



U.S. Food and Drug Administration

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Ischemia Reperfusion Injury - Day 1 - 09-08-2011

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Ischemia Reperfusion Injury and
Downstream Effects on Long Term Outcomes
in Kidney Transplantation

Sponsored by the Food and Drug Administration (FDA)

Monday, September 8, 2011

9:00 a.m.

Crowne Plaza Hotel
8777 Georgia Avenue
Silver Spring, MD 20910

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

2 DR. ALBRECHT: So I think we're ready to
3 begin, and actually just let me start by mentioning we
4 do have a transcriptionist, so please be aware that
5 this entire meeting will be transcribed and that
6 information will be available on the web, so if you are
7 presenting any confidential information, please
8 consider whether you are going to present it or whether
9 you need to self censor some of the information that
10 you'd like to provide. So I think we're ready.

11 So good morning, everybody. It is my
12 distinct pleasure to welcome you to the FDA's Workshop
13 on Ischemia Reperfusion Injury and Outcomes in Kidney
14 Transplantation. And I'd like to welcome you on behalf
15 of our office director, Dr. Edward Cox, from the Office
16 of Antimicrobial Products who joined us this morning,
17 as well as for myself and my colleagues from the
18 Division of Transplant and Ophthalmology Products and
19 also our colleagues from the Center for Device
20 Regulation and Health, Dr. Neuland and her staff who also
21 are part of this Workshop.

22 Now although FDA is sponsoring the Workshop,

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1 the agenda was actually put together by a planning
2 committee which included representation from various
3 groups, including the American Society of
4 Transplantation, for the American Society of Transplant
5 Surgeons, the Transplant Society, as well as
6 representatives from pharma. And I think the group has
7 come up with a really full and wonderful agenda, so we
8 hope that in the next two days you'll be able to enjoy
9 the presentations and participate in the discussions.

10 And in fact that brings me to speaking a
11 little bit about the agenda. If you look at it, you'll
12 notice that it's organized in a series of seven
13 sessions. And for the three sessions this morning and
14 early this afternoon and the three sessions tomorrow,
15 we actually have moderators who will introduce the
16 speakers at those sessions and then will lead a half
17 hour to 45-minute discussion session. And the reason I
18 bring up the discussion session is that there will be
19 an opportunity for an interactive exchange of ideas and
20 comments, and we will have the panel sitting around the
21 table participate. But we also want to invite the
22 audience to present their comments and their

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1 viewpoints, and to do that we have two mikes on the
2 floor in the audience, which if you're interested in
3 participating in the discussion we invite you to come
4 to the microphone, and the moderators will then be able
5 to recognize you for that.

6 Now, what is the purpose of the Workshop?
7 What we wanted to do is provide a forum where we can
8 hear the latest information and research and findings
9 in the area of ischemia reperfusion injury and outcome
10 in kidney transplantation with the long-term goal of
11 hopefully inspiring further research in drug and device
12 development in this area so that we can ultimately
13 provide management for prevention of ischemia
14 reperfusion injury in the kidney transplant patient
15 which is consistent with the FDA's goal of promoting
16 public health.

17 And I think at this point what I'm going to
18 do is stop and ask that we go around the table and
19 introduce ourselves. And I'm going to go ahead and
20 start the introductions. And Ms. Moser, I believe
21 you're going to have some slides that you're going to
22 project simultaneously. Do you want me to advance

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1 these? Okay, I'm going to resume my seat at the table,
2 and then we will --

3 DR. ALBRECHT: So good morning. I'm Renata
4 Albrecht. I'm the Director of the Division of
5 Transplant and Ophthalmology Products at the
6 Food and Drug Administration, and I have no conflicts.

7 DR. ZHOU: My name is Hongling Zhou, I'm a
8 statistician at the FDA, and I have no conflicts.

9 MS. HIGGINS: Hi, I'm Karen Higgins. I'm a
10 statistician of FDA supporting the Division of
11 Transplant and Ophthalmology Products, and I have no
12 conflicts to disclose.

13 DR. LORBER: Good morning. I'm Mark Lorber.
14 I am employed full-time at Novartis Pharmaceuticals.
15 Beyond that, there will be no Novartis products
16 discussed at this event.

17 DR. ARCHDEACON: Hi, I'm Patrick Archdeacon.
18 I'm a medical officer at FDA in the Office of Medical
19 Policy. As an FDA employee I have no conflicts.

20 DR. WOODLE: Steve Woodle. I'm a transplant
21 surgeon for the University of Cincinnati.

22 DR. VELIDEDEOGLU: I'm Ergun Velidedeoglu,

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1 medical officer at the FDA Division of Transplant and
2 Ophthalmology Products. I have no conflicts.

3 DR. LU: I'm Chris Lu. I'm a transplant
4 nephrologist at UT Southwestern. I have a research
5 grant from REATA Pharmaceuticals, so I will not be
6 discussing that work today.

7 MS. ALLOWAY: I'm Rita Halloway. I'm a
8 transplant nephrologist for University of Cincinnati
9 and a director of transplant clinical research. I have
10 no conflicts to discuss today, but we have research
11 grants with several industry representatives in
12 transplantation.

13 MR. IRISH: I'm William Irish. I'm a
14 statistician at CTI in Cincinnati, Ohio and was a
15 consultant for Y's Therapeutics although none of the
16 data or any results will be discussed at this session.

17 DR. RACUSEN: I'm Lorraine Racusen. I'm a
18 renal and transplant nephrologist at Johns Hopkins with
19 no relevant conflicts.

20 DR. HALLORAN: Phil Halloran from the
21 University of Alberta. I run the University Center.
22 We get a lot of a lot of interactions with industry and

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1 a consultant for industry and I have a slide of this
2 that shares in the diagnostics.

3 DR. MATAS: Arthur Matas from the University
4 of Minnesota. We have research grants with some of
5 this but no conflicts for today.

6 MS. MEYER: Dr. Abecassis isn't here yet this
7 morning. I'm Joette Meyer. I'm a clinical team leader
8 in the Division of Transplant Ophthalmology Products at
9 FDA, and I have no conflicts.

10 DR. LIGHT: I'm Jimmy Light. I'm a
11 transplant surgeon here in Washington, D.C. and I have
12 no conflicts.

13 MR. HERNANDEZ: Arturo Hernandez. I'm a
14 medical officer, Center for Devices and Radiological
15 Health at FDA. I have no conflicts

16 DR. SEGEV: I'm Dorry Segev. I'm a
17 transplant surgeon and epidemiologist at Johns Hopkins,
18 and I have no relevant conflicts.

19 DR. BONVENTRE: I'm Joe Bonventre. I'm the
20 chief of the Renal Division at Brigham and Women's
21 Hospital and I'm also this year President of the
22 American Society of Nephrology. I'm co-inventor on

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1 KIM-1 patents which have been signed partners and
2 licensed to a number of companies. I'm also a
3 consultant to a number of companies interested in
4 kidney safety biomarkers and drugs for acute kidney
5 injury.

6 DR. RABB: Hamid Rabb, Medical Director of
7 Transplantation at the Johns Hopkins Hospital. I have
8 no directly relevant conflicts of interest.

9 DR. CANTAROVICH: Marcelo Cantarovich,
10 Associate Director of the Multi-Organ Transplant
11 Program, McGill University, Montreal, and I don't have
12 any conflict to today's presentation, although we
13 receive educational grants from the cities from the
14 companies listed there.

