focus on the very
20 important pre- pre-clinical animal studies that
21 are necessary to help us look at the safety
22 profile of a new product, and then pre- IND

1 meetings where we have a chance without having a
2 clock ticking in the background to interact with
3 FDA and get our feedback, including the scientific
4 issues that we will be talking about today and
5 will come up during product development.

6 All of that culminates in an IND
7 submission, the very first clinical trials with
8 that product, proceeds through stages of clinical
9 trials, and then the goals are to have a license
10 application and lead to product licensure.

11 This is just a diagram of some of the
12 opportunities and interactions with people along
13 this clinical development pathway life cycle. I
14 mentioned pre- pre-IND interactions during the
15 developmental phase, pre-IND meetings, and then
16 the IND has a 30 day review clock.

17 It is good to take advantage of these
18 pre-meetings in order to help facilitate success
19 at the IND phase, and then a few other times when
20 meetings are sort of normal and expected. We are
21 also available for interaction when other
22 important questions come up throughout this

1 product life cycle.

2 I'm harping on the issue of how
3 important science is. These are the terminologies
4 that we apply to our different scientific review
5 disciplines. There is product, looking at how the
6 product is made, what the source of the materials
7 are and so on. Pre-clinical, looking at how the
8 in vitro and in vivo studies support the rationale
9 and the safety of a product, and clinical and
10 statistical.

11 We will be hearing people discuss each
12 one of these topics today.

13 The goals of pre-clinical testing are to
14 produce adequate information about the
15 pharmacology and toxicology both in animals or in
16 vitro, and that allows a sponsor to conclude that
17 it is reasonably safe to conduct a proposed
18 clinical investigation. There are a lot of
19 details that go into this, and I'll talk a little
20 bit more about that. Those are the goals of the
21 pre-clinical phase.

22 In the pre-clinical program, one of the

1 challenges is picking a relevant animal species
2 and model and relevant in vitro studies, and I
3 think Irv gave some really nice examples of how
4 one can go about that. It's not always so
5 straightforward, but that is an important and
6 challenging part of the science that supports
7 product development.

8 In these animal studies, both the
9 pharmacology and the safety are important. In the
10 end, again, if we think at the end of this that
11 it's reasonable to proceed to clinical trials,
12 these pre-clinical studies, if they point to an
13 acceptable risk/benefit profile, then we can go to
14 clinical studies.

15 The bottom line for pre-clinical studies
16 is follow the science, and what we really need to
17 know is what is the scientific rationale that
18 helps us look at this risk/benefit profile. We
19 want through pre-clinical studies to identify a
20 biologically effective cell dose range, and we
21 want to collect safety data associated with the
22 route of administration, the dose level range, and

1 the formulation.

2 It is also nice to know and important
3 perhaps more later in product development to start
4 understanding the mechanisms of action and look at
5 things like real time and quantitative cell
6 tracking, but the real issue is does that first
7 submission for the first clinical trial, the IND
8 phase one, contain sufficient information to
9 assess the risks to the subjects.

10 These are important scientific
11 endeavors. The stronger the science, the more
12 likely things will proceed as planned.

13 Now I'm going to switch a little bit to
14 product testing and development, what we often and
15 those in the industry call "CMC" or chemistry,
16 manufacturing, and controls. The goals of this
17 are to ensure product safety and ensure
18 consistency of process and product, and that can
19 be a challenge.

20 Ideally, predicted in vitro activity,
21 and this is a challenge, more of a challenge for
22 some of our products than for others, and I'm

1 going to be talking about some research that we
2 have done in that arena in just a few minutes.

3 Product testing really should be guided
4 by a detailed understanding of the manufacturing
5 process and the product, and this is what we term
6 generally as "characterization." Again, strong
7 science is what is needed here.

8 I mentioned this kind of life cycle
9 approach in the different phases, and we need to
10 know at the beginning what are you measuring to
11 say the product is what you say it is as an
12 identity, and then quality includes things like
13 what characteristics must the product have or lack
14 -- my timing is taking over my slides.

15 This includes microbiological safety and
16 product specific safety, things like remnant
17 undifferentiated cells that Irv mentioned in his
18 talk, are important things to consider for stem
19 cell based products. Purity, does the product
20 contain appropriate cell populations.

21 Often times, one of the things we say
22 and emphasize in our early interactions with

1 sponsors is we don't necessarily know that you
2 need one cell type to get the kind of clinical
3 effect that you want. That could be the case for
4 some products. It could be different for others.
5 This does say the appropriate cell populations.

6 Strength, how much will you dose. You
7 want to know that sort of going in or propose
8 those things. Then at the end, you really have to
9 know about identity, microbiological safety, and
10 potency becomes a challenging issue for cell based
11 therapies and purity.

12 Presumably at the end, you should know
13 what cells or cell types you want in your product
14 to get the kind of effect that you want.

15 What gets you into the clinical trials
16 at the beginning, if you don't continually try to
17 understand your product, at least in some cases
18 without an iterative understanding and approach to
19 developing the science behind your product, you
20 might not know how to characterize your product to
21 lead to success. I am going to illustrate that a
22 little later. Ideally, the testing should predict

1 the product performance in vivo.

2 Now I'm going to switch to multipotent
3 stromal cells, MSCs, and talk about a regulatory
4 science project that we have been doing here in
5 FDA labs.

6 We first started with kind of a survey
7 of what we actually see in regulatory applications
8 that come into our office. This resulted in a
9 publication, MSC-Based Product Characterization
10 for Clinical Trials: An FDA Perspective. I won't
11 go through that whole paper.

12 In the end, what people call MSCs is
13 quite diverse in terms of what people
14 characterize, how they manufacture them, what
15 source they take them from. The question really
16 is what are quality attributes that would lead you
17 to the kind of product understanding I've been
18 talking about, and what is the relationship to
19 what people are measuring to performance in
20 clinical trials, and those are open questions.

21 People often have a concept in mind when
22 they talk about mesenchymal stem cells, that they

1 are anti- inflammatory, they can undergo
2 tri-lineage differentiation. The question is when
3 they really isolate these cells and characterize
4 them the way they do, do they maintain those
5 properties that they kind of start out with as
6 their concept of how they are going to work.

7 So, the question is once you actually
8 take these cells and manufacture them, and you can
9 measure things about them, but does what you
10 measure -- how does that relate to their
11 biological properties and how does that relate
12 potentially to outcomes in the clinic.

13 It is an important question. This is
14 just a hypothetical but it's based on a lot of
15 observation on our end in seeing the information
16 in clinical trials, but it is a hypothetical
17 clinical response. There is a Y axis, and
18 comparing a control group to an active group, you
19 might look at this data and say there is
20 tantalizing evidence that there is clinical
21 effect. Clearly, some response and some
22 non-response.

1 The question is, is that due to
2 heterogeneity of the product or is it due to
3 heterogeneity of the patients, or a little bit of
4 both. So, advancing our knowledge in those arenas
5 might really help us to understand how you measure
6 the effect of products, and if you can do that,
7 you might figure out ways to manufacture
8 differently, enrich for, or somehow identify the
9 cells that lead to the clinical success and focus
10 on those.

11 We have undertaken a regulatory science
12 research project which we call our MSC Consortium,
13 and we started with bone marrow derived MSCs as a
14 proof of concept project. Our goal is to develop
15 strategies to determine identity/potency assays
16 that predict safety and effectiveness. That is a
17 rather ambitious goal, but we thought the kind of
18 studies that we are doing there could be broadly
19 applicable to a good number of cell therapy type
20 products.

21 What we did was purchase MSCs from
22 commercial sources. These are the lines, variety

1 of ages from 22 to 47, male and female, and
2 cryopreserved or analyze them at passages 3, 5,
3 and 7. This was based on say five or six years
4 ago, kind of common schemes of manufacturing for
5 MSC type products.

6 We did this manufacturing in my lab.
7 This was the overarching approach. We applied
8 genomics, single cell PCR, and qRT-PCR in the Moos
9 Lab, genomics in the Puri Lab, proteomics in the
10 Alterman Lab, in the Hurst Lab, epigenetics and
11 karyotypic analysis, high throughput.

12 We are looking to see if we can
13 correlate any kind of product signals that might
14 come out of these molecular analyses with in vitro
15 and in vivo bioassay systems, and the McCright Lab
16 is looking at in vivo and in vitro models of wound
17 repair. My lab was looking at in vitro
18 quantitative differentiation assays, and the Wei
19 Lab was looking at in vitro and in vivo
20 immunosuppression.

21 In my lab, we published several papers
22 looking at things like low hanging fruit

1 adipogenesis and showing you could measure the
2 progenitors, adipogenic progenitors in these MSCs,
3 and very interestingly, you could see that if you
4 took the MSCs from different donors, different
5 capacities to make adipocytes out of MSCs, and
6 then that capacity would diminish with passage.
7 These were surprising based on other people's
8 literature, but we did it for all eight of these
9 lines in a very systematic way, and reproducibly
10 quantitative.

11 We also observed the colony forming unit
12 activity decreased for all of these during
13 passage, and the size of the cells increased for
14 all these cell line passage. I won't show you
15 that data.

16 Clearly, when you take the cells out and
17 under the conditions that we used and the sources
18 of cells that we used, taking them out of the bone
19 marrow environment, manufacturing them had clear
20 effects on differentiation capacity, morphology,
21 stemness, that is used in the field.

22 I'm going to talk now about a recent

1 publication. I mentioned a second ago that we saw
2 increases in size in all these cells, so the
3 morphology was definitely changing, and it changed
4 differently for different cell lines, and we
5 thought maybe we could take advantage of that by
6 doing kind of a high throughput morphological
7 assessment of these cells.

8 We chose Xylenol Orange staining and
9 nuclear staining to kind of assess whether or not
10 we were seeing what some people say is an
11 important aspect of osteogenic activity. I know
12 it's not necessarily 100 percent correlation, but
13 this is a commonly used assay in the literature,
14 but what we did was assess the morphology at day
15 three after osteogenic stimulation and compared it
16 to just growth at day three, and then did all
17 these morphological signature collection, and then
18 subjected that to a principal component analysis,
19 and then compared that to the 35 day kind of
20 standard osteogenic conduction assay with
21 mineralization as the output.

22 We were able to show that two models --

1 you can take subsets of the measurements that you
2 use and subject them to models, and we developed
3 models from those, or even look at single
4 parameters, but we were able to show that two
5 models predict mineralization with 92 percent
6 accuracy.

7 This was done automated, high
8 throughput, three days rather than 35 days. It is
9 sort of getting towards this goal of making
10 predictive measurements about cell
11 characterization that have some either in vitro or
12 in vivo correlate. Of course, in vivo would be
13 better. We are working towards that.

14 We did this with an original set of
15 cells that we learned upon and then we applied it
16 to other cell types manufactured with different
17 serum concentrations, drugs, and so on, and were
18 able to show that this model still had that
19 predictive power.

20 One thing I wanted to point out also is
21 that if you look at the cell surface markers that
22 we saw in those INDs and that are kind of

1 community consensus markers for what people call
2 MSCs, I talked about the biological heterogeneity
3 of these cells.

4 This is an illustration, if you look at
5 passage 3, 5, and 7 for all the cell lines with
6 all of these different markers, you really don't
7 see differences. Using these kinds of approaches
8 as quality attributes might not give you the
9 information that you want with some kind of
10 correlation with biological activity.

11 This MSC Consortium, we have shown that
12 the consensus MSC markers don't correlate with
13 functional heterogeneity that we were able to
14 assess quantitatively. They're not responsive to
15 donor or tissue culture age differences.

16 We have had some success developing
17 assays to identify and qualify predictive product
18 characteristics, and we are publishing findings.
19 I've been talking about what came out of my
20 laboratory. I'll show you in a minute the
21 publications that have come out of this group.

22 The potential applications are you might

1 be able to identify differences between MSC
2 samples and work towards that goal I showed you
3 earlier with the hypothetical clinical outcome
4 thing.

5 Optimizing your manufacturing, figuring
6 out ways to differentiate between cells that work
7 and don't work, so you can evaluate the impact of
8 tissue culture conditions in duration. You can
9 correlate with other characteristics of MSCs. You
10 might be able to guide purification techniques to
11 help understand mechanisms controlling stem cell
12 differentiation and function, and that is kind of
13 an interesting biology behind this.

14 I'm not going to read all these papers.
15 They will be available in the slides that you will
16 get. There was a sector review. I mentioned
17 three different quantitative assays. Four papers
18 on proteomics, a paper on immunomodulation, some
19 outcomes of the genomic studies, and seeing some
20 predictive markers for proliferation and
21 senescence, and then genetic and epigenetic
22 stability studies that have come out of this

1 group. It's been the eight different labs I
2 showed you at the beginning.

3 In summary, you heard in the first talk
4 and in my talk about the importance of scientific
5 evidence, crucial for development of these 351
6 HCT/Ps. That applies to product and pre-clinical.
7 I think we will hear more about that, these other
8 disciplines, later today.

9 The regulatory framework in current
10 science allows development of these complex novel
11 products. We have licensed products using this
12 paradigm that I have been talking to you about and
13 look forward to doing more of that.

14 The science continues to evolve. It is
15 a challenge for all of us. It is important to
16 keep our eye on those targets.

17 This is contact information for myself,
18 and regulatory questions can be submitted. We
19 have a wonderful Web based webinar series called
20 "OCTGT Learn" for anybody who wants to learn more
21 about regulatory framework, then there is a lot of
22 information available on our Web site. You can

1 contact the Consumer Affairs Branch or
2 Manufacturers Assistance and Technical Training
3 Branch if you want. These are the places you can
4 find those resources.

5 Thank you. (Applause)

6 DR. BAUER: We are going to move on to
7 Session 2, and that session is about experiences
8 in product development.

9 I didn't intend to take any questions at
10 this time, but if you want to talk to me during
11 the breaks about the research part of this, I'd be
12 happy to do so.

13 I'd like to ask Dr. Galipeau to come up.
14 We are going to start Session 2: Experiences in
15 Product Development.

16 Jacques is a Professor of Hematology and
17 Medical Oncology at the University of Wisconsin at
18 Madison, relatively new, last week. As of
19 September 1, he became the Inaugural Director of
20 the University of Wisconsin Advanced Cell Therapy
21 Program, and Assistant Dean for Therapeutics
22 Discovery and Development.

1 His presentation today is entitled: How
2 Mechanistic Studies on Mesenchymal Stromal Cells
3 Inform Design of Human Clinical Trials for
4 Autoimmune Ailments - The Fitness Paradigm.
5 Thanks, Jacques.

6 DR. GALIPEAU: Steve, thanks for the
7 invitation, the organizers, to speak today. I'm
8 just going to jump straight into it.

9 Distinct from the hematopoietic stem
10 cells that Irv spoke of, mesenchymal stromal cells
11 are rare in bone marrow, maybe one out of a
12 million of nucleated cells in the marrow, and
13 probably the best reductionist marker that
14 identifies the MSCs.

15 These cells in life and in all of you
16 play an important role as nurse niche cells to
17 allow Irv's stem cells to survive long term in the
18 bone marrow space, but they also play another
19 role. They are sort of cops for the immune system
20 in the bone marrow. They play an important role
21 in regulating how lymphocytes come in and out, and
22 they can participate in tissue injury repair.

1 We now know a lot about how these cells
2 tick at least in regards to modulating the immune
3 response. When you tickle MSCs with Interferon
4 gamma, that is how they sort of sense in their
5 environment there is inflammation going on, the
6 human cells will massively up regulate an enzyme
7 in their cytoplasm called a IDO, it converts an
8 amino acid, and this small molecule blocks T cells
9 and also affects monocytes which are other cells
10 that circulate in your body.

11 Now, when you add Interferon Gamma, you
12 also have to regulate PD-L1, but also other genes
13 that are expressed, COX2, this is something that
14 is inhibited if you take Aleve, IL-6, HGF, and
15 these talk a lot to the monocytes, and they
16 secondarily, the monocytes, which are very
17 abundant, the MSCs are quite rare, the monocytes
18 in your blood are very abundant, start making
19 buckets of IL-10, and IL-10 is a profound immune
20 suppressant.

21 MSCs on their own, they are sort of the
22 match that lights the gasoline that leads to the

1 systemic anti- inflammatory effect, and because of
2 this, MSCs have been developed very robustly as a
3 method to hose down over exuberant inflammatory
4 disorders.

5 The reason MSCs are so popular as
6 opposed to say skin fibroblasts or something else
7 -- again, I'm a hematologist. You can take a
8 little bit of bone marrow, local anesthesia, not a
9 big deal, and as little as a couple of tablespoons
10 of bone marrow, you can grow in the lab a gram of
11 your tissue. You can grow in industry up to a
12 kilogram of these MSCs because of their big
13 proliferative potential.

14 Because of this property, everybody
15 basically was saying so, here's a solution, what
16 are the problems we can fix with it, because I can
17 make a kilo of Irv's MSCs. That being said, you
18 can grow them in the lab and you can harvest them.
19 I'm going to dwell upon immune modulation, not
20 talk about regenerative medicine.

21 In immune modulation, really the Eureka
22 moment was an anecdotal case report made by

1 Katarina LeBlanc at the Karolinska Institute in
2 Sweden, where a young boy had a bone marrow
3 transplant. He had leukemia. He developed graft
4 versus host disease. You get the diarrhea which
5 is the white spots [graph on slide], you get liver
6 dysfunction, that is a bilirubin [graph
7 on slide], and the young boy was
8 dying of graft versus host disease.
9 What Katarina did, she took marrow from
10 the boy's mom and gave the boy mom's MSCs i.v..
11 Here is a dose here. You see the liver
12 dysfunction and diarrhea went away, it came back,
13 another dose of mom's cells, went away, stayed
14 away.
15 Kids that have this die, it is as simple
16 as that. Adults that have this die quicker. This
17 was just an incredible Lazarus event that this was
18 really like, you know, the face of Helen launched
19 1,000 ships, so there were a bunch of clinical
20 trials done in academic centers in Europe that
21 were seeing actually very exciting phase 2 -- the
22 biggest one was the top one here, 55 patients.

1 Response rates, maybe 7 out of 10 patients were
2 getting MSCs, not from their mom's but somebody
3 else, were getting clinical response for their
4 graft versus host disease, which was basically
5 killing them. Multiple studies, virtually all of
6 them in academic health centers in Europe.

7 Now, the logical next step after some
8 development like this is deployment. A company
9 based in the U.S., Osiris, started making MSCs,
10 and this is from their Web site, from one donor --
11 I told you that you could generate a kilo, I was
12 not kidding. They say they can manufacture 10,000
13 doses from a single donor.

14 Please note that the European studies
15 are exciting, never manufactured more than 10
16 doses per donor. Remember that as we move
17 forward.

18 They went ahead and they did a clinical
19 trial, graft versus host disease, prospective
20 randomized trial, placebo controlled, in the U.S.,
21 the Osiris product, it did not work in their
22 hands, giving steroids only, which is the only

1 treatment that works, there is no FDA approved
2 treatment for graft versus host disease other than
3 steroids. It was no better in their hands.

4 This was presented as a press release
5 and in a poster, the paper has not yet been
6 published. This is in 2009.

7 What I haven't told you is there are
8 literally thousands of papers demonstrating that
9 mesenchymal stromal cells in mice will improve
10 just about any inflammatory tissue injury anyone
11 can think of, unimpeachable data published in top
12 journals from Nature Medicine down. Yet, you go
13 into people, and it don't work. Why is that so?

14 Do you just walk away and move on or do
15 you try to figure it out? We are university based
16 scholars, we tried to figure it out. Here are a
17 couple of things that we felt, our group, would be
18 playing an important role in why we could improve
19 things.

20 I want to dwell upon my favorite, which
21 is cryopreservation. If there is one thing you
22 have to remember this morning, stem cells are like

1 sushi, fresh is best. Why is that so? Usually, I
2 have a bunch of jokes at this point, since I have
3 only 15 minutes, I won't. I can give you the
4 jokes afterwards.

5 To come back to my point, the scientific
6 data using mice or sheep or monkeys, if you can
7 afford it, almost universally are positive, it
8 always works. Nearly all the MSCs that are being
9 used are syngeneic. That is a technical term
10 meaning because all these mice are inbred, so they
11 are like clones, if you take marrow from one mouse
12 and give it to the other, it is like giving the
13 marrow from the same mouse. They are all
14 syngeneic.

15 Virtually all the studies used fresh
16 cells, straight out of the culture. They don't
17 put cells in their freezer and then thaw them in
18 the vast majority of studies. The bulk, always,
19 always fresh cells directly from culture.

20 As in human clinical trials, MSCs,
21 nearly all the industrial studies, 100 percent of
22 the industry studies use allogeneic MSCs, not

1 their own, somebody else's. Academic studies are
2 about 50/50, your own or somebody else's.

3 Virtually the majority of studies
4 utilized frozen cells, and the way the frozen
5 cells are delivered is as follows: you take the
6 frozen cells out of the freezer, you put them in a
7 vat of warm water, you take that out, and
8 sometimes the cells are washed or not, and it is
9 given to a patient within four hours of thawing.

10 It's not that the cells are put back in
11 culture and allowed to recover emotionally, like
12 the astronauts in the movie Alien, none of that.
13 They are given right after thawing. All those
14 animal studies I spoke of don't do that. They put
15 the cells back in culture.

16 The question is is thawed allogeneic the
17 same as fresh. When you thaw cells, there's dead
18 cells, and that's standard, maybe up to 30 percent
19 are dead, and that's fine, versus live cells, a
20 little bit of dead cells, Trypan Blue really
21 doesn't detect that and Annexin PI does, and what
22 we found was -- this is a T cell proliferation

1 assay. These T cells are growing in a petri dish
2 after you tickle them. If you add live MSCs, you
3 block that proliferation. That is a standard sort
4 of assay, but if you take cells straight out of
5 the freezer, you thaw them, you put them on top,
6 don't work no more.

7 This is just different ratios of MSCs
8 and T cells. It's not that the thawed cells don't
9 work at all, they will, but their effect is
10 markedly blunted. If your end point is to achieve
11 statistical significance for effect, this is
12 something that will let you down.

13 We looked at human MSCs from different
14 subjects, and what we found was -- this is again T
15 cell proliferation, you add cells that were in
16 culture for a week, MSCs, you block T cell
17 proliferation, cells straight out of the freezer,
18 they don't work no more, no better than spit in
19 our hands, but if you put those exact same cells
20 in culture for at least a day, they fully recover
21 all their potential to block suppression.

22 It's not that they are permanently

1 screwed up post-op, they just have to recover
2 emotionally from the thaw.

3 Why is that so? When you take cells
4 straight out of the freezer and you tickle them
5 with Interferon Gamma, they cannot up regulate the
6 enzyme I spoke of, whereas after a day of culture
7 rescue, they can up regulate. Why is that so?

8 Interferon Gamma leads to
9 phosphorylation of STAT-1, and leads to the
10 Interferon Gamma effect. What we found was that
11 cells straight out of the freezer cannot -- the
12 protein is there, the receptor is there, the cells
13 can't respond. Why is that so? When you thaw
14 cells, this is three different volunteers, and we
15 looked at the heat shock proteins. The cells
16 undergo a heat shock response. Heat shock
17 proteins are to metabolism what P53 is to DNA.

18 This was described actually a quarter of
19 a century ago, a zillion years ago, when you take
20 cells out of the freezer, they undergo a heat
21 shock. It is called freezer burn effect. It is
22 reversible. These heat shock proteins, their job

1 in life is to tell the cell stop everything, let's
2 survive this insult, and then we'll move on.

3 What about homing of the freezer burnt
4 cells? We took human cells from the same donor,
5 froze/thaw them versus cells that were live, and
6 injected them in the tail vein of a mouse, and
7 when you inject in the tail vein, all the cells
8 wound up in the lung.

9 We asked can we detect human cells in
10 the lung of mice the day after we inject them, if
11 you take live cells, we detect the cells, this is
12 PCR signal, so it is counterintuitive, so yes, but
13 the thawed cells from the same human donor
14 injected in the mice, we could not detect any of
15 the cells, zero, in their lungs after 24 hours.
16 So, there is an accelerated clearance of thawed
17 cells.

18 Why is that so? MSCs are different from
19 hematopoietic cells because they have a skeleton,
20 it is called a cytoskeleton, that is how they
21 stick to things, and when you thaw cells, it
22 completely melts down their skeleton. This

1 skeleton spontaneously refurbishes itself, but it
2 takes 24 hours, and we have shown that for thawed
3 cells their cytoskeleton is markedly impeded, so
4 the structural integrity of the cells is messed up
5 post-thaw, and you can replicate this by using a
6 drug, Cytochalasin D, and although these cells are
7 both live, those with the busted up skeleton will
8 not biodistribute.

9 Again, showing this has nothing to do
10 with function and phenotype, this is structure of
11 the cell. You can only anticipate this by putting
12 this in a mouse in vivo.

13 We are not the only ones that say
14 thawing is not a good thing. Again, Katarina's
15 group showed MSCs thawed, if you put whole blood
16 on it, it generates blood clots, and they are
17 susceptible to complement mediated - complement is
18 the protein in your blood-- supposed to attack
19 bacteria. If you put that on thawed cells, it
20 lyses the cells.

21 What we found most recently, that we
22 just published, is if you take the thawed cells

1 and you add T cells on top, which is a standard
2 assay, the T cells start destroying the thawed
3 cells as opposed to live cells, which are not
4 destroyed. Even autologous cells can get
5 destroyed.

6 If the T cells and the MSCs are
7 mismatched, the T cells react to them and lyse
8 them in vitro. If you put activated T cells, and
9 there is a shield between them and the thawed
10 cells, the thawed cells are protected. It is only
11 if there is direct contact.

12 We went on to show T cells that have
13 direct contact with thawed cells kill them.
14 Thawed MSCs, they undergo a heat shock, they are
15 susceptible to killing, they are susceptible to
16 complement, increase coagulation, you have
17 abnormal membranes, abnormal cytoskeleton, but
18 otherwise, they are okay. (Laughter)

19 If you put them back in culture, all
20 this gets fixed. Don't forget, this is what is
21 done in mice, this is what is done in people.

22 I think fresh is best but fit is fine,

1 to come back to that.

2 How about those 10,000 doses? I told
3 you all that exciting initial data that was done
4 out of Europe. They were using MSCs generating no
5 more than 5 to 10 doses per volunteer donor versus
6 the industrial studies.

7 A massively expanded product, is it the
8 same as a non-expanded product, which comes back
9 to the presentation that Steve gave earlier. When
10 you split cells over time, it is basically an
11 experiment of an accelerated agent in a petri
12 dish, and we saw these cells stop growing. They
13 become big and fat, that is a characteristic of
14 senescence, and these senescent cells have a
15 phenotype that is identical to non-senescent
16 cells, again to Steve's point that the phenotype
17 is good for identity but not for functionality.

18 We found that senescent cells actually
19 were unable to block T cell proliferation. So,
20 there is a clear functional defect.

21 The last point that I want to raise in
22 my closing minutes is clinical trial design.

1 Steve pointed out there may be things that are
2 wrong with the cells, there could be, but there
3 are also aspects of who are the patients you
4 enroll in these studies because you want to give
5 the cells to patients that you think have a good
6 likelihood of responding and avoid giving it to
7 patients that won't respond.

8 If you look at the negative Osiris trial
9 for graft versus host disease, and Osiris was
10 acquired by Mesoblast, which is a public company
11 traded out of Australia that is now doing an
12 ongoing phase 3 study of MSCs for pediatric
13 steroid resistant GVHD in the U.S., and they have
14 learned, although they haven't published their
15 study, that their primary end point includes not
16 only a CR day 28 but a partial response.

17 We also know that kids do better than
18 adults. Restricting the enrollment to children
19 and young adults as opposed to the Orisis study
20 who went to older adults is a bias towards their
21 being able to observe a positive effect, and they
22 are also excluding people that had mild GVH

1 because GVH can affect the skin only, and those
2 typically can do quite well on steroids on their
3 own, so by excluding those, you are going to
4 increase the likelihood of getting a delta with
5 your control group, and they were also more
6 demanding. You had to be sicker. You had to have
7 at least bowel or liver involvement, and you had
8 to be getting worse on steroids to be enrolled,
9 and they were also doing it at a single site.

10 I think they designed the clinical
11 trial, but they are using the same product, the
12 frozen/thawed, but some don't work. I just think
13 in the setting it is not optimal. They are always
14 taking a chance they may not meet their primary
15 point, but the way it is set up, who knows.
16 Hopefully, it will move forward.

17 Compatibility is also a big deal. I
18 could take Irv's MSCs and give them to everybody
19 in the room and that is perfectly fine because
20 they are magically immune privileged. I think
21 that is not true.

22 In the setting of bone marrow

1 transplant, if you give -- MSCs are analogous to
2 mice under MSC transplant, the engraftment of the
3 donor hematopoietic cells goes up, but if you use
4 MSCs derived from the hematopoietic stem cell
5 donor, you make the outcome worse, so immunology
6 matters, the source of the MSCs and the immune
7 typing and compatibility with the recipient is a
8 big deal.

9 Are human thawed heat shocked senescent
10 allogeneic the same as mouse and genetically fit,
11 I don't think so. Learning from this informs what
12 we can do to improve the outcomes. If your Uncle
13 Bill has a heart attack or a stroke, you don't
14 have two weeks to grow his MSCs, because the
15 outcome is going to play itself out in the first
16 seven days. Allogeneic is the way to go but for
17 many ailments, chronic inflammatory ailments,
18 autologous makes sense, low passage meaning two
19 weeks of culture, not three months of culture,
20 fitness, and also clinical trial, rational
21 selection of subjects based on biomarkers.

22 To Irv's point, academic health centers,

1 not for profit, historically played a role in
2 development. I propose to this audience that
3 these same centers need to play an active role in
4 deployment, so we as academic health centers have
5 made available bone marrow transplants for almost
6 40 years because it works, and it has never been
7 developed by industry, industry is very, very good
8 at developing certain types of platforms, and for
9 reasons unrelated to effectiveness or outcomes may
10 not be able to effectively deploy other platforms
11 such as this like we can do in academic health
12 centers.

13 A short and narrow pathway to make that
14 feasible, I think, would be really useful. A lot
15 of data was generated when I was at Emory, I was
16 there for seven years, prior to my moving to
17 Wisconsin just last week.

18 Thank you for your attention.

19 (Applause) Now, I wasn't planning
20 to take any questions at
21 this point because Steve just gave us 20
22 minutes to speak, and being very vocal speakers,

1 we figured the panel at the end would be when
2 questions would come through, so I'm just going to
3 do a segue right now, if you can put Dr. Matthay's
4 presentation up, and introduce Michael Matthay,
5 who is a Professor of Medicine and Anesthesia at
6 UCSF, and will be talking to us about his use of
7 MSCs in acute respiratory distress syndrome.

8 Mike? *MESENCHYMAL STEM CELLS FOR TREATMENT OF
9 ARDS PATIENTS: CHALLENGES AND LESSONS
10 LEARNED IN PRE-CLINICAL TESTING, FDA APPROVAL, AND
11 ONGOING CLINICAL TRIAL

12 DR. MATTHAY: Thank you, Jacques. Thank
13 you very much for the invitation. I'm delighted.
14 I'd like to endorse what Jacques just said.

15 I believe very much in NIH and related
16 support for this field, just echo Jacques, what
17 you just said, I was going to ask you, but in the
18 interest of time won't, we don't know the details
19 of the Prochymal product from Osiris, it's not
20 published. FDA, of course, can't reveal that to
21 us. We don't know how they were modified. We
22 don't know how many passages they went through.

1 There are many issues there in all the private
2 world of how MSCs are managed. I couldn't endorse
3 the points you made more.

4 In terms of disclosures, I have no
5 conflicts. Basic science and clinical grants from
6 NIH and FDA, and research grants, two of them from
7 industry that are not in conflict.

8 What I'd like to do briefly is talk
9 about MSCs and the reason for our interest in
10 their relevance for acute respiratory distress
11 syndrome. The source of the MSCs, which I'll give
12 a little more detail on particularly in view of
13 Jacques' important remarks. The pre-clinical data
14 for efficacy that we worked on, which as you will
15 see advanced well beyond the mouse, and the issues
16 related for testing safety, which I think are
17 extremely important, and where we stand with the
18 phase 1 and 2 clinical trials, and some
19 conclusions.

20 Now, everyone knows that MSCs were
21 discovered by Dr. Friedenstein when the Russian
22 government compelled him to collect bone marrow

1 from volunteers in case of a Chernobyl or nuclear
2 war, but he discovered/noticed that these cells
3 that he thought were basically fibroblast
4 contamination were really part of the stromal
5 cells of the bone marrow, and subsequently they
6 have been described in placenta, cord blood,
7 adipose tissue, and other organs.

8 They do not engraft, almost for sure.
9 They could enhance proliferation of stem cell
10 niches. That is why the term "mesenchymal stem
11 cells" is misleading. They are really mesenchymal
12 stromal cells.

13 They do not normally express Class I or
14 II antigens, although that can be modified by the
15 presence of Gamma Interferon, so in general,
16 allogeneic preparations are well tolerated in
17 humans as far as we know.

18 This shows you our clinical focus for
19 MSCs, which is ARDS, which is a syndrome of
20 non-cardiogenic pulmonary edema where the patient
21 is hypoxemic because of the edema fluid. This is
22 not explained by heart failure, and the usual

1 causes are pneumonia, sepsis, aspiration, major
2 trauma, effects over 200,000 patients a year in
3 the United States, including the large pediatric
4 population.

5 We have made progress in treating this
6 syndrome with a lung protective ventilation
7 strategy, but we have no other specific
8 treatments.

9 Our experience with translating human
10 MSCs for clinical trials began with mouse
11 experiments, and as I am going to show you, we
12 tried to advance beyond the limitations of mouse
13 studies by using ex vivo perfused human lung
14 studies, some rat studies and some sheep studies
15 that FDA -- thank you -- recommended that we do,
16 and I will show you how important they were in
17 helping us and address some of the key points that
18 Jacques made.

19 Then our IND preparation submission
20 approval, funding from the NHLBI, and a phase 1
21 trial which is done, and our current phase 2-A
22 trial, which I will update you on.

1 dramatic effect on reducing lung injury when we
2 gave the syngeneic bone marrow mouse cells
3 intratracheal to mice after a high dose endotoxin
4 injury. You can see the marked improvement. This
5 was reflected by better survival, less lung
6 injury, and less edema.

7 In subsequent studies where we gave live
8 bacteria, a more relevant model for human lung
9 injury, we found the MSCs worked whether given
10 intravenously or IT. They worked in comparison to
11 appropriate controls with fibroblasts as well as
12 PBS. We blinded the investigators doing the study
13 so there couldn't be bias, and we actually gave,
14 as other investigators have, human MSCs, as well
15 as the mouse MSCs from Dr. Prokop's NIH
16 repository.

17 I'm going to move on to tell you what we
18 then did to try to really see if these cells might
19 be effective for human lung injury. Our
20 laboratory at the University of California, San
21 Francisco, receives about 60 pairs of human lungs
22 a year from the Northern California Transplant

1 Donor Network. These are lungs that are not used
2 for transplant. Only 20 percent of lungs from
3 brain dead donors are used for transplant. Most
4 of these lungs are actually not very severely
5 injured.