15 DR. CAVAILE-COLL: I'm Marc Cavaile-Coll,
16 Medical Officer from the Division of Transplant and
17 Ophthalmology Products at the FDA and I have no
18 conflicts.

19 DR. HARLER: Mary Beth Harler, Bristol-Myers
20 Squibb Global Clinical Research.

21 MR. HANTO: Doug Hanto, Transplant Surgeon at
22 the Beth Israel Deaconess Medical Center in Boston, no

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1 conflicts.

2 DR. DOSHI: Mona Doshi, a transplant
3 nephrologist at Wayne State University. I have no
4 conflicts.

5 DR. GRIFFIN: I'm John Griffin, a researcher
6 at Scripps Research Institute, and I'm a consultant and
7 advisory board member for Socratech and for ZZ Biotech.
8 I also have patents that are owned by Scripps Research
9 Institute.

10 DR. FENG: I'm Sandy Feng. I'm a transplant
11 surgeon at University of California-San Francisco. My
12 conflicts are doing clinical trials in ischemia-
13 reperfusion injury for the companies shown.

14 MS. GONZALEZ: I'm Gema Gonzalez. I'm a
15 biomedical engineer and clinical device reviewer at the
16 Center for Devices and Radiological Health, and I have
17 no conflicts.

18 MS. BALA: I'm Shukal Bala, microbiologist
19 with Division of Transplant and Ophthalmology Products. I
20 conflicts. And Dr. Stefan Tullius will be here later
21 this afternoon.

22 DR. LOBO: Peter Lobo from the University of

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1 Virginia. I'm a transplant nephrologist and I have no
2 conflicts.

3 MS. HOSGOOD: Sarah Hosgood, a research
4 scientist in the Transplant Unit, University of
5 Leicester, UK, no conflicts.

6 DR. ALBRECHT: And Dr. Michael Abecassis has
7 joined us. Dr. Abecassis, could you introduce
8 yourself, your affiliation and any conflicts?

9 DR. ABECASSIS: Michael Abecassis. I'm the
10 Chief of Transplant, Northwestern University, transplant
11 surgeon. I have no conflicts. I do have an IP
12 agreement with the company that does proteomics with a
13 kidney injury, past President of Society of Transplant
14 Surgeons.

15 MS. ALBRECHT: Thank you very much, and with
16 the conclusion of the introductions what I'd like to do
17 is turn this over to the moderators for the first
18 session, Drs. Christopher Lu and Dr. Ergun
19 Velidedeoglu.

20 Session 1: Pathophysiology and Contributing
21 Factors of Ischemia Reperfusion Injury (IRI) and DGF in
22 Kidney Transplantation

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1 MR. VELIDEDEOGLU: Good morning. We will be
2 starting our Session I. As we all know Session I is
3 the introductory session to the subject, and we have
4 four speakers in Session I. And our first speaker is
5 Dr. Christopher Lu, who is also co-moderating this
6 session. And he will be talking about pathophysiology of
7 ischemia reperfusion injury with special emphasis on
8 TOLL-like receptors.

9 MR. LU: Thanks. I appreciate the ischemia
10 reperfusion workshop organizers had a chance to present some
11 our work. I'm really humbled and honored to be sharing
12 the podium with a number of scientists who made some
13 major contributions in this area, and I look forward to
14 learning a lot during the course of this conference.

15 We have a kind of big charge today in the
16 course of the next 10 or 15 minutes, and I'll try to
17 keep my talk closer to that 10 minutes -- introducing
18 the area, which is absolutely huge, and also speaking
19 to an audience with diverse expertise. So I apologize
20 for kind of making things made too simple for some and
21 hopefully not too complicated for others.

22 These are my acknowledgments. These are the

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1 people when I do discuss the work from our lab, these
2 are the people who have actually done the work, Dr.
3 Jianli Chen, who's worked on the public work and
4 theorem reset project and John Hartono, who's worked on
5 the TLR4 Receptor project.

6 I think one of the major points that all of
7 us have learned over the last several decades is that
8 renal injury is not the result of just of the initial
9 injury. The very important concept is that there is a
10 maladaptive response to that injury, which magnifies
11 it. And hopefully, if we understood this maladaptive
12 response in greater detail, we would be able to design
13 -- we would be able to identify therapeutic targets
14 which would allow us to help our patients. Dr.
15 Albrecht asked me to review some of the maladaptive
16 responses, and I think really that's almost impossible
17 because there are so many. But nonetheless what I'm
18 doing here is just reviewing some of the major ones,
19 and those would be the maladaptive hemodynamics,
20 endothelia dysfunction, maladaptive mitochondrial and
21 other metabolic responses, reduction of excessive
22 reactive oxygen species from mitochondria and various

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1 enzyme systems, tubular obstruction of AKI and
2 maladaptive information. I'm going to concentrate on
3 this latter topic which is maladaptive information.

4 One way of looking at this -- and by the way,
5 I included more slides and references in my protocol
6 that I'm going to present, and I'm pretty excited about
7 that. But one of the protocols of doing that is to
8 give you places to go and references to read if you
9 want to learn more about this area. Reperfusion and I
10 also apologize to anyone in the room if I neglected to
11 put your references and your work on the list.

12 Renal injury occurs during ischemia
13 reperfusion. This injury elicits an inflammatory
14 response, which is maladaptive and can cause more renal
15 injury. And this inflammatory response when it occurs
16 within the allograft can participate in cause and
17 rejection.

18 So hopefully if we understood this
19 translation of injury to inflammation and were able to
20 interdict it, we would be able to decrease the renal
21 injury in allograft and also perhaps decrease
22 transplant rejection. And one way of looking at this

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1 is to restate the so-called danger hypothesis, which
2 was a major proponent of Paul Matzinger in a way that
3 was recognized about a millennia ago by Sun-tzu in his
4 treatise called the "Art of War." And during this time
5 China was divided into many, many small and large
6 states, and the idea was that you survived as a state
7 not only by having a great army but it was also
8 important to understand the politics that armies have.
9 It was important to know who you were, know thyself,
10 know thy enemy and know if and how to fight than we
11 could fight a hundred battles, win a hundred victories
12 in a war.

13 The immune system does a similar thing. It
14 recognizes self/non-self, and the important thing to
15 realize is that most non-self elicits no inflammatory
16 or immune response. It is also important to know if
17 and how to fight. So the idea here is that injury
18 elicits an inflammatory response. The inflammatory
19 cells arrive at the site of injury and assume that the
20 non-self present is the perpetrator of the injury and
21 then elicits immunity, and in the case of transplant,
22 this would be the non-self and rejection of the

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1 allograft.

2 So a major idea about how this inflammatory
3 response to injuries elicited is the damage associated
4 with a nephron pattern hypothesis. And according to
5 this hypothesis, cells such as renal tubular cells are
6 injured by the ischemia reperfusion which occurs during
7 the transplant. These injured cells release a number
8 of molecules, which are the damage associated whenever
9 the pattern molecules were alarmed. The best understood
10 is the HMGB1. The HMGB1 then interacts with a number
11 of different receptors including TLR4, endothelia,
12 macrophages and tubules.