6 We studied these lungs, both one,
7 isolating cells, and also doing a perfused human
8 lung model, and for these studies, we actually add
9 fresh blood to the perfusate to make it more
10 clinically relevant, and the lungs are perfused at
11 normal pressures, and the lungs are kept inflated
12 with 95 percent oxygen, 5 percent CO₂.

13 In the initial studies, we used high
14 dose endotoxin as in the mice, to injure the
15 lungs, then we used bacteria. What we found in
16 the initial studies was the remarkable ability of
17 the MSCs given intratracheal or intravenously one
18 hour after the endotoxin injury to reduce
19 endothelial permeability which had been markedly
20 increased by endotoxin back to a normal level.
21 Also, the pulmonary edema that was produced by
22 endotoxin was returned to a normal level, and even

1 the conditioned media had a beneficial effect.

2 Now, the other property that I alluded
3 to that is very important for the lung is the
4 ability to remove edema fluid from airspaces.
5 This is driven by active sodium transport, a
6 process we described about 20 years ago, and in
7 the presence of endotoxin, alveolar fluid
8 clearance, this goes to zero. Fibroblast did
9 nothing, but MSCs of the conditioned media
10 restored it to near normal, which explains why the
11 edema fluid was decreased.

12 Now, in these studies, we used initially
13 cultured MSCs, as Jacques had said is often the
14 case. Then we used cryopreserved MSCs, which had
15 been thawed, which I will tell you about.

16 At this point we were thinking about
17 translating the therapy, and we had various fora's
18 and discussions with industry about a source of
19 MSCs, but for a variety of reasons, I was not
20 satisfied with their candor, so we linked up with
21 Dave McKenna at the NIH Repository at the
22 University of Minnesota, and began to use his

1 clinical grade MSCs.

2 In the human lung studies, we took the
3 cryopreserved MSCs and thawed them, and we
4 centrifuged them, and we removed all of the
5 supernatant, which has the DMS cell, which I'm
6 going to come back to in a minute, as well as the
7 dead cells, and then re-suspended them.

8 At that point, we repeated all the prior
9 experiments with the chemical grade MSCs, with
10 endotoxin or live bacteria, and what you see here
11 is with intrabronchial or intravenous MSCs, the
12 alveolar fluid clearance with E.coli injury was
13 restored to three-quarters of normal, and
14 furthermore, the anti-inflammatory effect on
15 neutrophils was achieved, again giving the cells
16 in the perfused or intrabronchial one hour after
17 the injury. We extended these studies so we had a
18 lag time of two hours as well.

19 We had found in the mouse, as I alluded
20 to in the beginning, that these cells had
21 remarkable anti-bacterial effects. The MSC
22 treated mice with no bacteria had a markedly lower

1 number of bacteria. We found this was due to the
2 release of antimicrobial peptide LL-37, one that
3 we all have, and by increased monocyte
4 phagocytosis, but we wanted to see if this would
5 be replicated in the human system, and indeed, we
6 found again the MSCs had very strong anti-
7 bacterial effects related to increased monocyte
8 phagocytosis.

9 I think this is part of their
10 evolutionary adaptation, probably in the history
11 of evolution, the greatest threat to the bone
12 marrow was infection, and these MSCs probably
13 evolved as part of their properties to protect the
14 hematopoietic elements with these antimicrobial
15 properties.

16 Other people have confirmed this
17 antimicrobial properties, and it is an area of
18 quite a bit of scientific interest.

19 In the interest of time, I won't go
20 through the detailed mechanisms that have been
21 identified by our group and many others for how
22 they work, but the release of paracrine

1 molecules, such as fibroblast growth factor 7 or
2 KGF, and in our more recent work, the
3 pro-resolving lipid, Lipoxin A4, shows that they
4 can release factors that beneficially affect the
5 injured epithelium or endothelium.

6 They also release mitochondria, which in
7 a very nice Nature Medicine paper Dr.
8 Bhattacharya's group showed can be transferred to
9 the injured epithelium and restore the
10 bioenergetics of the injured epithelium resulting
11 in better function, and also they release
12 microvesicles, which turns out can enter in
13 macrophages in epithelial cells. It is quite
14 interesting, the different pathways by which they
15 work.

16 Finally, FDA said to me, Dr. Matthay,
17 wouldn't you feel better if we had a large animal
18 model before you introduce these MSCs into very
19 ill, critically ill patients with ARDS. I said
20 thank you, you're right. I appreciate the
21 suggestion.

22 We were fortunate to in fact partner

1 with Dr. Dan Traber, the late Dr. Traber, and Dr.
2 Enkhbaatar, and do some sheep studies at the
3 University of Texas. These sheep studies were 24
4 hour studies where severe pneumonia and sepsis
5 with pseudomonas aeruginosa, and we decided in
6 concert with the FDA's excellent advice to give
7 the MSCs exactly as we planned in the clinical
8 setting.

9 We shipped the cryopreserved MSCs from
10 the University of Minnesota. We thawed them. We
11 centrifuged them. We again removed the DMSO and
12 the cell debris and re- suspended them in
13 PlasmaLyte, and gave them in that way.

14 I'll just show you very quickly. The
15 first issue, of course, is always safety. We used
16 two different doses, 5 and 10 million MSCs per
17 kilogram. What I'm showing you here is for
18 systemic blood pressure after the severe pneumonia
19 and sepsis, the cells were given one hour later,
20 there were no adverse effects on systemic blood
21 pressure. In fact, at the end of the day, the
22 higher dose was associated with a better blood

1 pressure than the control.

2 The biggest issue would be pulmonary
3 arterial pressure. As an ICU physician my entire
4 academic life, we are always worried about
5 pulmonary hypertension. While we hoped for a
6 therapeutic benefit here, the risk would be that
7 if you give these cells into an injured pulmonary
8 microcirculation, maybe there would be a transient
9 rise in PA pressure and the right heart could
10 fail. That was what FDA was concerned about, it
11 is what we were concerned about.

12 We gave the cells. You can see here,
13 the blue is the control, the red is the higher
14 dose, and at the end of 24

15 hours, actually the PA pressure was
16 lower, fortunately, in the sheep treated with
17 either the lower or the higher dose of MSCs.

18 Briefly, from an efficacy standpoint, we
19 measured oxygenation like we would in patients.
20 Here the control sheep given PlasmaLyte, you see
21 this big drop in oxygenation reflected by what we
22 call the PaO₂-FiO₂ ratio, so this is severe

1 pulmonary edema, goes all the way down to 100, so
2 this is very severe respiratory failure. The
3 sheep are ventilated and managed like a severely
4 ill patient in the ICU, and here are the two doses
5 of MSCs.

6 I think you can get the impression that
7 oxygenation is better statistically at the end of
8 24 hours. It was better. We gave 10 million
9 cells, because FDA said look, you're planning on
10 giving 5 million cells, Dr. Matthay, we want you
11 to double the dose for safety.

12 Well, that turned out to be extremely
13 helpful, again, thank you to the FDA. We found
14 out when we measured the lung water, that it was
15 the higher dose which had a more beneficial effect
16 on the quantity of pulmonary edema. That is the
17 dose we selected for our trial.

18 When you thaw these cells, as Jacques
19 alluded to, about 65 to 70 percent of the cells
20 are viable. That is what we found with Trypan
21 Blue exclusion. You are certainly not giving 10
22 million cells per kilogram, you are probably

1 giving 60 to 65 percent of that in terms of live
2 cells.

3 One other key point I have shown in
4 these slides. When we did a few experiments in
5 which we did it the way Osiris did, and almost
6 every company in the field, where we just thawed
7 the cells and gave the cells with DMSO, no effect,
8 all the therapeutic effect was lost. We shared
9 that with FDA, and we talked about the long
10 history of how DMSO can be a problem, not in
11 hematopoietic cell transplant but under acute
12 conditions. We learned that, thank you again to
13 the FDA's directions.

14 Finally, the clinical trial called START
15 being run at Mass General in Boston, Pittsburgh,
16 Stanford, Ohio State, and of course, the home site
17 for us is UCSF. The phase 1 trial design was to
18 test standard dose escalation, three patients at 1
19 million, three patients at 5 million, and three
20 patients at 10 million cells, the target dose.

21 The enrollment criteria was moderate to
22 severe ARDS, defined by a P/F less than 200 on a

1 PEEP of 8, within 96
2 hours of developing ARDS. We excluded
3 patients with moderate to severe liver disease,
4 treatment for cancer in the prior two years
5 because there are still questions and concerns
6 that somehow the growth factors are other features
7 of the cells might enhance tumor formation,
8 chronic lung disease, pulmonary hypertension, and
9 children.

10 We very carefully identified with FDA's
11 input what would be pre-specified adverse events,
12 hemodynamic and respiratory. One of us, the
13 physicians, is at the bedside always during the
14 two hour baseline period and in the six hours
15 afterwards. We don't leave the bedside. There is
16 a coordinator, but one of the M.D. physicians,
17 usually myself, is there.

18 We had secondary endpoints for
19 respiratory, systemic, mortality, and biologic
20 markers. Of course, we are underpowered for that
21 in a phase 2-A design. The phase 1
22 results, fortunately, showed no safety

1 issues whatever, so we went on to the phase 2
2 trial.

3 We enrolled one last week, 51 of the 60
4 scheduled patients. The trial is 60 patients with
5 two to one randomization, 40 patients to receive
6 10 million MSCs, and the other 20 PlasmaLyte.

7 The safety endpoints are still primary
8 because in this field, we are very underpowered
9 for efficacy with only 60

10 patients. In conclusion, I would say
11 the pre-clinical

12 studies in several models, including the
13 human lung and the sheep, support the rationale
14 for testing MSCs in moderate to severe ARDS, in my
15 opinion, and an NIH or equivalent source of MSCs
16 is optimal. I'm very concerned about private
17 sources of MSCs where it is not in the public
18 domain what the passages were, how the MSCs were
19 modified so the company could achieve intellectual
20 property.

21 I'm far more comfortable with an open
22 NIH like support, and I would like to see that

1 supported more. I think it would help the field.

2 There is no question that our
3 consultation and input from the FDA has always
4 been extremely helpful. I couldn't also agree
5 more that studying the biology is critical. It is
6 only in the last two years, for example, that we
7 discovered these cells have the remarkable ability
8 to generate the pro-resolving lipids like Lipoxin
9 A4, resolving D1, a whole field developed by
10 Charlie Serhan at Brigham, which I think is
11 extremely important, and these lipid products,
12 very important.

13 It is one of those areas where the pair
14 of clinical trials and ongoing lab research is
15 critical. We will see what we learn from testing
16 safety and efficacy of the MSCs, and of course,
17 all this work is being done by a group of
18 investigators, both at UCSF, Dr. McKenna at the
19 University of Minnesota, and the late Dan Traber,
20 and I can't thank enough the investigators at
21 Stanford, MGH, Pittsburgh, and Ohio State for
22 their participation in the trial, the NHLBI, the

1 DSMB, and of course, most importantly perhaps, the
2 patients who consented to be part of our clinical
3 trials, and the ICU nursing and respiratory care
4 staff.

5 Thank you. (Applause)

6 DR. MATTHAY: Do we have a break now?

7 DR. ANATOL: We are going to try to get
8 back on time, so we will have our break and we
9 will come back at 10:40.

10 (Recess)

11 DR. GALIPEAU: Okay. So again, the
12 format is going to be 20-minute presentations.
13 We're going to hold questions for the panel
14 discussion that will follow at 11:40-ish.

15 It's a pleasure to introduce Greg
16 Russotti. Dr. Russotti is vice president of Tech
17 Operations at Celgene in Warren, New Jersey.
18 Plays a role in CMC, and he'll be talking to us
19 about drivers of methodology for making the cell
20 process changes.

21 Greg?

22 MR. RUSSOTTI: Thanks, Jacques. And

1 thank you to the FDA for the invite. It's a
2 pleasure to be here today.

3 So I'll talk about some of the
4 approaches we've taken to making process changes
5 within one of our cell therapy manufacturing
6 platforms. And at Celgene, there are several
7 different cell therapies we're interested in, and
8 there's two that are currently in clinical trials.
9 One is a mesenchymal-like cell product derived
10 from placenta called PDA002. And it's given
11 intramuscularly, and it's in trials of diabetic
12 foot ulcers with peripheral arterial disease and
13 diabetic peripheral neuropathy.

14 The other product currently in clinical
15 trials is also placental-derived. These are
16 natural killer cells. These are immune cells, and
17 we have a trial currently ongoing in AML, acute
18 myelogenous leukemia, and another trial for
19 multiple myeloma about to start. But the examples
20 I'll give today are really around the PDA002
21 product.

22 So let's just start by talking about why

1 you make process changes, and there's a variety of
2 reasons. Some proactive, some reactive. Whenever
3 you make process changes, the most important thing
4 to remember is product quality, and safety comes
5 first. Efficacy, if you have efficacy
6 demonstrated, is important to maintain, of course.
7 And process robustness. You want to make sure
8 that you have a consistent product and a process
9 that makes it consistently. Sometimes, and
10 hopefully this can be proactive as you
11 characterize your process as Dr. Bauer spoke about
12 earlier, you want to characterize and get ahead of
13 the curve. Sometimes it's reactive, solving a
14 problem.

15 Invariably, capacity needs increase as
16 you go through clinical trials, so if you have to
17 make more product, you either do things like
18 change a scale or change the way you make the
19 product, changing the operations. And one of the
20 examples I'll give today is about changing an
21 operation.

22 Cost becomes a factor, and this is

1 really not just about making more money; this is
2 about patient access. If you can't make a product
3 at a reasonable cost, then you can't make a
4 product.

5 So some of the things we focus on are
6 reducing labor. A lot of the things you'll do
7 initially to get into a trial involve processes
8 that are very labor-intensive, and the one example
9 I'll give today, the first example I'll give today
10 is about reducing labor. Raw materials are often
11 very expensive, so we can switch to less-expensive
12 alternatives. That's always a good thing. And
13 then you always look for opportunities to optimize
14 your process. Again, getting something that's
15 more consistent back to product quality.

16 So the challenge is that you understand
17 more about your product as you march through the
18 trial. So this is a timeline that shows starting
19 trials, the initial pre-clinical studies,
20 marching through ultimately towards commercial.
21 And as you gather knowledge on analytics, knowing
22 ways to better measure your product, as you

1 understand the product better, what makes it work,
2 what keeps it safe, as you understand your process
3 better, these things all increase as you go
4 through the trials. Tracking and trending refers
5 to the data you get as you make more and more
6 product for that trial in a very consistent
7 fashion. But the ability to make changes will
8 certainly decrease because your process evolution
9 should decrease as you march through the trials.

10 If you think about safety risks and
11 risks to your efficacy of your product, both the
12 regulatory concerns and the business concerns of
13 changing a product increase as you march through
14 the trial. So this is the challenge we face. We
15 know more as we go along, but we're less apt to
16 make changes as we go along.

17 So as we make changes, just to kind of
18 -- this is really a summary of my whole talk
19 really about how you go about doing it, and I'll
20 give a couple of examples of how we've made a
21 couple of changes in our placental-derived
22 mesenchymal cell. So most importantly, you need

1 to understand your process. To do prude process
2 characterization, the first thing you need to do
3 is be able to define the output. What are the key
4 product attributes they're trying to maintain?
5 And then from there you want to be able to define
6 acceptable ranges for your critical inputs,
7 knowing that if I stay within these ranges I'll
8 hit my outputs. That ultimately leads to process
9 validation.

10 We have a group of bioengineers and
11 biologists that comprise our process development
12 group and they complement our analytical
13 development and our production and QC groups, but
14 the engineers really take this methodical approach
15 to understand how the changes we make affect the
16 product, and thinking about things like effective
17 scale and other parameters, but ultimately, we
18 want to come up with an acceptable design space
19 that we know if we stay within this space, the
20 product should look the same. And I say "should,"
21 and then we'll prove it next with our
22 comparability tools. And there are a number of

1 tools listed here. I won't read these. These are
2 things people typically look at and measure. And
3 ultimately, you do want to look at some in vivo
4 performance when making a big change before you go
5 into clinical studies.

6 So at the end of the day, you want to be
7 thinking about all the effects of the change in
8 taking a risk-based approach. So what are the
9 physical effects on the cells, on your product?
10 What are the chemical effects on the cells?
11 Thinking about the micro environment. And then
12 other incidental things, like processing times.
13 And people don't often think about these because
14 you think about the most important things that
15 affect a cell and the changes you make, but you
16 don't realize that sometimes when you make a
17 change, whole times may increase, transfer times
18 of a product from one container to the next may
19 increase. You need to be thinking about all these
20 things.

21 So the analytical tools are very
22 critical, and I'm not going to go over all the

1 different tools. This is just an illustrative
2 slide that gives you an example of the things you
3 might consider, but it's really important to think
4 about what you want to measure. What change are
5 you making, what might be affected, and what tools
6 do you want to use? And you're not going to
7 necessarily use every tool for every change, but
8 you want to use the right tools. And how to
9 measure those things is important, too. And
10 there's a lot of choices there as well.

11 So let's dive into a couple of examples.
12 And this is just a schematic of the process we use
13 to make this PDA002 product, the placental-derived
14 mesenchymal cell. We start with placental tissue.
15 Do a primary culture after initial isolation.
16 You'll see a two-tiered banking system with a
17 master stock and a working stock. For those of
18 you who are not that familiar, this is really just
19 to allow the proliferative potential of the cells
20 to be taken advantage of so you can get a large
21 number of cells which you could never process in
22 one batch, so you freeze down at these

1 intermediate points and have a consistent starting
2 material for every batch you make.

3 As we march through the cell expansion,
4 we do start in cell factories. We've moved
5 towards this bioreactor approach growing cells on
6 microcarriers, which can be suspended in a
7 bioreactor, centrifuge the cells down to remove
8 residuals and other wastes, add our DMSO at the
9 latest possible moment, and then cryopreserve.

10 So the two areas that I'll focus on are
11 a change to the bioreactor and a change to the
12 final container circled on this slide.

13 So the first example is making this
14 change from growing cells on these static cell
15 factories. These are very much like T-flask only
16 scaled up in greater capacity. A good way to
17 start your trial. You don't want to spend a lot
18 of time making the perfect process when you start
19 a trial, but as you go forward and you think about
20 cost of goods and capacity, this is a very hard
21 thing to sustain. And we made a decision to
22 examine better platforms pretty early on once we

1 had a sense that this was something we were going
2 to go forward with. So the concept here is the
3 cells need a surface upon which to attach. They
4 can't be grown in suspension like a CHO cell like
5 you might use for monoclonal antibodies but they
6 can stick to a surface like a microcarrier which
7 you can suspend.

8 So the platform switch included a couple
9 of things. It included going from these cell
10 factories to the bioreactors, and also the cell
11 concentration step we had done in BAT centrifuge
12 mode. We switched it as kSEP system, which is a
13 continuous centrifuge mode. So today I'll really
14 just talk about the cell culture, the cell
15 expansion change, not the centrifugation change.

16 So as we did this we, of course, had
17 many reasons to make the change. The benefits
18 listed on the left, as I mentioned, scalability,
19 cost of goods. We think better robustness because
20 now you have one container making all your product
21 rather than a bunch of parallel containers which,
22 and if you think about cell factories, there's

1 going to be natural heterogeneities of the cells
2 within the cell factory. Within a bioreactor,
3 you're aiming more towards homogeneity. And then
4 the operational steps and controls are just better
5 and sterility risks should be less because again,
6 one container versus many.

7 But there are many risks. It's a more
8 complicated process. It's not like your t-flask
9 that you started in when you first discovered your
10 cell product and wanted to develop it. So you
11 have to understand your process better and put the
12 proper controls in place.

13 Comparability is key here. So we wanted
14 to define which parameters we wanted to look at as
15 input parameters because ultimately, we need to
16 minimize those differences in the final cell that
17 we make. And we have a variety of things that we
18 measure, and I'll talk a lot about those.

19 The other thing which I won't really
20 talk about today but I just want to highlight is
21 bringing microcarriers in added a whole new facet
22 to the drug product purity, and that's the fact

1 that microcarriers could bring impurities in. So
2 anything the product comes in contact with could
3 bring impurities in, but these microcarriers are a
4 new material. They do break apart. They don't
5 have a perfect uniformity when you buy them.
6 There's different sizes. So we had to make sure
7 we minimized the small particulates before we
8 cultured. We have process controls in place to
9 minimize those particulates once we purified our
10 cells and we characterize those particulates
11 extensively to ensure that the amount left -- and
12 there's always going to be something left.
13 Hopefully it's very little, but there will always
14 be something. The amount left was reasonable and
15 the type was reasonable for safety.

16 So again, it's a risk-based approach,
17 data driven. As Dr. Bauer said, it's all about
18 data. The science should be driving where you go.
19 So to do this comparison, of course we used our --
20 I put current release assets because this is what
21 was in our release panel at the time, looking at
22 how the cells grow, their viability and the

1 phenotypic purity. We had functional assays,
2 which were not part of our release panel yet, but
3 potency is the most important thing. And we had a
4 bead T-cell reaction, which is like a mixed
5 lymphocyte reaction except we use beads to present
6 the antigen as opposed to dendritic cells. And
7 some other potential potency candidate assays
8 which I won't talk about today.

9 We did further characterization as well.
10 Of course, we looked at the effect on stability,
11 both long-term in the freezer and short-term after
12 you thaw the cells before infusion. And then we
13 did some in vivo studies as well that were
14 relevant to the diseases we were going to be
15 studying in the clinic.

16 So just going through some of this and
17 how the data looked, the first is the functional
18 test, the bead T- cell reactions. So we look at
19 both CD4 T-cells and CD8 T- cells like you would
20 in the mixed lymphocyte reaction. And you can see
21 on the far left is the CD4 and the far right is
22 the CD8. And within each one you have your 50

1 liter bioreactor results versus your 10 tray cell
2 factor results. And you're looking at T-cell
3 suppression, and there really is no difference at
4 all here. So we've got great confidence that the
5 most important thing that is that the cells are
6 functional when we make this change.

7 Trypan blue viability is just a simple
8 measure of viability. No difference, but we think
9 there's much more sophisticated measures of
10 viability, and we did look at some of those. So
11 one in particular -- and I'm not going to talk
12 about all the data that we did, it's just a couple
13 of snapshots of the key things we looked at. We
14 did something called a cell health assay. This is
15 a flow cytometry assay that looks at both annexin
16 which is a marker of the apoptotic state of the
17 cells and TO-PRO 3, which is a much more sensitive
18 marker of membrane integrity than trypan blue.
19 And again, good news here. Things look very
20 similar across the two platforms.

21 And another thing is morphology. You
22 know, it's funny. I always the scientists and

1 engineers in my group, as you move towards these
2 more automated things, like using a Vicell counter
3 for cell counting, which is what we use, which
4 also measures the trypan blue viability, don't
5 forget to look and see what the cells look like.

6 And here's just a simple picture of
7 morphology. I don't know how well you can see it
8 but the cells do look similar in terms of their
9 shape, in terms of their density. The cells had a
10 bit of a growth lag in the microcarriers but then
11 caught up. And that's, we think, because of the
12 initial attachment time that's required in a
13 dynamic system like the bioreactor as opposed to a
14 static system like the cell factory.

15 Now, cell size is where we saw one
16 difference. And you can see the average cell
17 diameter in the top left graph a bit lower for the
18 cells growing in microcarriers as compared to cell
19 factories. And we looked at this a lot, and one
20 of the things we wanted to understand was were the
21 cells really inherently changed or was it just the
22 dynamics of the system, the sheer in the system

1 that was causing them to get a bit smaller.

2 And if you look at the graph on the
3 right, you can see the red line is cells growing
4 only in cell factories, so they maintain their
5 average size pretty well. The blue line of cells
6 grown in cell factories of passage five switched
7 to bioreactors in passage six, which is
8 representative of what we do. But you see if you
9 put them back into cell factories they recover
10 their size, so we think this is a transient effect
11 and not an inherent change to the cells, more just
12 of what they're seeing in culture.

13 The other most important thing in my
14 mind is if you look at size distribution, yeah,
15 the average changed but the spectrum of sizes that
16 these cells are no different in the cell factory
17 than in the bioreactor. So when you think about
18 the fact that we did clinical studies already in a
19 cell factory, the body had already seen cells of
20 all these sizes and we're just shifting the
21 spectrum a little bit. We also did some animal
22 studies which I won't get into today to give us a

1 better understanding of what cell size might do
2 when you infuse the cell. And at the time we were
3 thinking -- this change was made both for our
4 infused product or IV administered product, as
5 well as an IM product. But we were more concerned
6 about the IV and whether the cell size would make
7 a difference. And again, I won't get into that
8 today but we did some animal studies there.

9 So overall, just in conclusion, there
10 were a variety of studies done. I didn't show you
11 all of them today but in all, it looked like the
12 cells were not changed as far as their key product
13 attributes, and these other things like cell size.
14 We had a pretty good understanding of why they
15 changed and why it wouldn't make a difference.

16 I didn't talk about stability or post-op
17 preparation, but those were comparable as well and
18 the animal models also showed comparable results.
19 Just in the interest of time, I'm not going to
20 show those today.

21 So we have one other example. So the
22 first example is a nice example that showed you a

1 very comprehensive comparability strategy with
2 really a lot of good analytical tools that look at
3 the most important things and give us confidence
4 we're making the same product. This example is
5 really one about using proper engineering to
6 understand the effect of the change on the cells.
7 So this is switching our final product container
8 from blood bags, which is what they initially use
9 for a long time, to cryopreservative vials. And
10 this is a vial made by Aseptic Technologies. They
11 make them in a variety of sizes. In this study we
12 looked at both the 2 ml size and the 20 ml size.
13 And what you can see here is the differences in
14 geometry are quite difference. And the surface
15 area to volume area is quite different from a bag
16 to the vial.

17 So this is just some background on the
18 vial. If you want to know more, we can talk
19 later. But the beauty of these vials which came
20 out a number of years ago is that they can be
21 cryopreserved. They do come already sterile,
22 gamma radiated, and you can get your product in by

1 going through the septum which reseals, and you
2 can reseal it with a laser. It just actually
3 naturally reseals on its own after you puncture it
4 with a needle.

5 Many challenges with this. And you can
6 imagine it's a different product now that the
7 cells are coming in contact with the time of
8 filling, how you visually inspect, which is a
9 whole talk in itself which I won't really get into
10 today. Leachables, extractables are important.
11 What we're going to talk about today is the
12 geometry and its effect on freeze and thaw.

13 So when we first did our quick and dirty
14 study and said how will the cells do if we use the
15 same freezing program? And what's interesting, if
16 you look on the left and you look at trypan blue
17 viability and you compare viability of cells
18 frozen in the bag on the X-axis to viability in
19 the bag frozen in a vial on the Y-axis of course
20 from the same batch of cells made. You see really
21 no difference. It's all within a five percent
22 difference. So if you're just using trypan blue

1 you're going to fool yourself is the point of
2 this.

3 We had a potency measure at the time
4 which we thought was indicative of the efficacy of
5 our cells and the functionality of our cells, and
6 what we saw is that the potency of cells in the
7 vial was considerably less than that made in the
8 bag, as much as 30 to 50 percent less.

9 So back to Dr. Galipeau's point about
10 freezing and potentially damaging your cells.
11 It's very important you understand how you freeze
12 and what you're trying to have your cell do.

13 So we looked into this a bit, quite a
14 bit, and the graph on the left shows in the dash
15 line the freezing chamber temperature. This is a
16 control rate freezer. And because there's a lower
17 surface area to volume ratio in the vials, what
18 you can see on the red graph is a much longer time
19 to get through the freezing, and then what ends up
20 happening -- I don't think this pointer works.
21 Oh, it does work. There we go. What ends up
22 happening is then the rate of freezing here in the

1 vials is much greater than the rate of freezing in
2 the bags. And we did some separate studies,
3 independent studies which showed that the freezing
4 rate affects potency directly.

5 So once we saw this and looked at
6 differences, we started pulling apart what
7 differences were the ones that affected the cell
8 potency? And sure enough, it's freezing rate. So
9 then we went ahead and changed our freezing
10 protocol, changed the freezing chamber profile so
11 that we can match this freeze rate that we
12 previously had in the bags which gave us what we
13 thought was an acceptable potency. And when doing
14 that, our trypan blue viability still stayed the
15 same but now our potency numbers are much better.
16 Everything was within 10 percent in a vial as
17 compared to a bag.

18 So again, trying to understand, using
19 the right comparability matrix and then trying to
20 understand the physical effects of the system on
21 your cells, and then making the right engineering
22 changes so that those effects become minimized and

1 what the cell is seeing is now very much like what
2 it would have seen before.

3 So in summary, when you make these
4 changes, it's really important you understand your
5 process. Process characterization is something
6 you should be doing from day one as much as you
7 can. I always like to tell my peers and my
8 management, whatever resources we have that's
9 excess, we're going to just do more
10 characterization. We have some minimum we want to
11 do, but we're going to be opportunistic and do
12 more so that we can solve problems proactively
13 rather than reactively.

14 Engineering approach, you obviously have
15 to understand what's affecting your cells and
16 design your systems and your parameters so that
17 you can make the same cell. Understanding the
18 science. Back to understanding how the product
19 works. Measuring the right thing. How the
20 product is affected in your system. And that
21 analytical tools are the key. You have to have
22 the right ones and enough of them.

1 So when you consider making changes, I
2 mentioned earlier it's easier to make them earlier
3 in your clinical process than later, but it's not
4 impossible to make them at any time. And of
5 course, as you go later, you're going to have to
6 scale up, hopefully. So it's really important to
7 consider the benefit of the change to the risk
8 it's presenting and then the timing of that change
9 within the clinical development spectrum. And all
10 along it's important that you must maintain
11 product quality, whether it's safety or you
12 understand efficacy, but you have to make sure
13 that at the end of the day you're making a product
14 that's going to be safe for patients, and then if
15 it's efficacious, it continues to be efficacious.

16 So just to acknowledge in the groups
17 that all contributed to the study, we have the
18 Bioprocess Development, Analytical Development
19 groups. Our production group, we have a GMP
20 facility at our site in Warren, New Jersey, and
21 the quality operation groups that go with that.
22 And I just want to note a lot of these ideas and

1 approaches are published in an online journal,
2 which you can take a look at. It was published
3 earlier this year. This journal, Bio Insights is
4 doing a four-part series. This was in the first
5 part. A four-part series on the cell and gene
6 therapy manufacturing pathway, and I think the
7 third part is about to come out. Didn't have as
8 much -- the same examples, exactly, but a lot of
9 the methodologies are there if you want to know
10 more.

11 So thanks very much. I guess we'll take
12 questions on the panel. Okay, thank you.

13 (Applause)

14 DR. GALIPEAU: I think we have to do
15 here a PC to Mac swap, so while Dennis is setting
16 himself up, I'd just like to introduce Dr. Clegg,
17 who is the founding co-director of the University
18 of California-Santa Barbara, for the Center for
19 Stem Cell Biology and Engineering. He's the co-
20 principal investigator of the California Project
21 to Cure Blindness and multi-disciplinary effort to
22 develop stem cell therapy for age-related macular

1 degeneration.

2 Dennis?

3 DR. CLEGG: All right. Thank you. And
4 I'd like to thank the organizers for the
5 invitation to speak today.

6 So I'm going to tell you about
7 development of an embryonic stem cell-derived
8 product, retinal pigmented epithelium that we're
9 growing on a scaffold for the treatment of the dry
10 form of age-related macular degeneration.

11 And one disclosure, I'm cofounder of a
12 startup company called Regenerative Patch
13 Technologies with Mark Humayun and David Hinton at
14 USC.

15 So if you go to the Internet and search
16 for cell therapy, the first thing you might find
17 is a shampoo, but I'm not talking about that
18 today. Instead, we're talking about what some
19 have called perhaps the next pillar of medicine, a
20 third pillar of medicine to go along with small
21 molecule drugs and biologics. And of course, when
22 you're dealing with cells, it's a completely

1 different situation than a small molecule or a
2 biologic.

3 And according to the Alliance for
4 Regenerative Medicine, there are over 600 clinical
5 trials underway using cells and stem cells, and 74
6 approved products already. So it's keeping the
7 FDA very busy as I'm sure they will tell you.

8 I'm going to talk about blindness, and
9 the September issue of the National Geographic had
10 a beautiful story about sort of a global
11 perspective of blindness. Roughly one in every
12 200 people on earth, 39 million can't see, and
13 another 246 million have reduced vision. And in
14 the case of age-related macular degeneration, it's
15 actually a small percent worldwide that in
16 developed countries in the elderly population it's
17 one of the leading causes of blindness.

18 If you go into the optometrist or
19 ophthalmologist and they give you that bright
20 flash, they're taking a picture of your retina.
21 It's called a fundus photo, and it looks like this
22 in a normal eye. If you have the early form of

1 macular degeneration, you see these drusen yellow
2 spots. I don't know how well that shows up. And
3 that can progress to two forms of the disease, the
4 so-called wet form where you get improper
5 angiogenesis and bleeding and the dry form where
6 you get something called geographic atrophy.

7 About 10 percent of the wet form and 90
8 percent have the dry form. Now, there's some
9 pretty good treatments already using inhibitors of
10 VEGF for the wet form, but for the dry form
11 there's really no good therapy and that's what
12 we're targeting.

13 Now, in both cases, most people believe
14 -- and there's good evidence for the theory that
15 the disease is caused by the death of RPE cells,
16 retinal pigmented epithelial cells. And this is a
17 monolayer of epithelial cells, pigmented that lie
18 right behind the retina. And you can see in this
19 diagram the RPE here are at the top. And so as
20 these disappear during age-related macular
21 degeneration, they are important support cells for
22 the photo receptors, the rods and cones here, so

1 pretty soon the rods and cones die and you lose
2 vision.

3 So how can we engineer an RPE
4 replacement for the dry form of AMD? Well, I'm
5 going to talk about two general challenges that
6 we've faced. One is the cells. How do you make
7 the cells? How do you differentiate an
8 undifferentiated stem cell and expand it to make
9 enough cells for therapy? And then, two, how do
10 you deliver it? And there are two general
11 approaches that people are taking. One is to just
12 inject a suspension and the other is to implant a
13 graft that's grown on a monolayer. And of course,
14 there are considerations if you're going to use a
15 scaffold, should it be biodegradable or biostable?

16 Well, I'm going to tell you about work
17 that was carried out, funded by the California
18 Institute for Regenerative Medicine so-called
19 disease team project that we called the California
20 Project to Cure Blindness. It's led by Mark
21 Humayun at Keck School of Medicine. And myself
22 and David Hinton are co-principal investigators.

1 And it involves in addition to USC, UC-Santa
2 Barbara; University College of London;
3 Caltech-City of Hope; and the startup company,
4 Regenerative Patch Technologies. And we've
5 benefited greatly from Jane Lebkowski, who is
6 part-time consultant for Regenerative Patch
7 Technologies.