13 Now, our research in this area has tripled,
14 and there are a number of these damage-associated
15 molecules, and I think you're going to hear more about
16 these in the course of this morning. There are
17 molecules which result when the injured cell expresses
18 new molecules on the self surface and activates the new
19 response, the inflammatory response; when the
20 extracellular matrix is damaged and changed by reactive
21 oxygen species and by enzymes which are released by
22 damaged cells, and then these are recognized by the

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1 innate end response; by intracellular ligands released
2 by injured cells, and there are a number of these; by
3 intracellular signals such as reactive oxygen species;
4 and by molecules which are released by neutrophils
5 arriving at the site of the tissue injuries.

6 So the best understood of these is the ligand
7 receptor pair of the ligand donation B1 and receptor
8 TLR4. Now, a number of damage-associated ligands for
9 TLR4 have been proposed. There are a few where actual
10 profound physical interactions between the ligand and
11 TLR4 have been demonstrated, and HMGB1 is one of those.
12 Others have shown that intervention of HMGB1 ameliorates
13 ischemic acute kidney injury in mice, and this offers
14 the opportunity perhaps of doing the same in our
15 patients; intervention of TLR4 ameliorates ischemic
16 through kidney injury in mice. So ischemic receptor
17 for the ligand, and human kidneys with TLR4 mutations
18 where the signal of the TLR4 receptor is decreased,
19 have less delayed graft function at the transplant,
20 work done by Kruger and colleagues.

21 So our work is concentrated on the area of
22 the kidney which is the most susceptible to ischemic

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1 injury. So this is kind of a cartoon taken from
2 Heptinstall's textbook, a set of nephrons. And the
3 kidney, the focus it was, the filtrate, which is going
4 to become relearned, the tubules, and then on out to
5 the bladder. The area of the kidney which is most
6 severely injured by ischemic reperfusion is the outer
7 medulla, and in this area the major players are the S3
8 segment of postular tubular, the medullary (inaudible),
9 the blood vessels of the vasa recta, and any
10 infiltrating leukocytes. The work from our lab and
11 others supports this cartoon; that is that the renal
12 tubule from this area is susceptible to injury; the
13 Rhesus reactive oxygen species, and we've shown in our
14 laboratory that these reactive oxygen species calls
15 endothelial cells to express TLR4. The injured male
16 tubule cells release damage-associated marker pattern
17 modules such as HMGB1, and this demonstrated by Wu
18 Chadban and a number of other investigators.

19 This interacts with TLR4 on the endothelial
20 cell. The endothelial cell then is stimulated to
21 express adhesion molecules, such as ICAM-1. These
22 adhesion molecules facilitate the diapedesis of

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1 mononuclear phagocytes into the interstitial spaces.
2 These leukocytes produce TLR4 and are stimulated by the
3 DAMPs, and they make maladaptive molecules, which
4 result in more gap per damage to tubules and also make
5 if there is as a transplant, will solicit the
6 rejection response.

7 This is just an inside corporatization
8 showing the upregulation of TLR4 on the vasa recta.
9 The Delta staining with the marker for endothelial and
10 TLR4 showing at the tubular stem cells. I'm going to
11 skip through the next couple of slides because I think
12 we started late, and we need a lot of time for
13 discussions.

14 The last slide is showing work improvement
15 qualities. This was a study where recipients were typed
16 for TLR4, and then the kidneys were transplanted. And
17 those donor kidneys that had mutation of TLR4 such as
18 signaling ability of the TLR4 signaling was inhibited
19 or dysfunctional. Those kidneys had a much higher
20 likelihood of having immediate function. This is one
21 of their pictures showing TLR4 on the tubular cells,
22 and this is a depiction of the amount of cytokines and

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1 chemokines that were produced by those tubule cells
2 from the kidneys.

3 So just a cartoon to summarize the main
4 points that I'm trying to make. One is that one
5 mechanism of exacerbation of injury, translation of
6 injury into information is this cartoon where tubule
7 cells released and associated marker pattern molecules,
8 produce reactive oxygen species, stimulate endothelia
9 to express TLR4. The endothelia express adhesion
10 molecules which facilitate the diapedesis of
11 leukocytes in interstitial space. These leukocytes at
12 TLR4 respond to HMGB1 and other DAMPs. These cause
13 production of the after molecules and this injures the
14 kidney helps elicit a rejection response. There are
15 many DAMPs, there are many receptors which participate
16 in this process in addition to TLR4.

17 And then the major point to be made is that
18 it's not only the initial injury -- response to the
19 initial ischemia itself; in other words, the initial
20 injury is not the whole story. There is a maladaptive
21 response, including information and many other things,
22 which magnifies this injury, and the ultimate injury is

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1 the result of not only the initial injury but also the
2 maladaptive responses. And what we can hope is that
3 therapy which interdicts these maladaptive responses,
4 would benefit our patients. So I'm going to stop there
5 and I refer you to the reference list for you on the
6 desk.

7 MR. VELIDEDEOGLU: We thank Dr. Lu for this
8 nice presentation, and as we all know, we have a Q&A
9 session, Q&A part at the end of this session, so we
10 will save our questions and the discussion for that
11 part. Our next speaker is Dr. Peter Lobo, and he's
12 from the University of Virginia. He will be talking
13 about the role of immunity both innate and adaptive
14 immunity and the complement system, and the pathophysiology
15 of ischemia reperfusion injury.

16 MR. LOBO: I would like to thank Dr. Albrecht
17 for inviting me to this workshop. And I was going to
18 talk of some work that has not done by me but by my
19 colleague from University of Virginia, Dr. Racusen, but
20 I will spend a little bit of some of the work that I've
21 also done in this area. I will discuss the role of NKT
22 cells and polymorphic cells, a little and also the role

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1 of complement. And then I would also try to spend some
2 time comparing the pathophysiology of renal IRI and
3 discuss the differences between the renal IRI that we
4 have in animal models and what we see transplantation
5 in that function. And right now, I'm not sure whether
6 we really understand our enemy.

7 As Chris Lu has already mentioned, there are
8 four big layers in the ischemic reperfusion injury, and
9 once ischemia causes damage to the epithelial cells, it
10 activates the endothelial cells and then causes dormant
11 leukocyte cells, especially polys, to come into the
12 area of injury, and also the renal interstitial and
13 renal cells may play a role.

14 Here is an example and I hope you all can
15 see. You can see that in a normal kidney, in a mouse
16 kidney there are a lot of the unmated cells in the
17 interstitial surrounding the renal tubules. What Dr.
18 Okusa hypothesis was is that these diverted cells take
19 up some of the molecules released by their tubular
20 cells after this kidney injury and in his model, the
21 renal molecule is a glycolipid. And this is presented
22 by the dendritic cell CD1d receptor. And often one

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1 molecule is taken up by a dendritic cell, the dialytic
2 cell gets activated, releases cytokines and this
3 activates, this whole process of antigen and cytokines,
4 activates the natural killer T cells, and they produce
5 interferon gamma. And then this further activates the
6 polymorph nuclear leukocyte. And he has nicely shown
7 that for the polymorphonuclear cells to be active and
8 cause damage, you need both interferon-gamma and IL-17.

9 This is an interesting, what they analyze
10 whether leukocytes that entered the kidney during the
11 reperfusion time, and they nicely showed that at 24
12 hours you get maximum amount of neutrophils as well as
13 macrophages, but there is very little in the way of T
14 cells and B cells. And this is at 24 hours.