8 Now, I'll tell you about the different
9 contributions as we go through this.

10 Well, the first question we wrestled
11 with is what stem cell should we use to make RPE?
12 And you can make RPE from both IPE and ES cells.
13 You can't make RPE from adult stem cells. We
14 chose ES cells when we started this project back
15 in 2010, and I'm going to focus on the studies
16 that we've done with the H9 cell line from
17 Wisconsin.

18 Now, the first person to report that RPE
19 could be derived from HSC was a group at ACT and
20 Irina Klimanskaya, et al., showed this figure in a
21 paper in 2004. And what they did was to grow
22 undifferentiated cells in a dish and then just

1 simply remove the FGF. If you remove the FGF, you
2 start to see differentiation into all kinds of
3 different cell types. And after about six to
4 eight weeks, they saw little pigmented patches
5 that they could pull out and expand, and they went
6 on to show that it had a mRNA profile very similar
7 but not identical to fetal human RPE.

8 So we looked at this and collaborated
9 with ACT early on, and then went on to do studies
10 on our own asking can we increase the frequency of
11 differentiation toward RPE? And then can we speed
12 up the process to make RPE?

13 And to make a long story short, we tried
14 many different conditions with this so-called
15 spontaneous method where you just remove the FGF
16 and wait. And using the right substrate and cell
17 line and media, you can get conditions where about
18 40 percent of the cells start to make pigmented
19 colonies and then by selective enrichment and
20 selective culturing methods, you can get nice
21 homogeneous cultures that are 99 percent positive
22 for RPE markers. As shown on the right here, you

1 can see staining for PMEL, a premelanosome marker
2 in green and DAPI in blue where most of the cells
3 are PMEL positive.

4 And very importantly, we didn't see any
5 undifferentiated HESC markers in these
6 experiments, and we've devised several different
7 assays to look at potential contaminating cell
8 types. The one percent we think is probably
9 neural cells. We can see some that have a
10 neurophenotype. Those are not dividing as far as
11 we can tell and we're not too worried about them.
12 And they may be RPE precursors because RPE is
13 derived from the interior neural plate.

14 I'm not going to go over all the
15 characterization, but we've looked using a variety
16 of methods at mRNAs, proteins, and functions, both
17 in vitro and in vivo, and these cells are similar
18 but not identical to fetal RPE, which we can
19 obtain and use as sort of a gold standard to
20 compare our cells to.

21 Now, one problem with this method is the
22 current method that we're using to make cells for

1 the clinic takes about six months. It's quite a
2 lengthy process. It works, but one of the things
3 we've been looking at more recently is can we
4 speed this up. And one idea is to mimic what goes
5 on during development by forcing the cells to
6 become RPE by adding growth factors to bring them
7 through these stages that normally occur in the
8 embryo. And we just published recently a study by
9 Lindsay Leach and collaborators where after 14
10 days we can get cultures that are about 90
11 percent, are positive for early RPE markers by
12 using a late WNT pathway activation and
13 manipulating FGF and WNT pathways and TGF beta
14 pathways in a progression of times that are
15 similar to what goes on in vivo.

16 But I have to say at 14 days they're
17 still not mature and we need to grow them for
18 another 60 days before they start to express
19 mature RPE markers.

20 Okay. So now on to delivery. How do we
21 install these cells for therapy, suspension versus
22 monolayer? And we had done some studies early on

1 with Pete Coffey's group at University College of
2 London and Pete's now at UC-Santa Barbara. And
3 what we're trying to do is deliver these cells
4 into what's called the subretinal space, right
5 here between the RPE and the photoreceptors. And
6 when we tried suspensions, what happens mostly is
7 that the cells clump together and don't integrate
8 into the endogenous monolayer. And these are IPS
9 RPE stain for human-specific antigen in green.
10 And you can see these clumps. And one important
11 function of the RPE is to carry out phagocytosis
12 of the outer segments. You can tell if they're
13 doing that by staining for rhodopsin and looking
14 for the red fluorescents inside the green-labeled
15 cells. And occasionally we can see that, but we
16 don't see a lot of phagocytosis. And they're not
17 oriented properly to carry that out. The apical
18 side should be right next to the photo receptors
19 and it's not in most cases.

20 So our approach has been to grow the
21 cells on a biostable scaffold made of a substance
22 called parylene. Parylene is a xylene polymer

1 that's already approved for use in the eye. We
2 collaborated with engineers at Caltech, especially
3 Y.C. Ty, to develop a scaffold that has ultrathin
4 regions so that the permeability mimics the normal
5 Brooks membrane that the RP cells lie on. And we
6 coat it with vitronectin, which allows these cells
7 to grow and polarize, make tight junctions so they
8 have apical micro villi that can interact with the
9 photoreceptors and a normal basal apical polarity.

10 So why polarized RPE on a scaffold? We
11 grow these for 30 days before implanting, and
12 studies from David Hinton's lab have shown that
13 the polarized RPE behave much more like real RPE
14 than suspension RPE. They're more resistant to
15 stress. And if you look at growth factors they
16 secrete, for example, PEDF, here is staining from
17 a polarized monolayer and here's staining from a
18 suspension. And you can see much better behavior
19 of the cells in a polarized monolayer.

20 And the parylene, we've done a number of
21 studies using this. This is used in coating
22 stents and electrodes already in the clinic, and

1 the studies that I said, show the permeability is
2 similar to Bruch's membrane.

3 We've done side-by-side comparisons in
4 the nude rat of subretinal implantation of the
5 monolayer versus the suspension, and we see
6 improved survival when the cells are implanted as
7 a monolayer. And we've shown efficacy, at least
8 proof of concept, in the RCS rat model.

9 Now, one issue with studying macular
10 degeneration is there's no perfect animal model
11 for macular degeneration. Rats don't have a
12 macula, which is the center of the retina.
13 Different structure, slightly. They're nocturnal;
14 we're diurnal. But the RCS rat has a defect in
15 the RPE. There's a mutation in the MERTK
16 receptor, and the cells can't phagocytose those
17 outer segments that I told you about. So the rats
18 are born with vision but the RPE don't work so the
19 photoreceptors die over time after about 12 weeks.
20 And so the experiment is to put in the RPE and see
21 if you can rescue those photoreceptors.

22 And a lot of studies have injected cells

1 at day 21. We had to wait till day 28 because
2 we're putting in a patch. And we made a much
3 smaller version and it's actually quite a
4 challenging surgery, but we were able to measure
5 phagocytosis, photoreceptor survival, and visual
6 function over time in this model.

7 And so first thing, can they rescue
8 photoreceptors, and this is work from Biju Thomas
9 and David Hinton, and you can see in the area of
10 the implant -- here's the implant in this section.
11 You can see the nuclei of the photoreceptor layer
12 here that are rescued where as if you look away
13 from where the implant is, you don't see that
14 nuclear layer. And this is after two months after
15 transplantation we can see rescue of those cells.

16 Are the RPE working? Well, we can look
17 at phagocytosis using the assay I showed you
18 earlier, staining for rhodopsin, and in this case
19 now the RPE is oriented properly and you can see
20 phagosomes containing rhodopsin immunoreactivity
21 in the transplant itself compared to the native
22 RCS retina where you don't see any phagocytosis.

1 And that's 60 days after transplant.

2 And we wanted to look further to see are
3 these rescued rods and cones still connected to
4 the brain? And one thing you can do is to
5 actually put an electrode in the superior
6 colliculus and measure responses to light. And
7 what we found was the area in the superior
8 colliculus that responds to light is the same area
9 that corresponds to where the implant is in the
10 retina. And these luminescence threshold mapping
11 experiments were just published in the Journal
12 IOVS by Thomas, et al.

13 Okay. So that's our efficacy. And then
14 it was a real challenge. We just heard about
15 process development and making cells large scale.
16 You can imagine there are some specific challenges
17 using a scaffold with a monolayer. And we worked
18 with City of Hope and a manufacturer spin-off
19 company from Caltech called California Memstek to
20 make a scaffold suitable for humans that's 3x6
21 millimeters, a little smaller than a penny, that
22 has a frame where it can be excised off the frame,

1 has a handle that the surgeons can grasp, and we
2 built a tool to deliver it to the eye which I'll
3 show you in a minute.

4 We worked with City of Hope. We
5 transferred our protocol to the GMP manufacturing
6 facility at City of Hope, and we introduced a step
7 where we freeze down cells as an intermediate cell
8 bank in vials and then thaw those out, grow those
9 30 days on the parylene, and they're delivered in
10 a 37 degree incubator to the point of care and
11 implanted. And we were able to complete our
12 preclinical studies and submit our IND which was
13 3,300 pages long. And I'm wondering if anyone in
14 the FDA read it from cover to cover, but I know
15 they have large teams that do this.

16 We showed efficacy in the RCS rat, as I
17 mentioned. Very important, we looked at
18 tumorigenicity in the nude rat. We wanted to show
19 we could deliver this reliably, and for that we
20 used a pig study and human postmortem eyes. And
21 the IND was cleared.

22 And I'm going to show you an animation

1 of what this surgery looks like. What is done is
2 to go in and remove the vitreous first, which is
3 the goey stuff in the middle of the eye, and then
4 inject some fluid behind the retina. And you can
5 see it's creating a retinal detachment here. And
6 that's where we're going to put our implant. So
7 you have to cut a little hole in the retina.
8 We're going to come in intravitreally. And here's
9 the implant. The surgeon trims the handle, and
10 using this special tool that we've designed, pulls
11 the implant into a cannula, and it folds up kind
12 of like a taco which protects the cells. And then
13 that's inserted through a hole in the side of the
14 eye, through the hole in the retina, and the
15 implant is extruded where it unfolds, such that
16 the apical side of these cells is directly opposed
17 to the photo receptors. The retinal detachment is
18 then closed by adding oil to the center of the eye
19 to push the retina back down and the surgery is
20 complete. There's also a laser to seal the blood
21 vessels that might have been damaged in the
22 retinotomy and then the oil is applied.

1 Okay. So we've shown in the pig that we
2 can deliver this and we've used OCT to look at the
3 implant after delivery and then cut sections and
4 looked at the photoreceptors. We can see pigs
5 with good placement show good preservation of
6 photoreceptors. And included these studies in the
7 IND.

8 So we've begun now our clinical trial at
9 USC Tech School of Medicine. It's underway. The
10 startup company is the sponsor. And I don't have
11 much time to go over the details. We're looking
12 at 20 patients in the first phase 1/2A. The first
13 cohort of 10 is 20/200 or worse. We started at
14 20/400 and now we've gone to 20/200, which is
15 legally blind. And then the second cohort will be
16 20/80 or worse. And the idea is to intervene
17 early. We're not adding photo receptors. And
18 some of these patients that are pretty far gone
19 have already lost their photoreceptors. So we
20 have to add the RPE at an early stage to rescue
21 the photoreceptors.

22 Okay. So just to wrap up, I've showed

1 you that we can make the cells and showed you how
2 we're delivering them on a scaffold and told you
3 about this clinical trial that we're starting.

4 But looking forward, I wanted to mention
5 that we're not the only ones in this space. A lot
6 of folks think that this might be a good idea to
7 use stem cells to treat the dry form of AMD and
8 there are a lot of different approaches -- people
9 using suspensions, people using different kinds of
10 cells, and IPS cells that you may have heard about
11 as well, and people using different kinds of
12 scaffolds. So we'll just have to see how these
13 work, and it's a very exciting time as phase 1
14 trials are underway.

15 So I'll just wrap up by thanking the
16 wonderful team and the California Project to Cure
17 Blindness at all those universities I mentioned.
18 The folks in my lab, including my dog, whose name
19 is Iris, and our funding sources, especially the
20 California Institute for Regenerative Medicine.

21 Thank you for your attention.

22 (Appause)

1 DR. GALIPEAU: So thanks, Dennis. While
2 Chris sets himself up. So Dr. Breuer is a
3 professor of surgery at the
4 Ohio State University. He serves as the
5 director of the tissue engineering program and
6 also director of the surgical research at the
7 Nationwide Children's Hospital, and he'll talk
8 today about the development of translation tissue-
9 engineered vascular graft.

10 DR. BREUER: Well, good morning, and
11 thank you very much for this opportunity to share
12 some of my work.

13 My name is Chris Breuer. I'm a
14 pediatric surgeon and a researcher at Nationwide
15 Children's Hospital, and I'm the director of the
16 Tissue Engineering Program at the Ohio State
17 University.

18 Tissue engineering is a
19 multidisciplinary science that attempts to
20 leverage the cells and the ability to replicate
21 and to self-organize into functional units that
22 are called tissue.

1 One method of tissue engineering uses a
2 biodegradable scaffold onto which the cells can be
3 seeded. The scaffold provides sites for cell
4 attachment and space for tissue formation and can
5 actually serve as a template that can control the
6 formation of the tissue. As the scaffold
7 degrades, neotissue forms and the resulting
8 neotissue that can then be used by a surgeon to
9 either repair or replace tissues that have either
10 been damaged, diseased, or congenitally absent.

11 For the last 20-plus years, I've been
12 working with my collaborator, Dr. Toshi Shinoka,
13 trying to apply tissue- engineering principles to
14 develop devices for use in congenital heart
15 surgery. Taken together, congenital cardiac
16 anomalies represent the most common birth defect,
17 affecting nearly one percent of all live births.
18 And despite significant advances in the
19 surgical/medical management of these patients, it
20 remains the leading cause of death in the newborn
21 period. And one significant source of
22 complications are the fact that most major

1 reconstructive operations require the use of
2 synthetic manmade materials in the form of either
3 vascular grafts, vascular patches, or replacement
4 heart valves. And complications associated with
5 the use of these materials are a significant
6 source of post-operative morbidity and mortality.

7 We developed the first tissue-engineered
8 heart valve, and then subsequently the first
9 tissue-engineered blood vessel designed
10 specifically for use in children. Our scaffold is
11 fashioned from polyglycolic acid fibers, which are
12 coated with a copolymer of polycaprolactone and
13 polylactic acid, and they degrade by hydrolysis
14 once implanted in the body. It takes about six to
15 eight weeks for the scaffolds to lose their
16 biomechanical integrity and about six months for
17 the fibers to disappear completely.

18 My colleague Dr. Shinoka performed the
19 first implantation of the tissue-engineered
20 vascular graft in a child at his home institution,
21 the Tokyo Women's Hospital. In this particular
22 case, he used our original method where he

1 harvested a biopsy of a small blood vessel from
2 this child. He then isolated the cells by
3 explanting the tissue and then expanded the cells
4 by serially passing them in culture. Once he
5 achieved a significant number of cells, he seeded
6 the scaffold and then incubated the scaffold
7 outside of the body for a period of time before
8 implantation. And he used this to replace a
9 portion of the pulmonary artery in a child
10 undergoing congenital heart surgery and the
11 clinical results were excellent.

12 He used this technique on several more
13 children and it worked well, but ultimately, he
14 abandoned this technology for several reasons.
15 One is its utility was quite limited due to the
16 large amount of time required to make one of these
17 blood vessels that took a couple months. Two,
18 because the cells needed to be cultured for such
19 long periods of time, there were insignificant
20 risks of potential contamination or even malignant
21 dedifferentiation. But the real nail in the
22 coffin was the fact that sick people had sick

1 cells and he had multiple children that came in
2 for this procedure but he couldn't passage
3 adequate number of cells in order to create the
4 tissue-engineered vascular graft.

5 So we began to explore alternative cell
6 sources and came upon the fact that you could
7 actually use bone marrow, or more specifically,
8 bone marrow-derived mononuclear cells to perform
9 the same procedure. You could seed these cells
10 onto the scaffold and use them to form neovessels.
11 And the bone marrow-derived mononuclear cells had
12 the distinct advantage that they were available in
13 such abundance that they didn't need to be
14 expanded in culture. So from a single bone marrow
15 aspirate, we could obtain enough cells to actually
16 seed our scaffold and implant it immediately, and
17 this dramatically reduced the amount of time
18 needed to make one of these grafts.

19 Using this technique, he initiated the
20 first clinical trial evaluating the issue of the
21 tissue-engineered vascular graft in an operation
22 called the Fontan operation. And this particular

1 clinical target was chosen for two reasons. One,
2 it's one of the more commonly performed operations
3 in congenital heart surgery; and two, it had an
4 excellent safety profile. You see, in the Fontan
5 circulation, the graft is used to connect the
6 inferior vena cava to the pulmonary artery, so
7 it's a large blood vessel with a high flow, so
8 there's a low chance of catastrophic graft
9 occlusion due to thrombosis. And it's also
10 implanted in a low pressure system so the chance
11 of aneurism formation or graft rupture is
12 significantly lowered.

13 Clinical results, the one year follow up
14 on the first 25 patients implanted with these
15 grafts were quite good. There were no
16 graft-related deaths or graft failures. The one
17 graft-related complication as demonstrated in the
18 CT angiogram, a patient developed a partial
19 neurothrombosis, which was successfully treated
20 with anticoagulation and went away. Long-term
21 results were interesting. We demonstrated that
22 the tissue-engineered vascular graft did possess

1 growth capacity, making it uniquely suited for
2 these particular applications and for use in
3 congenital heart surgery.

4 Long-term follow up also demonstrated
5 that the primary graft-related complication was
6 stenosis, and now some of these patients are up to
7 14 years out and our incidence of stenosis is up
8 to about a third of these patients. Fortunately
9 patients that develop stenosis can be adequately
10 treated with angioplasty, but this is an invasive
11 technique, and as we move forward, if we really
12 want this to be widely used, we need to develop
13 tissue-engineered vascular grafts that possess
14 growth capacity but don't stenose.

15 In 2007, I recruited Toshi back to the
16 United States to join me and together we went to
17 the FDA. And not surprisingly, they had some
18 issues with our technique for making the grafts.
19 The grafts proceeded using a manual technique, and
20 the graft actually had to be palpated with your
21 hands in order to get the cells to go into the
22 hydrophobic scaffold. The FDA suggested that this

1 might not be the best method moving forward. So
2 we went back to the drawing board and developed an
3 operator independent method using vacuum seeding
4 to seed the scaffolds and developed GMP compliant
5 methods for making our tissue-engineered vascular
6 grafts. And in the summer of 2007, implanted the
7 first tissue-engineered vascular graft in the
8 United States in a little three-year-old girl who
9 had a single ventricle cardiac anomaly and was
10 undergoing Fontan surgery. And six months after
11 surgery, the patient was doing quite well, and
12 she's actually completed enrollment in the study
13 and is now five years out. And this is an MRI
14 demonstrating a widely patent graft that has
15 increased in length as this child has grown in
16 size.

17 As we would have predicted, some
18 additional patients in our trial have developed
19 stenosis, similar to the Japanese trial. You can
20 see an angiogram of one of these patients.
21 Fortunately, these patients have all been able to
22 be successfully managed with angioplasty and

1 continue to do well.

2 This is a post-angiogram picture
3 demonstrating that the stenosis can be cured with
4 the angioplasty. And this is that little patient,
5 Anderson, six months after his angioplasty.

6 About 12 years ago, with the help of the
7 NIH, we began a series of investigations that
8 tried to get at the cellular molecular mechanisms
9 underlying neotissue formation, and specifically,
10 the cellular molecular mechanisms underlying
11 stenosis to see if we could stop being so empiric
12 and actually enact rational design. And based on
13 a mechanistic understanding, develop methods for
14 making tissue-engineered vascular grafts that
15 might not stenose.

16 And to this end, we needed to develop
17 mouse models to take advantage of the vast number
18 of molecularly agents that are readily available
19 in mice that aren't available in other species
20 that can enable things like cell tracking.

21 We needed to develop methods for
22 fabricating our scaffold on a much smaller scale,

1 and we needed to develop murine models and
2 microsurgical techniques so we could, in fact,
3 study these. And we were ultimately able to
4 develop an inferior vena cava interposition graph
5 model that worked quite well for this purpose.
6 Results of implantations of the grafts in the
7 mouse models seemed to be fairly similar to our
8 human experiences and that some of the graph
9 stenosed. And we were finally armed with the
10 tools that would enable us to ask and answer some
11 of the basic questions that we had wondered about
12 for quite a long time.

13 Our first question was what was the fate
14 of the cells that were seeded onto the tissue
15 engineered vascular grafts? According to classic
16 tissue-engineering paradigm, the cells seeded onto
17 the grafts are supposed to be the source of the
18 tissue, the building blocks upon which the tissues
19 are made. To test this question, we created a
20 chimera by making our tissue-engineered vascular
21 grafts with human bone marrow-derived mononuclear
22 cells but implanting them in an immunocompromised

1 SCID beige mouse model that readily accepted the
2 xeno transplant. And then using human- specific
3 markers to track the fate of the cells. And what
4 we discovered to our surprise is that the cells
5 actually disappeared and disappeared quite
6 rapidly. Nearly 99 percent of the cells were gone
7 within the first day. We wondered if this might
8 be an artifact of this complex model, so we
9 repeated the study using several different
10 techniques, including labeling the cells with
11 superparamagnetic iron oxide particles, and
12 certainly monitoring the grafts with MRI over
13 time. And each experiment showed the same thing.
14 The seeded cells disappeared very rapidly.

15 If the seeded cells weren't the source
16 of the vascular neo tissue, what was? We had
17 multiple hypotheses, but one was that they might
18 be arising from the native vessel necks into which
19 the vascular graft was implanted. To test this
20 hypothesis, we took a cuff of labeled blood vessel
21 and sewed it to our tissue-engineered vascular
22 graft and then implanted this composite graft into

1 a nonlabeled host. And what we discovered is that
2 the cells within the tissue- engineered vascular
3 graft, the neo tissue, did possess label and
4 co-localized for markers for endothelial cells and
5 smooth muscle cells.

6 So ultimately, the vascular neo tissue
7 is arising from the neighboring blood vessel. So
8 this really resulted in a paradigm shift.
9 Originally, we had assumed that the cells that we
10 were seeding onto the grafts were very important
11 for the tissue formation, but instead what the
12 seeded scaffold was doing was enabling tissue
13 regeneration.

14 The next obvious question was did you
15 even need to see the cells at all? And in our
16 initial pilot studies with large animals we would
17 always include an unseeded graft, and frequently
18 these grafts would fail. But when we did a larger
19 study using our (inaudible) models, what we
20 discovered was that the seeded cells, in fact, are
21 not needed for vascular neo tissue formation. But
22 very importantly, they inhibited the formation of

1 tissue- engineered vascular graft stenosis. So
2 there might be something there in our efforts to
3 try and improve the design of this graft.

4 We also observed at this time that most
5 of the cells during the early period of tissue
6 formation were actually immune cells, specifically
7 monocytes and macrophages, and the degree of
8 monocyte and macrophage infiltration actually
9 correlated with a degree of stenosis. And
10 furthermore, the seeded grafts had less cellular
11 infiltration and better patency, suggesting that
12 perhaps this was an immune-mediated phenomenon.

13 To determine whether this was
14 correlative or causative, we went back to our
15 mouse model. And we implanted our
16 tissue-engineered vascular grafts and monitored
17 tissue formation. Then we used a type of drug
18 called quadrinate. Quadrinate liposomes, which
19 are a selected macrophage poison. We did this
20 with the hope that we could knock down the
21 macrophage infiltration and decrease the incidence
22 of stenosis. But to our surprise, this had such a

1 powerful effect that it actually stopped tissue
2 formation. There was no tissue formation in the
3 animals that were treated with the quadrinate,
4 suggesting that not only were the macrophages
5 important in the formation of tissue-engineered
6 vascular graft stenosis, but they were essential
7 for vascular neo tissue formation.

8 To confirm these findings and validate
9 this discovery, we used an inducible conditional
10 monocyte knockout mouse and implanted our
11 tissue-engineered vascular grafts and observed
12 exactly the same phenomenon.

13 So identification that the macrophages
14 are really the critical cells in this process
15 prove really to be a very important discovery and
16 have enabled us to start to perform rational
17 design.

18 From an engineering perspective, there
19 are only three ways that we can try and affect the
20 host macrophages. We can do it with our cell
21 seeding. We can do it with our scaffold design.
22 Or we can try to manipulate the host through

1 pharmacologic methods to alter the macrophage
2 response and control the formation of tissue.

3 Our studies into cell seeding have been
4 quite interesting. It's embarrassing that this is
5 a publication from this year, but we finally went
6 back and did the basic study of looking at cell
7 dose. And what we discovered is that the cell
8 dose, the more cells we see on the graft, the
9 lower the incidence of stenosis. So there is a
10 cell dose response. So this provides one viable
11 strategy for inhibiting tissue-engineered vascular
12 graft stenosis.

13 Altering scaffold designs, another
14 viable strategy. When the tissue-engineered
15 vascular graft is implanted in the host, it
16 induces a foreign body reaction, and it's well
17 known in the literature that the chemical
18 composition, in addition to the morphometric
19 characterization of the scaffolds are ways of
20 altering the macrophage response to the scaffolds.
21 So simple things like the fiber diameter of the
22 scaffold, the porosity of the scaffold, or even

1 the fiber alignment of the scaffold are effective
2 strategies for changing the degree of macrophage
3 infiltration and altering tissue formation.

4 But when you think about this, there are
5 so many parameters that if you try and take an
6 empiric approach and attack these one at a time,
7 there would be an infinite number of experiments.
8 So we've actually turned to computational modeling
9 and have now developed a mathematical model that
10 can actually accurately describe tissue formation
11 in our tissue-engineered vascular grafts, and we
12 are currently using this model to optimize the
13 design of our scaffold, and we think this holds
14 great promise for moving forward.

15 Finally, we've probably had our best
16 results by altering the host pharmacologically.
17 Initially, as I mentioned, we discovered that the
18 macrophages are critical to tissue formation. We
19 tried to modify or inhibit macrophage infiltration
20 using the quadrinate liposomes, which was an
21 effective strategy for inhibiting stenosis but it
22 was too heavy a hammer. So we began to look at

1 what other signaling pathways were involved within
2 these macrophages and discovered that the TGF data
3 pathways were very, very important. And
4 subsequently started looking at different
5 inhibitors of the TGF beta receptors. And we
6 discovered that a small molecule that inhibits the
7 TGF beta one receptor was actually quite effective
8 inhibiting stenosis but didn't adversely affect
9 neotissue formation, providing another strategy
10 for moving forward.

11 And interestingly, when we characterize
12 the macrophages from these cells, not only did it
13 alter the degree of macrophage infiltration but
14 there was a certain phenotype that was very, very
15 important and associated with the development of
16 stenosis versus nonstenosis.

17 Most recently, we've been able to do the
18 same thing using losartan. We think this is an
19 off-target TGF beta effect of the losartan, but
20 this is an important discovery because the use of
21 losartan is already FDA approved and has an
22 excellent safety profile in our patient

1 population.

2 We've also continued to try and do
3 process improvement, to modify the way we make our
4 grafts. One of the unintended side effects,
5 developing our GMP methods for making the
6 tissue-engineered vascular grafts is that it takes
7 a lot longer to make the grafts than in the
8 original Japanese studies. In the Japanese
9 studies, the grafts could be -- the cells could be
10 harvested, isolated, seeded, and the grafts were
11 ready for implantation within a little over two
12 hours. Currently using our technique takes us
13 about six hours, which is feasible but does
14 present some problems and some additional
15 potential complications for these patients.

16 One of the reasons why this technique
17 takes so long is because we use density
18 centrifugation and Ficoll and this is a
19 labor-intensive process that adds time and
20 complexity to the procedure. So we began looking
21 at alternative methods. There is a filtration
22 elution method, a filter that can be used to trap

1 the mononuclear cells from the bone marrow and
2 then these cells can be eluted off the filter and
3 collected in a seeding chamber. And we
4 demonstrated that while there are some differences
5 in the cell populations obtained using these two
6 different methods, that biologically they're the
7 same. They form excellent vascular grafts in both
8 small and large animal models, and that they both
9 function by altering the macrophage response. But
10 they have the added advantage that it's a much
11 simpler technique and can save substantial amounts
12 of time.

13 So how do we roll out these findings
14 from the bench to the bedside? Well, I think it's
15 already been mentioned that one of the primary
16 problems with any animal study is the question of
17 relevancy. You know, mice aren't small humans,
18 and sometimes discoveries made using murine
19 models do hold true for humans but other times
20 they don't. How can you actually validate these
21 discoveries?

22 Well, one method is to use human tissue.

1 And this year for the first time one of our
2 patients died from a non-graft-related
3 complication and consented to an autopsy. So for
4 the first time we actually have human neotissue
5 that can be examined. And the resulting vascular
6 graft is beautiful. The neovessel looks like a
7 real blood vessel, both grossly and
8 histologically. It's got a monolayer of
9 endothelial cells surrounded by concentric layers
10 of smooth muscle cells. It's got a similar
11 extracellular matrix. But being able to examine
12 this tissue and look at some of these
13 characteristics has been very helpful in trying to
14 validate some of our work.

15 A more traditional method in the United
16 States is to do validation work with large animal
17 models. For our tissue-engineered vascular graft,
18 we've developed a lamb model which seems to be a
19 very relevant and important model. And we've used
20 this to validate some of our discoveries or some
21 of the changes that we're trying to implement like
22 the use of a filter.

1 And finally, in some studies where the
2 risks are able to be calculated and are fairly
3 minimal, it can be appropriate to go directly into
4 man.

5 So how do we suggest putting all these
6 pieces of the puzzle together and moving forward?
7 Well, we feel we've reached a point in our study
8 where we know that stenosis is a critical issue.
9 And we're interested in carefully rolling out
10 these different strategies that we've developed in
11 the clinic. And we thought it'd be best to start
12 simple. We think some of our process improvement
13 measures, such as changing to the filtration
14 method, seeding more cells, and eliminating the
15 incubation period are logical and safe ways of
16 potentially bringing these discoveries into the
17 clinic. And then if, and as needed, adding
18 additional therapeutics, such as the use of
19 losartan in our patient population in an attempt
20 to improve the design and develop our second-
21 generation tissue-engineered vascular grafts.

22 So what lessons have we learned? Well,

1 I think one, this is a high risk, high reward
2 game, and that anything you do, or anything you
3 don't do, has very, very significant consequences.
4 It's important that we try and push forward but do
5 it in a safe and careful way.

6 Two, you always require a leap of faith.
7 No matter how robust your data, no matter how long
8 you've been doing this, at some point you just
9 have to move forward. And you know, this is the
10 sort of thing that causes handwringing and keeps
11 you up in the middle of the night but it's part of
12 the game.

13 Three, it's very interesting doing this
14 work with congenital heart surgeons. They're
15 about as polar opposite as you could be from
16 somebody trying to do a well-controlled study.
17 You know, it's in their DNA. Every single
18 congenital heart defect is different, and so when
19 they get in there they have to be able to change
20 on the fly. And you know, to come in with this
21 protocol or trying to do things the same way,
22 sometimes I feel like the guy in this video.

1 (Video shown.)

2 DR. BREUER: But the single most
3 important lesson that I've learned, and I think if
4 I had to say one thing today it's this -- it's
5 that translational research has to be a two-way
6 street. You need to be able to go from the bench
7 to the bedside and back again on a very routine
8 basis and that no matter how strong your data,
9 really at some level the experiments don't even
10 start until you get into humans. And at that
11 point you need to be able to identify where your
12 problems are and you need to be able to go back to
13 the lab and develop rational solutions for
14 overcoming your problems. And that's how we're
15 going to safely help our patient populations.
16 Thank you.

17 (Applause)

18 DR. GALIPEAU: So thank you, Chris. I'd
19 invite the speakers that spoke this morning to
20 come up front, please. So for people in
21 the audience, the idea of the
22 panel that follows now was to sort of

1 have an open-ended discussion with panel members.
2 And we felt that maybe a structured approach to
3 this would be productive to get a lot of ideas
4 out. At first we had some set questions that I'm
5 going to be posing to the audience, the panel, and
6 afterwards we can open it up to the audience if
7 there are some pressing questions from
8 individuals.

9 So let me kick it up here. So one of
10 the questions that we wanted aired was -

11 - and I'm asking everybody that's
12 sitting here. Based on your experiences, what
13 advice do you have for product developers, whether
14 it be academic or industry, promising
15 manufacturing changes? The idea of course is to
16 get a better mousetrap moving forward. So to the
17 panelists, what's your advice?

18 The guy from industry first. There you
19 go.

20 DR. RUSSOTTI: Thank you. So just one
21 point, I guess, I already made in my talk that I
22 think is first and foremost is I would not try to

1 make the perfect process to get into the clinic.
2 I think an important strategy is to get answers
3 quickly. So don't worry about costs and capacity
4 when you first start out. I think it's more
5 important to learn. Of course, you have to make
6 good quality product, and of course you care about
7 safety, but I think it's important, and I think
8 this leads to another question we're going to
9 discuss later about iteration. I think it's
10 important to get answers as quickly as possible
11 because as we heard this morning, animal data is
12 great but it's not always predictive. The best
13 data is in humans. So get in early, learn,
14 iterate in the background, then work on better
15 processes and plan for success when the time is
16 right.

17 DR. GALIPEAU: So Chris, actually, you
18 had to do like a full like 180. You started off
19 with a cellularized graft and then you realized
20 well, we don't need the cells because it's a host
21 immune response to the cellularized graft. How do
22 you manage that moving forward trying to get the

1 ball rolling because you're working on IND and you
2 want to treat people? So how was that interaction
3 and dealing with the FDA?

4 DR. BREUER: The FDA has been a
5 wonderful partner. You know, I think we're both
6 on exactly the same page. We want to help
7 patients. And I think the road to perdition is
8 paved with good intentions. I think everybody
9 goes into this and is driven by their enthusiasm.
10 They want to do the right thing. But it doesn't
11 always work out that way. And I think having
12 somebody that can second guess you and look at
13 your work critically and then, you know, provide
14 additional controls is very, very important for
15 moving forward and making good progress. I also
16 think it's incredibly important if at all possible
17 to understand mechanism. If you can understand
18 mechanisms of action, not only does it help you in
19 developing your process, but if things don't work,
20 a lot of times you can potentially throw out a
21 very valuable technology. And if you understand
22 how the mechanism of action works, then you can

1 figure out why something doesn't work and then
2 improve your design.

3 SPEAKER: Could I ask a quick follow-up
4 to that?

5 (Inaudible) by the way. I'm just
6 kind of curious. You mentioned
7 that the

8 FDA -- said that the two-hour procedure
9 was maybe not the best method and they recommended
10 the GMP method. The thing that I didn't
11 understand from that was I didn't hear you say
12 that there was a practical problem of doing it

13 (inaudible) complications. I'm
14 curious. It wound up being
15 disadvantageous to patients in the
16 sense it was six hours instead of
17 two as we've said. Was there some
18 reason that that alteration was
19 made other than the theoretical?

20 DR. BREUER: Fortunately, there were no
21 graft complications using the non-GMP method that
22 was performed in Japan, but I think it's only a

1 matter of time. And I think the added benefit of
2 doing things in a GMP-compliant method speak for
3 themselves. I mean, it was absolutely the right
4 thing to do and absolutely the right way to go
5 forward.

6 I think now the onus is on me to figure
7 out how to do it faster and better, and we're in
8 the process of doing that. But especially in the
9 early phases, you know, following and tracking all
10 the data and making sure we have all the quality
11 control and quality assurance measures put in
12 place and having good release and post-process
13 monitoring testing in place is the only way it can
14 make sense.

15 You know, the Japanese trial was very
16 intriguing, but it was very poorly performed.
17 There's excellent patient follow-up. All 25
18 patients have been followed up through now 14
19 years, but again, it's congenital heart surgery.
20 So you know, everybody was followed up in a
21 different way. There weren't great release
22 criteria, so the data's flawed. And I think doing

1 it the way that I developed it in collaboration
2 with the FDA is the right way of moving forward.

3 DR. GALIPEAU: So a follow-on question
4 to that was are there ways the FDA and academic
5 and industrial stakeholders can foster open access
6 for novel development of tools, the CMC,
7 toxicology, clinical? Now, open access is
8 actually big deal. And you know, Dr. Matthay
9 spoke to that point this morning that academics
10 are compulsive showboats and published and dock
11 publicly and posters and do everything else while
12 industry for, you know, obvious IP protection
13 reasons sometimes are going to be more discreet.
14 So maybe Mike, I'll let you just kick off. What
15 are your thoughts here?

16 DR. MATTHAY: Well, I think it's not
17 we're just showboats. We have to show for our
18 peer review publications the details of our
19 methods. And that's good. And we need industry
20 very, very much. We can't go without industry.
21 But I do think once the IP is established there
22 should be a mechanism in cell therapy for the

1 pathways that the particular industry or company
2 has used to be more in the public domain. I don't
3 think that would interfere with the patent, and I
4 think it would really help both the companies
5 involved and the academics. I'm not quite sure
6 how to do that. I'd like to know what FDA thinks
7 and what others think.

8 DR. GALIPEAU: So panelists, anybody
9 else who would like to -- Irv, you had some strong
10 feelings about those things.

11 DR. WEISSMAN: Well, I think I said at
12 least for the cell types that I've been dealing
13 with, the stem cells, they organize themselves if
14 you get them in the right place. So for the cell
15 types we've looked at, making scaffolds is not
16 necessary. You put blood-forming stem cells into
17 the blood. They have homing receptors that make
18 it to the bone marrow. We didn't know if you put
19 neural stem cells into the brain if they could
20 find the right place, and mainly we located them
21 where they should be. But in both of those cases,
22 blood forming and brain forming, academic success,

1 discovery, preclinical discovery, even early
2 successful clinical trials have not led to a
3 single therapy. It's not the FDA that's the
4 problem; it's our culture that we try to get our
5 discoveries out early.

6 Second, and this is really important,
7 NIH, although it wishes to support clinical
8 translation, hardly supports at the level that's
9 necessary. That's why we began proposition 71 in
10 California, to try to get funding in via the state
11 so that you could carry it in a not-for-profit
12 setting until you got into mid- to late-phase,
13 phase 1 clinical trials when any fool would notice
14 that you had a success. When I say "any fool," I
15 mean any fool. The most likely problem you have
16 when you try to build something that will be
17 therapeutic in humans is that you have your
18 leaders, your business leaders, even your CMOs,
19 that come from an industry that was small
20 molecule-based, not cell-based. And so they
21 always live by the culture they grew up with and
22 that made them successes in the recent past. But

1 it doesn't work.

2 So just as an example, not one of the
3 small molecule pharmaceutical companies developed
4 a protein therapeutic. There were new names --
5 Amgen, Genentech, Biogen. You know, all of those,
6 because the culture wasn't there. And none of the
7 protein therapeutics have even ventured companies,
8 have ventured into a cellular therapeutic. But
9 the cellular therapeutics as you just said,
10 requires a whole team, a herd of cats, people who
11 are MDs, who will try to take the lessons they
12 know about the pathology of the disease and advise
13 you how to go next to try to treat the disease
14 while you're trying to bring in your cellular
15 therapy.

16 Now, we do have cultures that create
17 silos. Companies are absolutely great at making a
18 silo so that research hardly talks to development,
19 hardly talks to operations. And hardly any of
20 them get to talk to a CEO who wants to funnel
21 everything and keep the process to him or herself.
22 I know I'm being very negative here but the stakes

1 are incredible. That is that we have developed
2 scientifically -- we, the community, not just me
3 -- things that should be making their way. And
4 the surprise was the FDA was our partner in every
5 one of them, not the barrier. The barrier is how
6 we finance clinical translation. How we train
7 people to be translators.

8 I went to medical school a long time
9 ago, but even the medical students at Stanford now
10 don't learn clinical trials. They don't learn
11 everything that starts with, I have an idea. I've
12 got to now set up a clinical trial. I have to go
13 talk in my pre- pre-IND. I have to worry about
14 pharmacology, PK/PD, viability. All of the issues
15 we don't train. That may be boring training if
16 it's didactic, so maybe it needs to have like
17 business or law, case-by-case approach so it's
18 exciting. But unless we move those fundamental
19 problems, I don't see how we're going to move this
20 fast enough to save the people while we're still
21 alive to watch it happen.

22 DR. GALIPEAU: So, Dennis, go ahead.

1 DR. CLEGG: Yeah. I just wanted to
2 follow up on something that Irv said, you know, in
3 terms of teamwork. That's been super important in
4 our project, and it's a concept that CIRM --
5 really embraced with their disease team grants and
6 provided the funding. But coming from an academic
7 perspective, that's a challenge. I mean,
8 academics are raised in a competitive environment
9 where they have to write grants and get their
10 papers out before their competitor. And we were
11 fortunate to actually approach our competitor and
12 collaborate with them, which turned out to be
13 great collaboration. But I know that's not always
14 easy. And I also want to second what Irv said
15 with regard to the FDA coming into it, I didn't
16 know what to expect from the FDA and they've been
17 super helpful and helped us all along the way.

18 DR. GALIPEAU: So actually, go ahead.

19 DR. RUSSOTTI: So just to comment on
20 some of Irv's thoughts about doing things in a
21 nontraditional way. I think he's absolutely
22 right. You can take a small molecule or even a

1 biologic mindset when developing cell therapies.
2 Obviously, you can take your learnings and apply
3 them. So I was very fortunate. I worked at Merck
4 for a number of years before I went to Celgene to
5 lead a process development group in cell therapy
6 and at Merck I worked on highly complex biologics,
7 live virus vaccines. So a lot of the principles
8 applied on the CMC side.

9 But I think when you look at the
10 industry players that have gotten into this, and
11 if anybody from large pharmacy that's been in and
12 out of it, I'd be curious to hear your point of
13 view because I think Celgene is becoming large
14 pharma, but when I started at Celgene, Celgene was
15 less than a thousand people. Now it's over 7,000.
16 But what Celgene did that was very smart was we
17 made a very independent vision of the company to
18 focus on cell therapies. And we were everything
19 from discovery to clinical, regulatory, commercial
20 strategy, and the CMC that I run. And I think by
21 doing that we've allowed ourselves to grow and
22 think out of the box and develop things in a way

1 that draws upon experiences from traditional, but
2 writes a new story. And I think that's why these
3 smaller companies, and I think of our subsidiary
4 like a smaller company. These smaller companies,
5 and I won't name names. You know who the players
6 are that are well funded and are thinking
7 differently, are the ones in the best position for
8 success.

9 And I also just want to comment that
10 it's really - - really should be commended at the
11 FDA is really thinking out of the box, and I think
12 our interactions with the FDA on this have been
13 nothing but outstanding because you take guidances
14 that were written in many cases for other types of
15 therapies. They've been adapted for cell
16 therapies but they've really drawn upon
17 experiences from traditional types of biologics
18 and small molecules. And the FDA has thought in
19 an evolutionary kind of way to adapt these towards
20 cell therapies. And we've thought with them. And
21 it's been a great partnership. And I think other
22 companies would probably say the same thing.

1 We've heard our panel members from academia saying
2 the same thing. So that's not the problem.

3 I think the problem is you have to have
4 -- the solution is you have to have all players
5 thinking outside the box and this is where big
6 pharma, smaller biotech, like Celgene, have to be
7 able to put the right kinds of groups together
8 that can think creatively. And I think the field
9 is going.

10 One other account I'll make -- sorry for
11 taking so long -- is I think on the CMC side,
12 there are efforts by academic players that are
13 trying to pull consortia together which will
14 include academic partners -- there's one being led
15 by Georgia Tech, another by Wake Forest -- to
16 really focus on the CMC questions. And I hope
17 that these consortia are being built across the
18 board, not just for manufacturing, because this is
19 where we'll get many of the key academic,
20 government, industry players to work together and
21 solve these problems. It's a new field. It's
22 going to take a long time to figure it out, and

1 hopefully we've stated to turn the corner now but
2 it's going to take people working together to
3 figure it out.

4 DR. GALIPEAU: Chris?

5 DR. BREUER: Yeah, I'm not so against
6 big pharma or big device companies. I think
7 they've made a lot of great products and saved a
8 lot of lives.

9 I think there's a special place though
10 for academics, and I think one of the things that
11 I've found very enabling is the Office of Orphan
12 Products, and that it provides a more streamlined,
13 less expensive way of bringing your technologies
14 to the clinic. And it enables you to really
15 target in on the population that might not be a
16 big commercial market but could potentially
17 benefit from your specific product. And I think
18 that's one of the things that I think has been
19 done that is just incredibly enabling. It's a
20 great thing and I hope more and more people can
21 take advantage of that, especially within
22 academia.

1 DR. GALIPEAU: So actually, I'll pose
2 this question to Michael because he spoke about
3 that. So Mike, what's the relevancy of
4 preclinical animal models of predictive value for
5 human cell therapy studies?

6 DR. MATTHAY: Well, it's a good question
7 that I think applies to all of us. And there's
8 been discussion in different models. It does
9 depend very much on the questions you're asking.
10 I really like Chris's last slide here about the
11 two-way street. I think we all experienced Dr.
12 Clegg talked about this, and of course, so did
13 Irv. How we venture into the clinical setting, we
14 learn from it, and we go back to do
15 problem-solving. But I think all of us have used
16 mouse work to establish some general efficacy
17 model in most cases, or to test the mechanisms as
18 Chris described in some detail. But then it's
19 clear that in some cases going to a larger animal
20 model really is helpful. And in our case, I think
21 it was really excellent. I actually began some of
22 my research career with sheep work but then long

1 true testing of certain technology,
2 especially for immune modulation,
3 is to go fairly promptly to first
4 in human clinical trials. Speaking
5 rhetorically here, the case report
6 that Katarina Le Blanc did in that
7 trial of Graft-versus-Host disease,
8 they went in with in vitro data
9 because there were no good animal
10 models at that time. So they went
11 from in vitro data to first in
12 human. Not to belittle the utility
13 of animals to attempt to predict
14 toxicity, but in their utility of
15 (inaudible) models, mice and rats
16 in particular, it should be
17 predictive of immunology, and in
18 particular it is extraordinary
19 challenging. And you have to be
20 cognizant of the limitations. I
21 don't know what's the experience
22 with others. Limitations, maybe,

1 of animal models, or how much or
2 how little should we be put to the
3 test before promptly moving forward
4 to the people.

5 Irv, you had a thought?

6 DR. WEISSMAN: So I'll differ with you a
7 bit, or a lot.

8 There's been conservation of gene cells
9 and cell functions that you can follow, and you
10 get pretty accurate results. And then there are
11 species differences where you can't follow them.
12 And so I think you have to be aware of that as you
13 try to apply it.

14 The reason back in 1986 to 1988 that
15 Mike McCune and I made the SCIDHU mouse was we
16 knew that the hormones or the cytokines or the
17 proteins in a mouse didn't always act on the
18 receptors for those hormones or cytokines or
19 chemokines in humans. So we put in the whole
20 human fetal organ.

21 I think I've just been subpoenaed
22 recently for the use of human fetal tissues in

1 experiments. And the reason I say that is that
2 society also brings in its own cultural
3 background, and doesn't always try to look at the
4 issue in a balanced way. Meaning, how can we go
5 from an understanding of the biology to medicine
6 rather than a political or religious or a moral
7 background to allow or not allow these things to
8 go forward. You may think it's minor, but I don't
9 think it's minor at all.

10 So I think if people had picked up on
11 making SCIDHU, as we did, you would have been able
12 to work with the subsets of human immune cells as
13 Mike McCune and I did for years. We were lucky
14 enough in that model that HIV, which didn't infect
15 any animal in a productive way, infected the
16 SCIDHU mouse's thymus, lymph node, and so on, so
17 that we could follow HIV and eventually know what
18 therapies didn't work. We couldn't find the
19 therapy that would work.

20 But the important point is to be able to
21 look at what animal model you need to use to study
22 what's going on. The fundamental principles I

1 believe are the same. The exact interactions of
2 defined subsets of CD4 T-cells may not be exactly
3 the same, but conserved behaviors will be
4 conserved and will predict.

5 DR. GALIPEAU: So we have precisely 10
6 minutes left, so I'd open it up to the audience.
7 Invite people to walk up to the microphones.
8 Madam, please identify yourself before a question.

9 DR. ELGENDY: Hoda Elgendy, LifeNet
10 Health. Actually, since we are witnessing a stem
11 therapy
12 avenues and more than 70 clinical trials
13 ongoing, I think it's time to hear and brainstorm
14 and know your opinion about cell dose, especially
15 you mentioned that cell dose affects your system.
16 And in addition to cell purity index from a
17 surgeon's standpoint. And also the systemic side
18 of toxicity, knowing that those cells are baby
19 cells. They live inside the body. They may go
20 into the blood stream. Even with a scaffold or
21 without scaffold. In suspension or on a
22 monolayer. We know that. They can go especially

1 in the eyes, you know. You put it in the eyes
2 fiber blast and it could migrate on that surface
3 no matter what. If it's God-made the fiber blast
4 will come and then it will lead to blind. I
5 understand that the patient is either to be
6 terminally ill or blind as some of you mentioned,
7 but at the same time we are doing something to
8 prevent that in nonblind or semi-blind people in
9 terms of the eye.

10 So I would like in a nutshell to hear
11 your opinion about cell does and purity index and
12 cytotoxicity. Short and long-term. Thank you.

13 DR. GALIPEAU: Do you want to grab this
14 one?

15 DR. WEISSMAN: I think purity is
16 important. Or you'll never understand what you're
17 doing. I think you can work out the dose. You
18 get an approximation from the animal study but
19 then the actual first-in-human trial in a dose
20 escalation rather than a dose de-escalation. I
21 think you can get at it.

22 Toxicity, hopefully you'll see,

1 depending on the cell type you put in. Toxicity
2 hasn't been the problem for us with pure cells.
3 Toxicity is a problem of impure heterogeneous
4 populations of cells.

5 DR. GALIPEAU: Dennis? C: Yeah. In
6 our particular case, using a
7 scaffold and growing the cells for 30
8 days, they form a mature polarized epithelium
9 monolayer where they're held together by tight
10 junctions and adherent to the scaffold. And we
11 see very little cell division. And for us that
12 was a desired outcome. We don't want them to be
13 dividing. We don't want them to be migrating.
14 It's known that if RPE cells get on the surface of
15 the retina they can become myelofibrosis and
16 contract and cause a retinal detachment. That's a
17 really important problem. And if you're injecting
18 them into the subretinal space, you can get reflux
19 out and cells can come out. So we approached it
20 that way.

21 And in terms of dose for us, it's "one
22 size fits all." We made the scaffold big enough

1 to cover the geographic atrophy lesion in
2 patients, and so we didn't have to worry about
3 dosing. And then peers, as I mentioned, you know,
4 we developed assays to look at the different
5 potential contaminating cell types that might be
6 there. And one nice thing about growing these on
7 a 3x6 millimeter patch, we can look at every cell
8 on the patch using automated microscopy. And we
9 can't detect any undifferentiated antigens, and of
10 course, we've done the tumorigenicity studies to
11 make sure that the cells are not tumorigenic.

12 DR. GALIPEAU: Thank you. You've got a
13 question? Microphone number two.

14 MR. WEISS: Hi, my name is Dan Weiss.
15 And I'm a physician scientist from the University
16 of Vermont, interest in long-regenerative
17 medicine.

18 One of the reassuring things that I'm
19 hearing from this panel, and I think reflects this
20 particular audience, is the underpinning of
21 careful science as a primary guide in terms of how
22 the cell therapies are developed and brought to

1 the clinics. We all believe in the incremental
2 progress and the two-way street and like, too, but
3 it's a real world out there. And so I'm curious
4 about the position of this panel on movements
5 afoot out there currently. We may hear a little
6 bit more about it this afternoon, but to almost
7 fast-track some of the cell therapies. Things
8 like have happened in Japan and that have been
9 proposed now here in the United States with
10 something called the Regrow Act, and a simple
11 consolidation of that is to take a product that
12 made it through phase one and phase two and then
13 skip the phase three. Go directly to marketing,
14 if you will, and bring that to a needy public. So
15 I'm curious as to thoughts on this. Should we be
16 doing this? Should we put a break on this and say
17 absolutely no way; it's the wrong thing to do?

18 DR. GALIPEAU: Okay, so everybody gets
19 to put their hand in a bucket of crabs here? You
20 know, let's give Chris at the end here a chance to
21 --

22 DR. BREUER: I think it's very

1 product-specific. If you've got a disease and
2 there's nothing you can do for it and the patients
3 are going to die then, you know, have at it.

4 DR. WEISS: But that's a compassionate
5 use. That's almost a separate equal issue.

6 DR. BREUER: But I think you can do that
7 with Orphan Pathway. So in the Orphan Pathway,
8 you know, you prove safety and then you can have
9 an HDE and continue to use your product and sell
10 your product but you study it at the same time.
11 So I think it's possible to do right now. And I
12 think for the right applications it's a wonderful
13 way of doing things.

14 DR. RUSSOTTI: So I'd sure love to hear
15 the FDA's response to this. I'm just going to tee
16 it up though. I'm not a clinician. I'm a CMC guy
17 and I have been at Celgene

18 years. There's one story at Celgene I'd
19 like to share. On one of the earliest therapies
20 that Celgene was

21 approved on from one of their first
22 IMIDs, which is very effective in the field of

1 multi myeloma and related types of hematological
2 cancers, and one of the first indications Celgene
3 got approved on was on less than 30 patients worth
4 of data because it was a very clear understanding
5 of a genetic disposition of a patient population
6 that was going to respond to this therapy. So you
7 can talk about Japan all you want and the Regrow
8 Act. I think the Regrow Act is very dangerous in
9 a lot of ways but I'm not going to comment any
10 more on that. I think what's important, back to
11 science. If the science is there and the data is
12 there, the FDA will fast-track. The FDA will find
13 creative ways to get things to patients quickly.
14 So again, if the FDA wants to comment, great,
15 because they probably have more tangible stories
16 than I do. I have one that I know of very well
17 but I'm not going to comment anymore on that but I
18 think it's all about the data and we can do it.
19 We just have to have the right data.

20 DR. GALIPEAU: So it's about the
21 science. We're not going to put the FDA on the
22 spot because this afternoon they're going to be on

1 the spot with all this stuff.

2 So microphone number one.

3 DR. BERTRAM: Yes, sir. Real quick
4 question. Following up on the previous one which
5 relates to

6 dose, I think dose selection, if you
7 look at that --

8 SPEAKER: Closer to the mic.

9 DR. BERTRAM: Closer to the mic. All
10 right. One of the key --

11 THE REPORTER: Please say who you are.

12 DR. BERTRAM: Ken Bertram, RegenMed.

13 Quick question for you, really relates back to

14 dose, which is a key issue. If you look
15 at dose in clinical trial failures, whether it's
16 small molecule, large molecule, or cell-based
17 therapy, dose selection is the key reason why a
18 clinical trial fails, and so we're unable to bring
19 a particular product onto market.

20 Two-part question for you. All of you
21 looked at dose. In the cell therapies itself, did
22 any of you see any evidence of any toxicity as you

1 escalated your dose? And if you did, if you could
2 give some examples of general toxicity effects
3 that you did see.

4 DR. BREUER: No toxicity other than that
5 in my case it's autologous, so if you're taking
6 more bone marrow, your chances of a transfusion
7 are higher but there's ways around that. You
8 could reinfuse the red cells, but no other
9 toxicity.

10 DR. WEISSMAN: There was no toxicity in
11 animals or in humans with purified hematopoietic
12 stem cells. You couldn't reach a dose, give an IV
13 that would lead to toxicity if you used stem
14 cells. If you used an impure product, it's
15 completely different. When you put the cells in a
16 defined region, as we did in the spinal cord or
17 the sub-retinal, or even into the brain of
18 children, we suspect there is a cell dose issue
19 even with pure cells, but we only suspected. We
20 never got to the dose with the amount of money
21 that was there to follow. So I think it's an
22 important issue. I think you can approach it for

1 toxicity in animal models if you have the right
2 animal models.

3 DR. GALIPEAU: So our experience using
4 autologous fresh cells in Crohn's Disease, we went
5 2/5/10 million cells per kilo without a problem.
6 But then if you use autologous cell therapies
7 there's a practical limit of how much you can
8 manufacture. The limit is not so much the dose
9 but the time it takes because if you've got a big
10 fellow like me, 10 million cells per kilo is a lot
11 of cells. So to go through 20/50 -- in mice we go
12 up to 50, 50 million cells per kilo. If you go
13 above that the mice start getting sick. The only
14 other cell type that you could go off scale would
15 be universal allogenic, and I guess the only
16 company that went to high dose was what, I guess
17 Athersys went up, what, 10 million cells per kilo
18 repeatedly with their product. And that's
19 probably the higher dose of the MSC-like cells.
20 I'm not aware of anybody going a higher dose IV,
21 IV, unless somebody else has some experience. And
22 they haven't disclosed any toxicities.

1 MR. BERTRAM: Maybe rather than putting
2 forward the second question which may take time
3 and others would like to ask, one question or one
4 comment, I guess I would give not only the FDA but
5 to us as scientists trying to bring something
6 forward and actually develop it and that is
7 thinking about our dosing paradigms different. I
8 mean, Irv, as you said, we use dose escalations in
9 clinical trials. We're all faced with randomized
10 control trials. I can't help but wonder if in
11 partnership with the science we bring the
12 understandings of science forward into our
13 clinical trials so that we look at different
14 dosing paradigms, possibly dosing metrics. I
15 don't know what it is, but when I look at all
16 across all different cell types, when we get into
17 the millions and hundreds of millions, that's
18 about where we start seeing a fax, and that's
19 about where most of us considered to be probably
20 the maximum to manufacture. It may be in
21 partnering with FDA one of the things to think
22 about is what different, unique dose metrics or

1 clinical trial designs might we use in order to
2 take this very safe product generally and start
3 and advance our protocols in the humans at a
4 higher dose and look at dosing regimens in a way
5 that will allow us to actually, rather than look
6 at unsafe methods which I agree with Greg on, I
7 think Regrow has got some safe issues, but to
8 actually allow us to be able to accelerate the
9 development of these products more quickly.

10 DR. GALIPEAU: I guess the point you
11 raise has to do with the open access we spoke
12 with. Academics will publish, but often their
13 industry studies or small startups are under no
14 obligation to publish. And that data typically
15 is, for obvious reasons, kept confidential.

16 So it comes back to microphone number
17 two.

18 DR. GROSSO: Yes, Rob Grosso, Bethany,
19 Connecticut.

20 I just had a question for the panel.
21 There seems to be a great interplay between the
22 FDA and small developers, but one thing that sort

1 of came out was structure and function of cell
2 therapies. And during the process of process
3 improvement, how do you guys feel, and ladies
4 feel, about FDA guidance on process improvement
5 with structure and function in cell therapies? Is
6 there a clear guidance for you all?

7 DR. RUSSOTTI: I am not sure if I fully
8 understand the question but I think it's just
9 about back to making changes that make sense. So
10 I don't know if you want to come back and help
11 elaborate because I really don't fully understand
12 the question. I think it's back to the FDA being
13 willing to listen to science and just doing things
14 that make sense. Can you just maybe rephrase?

15 DR. GROSSO: Sure. With Irv's
16 discussion about structure and function of cells,
17 maybe as you change from one process to the other
18 in development from early bench science through
19 clinical procedure you're trying to increase
20 production. How do you guys handle guidance on
21 process improvement versus totally different
22 product? What's the --

1 DR. RUSSOTTI: Well, I don't think you
2 can do a totally different product, unless you
3 want to start from square one. I think that's the
4 whole point.

5 DR. GROSSO: Right.

6 DR. RUSSOTTI: In my presentation I
7 talked about the fact that we were trying to make
8 the same product. You have to understand what
9 your product is, number one; how your process
10 affects the product, number two; and then do
11 things that won't change the key attributes.
12 There may be some attributes that are not
13 unimportant, right, but it's all about function,
14 really. I mean, structure is nice, too, but it's
15 all about what your cells are trying to do. So I
16 think it's operating within that paradigm that you
17 have to understand your product and your process.
18 And the more you understand, the better your
19 chance will be that you'll make a change that will
20 result in the same structure and function.

21 DR. GALIPEAU: So I apologize to the
22 rest of the people lined up at microphone two

1 because we're going to take the last question from
2 microphone one.

3 DR. JONES: Thank you. Alice Jones,
4 LifeNet Health.

5 I was curious. You were talking about
6 your graft growing. What sort of objective
7 measurements did you take to discern that it
8 actually grew and perhaps did not stretch?

9 DR. BREUER: Yeah, that's a really
10 fantastic question. You know, people always say,
11 well, how do you know it's not just dilation? And
12 then it's really, really complex because the
13 inferior vena cava is like a (inaudible) so it
14 changes size and diameter all the time. So I
15 think one thing is to look at length, and that's
16 really key. Marking your grafts when you implant
17 them with something. A radiographic marker is
18 also very key. But we've got some interesting
19 data now 14 years out where we, not on purpose,
20 but did an experiment that I've always wanted to
21 do. In my mind, if I wanted to do the experiment
22 to prove growth, I'd have to take the same thing

1 and put it in an organism that's supposed to grow
2 and see that it increases in size, and put it in
3 an organism that's done growing and show that it
4 doesn't increase in size. And when we compared
5 the rate of growth in our younger patients versus
6 our older patients there was a much steeper rather
7 of growth in the children that were implanted in
8 the two- and three-year-age range compared to
9 young adults and older adolescents who had had the
10 grafts in place.

11 DR. JONES: Interesting. Did you also
12 find any commonality in the stenosis formation in
13 the patients that did become stenotic? Was there
14 some common underlying clinical feature or
15 something with the dose of the cells that was
16 delivered? And also, do you see elastin in that
17 explant?

18 DR. BREUER: We see some elastin.
19 Whether it's functional or not is always the big
20 question. And we're doing some biomechanical work
21 trying to get at that right now. The cohort is
22 too small at this point to really know who

1 stenoses or doesn't stenose, but I can't imagine
2 it doesn't have something to do with the immune
3 system, that there aren't going to be patients
4 that have a higher rate of stenosis and other
5 groups of patients that have a lower grade.

6 DR. GALIPEAU: I'm just going to have to
7 stop you at this point here. Miss, I'm just going
8 to have to stop you because we're getting a bit
9 late.

10 I know there's a lot of terrific
11 questions coming from the audience. Please, our
12 folks are going to be here for the rest of the
13 day, so walk up to our panel members and ask them
14 questions.

15 I'd like to thank all the panel members
16 for their excellent contribution.

17 (Applause)

18 DR. GALIPEAU: I apologize we're
19 breaking late for lunch, but I'm sure that our FDA
20 sponsors would like us to start on time at 1:20.

21 This closes Session 2. Thank you.

22 (Recess)

1 DR. WITTEN: Could people come in and
2 take their seats, please. We'll start in another
3 two minutes. Okay, if people could come in and
4 take their seats we're going to start with our
5 first after-lunch session which is the "Views from
6 Professional Societies," and to start off the
7 session is Dr. Jonathan Kimmelman. He's an
8 associate professor at McGill University with a
9 specialty in biomedical ethics. His research
10 focuses on ethics policy in scientific dimensions
11 of drug and diagnostic development. He chaired
12 the International Society of Stem Cell Research
13 Guidelines and his talk today is on the regulation
14 of unproven stem cell-based interventions, the
15 ISSCR, and he will also serve as the moderator for
16 the rest of this session.

17 DR. KIMMELMAN: So now for some ethics
18 to help you digest your lunch. So first I want to
19 thank the FDA for the tremendous honor to address
20 you.

21 So over the last 10 years or so there
22 have been numerous reports about clinics that are

1 offering unproven cell-based interventions to
2 patients outside the context of clinical trials.
3 Now, most of the time when we've heard about this
4 it's been in the context of far-flung locations;
5 places like Italy, Moldova, Dominican Republic,
6 Russia, et cetera., but as people like Leigh
7 Turner and Paul Knoppfler have meticulously
8 researched and demonstrated most recently in a
9 publication in cell stem cell, there are an
10 abundance of clinics within the jurisdiction of
11 the United States that are offering unproven
12 cell-based interventions to large numbers of
13 patients outside the context of clinical trials.

14 Now, there are many who would see this
15 as a good thing and there are many advocates out
16 there who would like to see the reins on providing
17 cell-based interventions to patients loosen, and
18 indeed as we've heard earlier today there have
19 been some jurisdictions that have done exactly
20 that, so for example we know in Japan that there
21 is a policy that allows cell-based interventions
22 to patients for a fee after demonstration of

1 safety in very small clinical trials, and we also
2 know that in the United States there have been
3 policies that have been floated -- not yet
4 successfully taken root but nevertheless floated
5 -- in Congress namely through the REGROW Act that
6 would also authorize in the context of
7 regenerative medicine unproven cell-based
8 interventions to patients outside the context of
9 rigorous clinical trials.

10 Now, regardless of where you stand on
11 whether these are good developments or bad
12 developments, it really invites a question, an
13 ethical question about how regulatory authorities
14 ought to establish the benchmark or threshold for
15 making cell-based interventions available to
16 patients, again, outside the context of trials,
17 and so what I want to talk about in my 20 minutes
18 is first, what is morally at stake in establishing
19 a threshold for approval of drugs or cell-based
20 interventions, and then in the second part I want
21 to explain how that moral understanding of what's
22 at stake articulates with the guidelines written

1 by the International Society of Stem Cell
2 Research.

3 Okay, so let me start with part one.
4 Typically when people talk about what is morally
5 at stake with the demonstration of safety and
6 efficacy with whatever the regulatory standard is
7 for allowing a drug or cell-based intervention to
8 be marketed, there are sort of four kind of
9 narratives or typical arguments people tend to
10 hear that kind of organize the moral debates.

11 The first one is that there's a tradeoff
12 between private interest and public interest. On
13 the one hand you have the interest of patients who
14 have very serious life- threatening disorders.
15 You have them wanting to exercise their autonomy
16 to get access to potentially life-saving
17 interventions traded off against the interest in
18 the public in being protected from unsafe and
19 unproven interventions, and in this way of
20 understanding what's morally at stake you can
21 think of the drug innovation as kind of a zero-sum
22 game. Whatever you do to increase the private

1 autonomy, the personal autonomy of patients is at
2 the expense of the public interest.

3 Now, the second common narrative one
4 hears is that there's a tradeoff between caution
5 and innovation. You can have a really cautious
6 regulatory environment, one that keeps us really
7 safe but that doesn't really allow the flourishing
8 of research and innovation, or you can have a
9 highly-innovative environment, but if we're going
10 to do that we're going to have to make peace with
11 the fact that people may be actually harmed in
12 that process.

13 A third really common narrative one
14 hears and that context often, again, it's kind of
15 zero-sum game; whatever you increase in caution
16 you do at the expense of innovation. Now a third
17 common argument one hears is that it's really a
18 matter of patients versus bureaucracy, of patients
19 with felt medical needs, caregivers who want to
20 advocate for those patients versus governments
21 that had a logic that may be disconnected in some
22 way with the very intense needs and yearnings of

1 patients and other caregivers. And the third
2 argument one often hears is that it's really a
3 matter of demonstrating safety versus requiring
4 efficacy; that one option is to allow cell-based
5 interventions or drugs to be approved on the basis
6 of safety, leave it to the marketplace to sort out
7 whether they're efficacious, or we can have
8 regulatory standards that really require
9 demonstration both of safety and efficacy.

10 Now, what I want to suggest is that each
11 of these different ways of trying to frame what is
12 at stake in regulatory standards is really
13 deficient on understanding the problem. So first
14 let's take the issue of private versus public
15 trade-off. The fact of the matter is that the
16 vast majority of interventions that are put into
17 clinical development in areas where the clinical
18 need is the greatest fail to vindicate their
19 clinical promise in rigorous clinical trials. So,
20 for example in cancer, for every 20 new drugs that
21 are put into clinical testing only about 5 percent
22 will actually demonstrate safety and efficacy in

1 trials.

2 Now, once we move into the realm of
3 things like neurodegenerative disorders which is a
4 thriving market for unproven cell-based
5 interventions, the numbers have to drop to less
6 than 1 percent. There's very little we can do for
7 neurodegenerative disorders that at least have a
8 neurological basis of their cause.

9 And in fact where we have been able to
10 be successful with translating complex
11 interventions, it's taken an enormous amount of
12 time. So for example, the very first gene therapy
13 clinical trial was conducted in 1989. That was
14 the year that song "Love Shack" was at the top of
15 the charts, so you can imagine at this point to my
16 knowledge there are no FDA-approved gene
17 therapies. Is this correct? Okay, so although
18 there are some very, very promising and exciting
19 gene transfer techniques, some of which actually
20 show tremendous promise for very niche disorders,
21 it gives you some sense of the scale, the timeline
22 that it takes to unlock the clinical utility of

1 very complex interventions, so it's not clear to
2 me that patients -- the (inaudible) of patients
3 have access to unproven cell-based interventions
4 or drugs necessarily deprives them of medical
5 opportunities. It may deprive them of a choice,
6 but it doesn't deprive them of access to a
7 life-saving intervention.

8 The second issue about caution versus
9 innovation; this assumption is that regulation in
10 some way stymies innovation, but the fact of the
11 matter is, at least in my analysis, there are many
12 ways that oversight actually enables the very
13 conditions under which innovation occurs, and
14 there are a number of different arguments by which
15 I can cash this out. One that I'm going to make
16 right here is just the simple notion that if you
17 are a for-profit company and you know that you're
18 going to get data exclusivity, exclusivity on your
19 product, if you demonstrate safety and efficacy of
20 your product you have an enormous financial
21 incentive to generate high-quality evidence about
22 how to unlock the clinical utility of your

1 intervention. So, maintaining stringent
2 regulatory standards creates incredibly strong
3 financial incentives for companies to generate
4 evidence, and this is just one way that stringent
5 regulatory standards actually drive innovation as
6 opposed to impeding it.

7 Another critical way, just to mention
8 really quickly, is that it ensures that by
9 maintaining high standards requiring demonstration
10 of efficacy it ensures that you maximize the
11 information you get for exposing each patient to
12 unproven cell-based interventions; that is if you
13 only allow patients access in the context of
14 clinical trials you're gathering important
15 information about safety and efficacy. If you
16 allow that efficacy information to be collected
17 outside in the marketplace, you're diminishing the
18 efficiency with which we are actually gathering
19 important information about the properties of
20 these interventions.