15 Before I go further, I would like to briefly
16 discuss the renal ischemic reperfusion technique. Most
17 of his work was done on the C57BL6 (B6) mice, which
18 was six weeks old, is they all had anesthesia. And all
19 these mice at the time of surgery, they were kept on a
20 heated bed and the rectal temperature was maintained
21 around body temperature. And the kidneys were
22 approached from the back and not from the abdominal

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1 approach. And ischemia was induced by clamping the
2 renal vasa recta for 24 minutes to produce mild
3 ischemia or 32 minutes to produce severe ischemia, and
4 then the kidneys were reperfused for 24 to 48 hours,
5 and again this reperfusion was done at room
6 temperature.

7 And this experiment is to show that if you
8 take an antibody and you put it in presentation of the
9 glycolipid, you can inhibit this whole process. And so
10 he injected the mice with the one antibody that bound
11 to this receptor, and you can see that the mice
12 received this antibody, that it develop no renal
13 failure while the control mice had significant renal
14 failure. And his other experiments, he actually used
15 an antibody that eliminated an NKT cell. And you can
16 see that once you eliminated the T cell you can stop
17 this process, and again the kidney is protected and
18 they do not have any functional impairment.

19 Here's some data to look at importance of
20 interferon gamma, especially in the leukocytes. As you
21 can see, if you analyze the leukocytes 24 hours after
22 renal ischemia reperfusion injury, you can see that the

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1 T cells do not have much interferon gamma, the
2 macrophage stages have little interferon gamma, while
3 most of the interferon gamma is made by the reperfuse
4 and by the NKT cells. The CD21 receptor is the marker
5 for NKT cells.

6 So in his studies to prove that interferon
7 gamma was necessary, he put mice that were deficient in
8 interferon gamma and as you can see, the IRI, they were
9 protected. And even when he added more IL-17 because
10 these polys (inaudible) -- even after adding more
11 complement IL-17 he could not induce injury, clearly
12 indicating that these neutrophils require both
13 interferon gamma and IL-17 to cause the injury.

14 In other studies, he looked at IL-17 the
15 neutrophil IL-17 and it is and that red brown mouse,
16 which is deficient in T cells and B cells but they have
17 neutrophils, macrophages and there is natural killer
18 cells but not natural killer T cells. And as you can
19 see, that if you do ischemic reperfusion injury with
20 these mice, both groups of mice developed injury but a
21 little bit less in the red mice because they collect
22 the T cells. And you can see that in both groups of

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1 mice, there's a lot of infiltration of leukocytes with
2 this injury. However, if he injected them four hours
3 before the experiment an antibody to IL-17 in, he would
4 be able to ameliorate this injury. And what's
5 interesting is that the leukocytes did not migrate;
6 they actually stayed in the blood vessels and there was
7 no leukocyte migration in the tissue in the T cell IL-
8 17. And as we know, the leukocytes, there's a
9 leukocyte marker and we know the leukocytes in the
10 blood has a lot of IL-17.

11 So in his other experiments, he wanted to
12 really define the role of neutrophils, so as you can
13 see the IL-17 knockout mouse was protected. When
14 he injected these mice 24 hours before the experimented
15 with neutrophils, they had both interferon and IL-17 it
16 would produce a lesion. While injected the neutrophils
17 that had interferon gamma but no IL-17 he put his mice
18 they were protected. And they give one type
19 neutrophils that at the same time gave them an antibody
20 to IL-17 is a protector, clearly indicating that for
21 the neutrophils to migrate and to cause injury, they
22 require both interferon gamma and IL-17.

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1 I will now spend the next few minutes looking
2 at the role of B cells and renal IRI, and I was going
3 to suggest that we go in the Dr. Rabb's lab sitting
4 right there. And you can see there's conflicting data
5 between his lab and that of Dr. Coleman from . In their
6 studies, in Dr. Rabb's lab, they use a B cell deficient
7 mouse that is a new engineered mouse, and this mouse there
8 are no B cells and so they will not have any
9 immunoglobulin in their plasma. And ischemia
10 reperfusion injury, and clearly showed the big
11 difference that those that were B cell deficient had
12 formed the other cells; they were protected just by
13 being B cell deficient. And here is the histology
14 score as well. While Dr. Thurman's lab used the same
15 genetically engineered mouse and acquired it from the same
16 company, and it could not show a protective defect.
17 Actually, they showed that this mouse that was renal
18 and B deficient was actually a little bit more energy
19 deficient and actually a little bit more originally.
20 So the story with the B cells has not as yet been
21 resolved.

22 I will next go to the role of the complement

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1 cascade. As just to remind some of you, for complement
2 activation to take place and to form the net complex,
3 complement is activated through three different
4 pathways. The classical pathway activation occurs in
5 the presence of antibody, while injured cells can
6 activate complement through the open-ended pathway, and
7 as you can see, that the ischemic renal tubules, they
8 can activate complement through the open-ended pathway, and
9 once the complement occurs, an activation occurs,
10 you'll get some byproducts which for example C3 and C5,
11 which bind to receptors on leukocytes and activate
12 these leukocytes. And they can also prove (inaudible)
13 factor to activate the macrophages. The kidney also
14 has complement inhibitors to regulate the complement
15 cascade, and in the proximity to cells that most of
16 ischemic in cells occurs, there is an inhibitor called
17 Crry that inhibits this open-ended pathway, and I will
18 show you data to indicate that during ischemia, this
19 complement inhibitor that is in the proximal tubule, is
20 depleted and so it cannot inhibit this open-ended
21 pathway, and so there is activation of complement. On
22 the other hand, the other compliment inhibitors that

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1 reside mostly in endothelial cells in the glomeruli and
2 in the peritubular space, they're complement inhibitors
3 are not effective.

4 Here's an experiment by Dr. Thurman from
5 Denver, very nicely showed that during ischemia, the
6 basolateral Crry gets depleted, and as a result, you
7 get complement activation within first three to six
8 hours as been seen with radical organization in the
9 basolateral area. And as a result, complement cannot
10 be inhibited, and so there is -- hence, tubule damage.
11 And you can see that if you take mice that are
12 deficient in Crry, there is more renal damage. There
13 are others who have also done work to show that you can
14 take mice that are C3 deficient or C5 deficient and can
15 also protect mice. And here is one such example by
16 this group, already showed that if you take mice that
17 are C3 deficient, they are protected from renal
18 ischemia.

19 So in summary, we have shown that -- Dr.
20 Okusa's lab is showing that maneuvers that inhibit the
21 renal clinical response, just as Dr. Chris Lu had
22 mentioned, clearly indicate that 30 to 35 minutes of

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1 renal ischemia at body temperature, especially the
2 mouse model, is not by itself sufficient because of
3 ischemic renal injury. He tried to implement the cells
4 to actually cause the renal tubular injury. And just
5 to remind you, for example, in this experiment both
6 groups underwent ischemia, yet once you stop the
7 implemented response by giving these antibodies, the
8 tubules look very normal, and there was no significant
9 renal failure. It is the Interleukin cells that cause
10 renal failure.

11 Secondly, ischemia-induced activation in
12 ganglion cells, NK and NK2 cells and neutrophils and
13 complement has a protogenic ability in reducing renal
14 (inaudible) and Interleukin failure and Interleukini
15 cells, especially those requiring both interferon and
16 IL-17 when you (inaudible).