21 Finally, I think critics who would see
22 that there -- as an argument -- there's a tradeoff

1 between innovation and caution should address the
2 fact that the USA enjoys one of the strictest
3 regulatory regimes for drugs and cell-based
4 interventions and yet has one of the most vigorous
5 innovation enterprises, so it's not clear to me
6 that one can argue that stringent regulatory
7 standards by themselves stifle innovation although
8 of course there are some regulations that are
9 better than others.

10 Okay, what about the issue about
11 patients and bureaucracy? Certainly there are
12 many patients that organize patient groups who
13 argue vociferously that we ought to diminish the
14 standards or requirements for making cell- based
15 interventions available to patients, and I think
16 these are voices that we need to take very
17 seriously and we need to listen to, but it's not
18 clear to me that patients with these organizations
19 necessarily are democratically elected to
20 represent the opinion of all patient groups.
21 Certainly I know many patients in my personal
22 experience, in my family who have had serious

1 life-threatening disorders, who I think value
2 knowing that there is an agency making sure that
3 the drugs that they take are proven to be safe and
4 effective.

5 And finally the issue about safety and
6 efficacy -- what's always puzzled me about this
7 argument is this notion that you can have
8 something that's safe but not efficacious. Let's
9 just take the example of X-ray radiation,
10 something that's pretty safe in the context of a
11 patient who's being treated for a tumor but not a
12 particularly safe modality for a patient that's
13 being treated for a wart or a skin tag.

14 Safety is by its very concept
15 context-dependent. It depends on the value or the
16 utility of the activity that you are evaluating,
17 and moreover it's not clear to me that cell-based
18 interventions by themselves can generically be
19 called safe. There are all sorts of different
20 kinds of risks that we have to worry about; risks
21 of contamination, risks of cells integrating
22 inappropriately and disrupting organ activity, et

1 cetera., and there's certainly a number of cases
2 out there of patients who have been harmed from
3 receiving unproven cell-based interventions.

4 So, in a sense you can think of
5 regulatory standards as a pivot point that
6 determines how we as a society want to distribute
7 the burdens of medical uncertainty. Do we want to
8 put the burdens on health care systems and
9 patients, or do we want to put the burdens of
10 uncertainty on the backs of companies that are
11 expressly privileged to profit from marketing
12 those products? That's one question.

13 Another way in which you can think of
14 regulatory standards as a pivot point is in a
15 question of patient autonomy. If patients receive
16 cell-based interventions in the context of
17 clinical trials they're typically undergoing a
18 very rigorous informed consent process. They
19 understand what risks and benefits they're
20 receiving.

21 If they're receiving unproven cell-based
22 interventions in a care context, typically the

1 informed consent process is less stringent and
2 less demanding, and in that way I think there's a
3 very strong argument about why we would want to
4 restrict access to unproved cell-based
5 interventions to patients within clinical trials.

6 Let me explain how this kind of moral
7 understanding of what's at stake in drug
8 regulation fits with the ISSCR guidelines. Now,
9 just a few words about the ISSCR. The ISSCR is
10 probably the largest and most influential society
11 of stem cell scientists; about 4,000 members from
12 around the world. In 2008 the ISSCR issued a set
13 of guidelines on clinical translation. In 2016
14 the revised guidelines were released addressing
15 clinical translation as well as basic research,
16 and I chaired the effort to revise the clinical
17 translation guidelines.

18 Just a few words about the process. The
19 process involved a very large and diverse group of
20 individuals who represented different
21 constituencies, different expertise, different
22 countries, and also we strove to have as much

1 diversity, both gender balance as well as cultural
2 diversity within our working groups, and the
3 process started in 2014.

4 We issued the first draft of the
5 guidelines in the summer of 2015, received about
6 26 comments from various experts who we solicited
7 for a peer review, made some revisions, sent out a
8 draft for public comment and there we received
9 about 80 different comments. We addressed those
10 comments, incorporated these into revisions of the
11 guidelines, and then released the guidelines in
12 2016, and there are about 6 different core
13 sections of the ISSCR Guidelines that directly
14 speak to the question of how regulatory
15 authorities ought to oversee the process of
16 evaluating cell-based interventions.

17 The very first call out of regulatory
18 authorities is actually in the first section; the
19 section on principles. Two principles in
20 particular speak to the issue of regulatory
21 standards. The primacy of patient welfare;
22 there's a passage there that says it's a breach of

1 professional medical ethics to market and provide
2 stem cell- based interventions to a large patient
3 population prior to rigorous and independent
4 expert review of safety and efficacy.

5 In the section on social justice there's
6 a statement that says it's a matter of social
7 justice that the cost of proving the safety and
8 efficacy of a medical intervention be borne by
9 entities that are expressly privileged to profit
10 when such interventions are marketed. Again, it
11 gets to this question of how we want to distribute
12 the costs and burdens of medical uncertainty.

13 The second section that deals with
14 regulatory standards actually directly speaks to
15 the question of regulatory approval, and that
16 section states the introduction of novel products
17 into routine clinical use should be dependent on
18 the demonstration of an acceptable balance of risk
19 and clinical benefit appropriate to the medical
20 condition and patient population to which new
21 treatments are designed. Now, within the
22 expository language underneath that there's also a

1 statement that says that national governments and
2 regulatory authorities should maintain rigorous
3 review pathways to ensure that stem cell- based
4 products conform to the highest standards of
5 evidence- based medicine.

6 The third section is actually a warning
7 within the guidelines about the provision of
8 unproven cell-based interventions outside the
9 context of clinical trials and innovative care.
10 Basically it says this should not happen unless --
11 you should not be delivering unproven cell-based
12 interventions unless it's in a trial context or a
13 special innovative-care pathway.

14 What is an innovative care pathway?
15 Well, that's the fourth section that deals with
16 this. The ISSCR lays out conditions that need to
17 be met for a legitimate care pathway; small
18 numbers of patients. There needs to be a
19 protocol. The protocol has to undergo peer
20 review. Patients should be ineligible for
21 clinical trials. There needs to be a mechanism to
22 systematically collect information on outcomes,

1 and these outcomes need to be reported in the peer
2 review literature.

3 The fifth section deals with the
4 question of patient-sponsored clinical trials or
5 pay-to-participate clinical trials. Many of the
6 clinics that are offering unproven cell-based
7 interventions to patients are doing so in the
8 context of trials where patients pay to
9 participate in them, and the ISSCR guidelines take
10 a very skeptical and restrictive view of
11 pay-to-participate clinical trials on a number of
12 grounds. One ground is that it's hard to imagine
13 how pay-to-participate clinical trials incentivize
14 the kinds of rigorous data collection activities
15 that you would need to actually rigorously
16 evaluate the stem cell based product. After all,
17 it's hard to imagine patients paying to be
18 allocated to the Sham treatment arm, for example,
19 so the ISSCR take a very restrictive view of the
20 pay-to-participate clinical trials.

21 And the sixth part of the guidelines
22 that deal with regulatory standards is actually in

1 the section -- the penultimate section of the
2 guidelines that deals with communications, and
3 they are the guidelines that state regulatory and
4 law enforcement authorities are encouraged to
5 investigate and where appropriate restrict
6 unsupported marketing claims made by commercial
7 actors to the extent that these violate relevant
8 consumer protection truth-in- advertising
9 securities and commerce laws within a given
10 jurisdiction.

11 Now, these guidelines, I encourage
12 anyone who's interested in them to go online, to
13 download a copy of them. They're very easily
14 accessible or you can read very brief synopses.
15 We've published a series of these in major medical
16 journals. This is one that we published in
17 Lancet. There's another longer description of the
18 guidelines published in The Stem Cell Reports as
19 well.

20 Let me just close with a last thought.
21 You might be sitting there wondering why would a
22 professional society that's primarily devoted to

1 scientific research take such strong views on
2 regulatory standards for cell-based interventions,
3 and the answer is that the process of innovation
4 is an area that is as cutting edge as cell-based
5 interventions is very long and it's very arduous,
6 and it depends on sustained collaboration of many,
7 many different kinds of actors all of whom are
8 putting a lot of their interests at stake in that
9 collaboration and all of whom come to that
10 collaboration entertaining a different set of
11 goals.

12 So, for example, patients participate in
13 clinical trials not necessarily to make big
14 discoveries but to get access to cutting edge
15 treatments. Companies fund clinical trials not so
16 much to make big discoveries. They might like
17 that, but because of a prospect of earning
18 revenues from products that get regulatory
19 approval. Scientists conduct clinical trials
20 partly to burnish their CVs, to get publications
21 in medicine, so all these different actors are
22 coming to the collaboration entertaining a mix of

1 different kinds of motivations, some of the
2 altruistic and others self-interested, and in that
3 environment you really want to create conditions
4 where actors can trust that when they collaborate
5 with other actors who are pursuing other kinds of
6 interests, they know their personal interests are
7 not going to be undermined, that patients when
8 they participate in clinical trials when they
9 receive cell-based interventions that they're not
10 going to be putting their health and welfare at
11 stake.

12 And I would suggest to you that
13 regulators play a key function in establishing
14 those conditions where these different disparate
15 actors can trust that their interests are going to
16 be protected when they collaborate with people who
17 are utterly strangers to them. So, in that
18 respect I would encourage people to think of
19 regulatory authorities like the FDA not so much as
20 agencies that are there to protect the public from
21 unsafe and ineffective drugs, but to think of FDA
22 as probably one of the most important regulatory

1 agencies that is driving the innovative process,
2 that creates incredibly strong incentives to
3 generate the kind of information we need to
4 practice a high standard of evidence-based
5 medicine. Thanks. (Applause)

6 Okay, so we now move on to the next part
7 of the program. I assume there's no question now.
8 I think I'll take as a panel. Does that sound
9 right? Okay, good.

10 So I'm going to introduce the next
11 speakers. The next speaker is Massimo Dominici.
12 He's a clinical scientist at The University of
13 Modena and Reggio Emilia, Italy, developing
14 cell-based and gene therapy approaches for cancer
15 patients. Dr. Dominici served as President of the
16 International Society of Cellular Therapy from
17 2014 to 2016. He's currently Chair of the ISCT
18 Advisory Board and Chair of the ISCT Presidential
19 Task Force on Unproven Cellular Therapies. Thank
20 you.

21 DR. DOMINICI: Thanks for the
22 introduction and thanks to the FDA for hosting

1 myself coming from Italy. I've been working
2 around cell therapy for quite a while, and I'm
3 going to share with you some of the reason why I
4 start to work also on these improvements in cell
5 therapy as part of the ICT.

6 ICT's a global society dealing with
7 translational research in cell therapy including
8 immunotherapy, stem cell therapy, and since 2010
9 we felt the need I think, together with other
10 societies has been already explained, to take some
11 action regarding what in 2010 was called medical
12 tourism. That time the President Kurt Gunter felt
13 a need to act and to propose a plan that involved
14 the society to try and face the issue of medical
15 tourism, and since that time the society
16 established a task force regarding what we now
17 call proven cell therapy and why is that?

18 I think we should start with numbers.
19 It's a massive issue. Some estimates are
20 indicating there are -- the market regarding the
21 unproven cell therapy is very wide, and there are
22 2.4 billion of U.S. dollars that are involving

1 patients that are paying to be treated with a
2 single treatment can be paid up to \$40,000 U.S.
3 dollars. And that's, I think, is quite
4 significant. But this I would say is just a part
5 of the issue.

6 At some very recent publication from a
7 friend, John Ruskin, in Australia where they were
8 dissecting the numbers of stem-cell based clinic
9 that were available on the web, so they did some
10 web research and the intensity of the redness has
11 indicated the numbers of clinic for each country.
12 So you see that these three global challenge, and
13 the global challenge as I was saying, is related
14 to the type of diseases and to the cost of the
15 diseases. I was mentioning the cost of each of
16 these treatments. This 2009 publication of stem
17 cells, these authors who were essentially picking
18 up a series of clinics where there was a doubt of
19 proven cell therapy approach. They were calling
20 them asking some questions. One of the questions;
21 how much is the payment for the treatments, and in
22 some cases there was no answers, but the answer

1 that they got were between \$10,000 and \$40,000 as
2 I was explaining.

3 How about the clinical indication of the
4 2009 publication? As was said, the majority of
5 the cases are related to neurological disorders
6 because these are frontier for medicine, is a
7 frontier for regenerative medicine, and so we move
8 from multiple scleroses, Parkinson, stroke and if
9 we compared those data we'd -- a more recent
10 publication in 2016 realized the situation is
11 likely changed. This once again the stem cell
12 publication from John Ruskin, you see there's a
13 big difference.

14 There's something else that's been
15 incredibly increasing; that these treatment with
16 stem cells for aging. The majority of the website
17 were advertising treatment with stem cells just
18 for aging, considering aging as a disease. This,
19 I think, was to me at least -- it's very
20 surprising how the landscape of clinical
21 indication has been changing the last seven years.
22 Would aging (inaudible) the rest of disease

1 versus, you know, the neurological disorders that
2 are still appearing in the list here.

3 Neurological disorders are certainly a
4 big issue and we know all that, and the reason why
5 I personally have been involved in this unproven
6 cell therapy field is for a reason that is related
7 to my own country. I think the previous speaker
8 was showing one of the scripts that were present
9 in Rome at that time. This was 2012.

10 In 2012 I received a call from the
11 Minister of Health asking my lab to analyze a cell
12 preparation that was under investigation in a
13 public hospital in Italy, and for clinical
14 indications which were mostly related to
15 neurological disorders. This group of individuals
16 who were essentially performing the following
17 procedure as I show you here in the slides, so
18 they were starting from bone marrow aspirate.
19 They were isolating the cells in a regular lab,
20 forgetting about the CGMP or the CGLP regulatory
21 frameworks. They were amplifying the cells.
22 There were some testing. They were freezing down

1 the cells. They were keeping the cells for quite
2 some time in a nitrogen tank. They were
3 defrosting the cells and they were treating the
4 cells with retinoic acid for a couple of hours,
5 and then they were infusing the cells and
6 (inaudible) almost to size. One end is fine and
7 one (inaudible). The second (inaudible)
8 intravenously. The numbers of cells which was
9 used about 200,000, and we have been talking about
10 millions of cells this morning, so I (inaudible)
11 of cells in this indication. And this was -- I
12 mean I'm not certain here to question the way in
13 which the cells has been delivered. If you have
14 data that (inaudible) reporting the approach, this
15 is very fine. If you have data that are
16 supporting that you can get some amelioration of
17 your diseases just using this type of delivery,
18 then that's very fine. These authors did not have
19 any type of preclinical findings regarding this
20 type of infusion.

21 While I was more and more involved in
22 this story I realized that the protocol that we're

1 applying was very, very weird; not done in the way
2 in the cell types but in the way in which the
3 cells were delivered, so approximately or
4 currently about 40 patients have been treated
5 according to this protocol and the treatments were
6 very different from one to the other, so one
7 patient in this case, patient AB was receiving
8 patient cells in a sort of (inaudible) setting so
9 the bone marrow aspirates and then transplant.
10 This was the first infusion. The same patient,
11 patient AB was receiving cells from an (inaudible)
12 donor in an allergen A setting for the second
13 infusion, and then for the third infusion the
14 patient was receiving cells from another patient.
15 In a very weird manner the authors were calling
16 that multiple (inaudible) transplantation since we
17 forgetting like 60 years of immunology and more.
18 So this is essentially what was shocking me, and
19 this was why I start to work in this field as
20 scientist involved in cell therapy development.

21 And the cost of this treatment has been
22 estimated between 40,000 and 80,000 euros and the

1 patient had to make loans with a bank to pay the
2 treatment which was another shocking surprise to
3 be seen.

4 So we talking about unproven cell
5 therapy and why this protocol can be considered
6 unproven cell therapy. I would say there were no
7 scientific basis on mechanism of action. There
8 were no scientific basis for the proposed delivery
9 schedule. There was no evidence -- even
10 preliminary evidence of safety. One of these
11 patients actually died during the infusion. There
12 was a lack of primary data and expectation of
13 efficacy, and the ratio between risk and benefit
14 was not even taken into consideration and informed
15 consent was an option for these guys here.

16 And then the last part which certainly
17 one of the

18 (inaudible) is terrible is the pay
19 to be treated model, so this is why
20 I'm proving -- this why (inaudible)
21 protocols can be considered
22 unproven cell therapy. So this is

1 just a case and I leave myself with
2 my lab and with my country I would
3 say with the patients that were
4 starting to look for this type of
5 treatment, but if we trying to
6 dissect which are the (inaudible)
7 of the cell-based intervention I
8 think we can try to simplify some
9 -- apologize for
10 oversimplification, but certainly
11 we can have this type of example
12 unproven, unregulated medical
13 procedure which are marketed as
14 beneficial therapy without waiting
15 for
16 (inaudible). Then we have a
17 novelty medical care, non-approved
18 but possibly proven approach provided by
19 legitimate care givers which, you know, they take
20 their path of investigating the efficacy and the
21 safety, and I would say this is innovative medical
22 care. Of course then we have the clinical trials

1 development as we all know.

2 The problem that is emerging (inaudible)
3 cell therapy is that sometimes the first line and
4 second line a bit confused. So there's some
5 confusion of unproven cell therapy in the novelty
6 medical care, so we don't want to take this cue of
7 innovate to propose unproven approach. That's
8 something that should be clear.

9 So when we start work around unproven
10 cell therapy inside the ICT and also with other
11 colleagues involved in this field we started to
12 ask ourselves which are the key question on
13 unproven cell therapy because that was very
14 challenging. So the first question was how to
15 define unproven cell therapy. The second which
16 are the minimum level of biological evidence that
17 we can apply to a cell-based product to advance
18 this product into a clinical scenario, and then
19 which are the minimum requirement for cell
20 manufacturing and those things which seem to be
21 obvious for us but they are not, and we should
22 talk about that in this context and outside these

1 rooms.

2 And then which are the interaction
3 between the improvements in therapy in the global
4 regulatory frameworks which are very different
5 from one region to the other. And then what is
6 the role of pharmaceutical and biomedical industry
7 in this context, and once again, you know, what is
8 the role of scientific community in this field.

9 So we start with the definition of
10 unproven cell therapy. I think presenting this
11 (inaudible) protocol I went through
12 all these points and it certainly
13 unclear scientific rationales
14 (phonetic). I'm not going to
15 repeat this data, and what I think
16 should be outlined here is just
17 uncontrolled (inaudible) procedures
18 that are taking place in human
19 being.

20 Then I wanted to pick something else
21 that was shared and discussed inside the group.
22 This is dealing with the basic core practice for

1 cell therapy production. This is work that was
2 done by Paul Eldridge in collaboration with other
3 colleagues in the Society. There is certainly
4 some common sense guidelines on manufacturing, but
5 it's very relevant to be respected to generate a
6 product that is essentially standardized and ready
7 to be injected and reproduced in a variety of
8 patients for a precise indication.

9 Of course there are some risks related
10 to this direct to consumer marketing of cell-based
11 therapy. Patient arm, there's lot of
12 psychological impact in patients and in their
13 family. There is financial loss for sure that has
14 been also subject of justice-related issues.
15 Damage to the integrity of the entire healthcare
16 and of course this is generating unrealistic
17 expectations.

18 The way in which these clinics are
19 providing and approaching providing therapies and
20 approaching the community it's changing rapidly.
21 The way of communicating is changing, so they
22 generally use, you know, testimonials on websites.

1 They use social networks and they link stem- cell
2 based intervention to some sort of scientific
3 journals that they support their approaches.
4 Essentially they are identifying some sort of even
5 fake scientific societies or fake regulatory body
6 that can certify their structure. So it's very
7 diversified the way in which they can justify this
8 approach. What is generally happening is those
9 guys are outlining the benefits and hiding the
10 risk.

11 This once again is a 2009 publication
12 that I was mentioning to you at the beginning.
13 Essentially the authors were calling about 25
14 clinics asking questions regarding the benefits of
15 the approach and the risk of the approach. As you
16 can see here in the majority of the cases those
17 clinics were outlining vague positive claims of
18 efficacy and in the majority of cases they were
19 hiding the risk of those treatments. That's part
20 of 7 years ago publication, but it's still going
21 on in a more subtle way.

22 So which are the future steps and why I

1 like to share this work with the scientific
2 community. Of course we cannot stay closed in our
3 lab or stay closed in our scientific community.
4 We want to embrace patient organizations, other
5 professional societies, and regulatory agency to
6 outline the action to ensure the patients are
7 protected.

8 We'd like to -- it's something that
9 might not be easy but to implement a long-term
10 program to promote a global regulatory
11 organization which might not be easy to do in a
12 short time-frame, but is something that should be
13 a focus of different regulatory agency. We would
14 like to promote (inaudible) scientific development
15 in the field and cooperate with other society so
16 that we can try to speak with one single voice
17 because I think the success of this strategy will
18 come if there will be a global collaboration and a
19 unified voice regarding this relevant issue.

20 So, I'm ending here thanking once again
21 FDA for the opportunity and thanking all the
22 people which have been participating in the

1 process of establishing this debate inside this
2 society and am looking for the final debate to
3 listen to questions you might have regarding the
4 work that we have been doing, and we hope to
5 continue in collaboration with other society, so
6 thanks very much. (Applause)

7 DR. KIMMELMAN: Thanks so much.

8 DR. MANSFIELD: Okay, our next speaker
9 is J. Peter Rubin who's the Chair of the
10 Department of Plastic Surgery, the UPMC Endowed
11 Professor of Plastic Surgery and Professor of
12 Bio-engineering at University of Pittsburgh. In
13 addition to his active clinical program, Dr. Rubin
14 directs a basic science research program in
15 biology of adipose-derived stem cells and serves
16 as the Co-Director of the Adipose Stem Cell Center
17 at Pitt. Dr. Rubin is Co-Chair of the American
18 Society of Plastic Surgeons Task Force on
19 Regenerative Medicine and a regulatory chair of
20 that same society. Thanks.

21 DR. RUBIN: Thank you. Thank you very
22 much to the FDA for the opportunity and honor of

1 being here today. Talk about adipose therapies,
2 we're going to shift gears a little bit and talk
3 about the world of adipose-based therapies; where
4 we are now and where we're going with these
5 therapies.

6 The American Society of Plastic Surgeons
7 is the largest surgery-specialty organization in
8 the world for plastic surgery and represents 94
9 percent of all board certified plastic surgeons in
10 this country, and many of the adipose therapies
11 that are being conducted are being done within the
12 field of plastic surgery, and no financial
13 disclosures for this talk.

14 So at the University of Pittsburgh I
15 chair the Department of Plastic Surgery. I'm a
16 clinical plastic surgeon and I also do basic
17 science and clinical research. I sort of work in
18 all the different spheres of translation, and this
19 is really focused around adipose tissue where we
20 have the Adipose Stem Cell Center at Pitt, and in
21 this talk I'm going to cover two main themes that
22 are distinct but really interrelated, so we have

1 first the theme of autologous fat transfer, and
2 this is a surgical tissue grafting procedure where
3 we use particles of adipose tissue that are
4 generally two to five millimeters in size, and in
5 current plastic surgery practice these particles
6 of adipose tissue are implanted, and these small
7 particles are composed of all the components of
8 adipose tissue; adipocytes, stromal cells,
9 connective tissue and blood vessels.

10 And then the other part of this talk is
11 about adipose stem cell therapies, again which is
12 interrelated to autologous fat transfer because we
13 derive these isolated cell products from these
14 extractive fat particles. In these adipose stem
15 cell therapies adipocytes are excluded and we have
16 a population of very bioactive cells, and these
17 cells are really the biologic engine that are
18 responsible for a lot of the tissue remodeling
19 that we see in fat transfer procedures.

20 So, again, the first part of this is
21 going to be about fat transfer which actually has
22 a really long history. We talk about many cell

1 and tissue therapies and this is one that actually
2 goes back to the 19th Century with the first
3 publication on this topic coming out of Germany in
4 1893 where a surgeon used small grafts to treat
5 scars of the forearm, and in modern fat transfer
6 this has really become a very common clinical
7 practice using simple methodology and this has
8 broad-reaching applications in aesthetic and
9 reconstructive plastic surgery. Moreover, this is
10 something that's undergone many refinements over
11 the last two decades.

12 How do we get these particles out of the
13 patients? Well, this is a minimally invasive
14 harvest, and we use hollow-bore cannulas either
15 under hand-held suction or with machine-driven
16 suction, and you can see in this picture the tip
17 of the cannula which is about the same size as the
18 particle and those apertures really determine the
19 particle size. We often will use infiltrative
20 solutions containing epinephrine in the
21 subcutaneous tissues so that we can minimize blood
22 loss, and once we have this tissue extracted very

1 simple centrifugation at about 1,200 g and then we
2 can use blunt-instrumentation specially designed
3 to inject this material after we separate the
4 aqueous and oil layers. So here we have a photo
5 from my operating room showing many of these small
6 tubes of fat processed in the O.R. and ready to
7 go, and we can do this in fairly large volumes,
8 and when we do this with large volumes we'll
9 simply use larger instrumentation to extract and
10 deliver the tissue.

11 So there's a lot of variation in how
12 this is practiced, and that's given rise to a
13 veritable supermarket of devices that are out
14 there, and the cannula world from the harvesting
15 and injection steps up through the fat- processing
16 steps, and this is an example of a commercially
17 available filter canister that we can keep online
18 sterile in the operating room, and there are other
19 devices that will irrigate the collected tissue
20 with saline solutions, and there are very
21 expensive devices that we can bring into the
22 operating room as well but in its base form I've

1 really outlined these straight-forward steps.

2 And this was survey data that we
3 published from our lab a few years ago showing
4 that in the plastic surgery community there is a
5 fair amount of diversity in how surgeons will use
6 these different processing steps: centrifugation,
7 simple filtering, washing with saline, other
8 methods that remain undisclosed by the
9 participants in the survey and to no preparation
10 at all or just simple decanting of the material.

11 So why is this technology important in
12 reconstructive surgery? That's because fat is
13 actually our best tissue for reconstructive
14 surgery. It's our best soft tissue replacement.
15 It's a natural component of soft tissue that
16 defines form and shape throughout the body, so now
17 we have a method of doing this with minimally
18 invasive technique, less donor site morbidity, and
19 very importantly a tissue-remodeling affect, so
20 the current clinical applications will span
21 aesthetic facial volume augmentation where this
22 really got its start as sort of a not really

1 mainstream procedure many decades ago, and it's
2 now widely practiced in breast reconstruction,
3 buttock augmentation, scar treatment, cranial
4 facial reconstruction, limb reconstruction, just
5 to mention a few, and it has very important
6 applications in the treatment of radiated tissues
7 and reconstructive surgery as well.

8 So I want to highlight some of the data
9 that we've collected in our clinical trials or
10 clinical studies that are really geared toward the
11 devastating limb and cranial- facial injuries that
12 are seen in military trauma from IED blasts, and
13 this is work that is funded by the Department of
14 Defense through different programs including the
15 Armed Forces Institute of Regenerative Medicine
16 and the Biomedical Translational Initiative, the
17 Congressionally determined medical research
18 programs as well, so it's a very important area
19 for our wounded warriors.

20 And we did some very detailed analysis
21 in a cohort of 20 subjects that we treated with
22 cranial-facial deformities. Five of these

1 subjects underwent repeat treatments. There were
2 no serious adverse events, and one of the things I
3 want to really highlight with these adipose
4 grafting therapies is that the safety record is
5 overall very, very good, and the recovery for
6 these patients tends to be much easier than the
7 traditional open procedures.

8 All of the procedures were performed on
9 an outpatient basis in this cohort and we followed
10 the patients out through 9 months with a battery
11 of quality-of-life measures, high-resolution CT
12 scans, and a number of other assessment
13 instruments.

14 So this is a young woman, a trauma
15 victim who has a left temporal deformity that you
16 can see on this photograph, and we followed her
17 out through 9 months. This is with a single
18 outpatient treatment where we were able to restore
19 her facial form without having to use alloplastic
20 implants or a more complex procedure.

21 This is a patient with a more severe
22 mid-face injury where she had significant volume

1 loss in her mid-face that we were able to restore,
2 and this is about 9 months after the initial
3 treatment with these injectable therapies.
4 Moreover, on patients with severe scarring,
5 depressed scars such as this military veteran we
6 were able to attain a pretty significant
7 remodeling of the scar out through 9 months.

8 And in a more extreme example, this is a
9 young trauma victim who had a very profound
10 cranial deformity that would have required a
11 significant procedure using autologous rib grafts,
12 a free tissue transfer, very major surgery that
13 would have kept him in the hospital for probably a
14 couple of weeks and about a 10-hour surgery. So,
15 he was one of our patients that we enrolled for a
16 second treatment, and you can see with two
17 outpatient procedures that we were able to make
18 quite a difference for him. This is 24 months
19 after the initial treatment and 9 months after the
20 second treatment, so these are really evolving as
21 very important reconstructive tools for our
22 patients, and quality of life measures as expected

1 are greatly improved in all of these patients
2 going out over time.

3 When we look at the tissue healing with
4 high- resolution CT scanning where we can do very
5 detailed volumetric analysis we see that this is
6 characteristic of these adipose-grafting
7 therapies. We see that there is a loss of volume
8 of the tissue out to about 3 months and then a
9 stabilization of the volume from 3 months out to 9
10 months where things really level off, and the
11 volume and the form at 3 months is very predictive
12 of what we're going to see at(inaudible)

13 months. There's also a clustering of
14 these patients at around 65 percent retention of
15 the material, healing of the grafted tissue based
16 on what we inject measured out over time.

17 Interestingly the stromal vascular cell
18 concentration in the native tissue correlates with
19 graft retention really suggesting that these
20 stromal cells are playing an active role in the
21 healing of the tissues, and this is very
22 consistent with what we've seen in our animal

1 models that we published where we've been able to
2 do much more precise measures, and there's a very
3 strong correlation between the presence --
4 concentration of endogenous CD 34 positive, 90
5 positive, 31 negative, 45 negative cells and the
6 healing of the tissue over time. More on that
7 shortly as we talk about the adipose-cell
8 therapies.

9 So very importantly while volume and
10 form can be restored, what's really striking about
11 these therapies is the tissue remodeling that we
12 see, and above and beyond volume there are very
13 significant applications in treatment of radiation
14 injuries.

15 So this is a case that was published by
16 one of our colleagues, Gino Rigotti in Verona in
17 Italy where he had a patient with
18 osteoradionecrosis of the chest wall following
19 therapeutic radiation. This was a refractory
20 wound and with multiple injections of
21 lipo-aspirate fat grafting he was able to get
22 these tissues to granulate enough that he could

1 put a skin graft on the tissues and get them to
2 effectively heal. And these are principles that
3 we've carried over into treating our patients.

4 This is a patient of mine, a 54-year-old
5 woman with a very aggressive T4 squamous cell
6 carcinoma who had a full thickness cheek
7 resection, partial mandibular resection, and you
8 can see that bulge right off of her lip is a free
9 flap. It's from her forearm and this is how she
10 came to me. Very tight, constricted, contracted
11 tissues and by all standards her reconstruction
12 was over, and if we were going to do anything more
13 we would have to do another free flap, another
14 free tissue transfer in a patient who's not really
15 in the best shape. So, with three outpatient
16 procedures we were able to soften the tissues
17 sequentially and get her to this point which is a
18 pretty dramatic improvement in quality of life for
19 this patient.

20 This is another one of our patients, one
21 of our wounded warriors who was also a bilateral
22 amputee, and you're seeing at the base of his

1 thumb a skin graft that is adhering to the bone.
2 He needed that surface to push his wheelchair and
3 he had a lot of breakdown, so we were able to
4 provide some good, soft tissue there but most
5 importantly, actually get suppleness and new
6 elasticity to the skin on his hand, and that
7 really stopped the breakdown from pushing his
8 wheelchair.

9 I want to talk a little bit more about
10 breast applications, and again this has become
11 very widespread for use in breast reconstruction.
12 This is more survey data published from our lab,
13 and when we asked in 2013 the plastic surgery
14 committee how many of you are doing fat grafting
15 for the breast, 70 percent said that they were
16 using this practice and 88 percent of those were
17 using it for reconstructive applications.

18 So, here's one of my patients with a
19 lumpectomy deformity -- single treatment with
20 autologous fat grafting. This is a year out.
21 Another patient with very severe capsular
22 contractures. Some of these patients get severe

1 scar contractures around their implants. It's
2 very painful. The implants are in place in the
3 picture on the left. On the right a year later
4 they had been removed and replaced with her own
5 fat tissue, so this was a year after the
6 procedures.

7 And this is a patient who in any
8 practice 10 years ago would have had implants or a
9 free tissue transfer. This was a case done by one
10 of my colleagues who was able to affect a complete
11 breast reconstruction using injectable autologous
12 fat, and to put this in perspective this is the
13 treatment that every other patient would
14 ordinarily be having tissue removed in block from
15 the abdomen transferred by microsurgical technique
16 to the chest to get this result, and that case was
17 achieved with autologous fat injection.

18 What about oncologic issues in breast
19 fat grafting? There are some questions about
20 growth factor release, cancer surveillance,
21 malignant transformation. In some of the in vitro
22 studies, and this is from our lab, show indeed if

1 we culture malignant pleural effusion cells with a
2 feeder layer of adipose stem cells we're going to
3 get tumor nests. We're not sure what this means
4 because clinically none of the recurrence rates in
5 the large published series are any different, even
6 a good case controlled series, but we're looking
7 more closely at that under NCI funding. We're
8 looking at new experimental models to better
9 represent the scenario of residual microscopic
10 disease treated subsequently with fat grafting for
11 reconstruction.

12 What's our Society doing? One of the
13 really key things that the American Society of
14 Plastic Surgeons is doing is data collection. We
15 have a large prospective registry for fat
16 grafting, and all of our members are expected to
17 introduce data into this registry to really verify
18 our results over the long time.

19 So, I want to spend the last part of
20 this talk focusing on adipose cell therapies which
21 again are derived from these particles of fat,
22 only it's obviously a higher level of processing

1 and isolation because we're going to get the
2 non-lipid-laden cells separated from these
3 tissues, and if you look within the structure of
4 fat tissue you see that most of our cells of
5 interest, these 34 positive cells are Perivascular
6 and really within the stroma, so we're going to
7 use enzymes to digest these cells out, and here we
8 have our initial isolate we refer to as the
9 stromal vascular fraction. That's our fresh
10 isolate, our sushi as our friend from Wisconsin
11 would call it, and once we plate these cells we
12 get the adipose stem cell fraction that can be
13 expanded through many passages, and we can get
14 very significant cell numbers.

15 We've worked out GMP methodology through
16 PAC funding to do this by manual techniques, but
17 there are also automated machines that will do
18 this, and for our clinical trials currently we are
19 actually using one of the automated machines under
20 an IDE so we can bring this down to the point of
21 care and do rapid isolation, and we know that that
22 will be more transposable to other environments.

1 What do we get in our cell isolate?
2 Well, this was data or summary from a Joint
3 Position Statement from ISCT and the International
4 Federation for Adipose Therapeutics, IFAT, so it
5 was published in 2013. Dr. Dominici was one of
6 the co-authors on this paper, and we really get a
7 heterogeneous mixed population with parasites,
8 endothelial cells, stromal cells, a few
9 hematopoietic lineage passenger cells as well --
10 tissue monocytes and macrophages and those will
11 not adhere to plastic, so those tend to wash out
12 when we culture the cells.

13 So a lot of people in this room know
14 ISCT. IFATS is not as well known. It's really a
15 fat stem cell and regenerative medicine society
16 that's actually going into its 14th year right
17 now, but this is an event where we really focus on
18 the best science in adipose therapeutics.

19 Some of the very, very attractive
20 properties of these cells are the release of veg-F
21 under hypoxic conditions and other angiogenic
22 growth factors. This is data where we sorted out

1 the cells and looked at veg-F expression under
2 low-oxygen tension, and we're applying these
3 therapies in the pre-clinical phase for wound
4 healing, in porcine models, and also because of
5 the immunomodulatory properties and the ability of
6 these cells to be suppressive in MLR we've been
7 looking at them in rodent transplant models. So,
8 this is a hind limb transplant that is out past
9 100 days where we have just 30 days of FK506 and a
10 large cell load of adipose stem cells as well as
11 bone marrow stem cells and this is adapted from
12 some protocols that we've been doing in
13 Pittsburgh.

14 And our strategy right now for applying
15 these clinically is to really capitalize on the
16 bio-active properties of these cells, isolate
17 autologous adipose stem cells and mix them back in
18 with this fat graft to get a more cellularly
19 enhanced fat graft, so we're doing this under an
20 IDE.

21 This is some of our pre-clinical data
22 that we developed in our rodent models, and this

1 is applied toward treatment of traumatic
2 amputation sites where we have about 1,500 people
3 in our military population who have lost limbs
4 from IED blasts, so many of them have poor soft
5 tissue coverage and pain at their amputation site.

6 So, we're conducting a randomized
7 clinical trial with 30 subjects, randomized to
8 receive the cell therapy or the fat grafting alone
9 and following them out actually over

10 years, so this is an example of how
11 we're able to build up that tissue. This is a
12 patient who's now back on his limbs rehabbing.
13 We're able to get really good remodeling of the
14 tissue, and importantly 8 out of 9 of the patients
15 that we've treated so far have had resolution or
16 at least a great improvement of their phantom
17 pain, and that's something that's been very
18 difficult to treat.

19 So in summary, adipose tissue grafting
20 is a very powerful reconstructive paradigm in
21 current surgical practice and adipose stromal
22 therapy has really held a lot of promise for

1 tissue repair and we certainly want to move
2 forward with the responsible evidence-based
3 approach and deal with all of the challenges of
4 cost, dose, and potency, et cetera. Thank you
5 very much for your attention.

6 (Applause)

7 DR. MC FARLAND: So, I'm Richard
8 McFarland from the Office of Cellular, Tissue, and
9 Gene Therapies and we're going to switch before
10 the afternoon break one more time, and as the
11 title suggests get some views from government
12 agencies, and as my first speaker works her way up
13 here I'm going to tell you that these are just two
14 government agencies, the DoD and the NIH, from a
15 multi-agency group that coordinates our efforts
16 across regenerative medicine and tissue
17 engineering.

18 So the first speaker is Kristy Pottol
19 who's the Project Manager and Director of Tissue
20 Injury and Regenerative Medicine, Project
21 Management Office of the U.S. Army's Medical
22 Material Development Activity at Fort Detrick.

1 MS. POTTOL: Thank you, Richard. Thank
2 you so very much for inviting me to be here. It's
3 really my honor to be here to speak to you all
4 today. I first must disclose that these views are
5 my views alone, and I can't represent the
6 Department of Defense, so there you go. There you
7 have it.

8 About 25 years ago I was trying to pay
9 my way to go to school and it was really hard. I
10 didn't have any money. I had to do it all on my
11 own, and I got kind of hungry after a while. I
12 wasn't really certain if when school loans ran out
13 in the summer if I was going to actually have a
14 roof over my head. I started selling everything
15 that I owned just to have food the next day, and
16 it occurred to me that at least if I joined the
17 military I could have food and there would be a
18 paycheck and there would be a roof over my head.
19 That was pretty much my main objectives as a young
20 kid, and I went into the military.

21 What does that really mean when you go
22 into the military? You have no idea. It was

1 really simple little hierarchy stuff, but a couple
2 years ago I was standing next to General Caravallo
3 and he was -- when we launched AFIRM, the Armed
4 Forces Institute of Regenerative Medicine, he said
5 when these young men and women choose to join the
6 service they write a check to the United States of
7 America payable up to and including their life,
8 and they sign their name and that's co-signed by
9 their family.

10 As a little kid that was not on my mind.
11 I just really wanted to eat, but really listening
12 to the two-star say that now 25 years later it
13 really just impressed on me the importance and the
14 responsibility the Department of Defense takes for
15 these young men and women that are joining the
16 service, and then we want to return them back to
17 their homes in whatever community they live
18 whether it's Iowa, Michigan, or Texas. And so
19 that's part of the responsibility that we have in
20 medical research for the military is to make good
21 on that promise.

22 And so how do we think about medical

1 research and any technology space inside the
2 Department of Defense? What we really think about
3 in terms of -- I just titled this and try to make
4 it in English instead of in Army-speak, so we have
5 kind of occupational-driven research. Our
6 occupation just happens to be really different
7 than most people's occupation, so we try to really
8 think about what is it going to take to help these
9 young men and women be able to function and
10 survive and live when they're on flight decks or
11 they're out at sea or they have a blast happen or
12 a gunfire happen or they're jumping out of
13 airplanes or walking into an area where suddenly
14 there's Dengue or something like that. So, we
15 really think about what is the occupation that we
16 have and how do we develop and drive medical
17 solutions to help keep them healthy.

18 As a project manager for tissue injury
19 and regenerative medicine what we think about is
20 we need to get that to them right now. We need to
21 hurry up and be really focused. We think about it
22 in a very military way. How do we push forward?

1 How do we get there fast? We owe it to these
2 folks to help them be ready to go protect our
3 country. If they get injured while they're
4 protecting our country, can we save them at their
5 point of injury and help bring them back home and
6 give them -- restore form, function, and
7 appearance back to their life, and then can we
8 help them enter back into their own community to
9 be rehabilitated and restored?

10 It's a very powerful mission for us, and
11 it's something that we drive very hard when we
12 think about how to move forward. As we do very
13 well, we've saved more people in these last wars
14 than we've ever saved before, but we also have
15 more significant injuries than we've ever seen
16 before, so how do we continue to be innovative to
17 help restore form, function, and appearance to
18 help put these young men and women back together?

19 Well, we think about it in a couple
20 different ways. One is are there medical
21 solutions already ready today? That's really
22 important for us. The military's not a commercial

1 manufacturer, so whether there are already
2 solutions that are available today -- anywhere in
3 the world today -- that will help us achieve this
4 goal to keep these guys ready to do their jobs.

5 Are there ways that we can partner with
6 non-government entities, and that's where we often
7 see us working or the Department of Defense
8 working is in some partnership where we can't go
9 it alone, but we have a need so we need to partner
10 with somebody. And then there are cases where we
11 lead the military or lead the research and
12 development for very unique military needs, and
13 often you might see this in the chemical and
14 biological side.

15 So this our focus. Obvious the top is a
16 little bit cheaper for us than the bottom, but we
17 have to go through that order. Behind every one
18 of these is a mission is how do we drive forward.
19 But going back to that responsibility that the
20 General talked about is we really need to think
21 about how we do that responsibly for any one of
22 these folks that are anywhere in the world helping

1 to protect and defend our country, and so in that
2 responsibility we have the Food and Drug
3 Administration thankfully looking out for some of
4 the elements of safety and efficacy and all that's
5 involved with that, but the DoD also has a
6 requirement of regulations because if we buy
7 something it's got to be incorporated into our
8 whole system, and so what does that mean? And
9 that means that there's a ton of regulations out
10 there for sure.

11 We also bring a bit of a systems
12 engineering approach, so that framework that you
13 see up on the top is the same framework that we
14 would use to build new tanks, to build a new F35.
15 It would be how we'd make new radios. That's also
16 how we think about developing new medical
17 products, so that systems engineering approach is
18 very structured. It's definitely cumbersome, but
19 inside there are elements of how to make your
20 thinking more robust to ask more questions and in
21 that we want to fail fast. We need to get those
22 solutions out now and so we need to fail fast, so

1 we think about a lot of questions and probably the
2 biggest power that we have if you're working with
3 the Department of Defense is the power of the
4 question; trying to figure out where the gaps are
5 and how can we solve the problem in a different
6 way because we're very mission focused. We have
7 to solve the mission, so let's just figure out how
8 we're going to do it successfully.

9 We need to translate the research into
10 products. This slide is really just meant to say
11 that's something that we cannot do alone. We have
12 to work with academic institutions. We have to
13 work with patients. We have to work with
14 regulators. We have to work with other
15 researchers and scientists, other government
16 agencies, and it has to be an ongoing
17 conversation. It's not easy. It's, you know, we
18 always laugh at ourselves inside the DoD -- I
19 think the FDA, too -- when you ask us a question
20 we always say, "Well, it depends." Right?
21 Because it always depends. There's so many rules
22 and regulations specific on your product and

1 that's really for us all these gears and all these
2 people you have to talk to is how do you get to
3 the answer of "it depends?" You have to talk to
4 everybody to figure out what it depends on, and
5 then try to get to your next bit of information,
6 so we work very hard to try to figure out how we
7 work together and ultimately navigate the pathway
8 through to get to the final side.

9 And really where's the risk that's
10 involved? We need to work on that question
11 together. We really, truly need to be partners
12 together in what we're doing, and as we look
13 forward into the future in front of us,
14 particularly in these new product technologies
15 that we're talking about here today, what is it
16 going to take to get us to move forward? How will
17 we be able to get to the right side of this image
18 and help deliver products to our service members
19 so that they can continue to live happy lives and
20 also help us protect our country if that's what we
21 ask them to do?

22 And so in my shop what we've tried to

1 perfect is the power of the question. This work,
2 what we're doing and what you're doing is too
3 important to leave to chance. We want everyone
4 that's working in this field to be successful
5 because we need answers to these questions. We
6 need to be able to restore us back to full form
7 and function and appearance after you've given us
8 so much for our country.

9 And so how we think about not leaving
10 this to chance is taking a look at where can we
11 influence, where can we find partners? And what
12 are the questions? We talked a lot about science
13 here but it does not end at the science. It's not
14 just the regulatory questions that are important.
15 Is there a way to reduce costs of goods sold? Is
16 there -- you know, what's your profit margin?
17 What's your long-term sustainability plan? If you
18 don't have a sustainability plan I'm not going to
19 be able to promise these men and women five, ten
20 years from now, and that's important to us. How
21 are you going to get funding to continue on? How
22 will you be able to continue to innovate? Can you

1 scale up to match your marketplace that you intend
2 to do? Do you -- in that scale of how big of a
3 scale does that really need to be and do you have
4 sufficient facilities to do that, and what if it
5 gets better? Do you have a way to scale up from
6 that even still? How are you going to get paid
7 eventually for selling your product? If you don't
8 know the answers to that question now, at what
9 time do you think you're going to get the answer
10 to that question?

11 So we want to start asking those
12 questions now. It's really important to start
13 asking all those really hard questions, and it's
14 like beating your head against a wall because you
15 just don't know. It always seems to depend, but
16 at some point you've got to figure out the answer
17 to that question, and that's what we really try to
18 do.

19 One area in here is because it's so hard
20 and it's so complicated. The DoD did a request
21 for information and asked the United States in
22 some way where are you stuck in regenerative

1 medicine manufacturing? Where are your real
2 problems? Where are your real gaps?

3 And there's a pretty good response from
4 that and as a Presidential Initiative for the
5 National Manufacturing Institute they released a
6 funding opportunity announcement for the Advanced
7 Tissue Bio-fabrication Manufacturing Institute, so
8 the Department of Defense on behalf of the
9 President put \$80 million out to find answers to
10 those questions that we heard were important in
11 advancing tissue bio-fabrication.

12 What is it really going to take to have
13 standardize cells and material processes to create
14 platforms to find appropriate lot release testing,
15 inline testing, non- invasive testing? What is it
16 going to do to really create stability so that we
17 can continue to have products, so we can answer
18 these questions of scale up, so that we can reduce
19 cost of goods sold to be able to make a company
20 viable down the road? So that's (inaudible).
21 It's in open competition right now, but it's --
22 these are the questions that are important to us

1 to try to help to answer because of this
2 commitment that we're making back to our country,
3 and how do we restore form, function, and
4 appearance to our wounded war fighters that helped
5 us defend our country today.

6 And so with that I'd just like to say
7 that there are a lot of ways that we think about
8 solving the problem, but for us there's always one
9 goal. How do we take that young man or woman who
10 was at the point end of the spear and give them
11 back to their home, take them back home so that
12 they can be with their family again when they're
13 done. Thank you. (Applause)

14 DR. MCFARLAND: Thanks, Kristy. So the
15 DoD the last 10 years have been really
16 transformative in many of these fields of
17 regenerative medicine and tissue engineering. Our
18 next speaker is from -- someone who we all know --
19 National Institute of Health, one of the other
20 institutes that funds this. Martha Lundberg is
21 the Program Director of Advanced Technologies in
22 Surgery Branch in the basic and early

1 Translational Research Program in the Division of
2 Cardiovascular Sciences of the National Heart Lung
3 and Blood Institute, also known as NHLBI.

4 DR. LUNDBERG: Well, good afternoon and
5 thank you to the FDA and Richard and the MATES
6 group for inviting me here. I think it's an
7 important and timely topic. There's a lot of
8 things going on in the field, and it's great to
9 see you all here giving us your advice and
10 opinions on where we are.

11 Today -- let's see if I can work this
12 thing -- I'm going to talk about enabling
13 development of regenerative medicine and
14 technologies at the NHLBI. As a disclosure I am a
15 full-time employee of NHLBI as mentioned, and this
16 is delivered as part of my regular duties so
17 there's no disclosure.

18 I'm going to talk a little bit about the
19 resources we have at NHLBI as well as some of our
20 programs in the context of preclinical and
21 clinical studies, and just in terms of resources,
22 we do support a number of programs that are

1 available at no cost to investigators. But really
2 what we see is that the path to clinical
3 application is long and it's expensive. There's
4 funding gaps, lack of non-technical expertise, a
5 lot of knowledge gaps, and decreased risk
6 tolerance among investors at this point in time.

7 So what is NHLBI doing in terms of
8 addressing those problems? Well, we've developed
9 a number of in-kind resources. We put together
10 panels of advisory experts to help people think
11 about, you know, are we going to bring this novel
12 discovery to commercialization? Almost all of
13 these resource programs include a training
14 component and educational component, so we're
15 trying to train the new scientists in the field,
16 the innovators, with education and training so
17 that they can think about regenerative medicine in
18 a commercializable way.

19 And finally through our SBIR program we
20 participate in the investor forums to try and
21 facilitate and develop partnerships with those
22 that would be interested in carrying on the

1 preclinical studies that are ready for
2 commercialization or clinical application.

3 So, some of the resources -- these
4 resources can provide a great deal of value to
5 developers even though they're not direct grants
6 or funding. The resources are available to not
7 only academic investigators but companies,
8 non-profits, and other researchers that are in the
9 field of innovation.

10 One resource that is important to talk
11 about from our point of view is the Biological
12 Specimen and Data Repository Information
13 Coordinating Center which is BioLINCC. It's a
14 long mouthful for me, and it really provides
15 access to sample sets that are linked to clinical
16 data which can be useful to support an IDE or
17 marketing application to the FDA.

18 We also have IND-enabling programs. You
19 may be familiar with the Gene Therapy Resource
20 program, the SMART program, as well as the PACT
21 program which is the Production Assistance for
22 Cellular Therapies.

1 So these IND enabling in-kind services
2 provide GMP manufacturing, GLP foreign talks,
3 testing for gene therapy for small molecules,
4 biologics, and other therapeutic modalities. So
5 this can increase the value of the technology
6 really at no cost to the developer, and there are
7 some other institutes. NCATS is a new institute
8 at the NIH that also provide these kind of in-kind
9 resources, so folks would want to be able to check
10 with that particular institute at the NIH to see
11 what's available to them.

12 So PACT -- PACT is a long-standing NHLBI
13 funded initiative. I'd like to mention my
14 colleague, Liz Welniak is here in the audience, so
15 if there's particular programmatic questions that
16 you have she's here to help me answer those
17 questions.

18 It began in 2003. It renewed in 2010.
19 It closed for a brief period of time, but now it's
20 back up and running, and it currently has five
21 cell-processing facilities and a coordinating
22 center. And the primary goal is to provide

1 assistance with cellular therapy, translational
2 research, and manufacture of cell-therapy products
3 for IND-enabling preclinical studies.

4 This is a little bit different than the
5 first two iterations of PACT. Basically this
6 program wants to help investigators scale products
7 requiring more complex manufacturing than they
8 normally have at their institution. It's really
9 not designed to provide products for
10 administration to human subject in clinical
11 trials. That's the new change for the PACT-3
12 program.

13 So as I mentioned, PACT-1 and 2 was
14 really designed for preclinical through the phase
15 1, first in human studies, and looking at dose
16 escalation, safety and toxicity studies. These
17 were really, you know, safety studies that needed
18 manufacturing and a scale of validation release
19 criteria for the cells being used.

20 In PACT-3 which has just been renewed,
21 we're focusing on the preclinical phase which
22 provides all of the GMP manufacturing and support

1 needed for proper preclinical
2 (inaudible) studies that is
3 required by the FDA. Another -- I
4 need to bring to your attention our
5 SBIR Advisory Group and the Office of
6 Translational Alliances. These folks really have
7 expertise in the regulatory affairs that this
8 development aspects (phonetic), regulatory
9 strategies, and they're available pretty much to
10 anyone. You don't have to necessarily be an
11 SBIR/STTR applicant, and they provide answers to
12 questions that you may have in taking your
13 innovation all the way up through clinical
14 application and commercialization.

15 And there's really more than -- more
16 people than we can talk to one-on-one, so NHLBI is
17 also providing Small Biz Hangouts. These are all
18 archived on YouTube, and they're really focused on
19 the common issues that innovators face regardless
20 of whether it's a technology in our mission space,
21 so advisor experts here, Chris and others, Gary,
22 really are hanging -- holding these hangouts that

1 encourage everyone who has a need to figure out
2 how to find the information you need through FDA.
3 They're there to help you navigate the FDA website
4 and provide answers to questions. Again, these
5 are archived on YouTube.

6 Next I want to just briefly touch on the
7 fact that NHLBI sends their staff to a lot of the
8 investor forums, so these forums allow -- and
9 they're listed here, across the U.S., some of
10 them. They really -- our staff are there to help
11 bring together those investors with innovators in
12 the field, and we go to these events throughout
13 the year.

14 So switching gears a little bit, some of
15 the preclinical programs that we have ongoing is
16 an example -- is NHLBI Progenitor Cell Biology
17 Consortium, and this program was started in 2009.
18 It had a 7-year \$170 million commitment and was
19 just recently renewed for 5 years. It has now --
20 has a translational focus and renamed the
21 Progenitor Cell Translational Consortium. This is
22 headed up by Denny Buxton, and we have a team at

1 NHLBI that are working with the new center, but
2 the original goals of the consortium was to bring
3 together multi-disciplinary teams from the heart,
4 lung, blood, stem cell technology research areas
5 to develop the regenerative medicine field. It
6 has an administrative coordinating center, and
7 throughout the program it brought in additional
8 ancillary projects and pilot studies as well as
9 education and training to help develop the
10 regenerative medicine field.

11 A complimentary program is the Lung
12 Repair and Regeneration Consortium which was
13 funded in 2012, and basically this was to further
14 help the lung community to -- mechanisms that
15 control lung repair and regeneration. This did
16 also have a strong educational and training
17 component to help scientists in the field figure
18 out and navigate this very complex field.

19 The renewal of the PCBC, now the PCTC,
20 is really combining the Lung Repair Consortium and
21 the Progenitor Cell Consortium into one but
22 focusing on translation. The applications were

1 laid out, so-called road map, about how they plan
2 to address disease in our mission space and
3 barriers to progress, how they plan to overcome
4 these barriers, and when they expect to reach key
5 milestones.

6 The focus areas are patient-specific
7 disease models using genome editing to understand
8 disease pathology and to design therapeutics.
9 They expect to further the field of cell therapy
10 and tissue engineering using progenitor cells
11 including gene-modified cells and differentiated
12 progeny. An additional area of focus is to direct
13 reprogramming of cells in vivo to treat disease.

14 These are some of the resources related
15 to the PCTC, and I'm going to try to catch up on
16 our time and jump right into the clinical programs
17 that we have ongoing. These are just a few of
18 them and I'm not covering everything obviously.
19 We have a very large investment in this space.
20 The Cardiovascular Cell Therapy Research Network
21 or CCTRN, funded in 2007. Its aim was to provide
22 infrastructure to develop, coordinate, and conduct

1 multiple clinical protocols to facilitate
2 bench-to-bedside application in this area. It
3 performed three trials, time, late-time, focus,
4 which all demonstrated safety and can be found
5 online -- those results. These were all three
6 trials looking at autologous bone marrow
7 mononuclear cells. The renewal occurred in 2012.
8 There's seven centers, and the scope has expanded
9 to include peripheral arterial disease and to
10 focus on more innovative cell types that have the
11 potential for enhanced therapeutic efficacy.

12 One study, the Concert Study, is looking
13 at C-positive cardiac cells versus MSCs in
14 patients with ischemic cardiomyopathy. A second
15 study, the Seneca Study, is looking at allogeneic
16 MSCs in cancer survivors with anthracite induced
17 cardiomyopathy.

18 Another area that we're trying to focus
19 on is the cardio-thoracic surgical trial network
20 which just completed a phase 1 safety trial which
21 demonstrated safety of mesenchymal precursor cells
22 as adjunctive therapy in recipients with LVADs.

1 The network renewed in 2012 and they're now
2 currently enrolling a phase 2 trial of MPCs in
3 patients with end-stage heart failure, ischemic or
4 non-ischemic that are being evaluated for LVADs
5 for which to transplant or destination therapy.

6 And what's interesting to note here and
7 suggests a notion of a strong public interest is
8 the easy enrollment. We're ahead of -- in our
9 accrual and it really demonstrates or suggests the
10 notion that folks are eager to see the use of
11 these cells in improving their heart disease.

12 I'd just like to summarize that we are
13 using a number of mechanisms to promote this whole
14 area and move towards clinical translation
15 including our in-kind resources, educational
16 support, facilitating partnerships, and clinical
17 networks. And we also have independent, robust
18 portfolio which Chris Breuer is a nice example of
19 an independent investigator that has really
20 capitalized on the NIH system to promote this area
21 and really looking at science-based advances in
22 the field.

1 And finally I'd just like to thank the
2 folks at NHLBI that helped me put together this
3 presentation to be at the meeting. Thank you.

4 (Applause)

5 SPEAKER: We're going to take a short
6 break. I mean short, and reconvene at five after
7 three.

8 (Recess)

9 DR. WEISSMAN: Okay let's get started.
10 The moderator for our next session is Dr. Jeffrey
11 Kahn who is the Andreas C Dracopolous Director of
12 the Johns Hopkins Institute of Bioethics. He is
13 also Robert Henry Levy and Rider Hex Levy
14 professor of bioethics in public policy and
15 professor in the Department of Health, Policy and
16 Management in the Bloomberg School of Public
17 Health. So he's professor of bioethics, public
18 policy and public health and Dr. Kahn is going to
19 talk to us initially about societal perspectives
20 on development in oversight of novel cell based
21 therapies.

22 DR. KAHN: Thank you. I'm going to kick

1 off this part of the program and then I'll be
2 moderating the rest of the session this afternoon.
3 I don't have a disclosure slide because I really
4 have nothing to disclose except to say Dr. Bryan
5 and Dr. Witten know that I chaired a committee for
6 the Institute of Medicine, now National Academy of
7 Medicine that was sponsored by the FDA on the
8 first human uses of mitochondrial replacement
9 techniques. I disclose that really mostly as a
10 matter of information and also to say some of the
11 lessons that came out of that report and the
12 recommendation from that report are quite relevant
13 to the discussion here today. One more thing to
14 say about that my colleague Jonathan Kimmelman who
15 spoke before the break was a member of that
16 committee as well.

17 So I'm just going to make some quite
18 general comments about how first society and then
19 individuals who are involved in early trials of
20 cell based therapies might be thinking about the
21 issues and what we want in place as we move
22 forward.

1 Dr. Pottol's comments about being hungry
2 and a student made me recall that when I was a
3 graduate student I was also hungry and I didn't
4 enlist in the military I rather enlisted as a
5 research subject and made a fair amount of money
6 over a fair number of months doing things in
7 retrospect were probably not so wise. Most of
8 them early phase research trials. They were not
9 for cell based therapies of course given my age
10 but they were sort of novel approaches and part of
11 what it reminds me of is that we have to be
12 thoughtful about how we proceed. So let me dig in
13 here. You see I only have a few slides so really
14 you'll hear me more talk than you will see slides
15 for me.

16 So as we, the royal we, the society
17 thinks about moving forward in enrolling subjects
18 who are likely to be patients and then eventually
19 as we move to approval and introduction of these
20 new cell based therapies we want to make sure
21 certain things are in place. And society not only
22 ought to expect this but ought to demand that

1 these things be in place.

2 First, that there is a pretty clear and
3 established set based on evidence that safety has
4 been established in an initial way and that we
5 minimize to the extent that we can tolerate the
6 risk to the parties involved. So we want to make
7 sure and I think we don't get many chances to get
8 this wrong before we get it right. This is a
9 really important point in the development of a new
10 technology. Getting things wrong at the early
11 stage will lead to continued problems of trust and
12 willingness of the public not only to participate
13 but also to allow their tax monies to be invested
14 in new areas of research.

15 The second thing we want to make sure
16 after safety is that there is some established
17 evidence for the likelihood of efficacy based on
18 pre-clinical that is non-human based research
19 models and as the investigations go forward that
20 they are limited to the appropriate populations
21 and we don't see proliferation beyond the kind of
22 narrow research population certainly at the early

1 stages and probably even more as we move into
2 initial adoption as a matter of approved
3 therapies. So just sort of a signal about one of
4 the things I want to leave you with at the end of
5 my remarks and I hope we can talk about during the
6 panel is how to make sure that we don't have this
7 sort of proliferation of technologies out into the
8 public once something is approved in ways that are
9 not as responsible as we might hope. So what
10 effectively look like off label uses are not the
11 most responsible or in the best interest of
12 individuals or society.

13 The second thing I think needs to be
14 really focused on is that we move forward in what
15 is presumed to be a cautious way so sort of safety
16 first is a really important principle I think and
17 one that is an important one to honor as a matter
18 of societal interests. So go slow and do these
19 initial kinds of research introductions with as
20 few individuals as is necessary. So we don't want
21 to expose more people to risk than we need to. So
22 careful and small numbers to the extent it makes

1 sense to get the data that we need. If we're
2 talking about studies that are performed in more
3 than one place by more than one entity maybe even
4 funded by more than one company that the designs
5 are standardized in a way and to the extent
6 possible that we can compare and pull the data
7 that comes from them. So make the most use of
8 information that comes from what would be a
9 relatively few numbers of people in early stages.
10 So that is not typically done. You may have heard
11 this from others. This was among the
12 recommendations that came out of the mitochondrial
13 replacement techniques report. Because we are
14 talking about such small numbers that it is hard
15 to get good and useful data unless you're able to
16 combine data from multiple sources somehow.

17 The expanded version of that point is
18 the next bullet which is about data from places
19 that are outside of typical FDA jurisdiction or
20 FDA analysis that might be outside of this country
21 for existence and so we want to pull information
22 from as many places as feasible to support coming

1 to conclusions about both safety and efficacy as
2 we move forward into the research trial and into
3 eventual, potential approval.

4 Maybe most difficult if not
5 controversial is how to collect long term
6 longitudinal information from the people who are
7 involved in both research and maybe even in early
8 applications of approved therapies. How are we
9 going to learn over a long period of time what the
10 effects of these new kinds of therapies are going
11 to be? That requires somebody to pay for that
12 work. It is really hard to collect longitudinal
13 data. One you have to get people to agree but two
14 someone has to pay for it. But I think that is
15 something that society needs to be made confident
16 about. I'm not giving you ways to do it but
17 rather raising it as an issue that needs to be
18 addressed.

19 Switching from societal interests to
20 individual interests to what individuals need to
21 be thinking about and need to be informed about as
22 they are offered the opportunity to participate in

1 what would be early trials. There needs to be
2 special attention paid to communicating what are
3 the novel aspects of whatever the initial trials
4 are for a particular cell based therapy. So you
5 would want to know and be told whether this has
6 ever been done in humans before. So if you're
7 among the first human subjects to be participating
8 in a novel cell based therapy trial that is
9 important for you to understand and the
10 implications of that. So what information has
11 been learned from non-human models but of course
12 understanding that this is the first time for a
13 human and there will need to be some human trials
14 and we've heard a lot about that today.

15 A clear explanation and communication of
16 the risks involved that the potential benefits are
17 highly prospective if any in particular in these
18 early stage trials and a longstanding issue in the
19 ethics of research involving human subjects is the
20 misunderstanding and I don't mean that people
21 don't get it but rather the improper balancing in
22 people's minds about how much risk versus how much

1 potential benefit. So part of that is because
2 people want to perceive potential benefit in
3 research participation but part of it is because
4 the communication of that information is often
5 skewed at least historically it has been.
6 Empirical research probably now 10 or so years old
7 shows that there is a pretty consistent skewing of
8 information shared with potential research
9 participants overemphasizing potential benefits
10 and underemphasizing potential harms.

11 In the context of cell based therapies
12 we need to make clear the difficulty of what it
13 means to withdraw from research. You may be able
14 to no longer be in a trial but it is hard to get
15 the thing that you got as part of that trial to be
16 taken out of your body. It is not like a drug
17 that washes out it is not like a device that can
18 be removed and that is something that needs to be
19 communicated and made clear. For some people the
20 source of materials if they are controversial in
21 nature would be important and should be disclosed
22 just as a matter of information and people may

1 decide that that's not something they want to
2 participate in as a matter of their own
3 conscience.

4 Stepping back and talking both from a
5 societal perspective and individual perspective
6 the kinds of principals that ought to be part of
7 an oversight scheme for moving forward with novel
8 first in human early phase development of novel
9 cell based therapies.

10 First to the extent that we can figure
11 out how to do this and do it with transparency.
12 Share with the public in a timely way the
13 information coming out of these early phase
14 trials. It would be great if sponsors were
15 willing to commit to depositing the protocols and
16 of course the identified results in publically
17 accessible places so that it can be seen by people
18 who would like to see it. An exploration of the
19 views of stakeholders involved in the kinds of
20 research that we've been talking about and hearing
21 about today and that can be done in a variety of
22 ways. This country we're not terribly good at

1 public engagement around what are socially,
2 societally and sometimes individually
3 controversial areas of science and biomedical
4 research. European countries in particular have
5 had much better examples and experience and built
6 up approaches to doing this but this is an area
7 where I think we could do better and need to do
8 better. There needs to be partnership among the
9 regulatory authorities responsible for oversight
10 of this kind of science and I mean not only in the
11 United States but across borders. Just to
12 reiterate something that I said earlier enabling
13 sharing of data, pulling of data, cross
14 referencing of data, so maximization of data
15 quality to make the most use of the data that
16 comes from asking people to put themselves in
17 uncertainty if not in harm's way and take
18 advantage of that to the greatest extent possible.
19 So it is a privilege to do research on humans and
20 we should take the most advantage of it as we can.
21 I don't mean exploit the people but I mean take
22 advantage of the data.

1 That is the end of my remarks. I wanted
2 to just to a very general overview as I just did
3 and there will be lots of opportunity to talk with
4 as you see a number of people at the panel stage.
5 I want to move to the next part of the program. I
6 now have the privilege of introducing the
7 remaining speakers in this part of today's
8 program. The next of whom will be Dr. Brian
9 Mansfield. As you get the slides ready let me
10 introduce Brian. Brian is the Deputy Chief
11 Research Officer for the Foundation Fighting
12 Blindness a position he assumed in 2011. In that
13 role, he assists the Chief Research Officer of the
14 Foundation in directing the early translational
15 research investment program and ensures
16 implementation of the Foundation's research
17 strategic plan and manages day to day operations
18 of its science department.

19 DR. MANSFIELD: Thank you for the
20 invitation to talk today. What I'd like to do is
21 to outline a little bit about what the foundation
22 does, the patient perspective of their disease and

1 where we stand in our guidance not only in the
2 research that we support but also in the guidance
3 we give to our constituents when they approach us
4 about these therapies. So the Foundation Fighting
5 Blindness is a non-profit organization. Our
6 mission is to provide preventions, treatments and
7 cures for people who are affected by this group of
8 often retinal degenerative diseases. So these are
9 all awful diseases and these are for a small group
10 of people who feel they are not well represented
11 by the major efforts that are going on in the
12 large pharma companies. Our research budget runs
13 around \$28 million a year. We have a scientific
14 advisory board of about 100 experts in this field
15 who give us very good input and guidance in the
16 things we do and in our decision making. We fund
17 a lot of preclinical research and more and more
18 now we are starting to step into fund the proof of
19 concept studies in humans which we generally do in
20 a cofounding manner with another partner and we
21 are also looked upon to provide education and
22 support to our constituents who are affected with

1 these devastating blinding diseases.

2 So I just want to remind you that the
3 inherited dystrophies the IRD these are diseases
4 that affect the back of the eye. The eye is full
5 of fluid and there is only that small part of
6 tissue outlined partly by that white box there
7 where the retina sits. But the retina is a very
8 complex tissue. There are at least 10 cell layers
9 in there we'll come back to in a moment.
10 Different diseases affect different cells in that
11 complex and different parts of the retina are
12 reflected by different types of diseases. So you
13 can see if the disease affects the middle of the
14 eye there. There are macular diseases which are
15 distinct from diseases that affect the edge which
16 are the peripheral diseases.

17 Now these diseases are literally in your
18 face all the time every day. They are progressive
19 diseases so you can't avoid the point that they
20 are progressing and you are very well aware of
21 their progression each and every day. In the
22 peripheral diseases your vision just gradually

1 disappears from the periphery until you end up as
2 if you're looking down a very narrow tube
3 ultimately you lose vision. The macular diseases
4 are the opposite. They start in the middle, the
5 high central acuity part of your eye where you
6 really depend on a lot of color vision, a lot of
7 ability to read and see detail and then that area
8 of blindness expands out until you lose all
9 vision.

10 So one of the things that we're very
11 focused on is the importance of vision to our
12 constituents and recently we held a patient
13 reported outcomes meeting with them where we were
14 asking about quality of life, what they want out
15 of therapeutics and what is most important to
16 them. I'm going to summarize on the next few
17 slides a couple of these findings.