17 Now, this comes from the last part of my
18 talk, and we have to ask this question. Could there be
19 an additional pathophysiological mechanism to explain
20 post-transplant acute renal failure as seen in
21 (inaudible) to get the function. And we started asking
22 this question because of three different observations.

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1 Firstly, the histological appearance of the renal
2 tubule injury in renal malfunction is mild compared to
3 the renal IRI. And secondly, the extent of renal
4 tubule injury in renal malfunction as defined
5 histologically is not significantly different from
6 other grafts that function mutually. And here is an
7 impressive study where they looked at the C zone of
8 rats, that those that they followed the function of the
9 (inaudible) and those that sustained molecular function
10 and they looked at the extent of renal tubule injury --
11 not intratubular cells, just tubule injury both on day
12 0 and day 7. And you can see that when they measured
13 IgM GFR, the kidneys that we followed had a finding to
14 GFR, and was also probably the leading donor grafts,
15 while those that had irregular function their GFR was
16 still very low. But when you look at different aspects
17 of renal tubular injury, you will find that there's no
18 significant difference between those that recovered and
19 those that had delayed renal function, even those from
20 living donors, indicating that there is something more
21 that we really do not understand, and we should not
22 easily accept what we see in the renal model.

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1 And the second observation is that one cannot
2 easily explain the (inaudible) allograft function in
3 different patients, receiving organs from the same
4 donor. So this is again a perplexing question. And
5 the third observation is repeating T cells that are
6 formed from reperfusion, for example, giving
7 immunoglobins or other antibodies, has failed to
8 significantly reduce renal function with renal
9 allografts from optimal donor. So even though with
10 this immunoglobulin, you might decrease the reperfusion
11 injury, yet there are patients who still have irregular
12 function.

13 So we wondered whether the differences in
14 pathophysiology injury or acute renal injury to be non-
15 transplant and transplant kidneys, whether they could
16 be explained by reperfusion and cold temperatures. As
17 you can see, there is a non-transplant in a patient who
18 develops high potential and renal failure, and here is
19 a transplant situation. Ischemic event occurs in the
20 patient here. We see the role of the transplantation.
21 The reperfusion event occurs in the same patient, and
22 the reperfusion temperature is at body temperature;

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1 while in the transplant model, although the ischemic
2 event occurs in the donor, the reperfusion event occurs
3 in the recipient and the temperature is in the cold.
4 And this made us wonder whether the cold temperatures
5 could be also producing another factor.

6 So we wondered whether renal malfunction
7 could be result from injury to small blood vessels,
8 especially since the tubular cells, they could not
9 discern any big difference between the tubular cells
10 and hence explain the lack of significant reasonable
11 renal tubular injury, and could the recipient blood
12 components cause frontisian (phonetic) damage to small
13 blood vessels in cold renal allografts, and could the
14 culprit be cold reactive IgM off of antibodies?

15 So what are cold reactive natural IgM
16 antibodies? As you can see, they're produced by B1
17 lymphocytes and they're detectible at high levels in
18 all individuals at birth but decrease in age. The
19 increase in chronic and this IgM are formed formal, and
20 they bind to different receptors on leukocytes and
21 material cells and leukocytes. And here's an example
22 where we can show these antigen antibodies binding to

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1 leukocytes. Here you can see okay, and you can see my
2 flow. Here are some of our suspicions where at the time
3 of crosstalk we looked for these cold antibodies that
4 come from -- they are present in their serum, and you
5 can see that some patients have very high levels of
6 antibodies but other patients do not have these
7 antibodies. Just one brief, and I'll finish up.

8 These natural IgM antibodies, they bind at a
9 cold temperature and this is what Suchy (phonetic) had
10 shown 20 years ago, that under cold temperature these
11 IgM antibodies, after they bind to the receptor, they
12 activate, complement, and damage their nuclear cells,
13 while at body temperature which is that physiological
14 function, they actually bind to receptors and actually
15 inhibit receptor activation but did not cause damage.

16 Here is examples of the graft where we put
17 one hour after their transplant I did renal biopsies,
18 and you can see that in those patients they had no cold
19 IgM antibodies. Their endothelial cells in their
20 medulla was well preserved, while in those that had
21 weak IgM cold antibodies, there was some damage, and
22 occlusion of the globular line, while in those with

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1 strong antibodies there was good IgM staining in their
2 endothelial cells and the globular lining were
3 completely occluded.

4 There's another group from Indiana that raise
5 similar observations, just about two or three years ago
6 showing that when they did one out of post-transplant
7 biopsies, they could find that there were patients
8 where severe and repeated cell injury they could detect
9 one transplant factor in the back. And what we went on
10 to show is that those who had these antibodies also had
11 glomular lesions and they lived to function, about half
12 of them, while those who didn't have any of these
13 antibodies, very few of them had live to function. So
14 we did one final experiment, which we auditioned onset
15 in the early '80s, where we actually took recipients
16 that had got a cold antibody and actually bonded a
17 kidney. And you can see that -- sorry here, where they
18 bond the kidney and here we did not warm the kidney.
19 And you can see that warming the kidney decreased the
20 incidence of the delayed renal function.

21 And here is the final slide, where we had six
22 recipients getting to this from three to ten donors.

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1 All of the six recipients had cold antibodies, and in
2 one of the recipients, since we were measuring from
3 these cold antibodies, in one of them we warmed the
4 allograft; in the other one we did not. And you can
5 see that the ones that we warmed have lesion graft
6 function. Similar observations were made by Belzer
7 group, where we looking for cold antibodies to bind to
8 red blood cells. And here's an interesting study that
9 they are done. They are done in transplant from a
10 donor with cold antibodies. And you can see there was
11 no blood flow. And so they took the second kidney from
12 the same category donor, which was by now 40 hours old,
13 and this time they warmed the kidney and you can see
14 that even though the kidneys were older, they had
15 improved graft function just by warming the kidneys.

16 So this is my last slide. So the conclusion,
17 (inaudible) renal function may not be the same as renal
18 IRI. (Inaudible) as renal IRI and delayed renal
19 function and fetal cell injury will be decreased could
20 have a problem and experiencing acute renal failure
21 regardless of renal failure from the injury. And the
22 second IgM natural antibodies could cause the cell from

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1 weakening and material cell injury and receding blood
2 flows from the cold organ. Thank you.

3 MR. VELIDEDEOGLU: Dr. Sandy Feng from
4 University of California-San Francisco, is our third
5 speaker She will be talking about donor factors and how
6 they influence the occurrence of DGF and ischemia
7 reperfusion injury.

8 MS. FENG: Thank you very much. It's a
9 pleasure to be here. It's exciting to think about
10 moving the ischemia reperfusion injury forward from a
11 clinical perspective.

12 Terrific. So, I'm going to focus my talk on
13 the donor factors alone, because there's a recipient
14 talk to follow and also to focus on DGF as opposed to
15 outcomes, but there is obviously going to be some
16 overlap. My disclosures have been discussed
17 previously.

18 So I think we know that donor quality factors
19 such as age, family, medical history, cause of death
20 and biopsy findings are the primary issues related to
21 DGF, and I think there's also the issue of the ischemic
22 injury that's sustained, which is reflected by whether

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1 the donor's a cardiac death or brain death donor.
2 What the CERF RAP mean is and also cold ischemia time.
3 My talk will focus on age, biopsy findings, DCD status.

4 So if we look at donor age, I think it's
5 already ruled as a potent risk factor. It's many
6 intuitive physiological reasons as shown here,
7 including just natural loss of renal function, an
8 entity's burden of comorbidities for the less healthy
9 person and a greater vulnerability to the injury that's
10 going to happen. In terms of trying to study the
11 impact of donor age more in isolation, we actually
12 looked at donor age in a living donor study where the
13 ischemic injury is minimized so then we can really kind
14 of focus more on issues of donor quality.

15 We looked at 469 living donor kidney
16 transplants performed at UCSF over a five-year period
17 where we had a 4.7 percent DGF incidence and a 10.7
18 percent incidence of slow graft function defined as a
19 creatinine greater than 3 of PSAT of 5. What we found
20 in a univariability model, looking at donor factors
21 again, was that donor age was a significant predictor.
22 By year it's 1.03 with a P value of .037. However, if

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1 we include some recipient factors into the model and
2 looked at all variables, donor age loss as significant.
3 So I think this tells us that donor age is very
4 important, because it's sort of a measure of surrogate
5 of the quality of the kidney, even in the healthiest
6 patients. But it may not be a dominant factor in
7 living donor transplantation where there is a minimal
8 amount of injury.

9 So I'm now going to switch to biopsy
10 findings, because again, donor age is probably a
11 surrogate in many ways for quality and the biopsy's
12 going to let you look at the quality. (Inaudible)
13 biopsies were studied in 172 transplants, and in this
14 cohort there was a 32 percent incidence of delayed
15 graft function. The criteria that were assessed are
16 shown here. What they found was that in uni and
17 multivariable models arteriolar hyalinization emerged
18 as sort of the biopsy finding most correlated with
19 delayed graft function. Donor age was certainly
20 significant, and you can see that the DGF patients
21 received older donor kidneys than the non-DGF patients,
22 and there were other significant factors, the usual

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1 suspect, such as cold ischemia time.

2 However, if you looked at the biopsy findings
3 that they studied, two factors emerged: arteriolar
4 hyalinization and arterial intimal fibrosis. What they
5 also showed was that the impact of arteriolar
6 hyalinization, if you had no arteriolar hyalinization -
7 - here's the odds ratio for arteriolar hyalinization,
8 AH, and again, it's very significant.

9 The intimal fibrosis in this multivariable
10 model no longer was a significant factor. So their
11 conclusions were that arteriolar hyalinization is an
12 independent predictor of delayed graft function. These
13 two lesions are elementary lesions of vascular
14 nephrosclerosis. They were considered a marker of
15 early onset atherosclerotic disease. In this
16 particular study of 172 kidney biopsies, it was not
17 correlated with donor age, and they felt that the
18 presence appears to increase the vulnerability to other
19 factors related to ischemic reperfusion injury such as
20 cold ischemia time. So if you look at kidneys that did
21 not have arteriolar hyalinization, cold ischemia time
22 did not seem to be a factor in delayed graft function.

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1 However, in patients with arteriolar hyalinization on
2 their donor kidney biopsy, cold ischemia time figured
3 in the occurrence of delayed graft function.

4 So there's a larger more recent biopsy study
5 published last year, looking at 541 of 633 implantation
6 biopsies. They were all treated in the same way and
7 scored again for many of the same factors. And again,
8 arteriolar hyalinosis emerged as a DGF risk factor. In
9 this study, donor age was significantly associated with
10 all of the chronic scores that were measured on the
11 biopsy, and associations were also observed between
12 histologic scores and medical history and mode of
13 death. And so here you can see that in their
14 multivariable model, arteriolar hyalinosis and fibrous
15 intimal thickening both emerged as factors pre-
16 disposing to delayed graft function.

17 So again, I think that donor age is more
18 predisposed to showing kidneys with vascular changes.
19 The presence of the vascular disease is strongly
20 correlated to important graft outcomes. The
21 relationship between the presence of vascular disease
22 and delayed graft function is very potent, because when

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1 these factors are in the model, donor age is no longer
2 a significant predictor. Interestingly, we've all been
3 focused historically on glomerulosclerosis, but
4 glomerulosclerosis as well as intimal fibrosis in
5 tubular atrophy were not independently associated with
6 graft outcomes.

7 Limitations, however, of vascular assessment
8 on a frozen section biopsy are significant, and this
9 needs to be considered because obviously there are time
10 constraints in evaluating donor kidneys. There are
11 sometimes insufficient material because you require
12 nice arterial cross-sections. There's poor
13 reproducibility in the reading. It may be
14 significantly dependent on the biopsy technique,
15 because you need deeper cortical sampling to assess
16 these findings in arcuate or proximal interlobular
17 arteries, and therefore it's underestimated by wedge
18 biopsy and requires core biopsy. And then finally, the
19 frozen tissue setting is very challenging.

20 What about donor renal function, most often
21 examined as serum creatinine, typically the terminal
22 serum creatinine. There was an SRTR database analysis

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1 of transplants over a long period for time. Kidney
2 grafts were characterized by not only SCD and ECD
3 status, but also their terminal creatinine. And the
4 endpoints examined in this study was delayed graft
5 function as well as long-term graft survival. What you
6 can again see was that there was a differential impact
7 of terminal creatinine on standard versus expanded
8 criteria donor kidneys, again suggesting that there's -
9 - the parenchymal quality that may be different between
10 SCD and ECD kidneys is reflected. So for the DGF
11 endpoint, you can see that for SCD kidneys, there was a
12 very steep relationship of DGF to the serum creatinine;
13 whereas for ECD kidneys compared to a reference group
14 of normal creatinine donors, high serum creatinine
15 donors did have increased delayed graft function, but
16 the relationship was less potent and less steep.

17 If you look at overall graft survival, you
18 can see that donor serum creatinine was a significant
19 factor only in the ECDs and donor serum creatinine had
20 no impact on overall graft survival for SCD kidneys.
21 So this differential impact of a high terminal serum
22 creatinine on the two classes of kidneys led to a

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1 hypothesis that increased serum creatinine is really a
2 surrogate for different processes. In SCD kidneys it
3 may well be a surrogate for reversible ischemic hypoxic
4 or nephrotoxic injury; whereas in ECD kidneys it may be
5 that injury on top of some chronic parenchymal damage,
6 poor parenchymal quality, that leads to the
7 differential impact of a high serum terminal
8 creatinine. And I think whenever we look at these
9 studies, we also need to keep in mind that there's a
10 strong potential selection bias because obviously not
11 all high serum creatinine kidneys are being used and
12 entered in the database.

13 Dr. Irish, sitting here, looked at the impact
14 of serum creatinine over time. There was a nomogram
15 developed and published in 2003 to predict DGF, which
16 was subsequently updated seven years later to better
17 reflect the current climate of kidney transplantation.
18 The differences in the two populations studied show
19 that there was a steep increase in donor age, a
20 substantial increase in the recipient wait times and
21 obviously changes in immunosuppression management.
22 What was found when you compared the two different

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1 nomograms was that there was very high consistent
2 impact of specific factors, such as donor age; for
3 example, 1.018 compared to 1.017. Cold ischemia time
4 had a very similar impact. But interestingly terminal
5 serum creatinine had a lesser impact in the earlier
6 cohort and a greater impact on DGF risks in the more
7 recent cohort.