18 The first thing that comes out broadly
19 is nearly everyone with this disease tries to hide
20 the fact that they have it because of a number of
21 societal things such as fear of loss of
22 employment. If you depend on computer use or

1 reading and your employer senses you may not be
2 able to do that efficiently that creates a great
3 fear. And particularly if you lose your job will
4 you get reemployed. There are concerns about
5 health insurance. What is the insurance
6 consequence of discovering that I have a disease
7 like this? By the way there are no treatments for
8 these diseases. There is one prosthetic which can
9 treat a small minority of diseases but there are
10 really no therapeutic choices for these people at
11 all. And then there is discrimination. These
12 people look different. They will often wear
13 tinted glasses, fat glasses, they will use a cane,
14 they will be less confident in their movement,
15 many different things make them stand out and they
16 are particularly aware of that difference.

17 Vision is also important to social
18 interactions. Think about how someone can say
19 something but depending on whether they smile or
20 frown it has a completely different meaning to
21 you. When you don't have good vision you lack
22 that context that it comes with. It is obviously

1 important for our interaction with others. For
2 instance, if we don't have peripheral vision and
3 someone walks past us and we don't acknowledge
4 them that can be considered perception of being
5 rude to them. That has horrible consequences
6 downstream. There is also the perception of
7 disability. The number of people who say when
8 they're out with their partner the person talking
9 to them is either talking to their partner or is
10 shouting at them. As they say it is a vision
11 problem not a hearing problem. Vision loss also
12 affects daily life. The biggest thing here is
13 they can't drive. In our society being able to
14 drive is independence and particularly if you have
15 a young family where you have to pick up the kids
16 and take them to their activities this is a major
17 consequence when you get to a stage where you
18 can't drive. And then there are other consequences
19 which are harder for us to appreciate maybe such
20 as July Fourth fireworks photoxia which should go
21 on whether your eyes are open or closed it just
22 keeps going.

1 So what do constituents want? Well it
2 is graded. Of course they would love to regain
3 lost vision but most realize that is not possible
4 at the moment. They would like to stop that loss
5 of vision at least stop it where it is now or
6 possibly slow it down. Most people are looking to
7 finish a productive life. They would like to get
8 through to retirement or they would like to see
9 their daughter married or something like that.
10 There are always these things that they look
11 forward to so any of these outcomes would be
12 valued to them.

13 When we ask them what functional outcome
14 they want the majority of them say they want to
15 drive but when you talk more about this they
16 really want independence. The ability not to have
17 to ask someone to do everything for them all the
18 time. A number of them or 40 percent of them also
19 reflect the need to improve a social interaction
20 and to be able to remain active in their careers.

21 When we ask them about therapies safety
22 is really a prime one that they all bring up not

1 only for the eye but they also are worried about
2 what more generic effects this may have on my
3 body. I don't want to suffer a heart attack
4 because of something I've taken for my eye. That
5 is going to be an adverse consequence for me. The
6 risk tolerance to what they will do varies. If
7 they have very little vision loss but they know
8 they're going to lose it, they are often open to
9 being a guinea pig because they feel they can
10 afford to lose a little vision if it will benefit
11 someone else. That is great for pharmacological
12 treatments probably not for the self-therapies.
13 If they have a large vision loss, there is often a
14 reluctance to do anything because they really hang
15 on to just seeing the sunrise and knowing it is
16 daytime again.

17 So the stem cells for the IRD that we
18 support fall into three categories. There is the
19 neurotrophic support where cells are generally
20 injected as a bolus. They are not intended to
21 migrate or differentiate or proliferate but they
22 produce neurotrophic factors that we hope will

1 keep the retina healthier and maintain vision,
2 slow or stop that degeneration. An example of
3 work that we funded led to the neurotech device
4 which is the small encapsulated device that
5 contained cells genetically engineered to release
6 a neurotrophic factor and that is placed just
7 inside the eye in that watery compartment and
8 diffuses proteins across to the back of the eye.

9 The second sort of stem cell therapy
10 that we support is cell replacement therapy where
11 we are looking for migration, integration,
12 differentiation and the creation of productive
13 connections in the eye. And as you've heard from
14 Dr. Clegg and others formulation may involve bolus
15 injections, a single sheet of cells, 3D layers
16 where you provide a matrix to support some of
17 these spindly cells and help them be more secure
18 and you may look at a single cell type or you may
19 be looking at trying to put in several of those
20 different layers together as an architecturally
21 structured component.

22 Again, just to give you a flavor of sort

1 of the work that we have cofounded most of it is
2 preclinical. We support autologous and allogeneic
3 work induced pluripotent stem cells, embryonic
4 stem cell work, fetal retinal precursor stem cell
5 work and you'll notice that second to bottom we
6 did support autologous non-homologous use for
7 CD34+ stem cells. We'll come back to that in a
8 moment.

9 We support a number of primary
10 indications. The technologies you can see range
11 across the different matrices protocols trying to
12 get optimization and better differentiation
13 protocols. Some of the work that we have
14 supported has ended up in the clinic.

15 The third stem cell we support is in
16 situ differentiation where you're trying to
17 encourage native cells in the retina to
18 differentiate into a different type of cell to
19 replace the damaged cell. So for instance we can
20 induce the

21 (inaudible) expression or we can
22 use small molecules to manipulate

1 permanent expression for
2 transcription factors.

3 Now as I said the retina is a complex
4 tissue. There are six primary cell types but
5 actually 59 distinct subtypes so when people start
6 going and putting cells in there be aware this is
7 a very complex environment you're putting things
8 into. Placement of the cells and migration
9 differentiation integration are critical. This is
10 a highly organized structure. There are very,
11 very precise connections going on in there and
12 when those synaptic connections go wrong we don't
13 know what is going to happen to the perception of
14 vision. Certainly in the diseases as they
15 progress further and further those synaptic
16 connections change and that is obviously a
17 challenge in that you would like to see those
18 rectified in a therapy that is addressing that
19 stage of disease.

20 The other thing to realize is that this
21 structure is actually essentially a computer as
22 well. It is already starting to synthesize and

1 interpret shades, contrast, edges in your vision
2 before it is even communicated to the brain. We
3 must be aware that some cells if inappropriately
4 activated can have negative consequences. For
5 instance, glia, activated glia can lead to
6 scarring so this is not something to go into
7 lightly when you start playing with cells.

8 So what are the key challenges facing
9 our therapy? I think we've heard other speakers
10 talk about these. Key to us is how do you get
11 stem cell differentiation to a particular cell
12 type you wish to replace, where do you place it,
13 how do you promote the functional synapse
14 connection to make sure the signal gets back to
15 the brain in a sensible way. What is the function
16 of creating a synapsis which is not native? Where
17 do cells go I think we all have that and the
18 ability to trace them.

19 Now we are particularly concerned about
20 non-homologous therapies that are appearing on the
21 market where people are starting to take bone
22 marrow and inject back into the eye for a fee.

1 There are many studies which are poorly
2 characterized. The cells not well characterized
3 by type, consistency, purity, quality. Route of
4 administration is often poorly defined. In fact,
5 often some of these protocols will suggest there
6 are five or six different things they may do
7 depending on the clinician. There is no disease
8 focus. Most of these therapies that we are aware
9 of are offering to treat nearly any retinal
10 disease. That doesn't seem realistic as this is a
11 complex tissue. There is a cost to the patient
12 and generally there are few or no peer review
13 publications showing anything about preclinical
14 evidence with safety, efficacy, dosing, or
15 administration route.

16 So we are very worried about the safety
17 and oversight concerns. Some of these studies for
18 instance are listed on clinicaltrials.gov and I'm
19 particularly concerned that they can give the
20 impression that they are federally mandated. You
21 find the health authority being defined by a
22 variety of different terminologies. There is in

1 fact no way when you go on clinicaltrials.gov of
2 finding whether there is an IND for this procedure
3 and whether it is FDA authorized. And clinical
4 trials can tell you you can sort of get there but
5 you can never be certain. You actually have to
6 ask the person doing the procedure.

7 So what is our perception on this. Well
8 there are very few as I say published outcomes and
9 it worries me when we start seeing a lot of
10 promotion in social media, in the mainstream
11 newspapers where they're talking about the
12 publication of a single case study but notice that
13 the PI says he's treated 278 patients and 60
14 percent respond. Well why that one? Why did he
15 publish on his 278? This really bothers us. We
16 have to be careful though. There are some studies
17 which do have regulatory oversight which do use a
18 similar source of material maybe slightly more
19 enriched and refined so we have to be very careful
20 that we don't use a broad stroke to wipe out all
21 these sorts of studies.

22 So what is our perspective on these sort

1 of procedures? Again, very much what other people
2 have said. We very much support the regulated or
3 careful approach that the FDA has understanding
4 mechanism action if you can, defining your cells,
5 defining your procedures, understanding toxicity
6 distribution, efficacy and preferably having that
7 peer reviewed and open.

8 So what do we tell our constituents
9 because I often read an article in the paper and
10 say you should be jumping for this this is the
11 treatment you want and we tell them our studies.
12 Is it on clinicaltrials.gov but be aware of what
13 that really means. Is it authorized by the FDA
14 when you know there is going to be an emphasis on
15 safety. Is it focused on the world defined
16 condition or is it a fix all. Are the clinicians
17 experienced preferably knowing the complexity of
18 the retina and therefore specializing in the IRD
19 and talk to your own specialists before you go
20 jumping into another study or clinical. Be wary
21 of personal testimonies. They are often taken
22 immediately after treatment where this is a strong

1 incentive to say it is working, it is good, it is
2 beneficial. You don't know what happened later on
3 and you don't know what their perception of it is.
4 And we feel very strongly that participants should
5 not be paying for any of these out of pocket if it
6 is said to be a clinical trial study.

7 Finally, think of your risk tolerance.
8 This is a trial, it is not approved and don't
9 forget once you've been in a cell therapy trial
10 you are going to be excluded from any of the other
11 trials that are coming down the road probably for
12 10 years. So if you really think that there is
13 something else on the horizon think very carefully
14 about your risk tolerance as you enter into these
15 trials.

16 So in conclusion, the Foundation for
17 Fighting Blindness seeks to make our constituents
18 scientifically aware of the issues. We believe in
19 the potential of stem cell therapy, absolutely.
20 But we believe it will come through well
21 controlled peer reviewed studies on cell therapy.
22 We have supported some of these autologous bone

1 marrow cell transplant experiments but they have
2 been under the oversight of the FDA. We are aware
3 that some of the procedures that have been out
4 there have had complications and I believe you may
5 hear about them soon and we advocate that all of
6 the therapy should have (inaudible) data and have
7 that regulatory oversight. Again, we do not
8 advocate the use of pay policy for these sort of
9 studies.

10 DR. KAHN: Thank you Dr. Mansfield. Our
11 next speaker is Thomas Albini. Dr. Albini is an
12 Associate Professor of Clinical Ophthalmology at
13 the Bask and Palmer Eye Institute in Miami.

14 DR. ALBINI: Thank you very much for the
15 invitation to speak here. Thanks to the FDA and
16 Dr. Kahn and it is also a pleasure to be following
17 after Dr. Mansfield and my colleagues at Baskin
18 Palmer Eye Institute and myself have been familiar
19 with Foundation for Fighting Blindness. I've
20 worked with them for years and I have to say I
21 have very little of substance of what he said from
22 the patient's perspective. I think it is a great

1 organization in really helping patients who have
2 these blinding conditions. But what I'm going to
3 share with you is what I think is a very rare
4 instance of a dreadful outcome from a "health
5 provider" in South Florida where I think there was
6 really demonstrated neglect for both patient
7 safety and for any sort of scientific integrity
8 from what was being done. Just to discuss a real
9 case scenario with three patients who were
10 treated, came from elsewhere in the country, were
11 treated in South Florida and then were seen at my
12 facility within two or three days after the
13 treatment because of complications and of note
14 this happened three times not just once. It was
15 really a very horrifying situation. I have no
16 relevant disclosures.

17 We've heard already about macular
18 degeneration this morning and a little bit in the
19 last talk and its important to say that for most
20 patients with macular degeneration they preserve
21 their vision for quite a long time. Dry macular
22 degeneration especially in its early

1 manifestations is really consistent with retained
2 vision for decades for the vast majority of
3 patients. But for about 10 percent of the
4 patients they will go on to develop one of the
5 severe forms. There is the wet form of macular
6 degeneration. This is the form where patients are
7 routinely getting monthly injections of various
8 biologic agents to control the fluid that
9 accumulates underneath the retina within the
10 retina and causes vision loss. Another 10 percent
11 of the macular degeneration patients will develop
12 severe dry form macular degeneration where there
13 is atrophy of the retinal pigment epithelium as we
14 discussed earlier this morning.

15 Now these patients will go on to severe
16 vision loss for the vast majority of them if left
17 untreated. We have very good treatment now for
18 the wet form. For the dry form we still don't
19 have a very good treatment. So the story is the
20 patient moves to Florida and is getting excited
21 about taking up golf as their main retirement
22 activity and then loses the ability to drive, read

1 and recognize faces. These patients maintain good
2 peripheral vision so they can get around a room
3 but they lose their central vision.

4 So the wet macular degeneration outcomes
5 these are outcomes from pivotal trials for a drug
6 called Ramibizumab that was introduced by
7 Genentech back in 2006 and really have shown
8 marked improvement of visual acuity from baseline
9 whereas in the control groups the patients lost
10 visual acuity. This is maintained out at least
11 through the first three or four years, we've got
12 data through seven years. You lose a little bit
13 of vision but if you continue with these monthly
14 injections of biologics you can really maintain
15 that visual acuity for a long time.

16 In dry macular degeneration the number
17 of different strategies that are out there trying
18 to find a treatment including biologics, small
19 molecules, gene therapies and cell therapies as
20 we're talking about here today. Perhaps these
21 embryonic stem cell derived retinal pigment
22 epithelial cells much like the cells that were

1 discussed earlier today. But provided from
2 another source a company called Ocata Therapeutics
3 that published their results in The Lancet, this
4 is for dry macular degeneration and really showed
5 some modest but apparently real visual acuity
6 gains and some other biologic findings on various
7 imaging studies demonstrating that these cells
8 actually took residence and where the retinal
9 pigment epithelium should be in the sub-retinal
10 space and had some demonstrated function as well
11 in that space. So we are having some victories in
12 this field. They are coming slowly but I think
13 this is very welcome news that there is some real
14 data that stem cells are working for dry macular
15 degeneration.

16 Now one of the delivery methods that we
17 haven't talked about today is just intravitreal
18 delivery which is perhaps the simplest form of
19 delivery. It is the form of delivery that we use
20 for intravitreal injections of biologics for wet
21 macular degeneration like that drug Ramabizumab
22 that I just mentioned. In this case these four

1 different trials that are listed on
2 clinicaltrials.gov are looking at taking stem
3 cells and delivering them straight into the
4 vitreous cavity. One of these studies was using
5 adipose derived stem cells where the adipose
6 tissue was harvested on the same day that the
7 intravitreal injection was done and was then
8 processed in a very quick fashion under an hour.
9 In the same procedure injected them bilaterally
10 into both eyes. It is the outcome of this
11 procedure that I'm going to be talking about.
12 This company that was doing this unbelievably
13 without an ophthalmologist directly involved in
14 what was happening without an M.D. injecting the
15 cells. They were injected by a nurse
16 practitioner without M.D. oversight. This has
17 resulted in really bad outcomes and as I said
18 again demonstrated a complete lack of regard to
19 the patient safety and to any sort of scientific
20 integrity. They did have a trial that was posted
21 on clinicaltrials.gov. The patients when I saw
22 them and they came to the hospital a day or two

1 after this happened, by the way this was a very
2 painful procedure for them which is not typical
3 for injections. They are usually somewhat painful
4 but not the type of profound pain that these
5 patients were describing. They were under the
6 impression that they had participated in a
7 clinical trial. When we finally were able to see
8 the informed consents that the patients had signed
9 the informed consents actually weren't for any
10 clinical trial they were just for a basically fee
11 for service procedure which was explained to the
12 patient to have the possibility of resulting in
13 blindness and that it was outside the standard of
14 care of treatment. That's how this particular set
15 of injections was performed.

16 So we're reporting here three cases of
17 bilateral vision loss after bilateral intravitreal
18 injection of stem cells in a stem cell clinic.
19 All patients underwent intravitreal injections of
20 the usual dose of volume that is injected with
21 autologous adipose tissue derived stem cells. All
22 three of the patients paid \$5000 for the

1 procedures. One of the patients also had the same
2 stem cell preparation injected into both of her
3 knees on the same day for an extra \$1200. They
4 signed a consent form for the procedure but not a
5 study consent and all three of the patients here
6 had seen the clinicaltrials.gov website. One of
7 the patients, the first patient I'll describe was
8 a statistician who had been involved in clinical
9 research and these patients were under the
10 impression that the clinicaltrials.gov website
11 lended some credibility to the study.

12 The first patient is a 72-year-old
13 female with a history of dry macular degeneration
14 and vision of 20/60 and 20/40 which is pretty good
15 vision. 20/40 is good enough to drive if that
16 were your only eye at least in the State of
17 Florida and it is good enough to read standard
18 newspaper print. This is not perfect vision but
19 it is very functional vision. She came in with
20 three days of decreased vision, pain and vomiting
21 and nausea. Visual acuity on presentation was
22 hand motions only, she couldn't see the large E on

1 the eye chart out of either of her eyes and she
2 had extremely high intraocular pressures. What we
3 found in this particular patient these are
4 ultrasounds showing anterior displacement of the
5 crystalline lens which the zonules that hold the
6 lens in place apparently became loose somehow.
7 This is probably not because of the needle or a
8 direct pushing or ripping of the lens but we think
9 it is an enzymatic digestion that something that
10 was injected into the eye. Trypsin for example is
11 known to digest the zonules and used to be part of
12 standard intracapsular cataract surgery. It is a
13 way to remove the lens. But some protein that was
14 injected in the eye probably dislodged these
15 lenses that pushed forward that causes the
16 obstruction of outflow of fluid from the eye,
17 increases the pressures in the eye which of course
18 is bad for the optic nerve that causes an acute
19 glaucoma. She was found to have a vitreous
20 hemorrhage in both eyes there was no view to the
21 back. We had to remove the lens emergently,
22 remove the vitreous that was in the back of the

1 eye and remove the blood that was there. She was
2 found to have a retinal detachment in the right
3 eye and over one week her vision dropped down to
4 no light perception in either eye. She ultimately
5 had retinal detachments in both eyes that needed
6 to be fixed. Here you see a lot of intraretinal
7 hemorrhage all throughout the fundus, retinal
8 detachment, displaced lenses, really a disastrous
9 outcome that you never see after routine injection
10 of biologics for wet macular degeneration.

11 The second patient is a 78-year-old
12 female. She had wet macular degeneration which
13 was well controlled. She hadn't required an anti
14 veg-F injection for two years prior to undergoing
15 this therapy. Her visual acuity in the right eye
16 had just dropped to a point where she was losing
17 her driver's license and therefore sought out this
18 treatment as a potential remedy for herself that
19 her daughter found on the web. Again, from the
20 web was referenced to the clinicaltrials.gov
21 website and mentioned that when we spoke to her.
22 She was also under the impression that she was

1 participating in a clinical trial. Similar
2 diffuse hemorrhage in both eyes worse on the left
3 than right. She presented without retinal
4 detachments. Also very bad vision, counting
5 fingers again not formed vision in either eye.
6 She was initially observed and eventually
7 developed retinal detachments in both eyes
8 requiring treatment and now at least has one eye
9 with visual acuity of 20/200 and the other one
10 doesn't have any formed vision.

11 This is the third patient 88-year-old
12 female, dry macular degeneration. Had a visual
13 acuity of 20/40 again relatively good vision in
14 the right, 20/200 in the left eye prior to
15 injection. She came in seven days after the
16 procedure with light perception vision only in the
17 right eye, 20/200 in the left eye. A very mature
18 looking retinal detachment with what we call PVR,
19 Proliferative Vitreal Retinopathy which one of the
20 reasons the retinal detachment surgery fails is
21 that you get a growth of scar tissue on the
22 surface of the retina fibroblast that contract and

1 pull the retina back off of the wall of the eye.
2 It is possible that the stem cells which in some
3 of the imaging that we have seen to take residence
4 on the anterior surface of the retina and they may
5 be actually pulling the retina off and being the
6 reason why all these patients eventually developed
7 retinal detachments in both eyes as this patient
8 did in her left eye about a month later.

9 So these were the initial vision of the
10 patients ranging from 20/40 to 20/200. Their
11 presenting visual acuity when they came to the
12 clinic ranging from 20/200 to light perception.
13 Five of the eyes had lens subluxation, some were
14 along their course. Four eyes had severe
15 intraretinal hemorrhages. All of the eyes
16 eventually developed retinal detachment and the
17 ultimate visual acuity was legal blindness in all
18 three of these ladies. We had a one year follow
19 up and unfortunately none of the patients have
20 gotten any better.

21 So what are the potential causes for
22 these findings? Well they include contamination

1 of stem cell with toxic substances during
2 preparation. Use of trypsin or collagenase during
3 stem cell isolation which we're looking at because
4 of that zonular weakness that we've seen and maybe
5 it is not appropriately washed out. And there may
6 be some genuine affect from growth factors in
7 cytokines and the vitreous and blood derived
8 undifferentiated stem cells to myofibroblast cells
9 resulting in detachment of the surface of the
10 retina. There is some biologic effect of these
11 cells and some of the phase one studies have also
12 been stopped because of retinal detachment where
13 there has been inadvertent seepage of cells that
14 were injected into the subretinal space coming
15 back into the vitreous cavity and then retinal
16 detachment was seen in a lot of those. So there
17 may be some danger from this mode of delivery.
18 There is real science being done on intravitreal
19 injection of stem cells so I certainly don't want
20 to put any hindrance to that. There may be a good
21 way to deliver intravitreally but we hypothesize
22 that intravitreal delivery at least in these cases

1 may have caused some of the problems.

2 The patients were referred to
3 clinicaltrials.gov which listed an IRB approved
4 study however the patients were not enrolled in
5 the study. Injections were being performed
6 without FDA oversight. There was no IND obtained
7 by this clinic. These were patient funded
8 research procedures and we've talked about the
9 dangers of that. Unbelievably, an American
10 licensed physician was not involved in the care
11 and the injections were performed by a nurse
12 practitioner.

13 Sorry to share this with you but I think
14 it is an important thing for patients to know and
15 as I've learned today the extent of the industry
16 that is around these unregulated stem cell clinics
17 I hope we don't see more of this with intraocular
18 delivery. Thank you.

19 DR. KAHN: Thank you. Our last speaker
20 for this session before the panel is Dr. Michael
21 Miller. Dr. Miller is a Senior Clinical Fellow in
22 neuropathology at the Brigham and Women's Hospital

1 in Harvard Medical School in Boston.

2 DR. MILLER: Good afternoon. I'd like
3 to thank the organizers for the opportunity to be
4 here today and to present on this very interesting
5 and unique case that we saw recently at our
6 institution. I don't have any conflicts of
7 interest to declare.

8 I'd like to start with I think the
9 reason we were contacted to present here is
10 because when our case was reported a couple of
11 months ago in the New England Journal it received
12 a fair amount of press coverage about stem cell
13 tourism and such and so I'd like to take the
14 opportunity today to go into some detail about
15 this case. What were the things that we learned
16 from this patient and what types of conclusions
17 might we be able to draw about stem cell research
18 and the potential risks of tumors and other such
19 outcomes?

20 So let's take a step back and look at
21 the history of this patient. So this is a highly
22 educated man who had worked as an attorney and at

1 the age of 60 he suffered an MCA ischemic stroke
2 which resulted in hemiplegia on the left side of
3 his body. Over the next bit of time he underwent
4 physical therapy, a standard treatment after a
5 stroke and saw some improvement in the strength of
6 his left leg and he was able to then walk with
7 some assistance but his left arm remained
8 paralyzed. He also underwent a number of other
9 procedures not necessarily done in the
10 conventional setting including acupuncture as well
11 as other physical therapy and off label use of
12 anti-TNF therapy. These did not produce any
13 improvement in his weakness. So then he traveled
14 around the world to receive a series of stem cell
15 treatments and I should note that all of this is
16 reported by the patient. Unfortunately, we don't
17 have any official records of what therapies he
18 received and the patient was not willing to
19 furnish literature such as dosages or other
20 information nor was he willing to report the names
21 or locations of the clinics. According to what
22 the patient did tell us he went to China and

1 received embryonic stem cells and also in China
2 subsequently received and also mesenchymal stem
3 cell preparation that was injected intrathecal to
4 the area around the spinal cord inside the dural
5 sac. He then subsequently over the years traveled
6 to Argentina and received autologous mesenchymal
7 stem cells as they were labeled and then traveled
8 to Mexico and also received mesenchymal stem cells
9 and neural stem cells. A few things to note, one
10 is the autologous stem cells that he received in
11 Argentina, these were actually injected into his
12 carotid artery I guess with hopes that they may
13 reach the MCA distribution in the area that was
14 affected and reconstitute some of the dead
15 neurons. Then the treatments in Mexico he
16 received two sets of them. After the first set he
17 thought that he had some improvement which lasted
18 about a month and then regressed but it is not
19 clear whether there any physicians involved in the
20 evaluation in these therapies. One of the real
21 tragedies of this is the expense that he underwent
22 himself as well as the risk that he took and the

1 fact that the community as well as the patient has
2 not really gained a lot from this. This underlies
3 the point of a lot of speakers that the
4 investigation of these therapies really benefits
5 from being in a controlled setting where we're
6 surveying and gathering information that can then
7 be offered to the broader community.

8 So subsequent to this he presented to
9 our hospital with progressive lower back pain,
10 lower extremity weakness that was not bilateral as
11 well as sensory loss and urinary incontinence all
12 of which raised concern for a lesion involving the
13 spinal cord. So an MRI was performed. Here you
14 can see that there is a lesion that extends from
15 T12 to L5 and the superior and inferior extent of
16 the lesion are marked there with arrows. It is
17 contrast enhancing and in this axial image you can
18 get a sense that the lesion is encasing the spinal
19 cord within the dural sac.

20 The patient was taken for neurosurgical
21 exploration and the image at the left shows the
22 epidural exposure so the dura mater has not yet

1 been opened here but they noted tightness and
2 appearance that suggested it was bulging. Then
3 when they sectioned and sliced through the dura
4 the image at the right shows the exposure beneath
5 the dura. They noted that the arachnoid mater was
6 abnormal. I see the tortuous blood vessels here
7 and the spinal nerve roots where the arrow points
8 appeared to be caked together by some sort of
9 substance. So they took a series of biopsies and
10 this is from a specimen that they indicated was
11 part of this intra-dural mass and here we see a
12 large number of cells. This is very hyper
13 cellular for an adult spinal cord. The cells
14 appear as these purple structures, the nuclei of
15 the cells and they have a primitive morphology
16 that is they have a very high nuclear to
17 cytoplasmic ratio and they resemble cells that you
18 might find in a developing fetus as well as stem
19 cells.

20 In another specimen that was nerve root
21 you can see part of peripheral nerve there we also
22 saw tumorous cells that were encasing the nerve

1 root. And then in a portion of another specimen
2 there was an area of the tumor that was
3 differentiated. So rather than these primitive
4 cells with a high nuclear to cytoplasmic ratio and
5 minimal cytoplasm in this particular area we saw
6 tumor cells with a glial morphology here
7 resembling astrocytes as well as this structure
8 here which is known to pathologists as vascular
9 proliferation and that is a hallmark of
10 glioblastoma.

11 So next we used immunohistochemistry to
12 better characterize the lesion and here in each of
13 these images the pale blue is background staining
14 of the nuclei of cells and the brown is a positive
15 result where the antibody has detected the protein
16 that we're interested in. So GFAP indicated that
17 it was expressed positive and indicated that the
18 tumor cells were forming astrocyte like cells.
19 oligo-2 was also expressed in some cells
20 suggesting a glial differentiation. A number of
21 the cells expressed sox-2 which is found in
22 (inaudible) as well as neuro stem cells. The

1 cells were also highly proliferative expressing
2 the proliferation marker NIB-1. This is an index
3 found in only very aggressive cancers and in the
4 normal brain or spinal cord it is less than one
5 percent.

6 The cells were negative for neuronal
7 markers such as NEUN and synaptophysin and also
8 negative for CD-34 stem cell marker and negative
9 for CD-45 a marker of leukocytes because a tumor
10 like this could be a lymphoma if you just look at
11 the way the cells look but it doesn't look like
12 that according to the immunized chemistry.

13 So based on this information just
14 looking at the histology there is a very broad
15 differential diagnosis for a tumor like that. It
16 includes a lymphoma, glioblastoma, perhaps a
17 primitive neuroectodermal tumor which we're now
18 referring to as primitive neuronal or embryonal
19 tumor. So the data that we have indicates quite
20 clearly this is a malignancy and that is comprised
21 of rapidly proliferating cells and they seem to
22 have some glial differentiation. However, it

1 doesn't clearly fit the phenotype of any known
2 tumor entity that is currently accepted in the WHO
3 book of tumors. So we gave it the name of
4 glioproliferative lesion to try to give our
5 clinicians some sense of what this was to assist
6 them in making decisions on how to treat the
7 patient. So there is a series of questions we
8 then proceeded to try to ask. One is are the
9 lesional cells from this patient or are they
10 exogenous? So to address this we used short
11 tandem repeat genotyping this is the same type of
12 test that is used in paternity testing as well as
13 in forensic testing and it uses loci across the
14 genome on multiple chromosomes that are known to
15 be polymorphic and they have a different number of
16 repeats in different individuals. So here is one
17 locus, the Penta E locus and in the peripheral
18 blood of this patient we noted that there were
19 alleles with 13 repeats and
20 these two peaks here. And in the tumor
21 we saw these same peaks indicating that some of
22 his cells were there but we also saw 10 repeats

1 and 16 repeats indicating that the DNA of another
2 person with those alleles was present there. Then
3 when we put all of the alleles together we found
4 that in the peripheral blood of this patient there
5 was no non-patient DNA so his peripheral blood
6 contained all his own DNA. However, in the tumor
7 62 percent of the cells were foreign. So in our
8 specimen the majority of the cells there were from
9 another person presumably one of these stem cell
10 injections.

11 Next we asked which genetic aberrations
12 are present in the tumor cells. So the field of
13 tumor pathology has evolved quite a lot over the
14 last 10 years and now a large number of tumors can
15 be understood in terms of the genetic mutations
16 that they have. For example, most glioblastomas
17 have an extra copy of chromosome 7 and often have
18 amplification of the EGFR locus. So we were
19 looking for characteristic genetic changes that
20 might help us to understand this tumor. So we did
21 targeted exome sequencing using a panel of 309
22 tumor associated genes. At our institution we

1 call this Onco Panel and we found no mutations or
2 copy number changes of known clinical significance
3 in these genes. We did find some variance but
4 none of them were a classic variance of any clear
5 clinical significance and some of them may have
6 just been polymorphisms. So we weren't able to
7 fit this into any known tumor entity based on this
8 data.

9 So again putting this all together we
10 call this a glioproliferative lesion. We were
11 able to conclude that it was derived from
12 non-patient cells. So this is a schematic that
13 shows how a pluripotent stem cell can
14 differentiate into mature forms as has been
15 discussed in various aspects today so you can have
16 pluripotent stem cells that can differentiate into
17 neural stem cells which can then differentiate
18 into forms like neurons, astrocytes, and
19 oligodendrocytes. And so I'm going to take a look
20 at the markers that I showed you earlier and we'll
21 try to get a sense of what line of differentiation
22 these tumor cells were showing. So they were

1 Sox-2 positive but negative for Oct-3/4 suggesting
2 that they were not induced pluripotent stem cells
3 or embryonic stem cells. They did express OLIG-2
4 found in neural stem cells. They were negative
5 for neuron markers and positive for astrocyte
6 markers and for oligodendrocyte markers. So based
7 on this data at the time the patient presented to
8 us the lesion appeared to be acting like neural
9 stem cells. That being said we can't say exactly
10 whether that was the state of the cells when they
11 were transplanted into the patient. It is
12 possible that less differentiated cells were
13 transplanted and then subsequently differentiated.

14 For a clinical follow up the patient was
15 seen by our colleagues in neuro-oncology and
16 radiation oncology and they made the decision to
17 treat the tumor with a three phase technique of
18 radiation from cervical level C to the thecal sac.
19 The patient did show some improvement of their
20 spinal cord symptoms and on MRI three months later
21 there was a modest decrease in the tumor bulkiness
22 although subsequently it has grown in size. But

1 the patient is still alive at this point.

2 So I'd like to take a few minutes after
3 sharing this case to talk about some other reports
4 of stem cell derived tumors. One that received a
5 fair amount of attention a few years ago now was a
6 9-year-boy with a genetic disease ataxia
7 telangiectasia. He was given fetal neural stem
8 cells. He traveled from his home in Israel to
9 Russia and four years later presented with severe
10 headaches. He was found to have two separate
11 lesions. One in the posterior fossa adjacent to
12 the cerebellum and the second one in the lower
13 spinal cord. Examination of this lesion showed
14 there were cells with neuron like differentiation
15 with the marker new N as well as cells with
16 astrocyte like differentiation expressing GFAP as
17 well as areas that resembled the cells that line
18 the ventricles within the brain. So this group
19 described this as an extra axial multifocal
20 glioneuronal tumor hinting at those dual lines,
21 multiple lines of differentiation. They did note
22 that it did have a low proliferation rate and that

1 it was well differentiated. So this overall is a
2 better behaving tumor than in our patient where we
3 saw very aggressive characteristics both in the
4 clinical realm as well as pathologically.

5 Another case that has been reported was
6 a 50-year- male with Parkinson's disease. He was
7 transplanted with fetal neural stem cells, a
8 procedure that has been done in a variety of
9 places and has produced some very interesting
10 science. He presented two years later with
11 progressive lethargy, breathing difficulty and
12 then suddenly passed away. I apologize, these
13 figures were from 20 years ago so they're in black
14 and white. In the occipital lobe and in the
15 fourth ventricle we see that there is material
16 that is filling the ventricles, filling these
17 ordinarily empty spaces with cerebrospinal fluid.
18 When these areas were examined microscopically
19 they noted that some areas looked like cartilage
20 and other areas looked like hair shafts. So we
21 have two different lineages mesenchymal and
22 ectodermal lineages. Interestingly, they didn't

1 find any neural tissue even though supposedly the
2 patient received fetal neural stem cells. So they
3 described this as differentiated intraventricular
4 tissue of unclear origin and offered a number of
5 explanations perhaps contamination by other cells
6 during the procedure or perhaps the fetal neural
7 cells de-differentiated and matured but it wasn't
8 clear exactly how they got there but a fatal
9 effect of this therapy.

10 We should not be surprised that stem
11 cells can form tumors. It has been well known in
12 animal experiments that when embryonic stem cells
13 are injected into mice that they have the capacity
14 to form teratomas in which a diverse range of
15 differentiated cell types can be formed such as
16 gut, neural, bone and so on.