8 The conclusions from that study was that the
9 overall rate of DGF remained comparable between the two
10 cohorts. However, there were compensatory changes.
11 Immunologic factors were attenuated; whereas there was
12 an increased relative impact of terminal creatinine,
13 suggesting that suboptimal donor quality may have
14 worsened DGF rate while immunologic factors and their
15 attenuation may have improved DGF rate leading to no
16 overall change in DGF rate over time. So again, this
17 shows that in a more modern cohort the terminal
18 creatinine is a more potent factor for DGF, perhaps
19 because we're using lower quality kidneys.

20 A more extreme version of looking at this
21 terminal creatinine story is to look at using kidneys
22 from donors with basically acute renal failure. Here

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1 defined as terminal creatinine greater than 2.0 along
2 with doubling of this serum creatinine compared to
3 admission. This particular study published two years
4 ago, looked at 25 such kidneys, and in addition to
5 having acute renal failure, they were highly selective
6 and basically trying to pick donors who had no
7 significant risk of poor parenchymal, intrinsic
8 parenchymal quality. When they looked at their
9 experience, basically it was a predominantly pumped
10 experience. The parameters from pumping were also used
11 in an assessment tool. They had 92 percent one year
12 graft survival, 4 percent PNF and 32 percent DGF, which
13 is not a very high rate of DGF when you think about it.
14 And what they found was that compared to their nonacute
15 renal failure SCD kidneys, there was no differences in
16 anything, including DGF rates when you use kidneys with
17 high serum terminal creatinines. And their conclusions
18 were that kidneys from highly selected donors with
19 acute renal failure yield good outcomes, that the
20 admission creatinine, perhaps a better reflection of the
21 intrinsic quality of the kidney, is more important than
22 the terminal creatinine, and they also went on to say

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1 that the trend at the time of procurement, was it
2 improving, was it increasing, was it decreasing, did
3 not appear to be important. Again, these are
4 predominantly standard criteria donor kidneys with
5 probably good intrinsic donor quality.

6 DCD kidneys. DCDs are obviously increasingly
7 used. It's a potent risk factor for DGF. And overall
8 outcomes, however, have been reported to be comparable
9 compared to standard criteria donor kidneys. This was
10 examined a little bit more in detail, which shows that
11 if you look at DCD kidneys from donors less than 50
12 years of age, they perform like SCD kidneys. If you
13 look at DCD kidneys from donors greater than 50 years
14 of age, they perform like ECD kidneys. Well, as we all
15 know, many ECD donors are also just over 50 years of
16 age, so this basically shows that there's fairly
17 comparable outcomes between DCD and non-DCD/DBD
18 kidneys.

19 Interestingly, there's a bit of a conundrum,
20 because DCD kidneys have more DGF. The increased
21 incidence of DGF, however, does not appear to translate
22 the worse overall graft survival. DCD kidneys appear

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1 to "tolerate" DGF better than DBD kidneys. There's a
2 decrease in the risk of graft loss for those kidneys
3 that experience DGF.

4 So this is really part of the DCD conundrum,
5 and it leads people to raise the question as to whether
6 the DGF that occurs with DBD kidneys is fundamentally
7 different than that with DCD kidneys. DCD kidneys may
8 be more of a pure ischemic injury; whereas the DBD
9 kidneys, we know that brain death sets off a whole
10 cascade of reactions, and so I think that this is a
11 very interesting question that bears some thought, that
12 ischemia reperfusion injury occurring in different
13 settings may actually have different overall long-term
14 impact.

15 I think that if you look at DCD kidneys in
16 isolation, this experience from the New England organ
17 bank identified that the hemodynamic profile is the
18 predictor of delayed graft function in DCD, and
19 specifically it relates to the duration of hypotension,
20 that warm ischemia time, whereas O₂ saturation, cold
21 ischemia time, time from extubation to cisile (ph) did
22 not actually correlate with DGF risk. And this is more

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1 data showing that while the duration of hypotension
2 associated with DGF here, it was not associated with
3 longer term outcomes. So again, this is a disconnect
4 between risk factor for DGF and its impact on overall
5 outcomes.

6 Finally, in DCD kidneys, biopsy findings,
7 while predictive for DGF in brain dead kidneys, they
8 were not predictive in DCD kidneys. So I think if we
9 think about DGF, we really need to perhaps separate out
10 brain death and cardiac death. Fundamentally, I think
11 cardiac death kidneys probably are again a higher
12 intrinsic donor quality sustaining ischemic injury, and
13 these differences we should really keep in mind. So to
14 conclude, I think, I've tried to highlight because the
15 factors, the donor factors are actually fairly
16 straightforward. They're all well-known to everybody
17 in the room, that there are issues related to the
18 fundamental parenchymal quality which we're not going
19 to be able to change because donors come as they are.
20 And then there's this issue of the injury that occurs,
21 which may be amenable. And I think there's that
22 connection between the quality and the injury, which is

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1 the vulnerability to the injury, and whether, how are
2 we going to figure out how to decrease the extent
3 and/or enhance the recovery from this injury, and I
4 presume that's what most of this conference is all
5 about.

6 On the donor side, I just want to put in a
7 word for my concerns about the significant ethical and
8 logistical, in addition to the scientific challenges of
9 performing intervention trials and donors, which I
10 tried to highlight for the tenth anniversary of the
11 AJT. And I hope we have some time to discuss how we
12 might be able to do donor intervention trials and how
13 that affects the recipient and in terms of informed
14 consent and just a lot of practicalities and logistics.
15 So I really look forward to the rest of this
16 conference. Thank you very much for your attention.

17 DR. VELIDEDEOGLU: Dr. Mona Doshi from Wayne
18 State University is our last speaker, and she will be
19 talking about recipient factors.

20 MS. DOSHI: Good morning. I would first like
21 to thank the organizers for inviting me to this
22 exciting workshop and hopefully collectively we can

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1 come up with some solutions for this important topic.
2 So today I'm going to be talking about recipient risk
3 factors for delayed graft function, and I have nothing
4 to disclose.

5 As Dr. Feng already alluded to, donor factors
6 or donor quality plays a very important role in
7 development of delayed graft function. So studying
8 recipient risk factors leading to delayed graft
9 function have been quite challenging. So what myself
10 and Dr. Perev Fencher (ph) undertook -- sorry about
11 that. So in order to study the recipient risk factors
12 leading to delayed graft function, we looked at pairs
13 of kidneys that came from common donor but went to
14 recipients that were discordant which had discordant
15 occurrence of delayed graft function. So we controlled
16 for donor's factors, two kidneys from each single
17 donor, one went to a recipient that had delayed graft
18 function, the other recipient did not have delayed
19 graft function, suggesting that the discordant
20 appearance of delayed graft function was because of
21 recipient factors. So we exploited this and evaluated
22 recipient risk factors that lead to delayed graft

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1 function. So this is the table for the setting. On
2 the extreme left side is the characteristics. In the
3 middle is the univariate analyses; on the extreme right
4 is the multivariate analyses. What we found is that
5 recipient age did not correlate with occurrence of
6 delayed graft function. However, male gender, African
7 American race, and increasing BMI were related to
8 occurrence of delayed graft function, both in
9 univariate and multivariate models. Also, recipients
10 having diabetes as cause of end stage kidney disease
11 and recipients with high PRA and those who did not have
12 a pre-emptive kidney transplant and with longer wait
13 times had increasing incidence of delayed graft
14 function.