17 I'd like to also step out of the stem
18 cell area for a moment just to note that neoplasms
19 can be transmitted between humans under certain
20 circumstances. There are reports of transmission
21 during solid organ donation. A preexisting
22 neoplasm in the donor was transmitted to the

1 recipient generally requiring immunosuppression in
2 the recipient and it has also been reported that
3 in umbilical cord blood transplantation that
4 leukemia has been reported. There is also a
5 report of transplacental transmission from the
6 mother to the fetus of a lymphoma.

7 So in summary, I presented a case of a
8 66-year-old male with a glioproliferative lesion
9 of the intradural space and we found that this
10 appeared to be derived from donor stem cells those
11 it is not exactly clear which type of stem cell it
12 came from. There are multiple previous reports of
13 other tumors coming from stem cells and other
14 exogenous sources that have grown in humans
15 although none showed the same high grade
16 characteristics that the case we saw demonstrated.

17 So as a closing point it is clear that
18 stem cell therapy does hold great promise but must
19 be balanced against the potential adverse effects
20 and for this reason the clinical use and
21 investigation of these therapies really needs to
22 be evaluated in a rigorous setting and follow up

1 surveillance and standardized assessment by
2 physicians and other professionals is really a
3 critical part of this if we're going to be taking
4 risks with patients' lives.

5 I'd just like to thank the others at
6 Brigham and Women's Hospital as well as at the
7 Dana Farber Cancer Institute who have been
8 involved in various aspects of working up this
9 case.

10 DR. KAHN: So I think now we're going to
11 move to the panel. Everybody who spoke after
12 lunch please make your way to your seat where
13 there's a tent card. There is going to be more
14 people at the table than the audience but we'll
15 manage that. So we have about a half hour is that
16 correct? So I think we'll also obviously have
17 some time for questions from the audience so be
18 thinking as we get settled here. I guess we'll do
19 what has been done through the course of the day
20 and have people line it up and we'll manage it
21 that way.

22 So I've been thinking as we've been

1 listening to the afternoon presentation and we've
2 had sort of how to be responsible from the
3 professional society prospective, how to manage
4 both moving forward responsibly and making sure we
5 do so for the people who need new therapies from a
6 government perspective. Then we just heard two
7 very cautionary tales which makes me want to ask
8 the following question and I hope you all can
9 opine about this. In the history of research on
10 human subjects the emphasis in the past going back
11 to the 1970's when the regulations were first
12 promulgated the emphasis was on protecting people
13 from being taken advantage of and making sure that
14 they weren't exposed to too much risk for the
15 benefit of other people and not to themselves.
16 Over the course of this decade there has really
17 been a shift to talking about people as
18 participants and partners in research. But the
19 stories we're hearing sound a whole lot more like
20 we need to protect people then we need to make
21 sure they are partners that have access to the
22 benefits that research offers. So let me ask you

1 whether you think we just haven't got it right for
2 this particular category of research or whether
3 we've got it right but there just needs to be an
4 assertion of control, establishment of parameter,
5 something or some third option that I haven't
6 thought of.

7 DR. KIMMELMAN: So it is true that
8 historically research ethics has been built on a
9 premise that the fundamental function of research
10 ethics is to protect the welfare of the human
11 subject. But I think in a contemporary era where
12 so much hinges on the quality of evidence our
13 healthcare system solvency depends on it, our
14 ability to deliver appropriate healthcare to
15 patients hinges on having reliable evidence. I
16 think it is time for research ethics to be
17 thinking a lot about the downstream consumers of
18 evidence. At the end of the day when you conduct
19 clinical research it is not strictly a private
20 transaction it is a public transaction. There are
21 stakes that exceed or transcend merely the dyad of
22 the patient and caregiver and those ought to

1 factor in to how we make decisions to risk,
2 benefit and access. So I think Jeff really
3 eloquently in his remarks noted that. For many
4 novel scientific endeavors, you only really get
5 one at bat. You conduct a clinical trial. If you
6 don't have your conditions optimized, if you don't
7 have good preclinical evidence behind it you go
8 into a trial prematurely, you get a negative
9 result and potentially you have withdrawn funding,
10 public support, et cetera and that potentially can
11 really set back what might otherwise be a very
12 promising scientific endeavor and I think it is
13 those kinds of considerations of public interests
14 that ought to be driving in part our decisions
15 about how we set regulatory standards rather than
16 merely the question of how we protect patients
17 from risk.

18 DR. ALBINI: I think it is difficult to
19 be transparent about what level of regulatory
20 standards you have and I think what the South
21 Florida story shows, one of the things is that the
22 patients assumed that there was a certain level of

1 regulation and a certain level of quality and
2 science that they were buying into. They weren't
3 aware of the tell-tale signs that it really wasn't
4 there like the fact that they were paying for it,
5 that there was no doctor involved. I mean some
6 things in retrospect you say how on earth could
7 you let this have happened to you. But they'll go
8 back to well it was on clinicaltrials.gov and it
9 turns out they weren't even in a research study.
10 There was no outcomes data that was planned to be
11 obtained. They didn't even follow up with the
12 patients. It was just mind boggling. It was
13 clearly just fee for service procedure without a
14 doctor and I think that there just needs to be
15 more transparency or more awareness in the public
16 to what they're getting involved in. If you're
17 going to deregulate it has to be very clear
18 somehow to the participants in the trials that
19 this is not the same as the type of clinical
20 trials that they've been used to.

21 DR. KAHN: So only because I can't see
22 all the way down to where Mike is but why don't we

1 just move serially from Dr. Dominici.

2 DR. DOMINICI: So I think you comparing
3 the current situation with the seventies.
4 Specifically, in this field there was a revolution
5 in the way in which we can essentially isolate and
6 amplify the cells. It is relatively easy and it
7 is relatively cheap to do that if we compare with
8 what was done in the past. You can take bone
9 marrow, you can take fat and it is cheap and it is
10 easy. That one side is a good thing because we
11 can work in the lab and do things that were very
12 difficult to do in the past. On the other side
13 this is allowing those types of treatments in an
14 environment that are easy and once again cheap to
15 be approached. That is one of the problems I
16 would say. The second problem which is part of
17 the (inaudible) that we are being see on
18 information on the web. In the seventies we
19 didn't have that. These people have access to
20 clinicaltrial.gov and they look at that as we
21 learn. Those types of web based information can
22 be misused and the patients may essentially be

1 captured by the fancy images that are related and
2 are included in the website. They can't dissect
3 the good and bad information. So I think the
4 scientific society should be collaborating with
5 patient associations and with the other stake
6 holders in trying to clarify and work and starting
7 from the source of information that the patient
8 can get and provide resources. I think we should
9 move along with the technological improvement to
10 provide services for patients.

11 DR. RUBIN: I think the standards are
12 not elusive. In fact, Jeff, you laid them out
13 really eloquently in your talk and a lot of the
14 issues of transparency and informed consent
15 they're just so intuitive and all the things that
16 we as a doc would want to do when we have to look
17 a patient in the eye and say whether it is
18 experimental or not, these are the risks, these
19 are the benefits and lay it out and really have
20 that transparent decision making process is really
21 important. But there are mechanisms obviously to
22 circumvent the standards that we've heard about in

1 the last few talks that therapeutic misperception
2 of a patient funded trial or pay to participate
3 trial combined with the desire for hope with
4 patients who don't have a lot of hope. In fact,
5 when patients call me and they want regenerative
6 therapies that can't be done and I say it can't be
7 done they get angry with me. And the no
8 discussion is longer than the yes I can help you
9 discussion because they get angry and they want to
10 know why can't you help me, when can you help me,
11 what do you mean you can't help me. So it is very
12 easy, I could see how easy it is for them to show
13 up in someone's office and be treated with
14 standards that are less than what we would desire
15 because of what they want from it. Those
16 mechanisms and the people who are out there not
17 adhering to the standards is a problem.

18 MS. POTTOL: I can appreciate the point
19 where the patient is a little bit more difficult
20 than it is for us. At least at my office I sit a
21 couple of steps behind the scenes in an office and
22 I don't see the patients. In the DOD we do have

1 one additional hurdle there to try to really
2 making sure the clinical trials are in the best
3 interest of the patient and that is with an
4 additional layer of our human resource protection
5 office on top of the standard IRB's and the FDA.
6 So I think that it certainly takes a little bit
7 longer to get a trial started but it helps us ask
8 additional questions on what is right for the
9 patient and are we doing all those things to care
10 for them. The other challenge is are you
11 challenging yourself to make sure that you're
12 staying responsible, you're close to your
13 research, are you having enough different voices
14 involved to challenge you to make sure that the
15 decisions that you're making are the choices that
16 you're putting in there for your patient that you
17 bring maybe opposing views so you can help place
18 your own self and your own thoughts being too
19 close to the work that you're doing.

20 DR. LUNDBERG: So I agree with a lot of
21 what has been said already. I think another
22 challenge which we haven't really touched on is

1 the fact that again with the internet being so
2 available is that the problem is larger than just
3 the U.S. As the example of the spinal cord tumor
4 people are going outside of the U.S. and the
5 access is just out there so that's a challenge
6 that I think we as a group should be thinking
7 about in ways how can best protect U.S. citizens
8 from this kind of impact.

9 DR. MANSFIELD: I think engagement of
10 the patients is very important. I think that the
11 foundations and other organizations that fund some
12 of this research and that support the patients
13 have really got to have a strong educational role.
14 They've got to help these people to understand
15 what is involved, what the risks are. As a person
16 who interacts with people with a disease we're
17 very much aware of this real urgency that they
18 have to get a treatment. Understanding the
19 scientific process is very hard. We all know that
20 you don't go from a concept to a drug in a year or
21 two years it is a very long process with a defined
22 set of steps and it needs to be done carefully.

1 And when there is an urgency for treatment it is
2 very hard to understand why is it taking so long.
3 One of the questions that we had when we were
4 supporting gene therapy was once one gene therapy
5 was successful they wanted it to be plug and play.
6 Why can't you just cut it out and put it into the
7 next, next one, next one and solve it all for us
8 now. So there is this urgency, there is a need to
9 educate to understand the time involved in these
10 developments but I also think there is a need to
11 control the development of the non-homologous use
12 of autologous cells. I think that is a particular
13 area that needs particular attention. That would
14 be my thought. I think the existing regulatory
15 framework that we have in general is good.

16 DR. KAHN: Yes I agree with a large
17 amount of what has been said and I think one of
18 the critical things that the speakers have done
19 today is to lay out an ethical framework for how
20 to address these questions. I think in one
21 particular case there were two things that were
22 very difficult. One is that there is great

1 variation in patients in terms of the degree with
2 which they're willing to accept risk and the way
3 that they see benefit. I think the second thing
4 is to really be realistic about expectations to
5 not be over promising. In the case of our patient
6 he actually was highly motivated to seek
7 treatments to the point that he traveled all
8 around the world and spent potentially hundreds of
9 thousands of dollars on these treatments. I think
10 one thing that is very interesting even after all
11 of this and even after the tumor he doesn't regret
12 having taken this action. As some of you may have
13 seen he volunteered to be interviewed by the press
14 after our paper came out and on some level I think
15 he was happy that he took this risk and it was a
16 risk that he felt was worth I which I think it is
17 important to respect the patient autonomy in that
18 way but it also may still reflect over promising.
19 Even if no individual physician has promised him
20 something unrealistic from advertising from the
21 way that scientific papers come out clearly he was
22 expecting the potential benefit that made it worth

1 it for him and the amount of money and risk to
2 himself.

3 Jeffrey Kahn: So I see we've got a few
4 people at the microphone. I just want to make one
5 observation and then we'll turn to the question
6 which is at a time in our history when it seems
7 like pressing government is not at its all-time
8 high that one of the explanations for why people
9 thought these cases we heard about were worth
10 pursuing was because it was on a government
11 website that seemed to endorse it as safe or
12 something that would not harm them. So I think it
13 really comes back to this notion of trust and
14 we've said this over and over in the course of the
15 day. It is very easy to lose trust and it is very
16 difficult rebuild it. This particular area of
17 biomedicine is kind of at a tipping point for
18 moving forward and this notion of trust really
19 cannot be squandered. Let's go to the second
20 microphone because you're been waiting.

21 DR. RODRIGUEZ: Yes my name is Ricardo
22 Rodriguez and I'm from Baltimore. I got approval

1 for a grant for a human study using SVF three
2 years ago and we have gone through the process of
3 INDs and IRBs which I believe is right and has
4 made us think about our process very carefully.
5 As I have been going through this process what
6 strikes me as how many people are out there sort
7 of doing it on whatever basis they can. So for me
8 the problem as I see it at large is not so much a
9 regulatory schema as it is, rather how those other
10 people are flouting the existing regulatory scheme
11 and that a quicker way of tackling this problem is
12 identifying and bringing to light those people and
13 publishing the information rather than complicated
14 regulatory overhauls.

15 DR. KAHN: Okay we will go to the first
16 microphone.

17 MR. CLEGG: His Dennis Clegg, UC Santa
18 Barbara. I had a question for Dr. Miller and
19 maybe you mentioned this and I missed it. Did you
20 determine that the transplanted cells or the cells
21 with the different DNA were human? Could they
22 have been animal cells?

1 DR. MILLER: They were human. From the
2 STR we were able to confirm they were human as
3 well with the deep sequencing even though we
4 didn't find pathogenic mutations.

5 MR. CLEGG: Okay. And then a general
6 question for the panel. What can be done about
7 clinicaltrials.gov? That really surprises me that
8 they're listing these kinds of trials.

9 DR. KAHN: I'm not an expert about
10 clinicaltrials.gov but maybe Jonathan you can
11 opine.

12 DR. ALBINI: Well I think that one thing
13 that could be done is you could just say on there
14 this doesn't condone any government approval. I
15 think the supposition is that somehow this is
16 government approved. The purpose of the site is
17 really just to make sure that everybody is aware
18 of any clinical trial that is being done so
19 anything can be put on there and it is not
20 verified. So I think if there were a disclaimer
21 that was written in English easy to understand by
22 most patients on there than that would be a great

1 way to start. The other recommendations that
2 we've had are to list whether or not an IND was
3 obtained. For example, this group that I dealt
4 with while they had IRB approval they didn't go
5 through getting an IND they thought they didn't
6 need it. But to the point of enforcing the
7 regulation that we already have I mean the fact
8 that this clinic was able to do this three times
9 was very frustrating to me because as we saw the
10 patients coming in we notified the Florida
11 Department of Health and we notified the FDA and
12 they all have mechanisms in place to investigate.
13 But they are all slow going investigations and
14 they didn't stop. The company is still around
15 that is doing these things. They stopped doing
16 eye research but they are doing other treatments.
17 But really besides call the police there is no
18 other way to regulate or do anything about it.

19 DR. MANSFIELD: I'd like to add that
20 clinicaltrials.gov if you do have an IND it is
21 actually captured on there it is just not visible
22 to the public. I don't know why that can't just

1 be declared. You don't have to reveal more than
2 it has been applied for.

3 DR. WEISS: If I may interject something
4 on that. Is there not legislation pending that is
5 meant to upgrade clinicaltrials.gov for all these
6 reasons that are being articulated. If I'm not
7 mistaken there is a motion afoot to number one
8 tighten the requirements for entry of anything
9 onto clinicaltrials.gov. Number two to tighten
10 the reporting requirements because that is the
11 flip side of course you need to know what happened
12 with these trials. So all of these sentiments are
13 good but what disturbs me a little bit is that we
14 as the experts in the field in this room don't all
15 know what each other are doing number one. Number
16 two, we're not communicating and presenting as
17 best we could a unified front. The ISSCR, the
18 ISCT et cetera should be hand in hand with the
19 NIH, the FDA, loud and clear, consistent broadly
20 circulated to have a loud message to patients and
21 caregivers about the dangers of unproven cell
22 therapies and where to go for the information.

1 This is where transparency, communication,
2 visibility can go a long way. So the fact that
3 nobody up here seems to know about pending
4 legislation in the clinicaltrials.gov reporting
5 and entry system is a little disturbing. So how
6 can we all best learn from this. The other thing
7 I'm curious about is the point you made. The FDA
8 we spent a lot of time tracking down snake oil if
9 you will that is on the web. We reported it to
10 the FDA and they go through their diligent
11 processes but there are no teeth in the FDA. They
12 can't necessarily enforce anything it has got to
13 go to the justice department to go out and take
14 the action to throw these people in jail. It
15 happens rarely and not frequently enough and so
16 one of the things that we as a group can hopefully
17 send a strong message is to the people that would
18 have the power to shut these places down. There
19 is a range of things out there and none of us can
20 put ourselves in the shoes of a patient who is
21 desperate or a family. We're not saying that. No
22 one is trying to play God. What we're trying to

1 do is to identify the more egregious snake oil
2 people out there and just shut them down as best
3 as possible. Now one thing I'm curious about is
4 the ISSCR experience a few years ago. You all
5 gave a solid go at trying to do this and then you
6 got threatened somehow and you had to back off.
7 How can we as a community again learn from that.
8 What happened to you? Why did you have to back
9 off? How can we move around that to try to again
10 wipe some of this garbage off the map?

11 DR. KAHN: That's a bunch of things. Why
12 don't we start with ISSCR and maybe we'll move in
13 reverse? Go ahead Jonathan.

14 DR. KIMMELMAN: I'm guessing Irv can
15 probably better answer this question better than I
16 can. This actually preceded my time here but Irv
17 was president during this period.

18 DR. WEISSMAN: So in 2009 when I was
19 about to retire as president of ISSCR I wrote an
20 article about unproven clinics and that it should
21 be the ISSCR as the agency that looks at it. So
22 we had a group of people who looked at unproven

1 therapies. And we decided at the end to warn the
2 patients and warn the caregivers because we
3 couldn't be another FDA for the world. We
4 couldn't take on the expertise to judge which one
5 was good or bad so we said you as a caregiver or
6 you as a patient should ask two questions of the
7 people who are about to give you a therapy or
8 charge you for a therapy. The first is the name
9 of the head of the institution review board that
10 oversaw the in house first in human clinical
11 testing. And as you know IRB is responsible
12 prospectively and during the early part of the
13 trial for the safety does not judge the efficacy.
14 The second question you should ask is in your
15 country or in this country you find out the
16 documentation from their FDA or their FDA
17 equivalence that was responsible for overseeing
18 the three phases of safety and efficacy. That's
19 all we asked. We didn't take on anything. And we
20 set up a website called A Closer Look and had
21 many, many hits and we said we will even help you
22 if you don't know who to ask the question. We'll

1 ask the question for you. So a few months later I
2 was still head of ISSCR. I had the most
3 distinguished board of scientists, stem cell
4 scientists around the world with me and at a board
5 meeting the executive director showed us a letter
6 from an attorney in Chicago that said by what
7 authority are you asking my client these two
8 questions. And all of that board of distinguished
9 physicians and scientists except two of us and the
10 administrative head of the society said we're
11 closing the site. They were afraid of litigation.
12 We are afraid of litigation. So it takes courage,
13 it takes the resources of the FDA maybe to step in
14 and say these are the questions you should ask or
15 have us ask because this is a most serious defect
16 and for me it was an alarming revelation of my
17 colleagues who were the leaders of the field.

18 DR. KAHN: Anyone want to comment? I
19 will say in response to the previous comment about
20 clinicaltrials.gov and reporting of results the
21 NIH is moving towards a policy to require result
22 reporting of all clinical trials that they fund.

1 So we've moved towards greater and greater
2 transparency and of course the idea behind
3 clinicaltrials.gov in the first place was to give
4 people greater opportunity to understand what
5 trials were available. To the point that people
6 see it and they think therefore it is endorsed.
7 That wasn't ever the point. So somebody is taking
8 advantage. It isn't so much the site that's the
9 problem it is the people that are taking advantage
10 of what the site does as a way of exploiting
11 desperate patients. I don't know how more bluntly
12 to say it than that. Anymore comments or
13 questions?

14 DR. BERTRAM: Tim Bertram, Region
15 Medical. I was musing on the last statement
16 because it is kind of interesting as we've debated
17 here today it has been interesting to see as we've
18 looked at the different things and the
19 expectations of the agencies and what I was really
20 struck by is the ocular changes that we saw as a
21 result of that implantation. A couple of points
22 was it was done by a nurse practitioner. It

1 reminded me as I was listing to the story of the
2 Maturini case that has been carried on, a fair
3 amount of notoriety that took place in Europe
4 where in fact is was also a medically trained
5 professional. What I'm wondering about if there
6 was no conversation here about how we are training
7 our professionals to actually communicate with the
8 patients. So maybe the papers and there is always
9 going to be a nefarious aspect and I'm not saying
10 no regulations here, I'm just saying there is an
11 element that we will not be able to control. But
12 in one part what we haven't discussed here today
13 is how are our physicians being trained in order
14 to go forward. We've got some very illustrious
15 physicians that have presented but is it a general
16 training that is going on because as this therapy
17 comes forward there is obviously going to be the
18 use, ultimately the misuse but more significantly
19 the inappropriate use and I'm just curious what
20 the board thinks.

21 DR. ROSS: Duncan Ross from Chimera
22 Labs. As far as the training is concerned I was

1 wondering if we saw that result with the
2 collagenase. In the case where we saw that result
3 with collagenase have we seen that collagenase in
4 other labs and when we talk about the training I
5 know that that group has a training operation.
6 I've come in and found various discrepancies. So
7 when I think about taking collagenase away from
8 the field I think that there needs to be better
9 training. Maybe we could form some kind of
10 training system.

11 DR. ALBINI: I can't speak to the
12 enzymes but what I can speak to is that as a
13 retina surgeon I don't think that my colleagues
14 were aware this was going on. This was sort of
15 off the map. So in terms of what we're training
16 retina specialists I think the answer is nothing
17 because I think there just wasn't awareness of
18 this. When I've presented these cases at retina
19 meetings everybody has been in shock and is
20 unaware of other problems or that clinics like
21 this even exist or what the market place is for
22 stem cell clinics and so forth. So that's not out

1 there and the only thing I can say is that I do
2 think probably a minority of retina specialists
3 would recommend to their patients to try something
4 like this. I can imagine I don't know how small
5 the minority is but I can imagine and I think I've
6 heard of some physicians who have recommended to
7 patients where there are no other options why
8 don't you try this -- not the particular one that
9 I discussed but why don't you try some sort of
10 stem cell therapy. I think that just comes out of
11 the fact because we as retina specialists don't
12 really talk about any of this. So I've learned a
13 lot today and I think there probably should be a
14 mechanism that some of what I've seen here today
15 be communicated back to my colleagues.

16 DR. KAHN: Okay really, really, last, do
17 you want to say something?

18 DR. KIMMELMAN: I just want to say two
19 things about this. So first of all, I'm not a
20 physician, I don't dispense medical advice but it
21 seems to me that physicians dread having to tell
22 patients that their options are incredibly thin

1 and I think when we talk about training it is not
2 merely in terms of helping physicians to convey to
3 patients the dubiousness of some of the medical
4 options that they may be hearing about but also
5 maybe training physicians to have those kinds of
6 uncomfortable conversations with patients. That
7 is my first comment and the second comment is one
8 thing that we haven't talked about here is
9 journalism and media coverage because of course
10 patients get a lot of their information not from
11 physicians but from news stories. Just the other
12 day there was a wonderful story in USA Today about
13 Bart Starr going to a clinic in Florida or
14 somewhere else. Not exactly a hard hitting good
15 scientific coverage and I think we could probably
16 be doing more to be training our journalists on
17 how to cover cutting edge science as well.

18 DR. WEISS: One last thought to add to
19 that. So the training point is an excellent one,
20 the journalism point is an excellent one. It is
21 hard of course to implement training in an
22 effective way across entire disciplines. It is a

1 good goal and a worthy goal that will take some
2 time. One parallel that could be and hopefully is
3 being effective is to utilize the professional
4 societies. Parallel with the ISSCR and the ISCT
5 have your American College of Retinal Surgeons,
6 the American College of Cardiology, plastic
7 surgeons take a visible and uniform stance such
8 that on their respective websites at their annual
9 conventions there is prominent visibility. Just
10 by hammering away at it that you're going to
11 eventually get the message across. This isn't
12 something that is going to permeate the entire
13 medical profession quickly but it needs to be a
14 consistent concerted effort. So to give an
15 example --

16 DR. KAHN: I think we need to give Irv
17 the last word here.

18 DR. WEISS: Ten seconds. So as an
19 example in the lung world we've just published an
20 editorial against stem cell medical tourism in the
21 flagship journal of the American Thoracic Society
22 that is on the website but most importantly it is

1 a joint statement that is now shared on the
2 website of probably 50 different respiratory
3 disease societies ranging from private, non-profit
4 foundations to patient advocacy groups to the
5 actual foundations. It is an example of at least
6 a small step in the education process against stem
7 cell medical tourism.

8 DR. KAHN: Thank you. Thank you guys
9 all eight of you. I'm going to turn it back over
10 to Irv.

11 DR. WEISSMAN: So first I want to thank
12 the FDA for organizing this session. When you
13 hear so many negative stories about stem cells and
14 tumors that are derived from not proven stem cells
15 you may start to get disappointed about the field.
16 It is an anomaly that right now this field is
17 busting wide open and it is moving better and
18 better towards rational scientific based animal
19 model studied clinical therapies and clinical
20 trials. But we must have funding for the basic
21 science to do this. And you may have thought well
22 don't you have enough stem cells? So far we have

1 blood forming stem cells. We can prospectively
2 isolate transplant not in clinical trials. We
3 have brain forming stem cells. Some people think
4 we have skin forming stem cells I'm not sure. And
5 in humans that's all we know. But we know by
6 other kinds of developmental biology or what we
7 call lineage tracing experiments that stem cells
8 exist for every tissue. So obviously if we're
9 going to move the field we have to fund the field.
10 That's NIH. And NIH has to do it and the best
11 method of scientific inquiry that is Fund R01,
12 investigator, initiator, research and make sure
13 there is enough funds in this area to do it.

14 So that is tissue stem cells and I've
15 told you that we've now had since the 1990's the
16 understanding that pluripotent stem cells can turn
17 into all tissues and go through tissue stem cells
18 to get there. So that is our opportunity to fast
19 track the identification of the tissue stem cells.
20 Embryonic stem cells cause teratomas. They are
21 not therapeutic objects. When you purify a
22 differentiated stem cell say bone and cartilage

1 stem cell you have to be able to differentiate it
2 and then you have to purify it away because even
3 one in a million cells could make a teratoma. So
4 it is the responsibility of the regulatory
5 agencies to look carefully at that proof of
6 principle. Because the neuro tumor you described
7 of the child coming back from Russia almost
8 certainly came from a very undifferentiated cell
9 or a poorly regulated cell that had been grown and
10 was abnormal.

11 The next step I already told you is for
12 this field to move forward we have to find ways
13 like we are trying to where you remove life
14 threatening chemo therapy or radio therapy to
15 prepare the patient for a stem cell transplant.
16 Hematopoietic tissue transplants were invented by
17 the oncologists so they could give super lethal
18 doses of chemo therapy. But now we have this
19 other side to it, regenerative medicine. And we
20 and I hope others are going to do that and again
21 every single antibody we use will have to vetted
22 through the FDA as being safe. One of the

1 difficult issues for any stem cell therapy is if
2 you make a cell line and it goes bad and you have
3 to make another cell line how can you guarantee it
4 similar, biologically similar and biologically
5 effective. That is really important.

6 The major focus of this meeting, oddly
7 but I can understand it, is around mesenchymal
8 stromal cells. And as Jacques said at the
9 beginning why were people trying to put these
10 cells in all the tissues. Well I know at the very
11 beginning with Arnie Kaplan at Case or Cleveland
12 trying to make the bone healing cell. One of the
13 amazing things about getting that cell out in
14 culture is it is easy. It grows like mad. So
15 when the commercial outfits came into it they went
16 where the light was. The easy cells and then kept
17 trying them and many different things. I think it
18 is a miracle that they've turned out to be great
19 or at least interesting anti-inflammatory cell
20 types. But that doesn't substitute for the hard
21 research to find the other tissue stem cells.
22 What we saw was a lot of the nitty gritty about

1 what will be important to the patients, what will
2 be important to the FDA is how can we make these
3 cells better, how can we manufacture them safely
4 and because money is always involved how can it be
5 done with a margin that will keep funding going
6 for the company. And delivery of the cells of
7 course as well.

8 Now I will say going back over the
9 mishaps that we've seen on cells that cause
10 tumors, cells that cause problems is you need to
11 purify the cells. We should no longer be in an
12 era that we accept all of the bone marrow or a
13 homogenate of liver being the cell type that you
14 use in a therapy. You should learn what the stem
15 cell is, learn how to purify it and if it tests
16 out right in the right models then carry that
17 forward. Because most of the whole field of bone
18 marrow transplant since the late seventies when
19 Don Thomas and others invented it has not advanced
20 very much at all. It is a little bit of this
21 combination, a little bit of that but it is still
22 mixtures of cells. Twenty-five years after it is

1 possible to isolate the cells. I don't want to
2 make this all self-referencing.

3 By the way I forgot to put up a conflict
4 side. I was the founder of Systemics bought by
5 Novartis I have no financial interest in Novartis.
6 I started at least two other companies that are
7 dead or dying. Stem Cells Inc. that did brain
8 stem cells and just recently ran out of money
9 before it ran out of trials to do, closing down.
10 So I guess for those I don't have a conflict of
11 interest but I just formed another company called
12 Forty Seven and I mentioned it in one of my talks
13 that antibody to CD47 currently in clinical trials
14 for cancer could also go into clinical trials for
15 stem cell transplants.

16 I want to go back to terminology. I
17 can't imagine why we're sloppy that we allowed the
18 whole bone marrow transplant community to say they
19 were stem cell therapists in which led of course
20 to the cord blood community saying yes and the
21 stem cells we have can probably give rise to all
22 cell types in the body but they don't. They only

1 have cells that give rise to blood and if a few of
2 them have enough mesenchymal precursors to
3 mesenchyme. They do not give rise to brain, they
4 do not give rise to heart and so on. We allow our
5 clinicians, our journals and our journalists to
6 get away with calling stem cell therapies when
7 they're not stem cell therapies they are bone
8 marrow or some other cell type. I'm an M.D. and
9 like most M.D. I had to compete with the pre-meds
10 to get into medical school. So I remember those
11 people. They were the great memorizers. And all
12 the time during medical school and after they
13 advanced because they could memorize way better
14 than I could. Those are the people who are asked
15 to judge whether the therapy will work or go
16 forward. Those are the people who added the word
17 stem cell to all of these therapies. So somebody
18 is going to have to insist if you advertise that
19 you just had a stem cell therapy for breast cancer
20 that you really did a stem cell therapy. Because
21 the other memorizers will read the title and say
22 well stem cell therapy doesn't work for breast

1 cancer.

2 We've had the answer since 2000 that
3 one-third of our patients in a tiny trial were
4 cured. But we can't get anybody to spread it
5 because they read a paper by Statenauer and they
6 read a New York Times article by Gina Colada that
7 says this was all a fraud and a sham and it cost a
8 lot of people a lot of trouble and they missed the
9 boat. They threw the baby out with the bath
10 water. So we should insist the same standard of
11 terminology that we would insist for any chemical
12 or any drug.

13 So you heard a little bit about the
14 unproven, a lot about it. It is a very serious
15 issue. It is not going away. I gave you the
16 example of the question that I think still should
17 be asked. We just the ISSCR wasn't the group who
18 knew how to ask it or had the courage to back it
19 up because we didn't have the resources to cover
20 litigation, at least that's what they told me.

21 So maybe one way to do this is to have
22 more of a global interaction between three bodies

1 that are really relevant to these kinds of
2 advancement of medicine. First and foremost is
3 the FDA. I am absolutely against the Regrow Act
4 that takes away from the FDA the possibility that
5 they oversee whether it is effective not just
6 safe. If the FDA had an alliance with all of the
7 FDA like bodies and I know you talk but I don't
8 know how strong the alliance is then maybe you
9 could get a handle on it.

10 I was called about eight years ago by
11 the pulmonary acute care physicians that an
12 18-year-old girl was in the Stanford Hospital with
13 pulmonary emboli. A day before she had been in
14 the Dominican Republic where a South Florida
15 doctor injected into her mesenchymal cells grown
16 either from her or another source. So I called my
17 Dean and I called the hospital administrator and I
18 said what can we do about this. They said it was
19 done in the Dominican Republic? Well there's
20 nothing we can do about it. We can't do anything
21 in Florida because we're in California and Florida
22 covers the medical licensure. So medical

1 licensure should be dependent on non-participation
2 in unproven therapies no matter where it happens
3 in the world. Whether you send the patient to
4 that place or you go there to help the trial or
5 you collect money for the trial. Licensure should
6 be at risk.

7 The final part of it which surprisingly
8 I heard first in Thailand when I gave a talk and
9 the head of the FDA and also the head of licensure
10 which was under the emperor of Thailand. He said
11 well we've added something. We've added no false
12 advertising. I'm not sure if that is under FDA
13 purview. I don't think so but you guys can tell
14 me afterwards. So the triumvirate of a strong FDA
15 that demands not only IRB but phase three trial
16 with efficacy and comparative efficacy the risk of
17 losing medical licensure and a penalty perhaps a
18 very severe penalty for false advertising in the
19 stem cell field. Maybe then when you Google stem
20 cell therapy the first 100 won't be phony stem
21 cell clinics. I think that that's most of the
22 important part but we've heard over and over again

1 that there appears to be a small defect in
2 clinicaltrials.gov, perceived or real so that that
3 needs to be fixed. So that people can look at it
4 and know whether an IND supported type clinical
5 trial.

6 Then I will say the final one and it is
7 mainly by Steve Bauer's early discussion on how
8 they were characterizing the cell lines at the
9 single cell level and then talking with a number
10 of people at the break the FDA has to be funded to
11 continue to do research in the relevant area. So
12 it is not only a regulatory and oversight body and
13 I know it is funded, I don't know the extent to
14 which it is, but it is critical to have people who
15 are also confronting the difficulties of digging
16 secrets out of nature. How hard it is and how
17 important it is to be part of the discovery
18 apparatus if you're going to regulate it. So
19 those may be more opinions than summaries but I
20 want to thank you very much.

21 DR. WITTEN: I'd like to thank all our
22 speakers and I'd like to thank the audience for

1 attending, thank you.

2 (Whereby, at 5:05 p.m. the
3 PROCEEDINGS were adjourned)

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1 CERTIFICATE OF NOTARY PUBLIC

2 COMMONWEALTH OF VIRGINIA

3 I, Carleton J. Anderson, III, notary
4 public in and for the Commonwealth of Virginia, do
5 hereby certify that the forgoing PROCEEDING was
6 duly recorded and thereafter reduced to print under
7 my direction; that the witnesses were sworn to tell
8 the truth under penalty of perjury; that said
9 transcript is a true record of the testimony given
10 by witnesses; that I am neither counsel for,
11 related to, nor employed by any of the parties to
12 the action in which this proceeding was called;
13 and, furthermore, that I am not a relative or
14 employee of any attorney or counsel employed by the
15 parties hereto, nor financially or otherwise
16 interested in the outcome of this action.

17

18 (Signature and Seal on File)

19 Notary Public, in and for the Commonwealth of
20 Virginia

21 My Commission Expires: November 30, 2016

22 Notary Public Number 351998