15 However, of note, the PRA was not
16 statistically significantly associated with delayed
17 graft function in the univariate model, but did appear
18 significant only in the multivariate model. Moving
19 along, what about the transplant factors such as HLA
20 mismatches? Increasing number of these HLA mismatches,
21 after three, was associated with more increased
22 propensity to development of delayed graft function.

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1 However, this significance was lost, or this
2 association was lost in the multivariate model. Also
3 there was a center volume effect that is centers
4 performing lower amount of kidney transplant had
5 greater incidence of delayed graft function.

6 So to summarize our findings, what we found
7 was male gender, African American race, higher BMIs
8 greater than 30, recipient history of diabetes, higher
9 peak panel reactive antibodies more than 10, longer
10 duration of dialysis, greater frequency of HLA
11 mismatches, and low center volume were all associated
12 with the occurrence of delayed graft function.

13 What I'm going to do in the upcoming slide is
14 I'm going to take some of these factors and piece it
15 out more into detail as how they lead to delayed graft
16 function. So to begin, I'm going to start off with
17 race. What are some of the postulated mechanisms for
18 delayed graft function in African Americans? Some of
19 them are written here. African Americans are
20 proclaimed to have unique HLA leading to poor HLA
21 matching. As we know, over 70 percent of donor pool is
22 Caucasian, so of course they're not well matched with

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1 our African American recipients. African Americans are
2 also known to have hyperimmune response. We all know
3 they're also known to have more incidence of non-
4 compliance, poor socioeconomic factors. Therefore,
5 they don't take their medicines, leading to adverse
6 outcomes and prolonged duration of dialysis as my
7 earlier slide showed, that increasing duration (ph)
8 duration of dialysis leads to more increased frequency
9 of delayed graft function.

10 So Ojo, et al., in 1995, published this
11 beautiful article, trying to account for all these
12 factors. What they looked at is they looked at the
13 UNOS database, and they restricted their studies to two
14 haplotype match living donor transplants limited to
15 African Americans and Caucasian recipients. So by the
16 fact that it was two haplotype match, we got rid of the
17 unique HLA in the African Americans, the HLA matching.
18 These were first transplant recipients, first timers,
19 so hopefully did not have high PRA. They looked at the
20 outcomes only during the initial hospitalization prior
21 to this chart, so noncompliance was not a factor
22 because these patients were given medicines throughout

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1 their stay and their hospitalization. Even
2 socioeconomic factors were overcome by this method, and
3 since they were living donor transplant, the duration
4 of dialysis was pretty minimal in this cohort.

5 So let's look at the outcomes. This table
6 shows you the incidence of acute rejection rate and
7 delayed graft function in African Americans and whites.
8 What we see here is despite all these adjustments,
9 perfectly matched -- two haplotype matched renal
10 transplants from a living donor. During the initial
11 hospitalization stay, African Americans had higher
12 grade (pH) of acute rejection, 13 percent, versus 7
13 percent in Caucasian. What about delayed graft
14 function? Numerically, the African Americans tended to
15 have higher incidence of delayed graft function but
16 that difference did not read (pH) statistical
17 significance. So what this study alludes that, the
18 African Americans have a different immune response
19 maybe to ischemia reperfusion injury, or are more
20 likely to have acute rejection that may manifest as a
21 need for dialysis within the first week.

22 Moving along to the next risk factor; that is

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1 obesity. What the impact of obesity in the early post-
2 transplant outcomes? Now, obesity or increasing BMI,
3 in different studies have shown different results. I'm
4 going to show you this first one, which is from Albany
5 Med, where they looked at only 56 recipients from a
6 single center where again, they looked at paired of
7 recipients that card (ph) kidney from the same donor.
8 So they're adjusting for the donor factor where one
9 kidney went to a recipient with BMI less than 30;
10 another kidney went to patient with BMI more than 30.
11 So if you look at this, Table 1 shows you the recipient
12 characteristics, which were no different between the
13 two groups except for difference in BMI. So just the
14 BMI was the only difference between the two groups,
15 versus down here in Table 2 what we see here is the
16 incidence of delayed graft function was not different
17 between the two groups. Now, this was a small single-
18 center study, but they controlled for a lot of factors,
19 such as same donors, small immunosuppressive protocol,
20 same surgeon, same handling technique.

21 Now, on the flip side, a more recent study
22 that was just published in Kidney International which

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1 looked at SRTR database, over 50,000 patients where
2 they looked at deceased donor kidney transplant and
3 looked at effect of weight and BMI on occurrence of
4 delayed graft function. So on the extreme left is the
5 BMI in the weight; in the middle is the unadjusted
6 model and then subsequently the last three columns are
7 the adjusted models. What we see here is as the weight
8 increases by a kilogram, the odds of having delayed
9 graft function, both in univariate and multivariate
10 model increases. So with BMI, as the BMI goes up, so
11 does the risk of delayed graft function goes up, too.
12 And in the last four lines down here, they show that as
13 the BMI goes up, there's progressive increase in odds
14 ratio for development of delayed graft function. So
15 these authors or investigators here, showed a linear
16 relationship kind of between increasing BMI and the
17 occurrence of delayed graft function.

18 So what are the possible mechanisms for
19 having such findings? Maybe patients who are obese
20 have longer operative time, have longer sewing time,
21 but nobody has been able to show that definitively.
22 Maybe obese patients have higher (inaudible) activity

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1 leading to more vasoconstriction. And on top of that,
2 if they were to be dosed, CNI was dosed according to
3 the actual body weight and not ideal body weight, then
4 they would be perhaps CNI toxic, again leading to more
5 renal vasoconstriction and therefore manifesting as
6 poor allograft function early on.

7 Also, another mechanism proposed is
8 endothelial dysfunction. And this same hypothesis is
9 extrapolated to development of DVTs in obese patients
10 around the time of their surgery. So perhaps these are
11 the possible mechanisms that may explain the
12 correlation between delayed graft function and high
13 BMI.

14 What about the recipient risk factor of
15 diabetes? What about cause of diabetes mellitus as
16 cause of end stage kidney disease? Koren (ph), et al.
17 recently, maybe last year, published in AGT where they
18 looked at pairs of kidneys again, pairs of kidneys
19 coming from common donor, one kidney going to a
20 recipient who had diabetes, another kidney going to a
21 recipient who did not have diabetes. So again you're
22 controlling for donor factors and you're looking at

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1 outcomes. This table shows you the differences between
2 the baseline characteristics between the diabetic group
3 and the non-diabetic group. What we see here is the
4 diabetic group, of course, was older and were more
5 likely to be males, versus in the nondiabetic group,
6 they were younger and more likely to be sensitized and
7 have high PRA.

8 In the multivariate model for risk factors
9 for delayed graft function, defined again as need for
10 dialysis within the first week, diabetes had -- a
11 recipient history of diabetes had odds ratio of 1.675
12 for occurrence of delayed graft function. That is
13 diabetics were 67 percent more likely to develop
14 delayed graft function than nondiabetics.

15 So what I showed you so far was a
16 retrospective analysis. This is a study from Iran that
17 looked at 81 patients who came in for diseased donor
18 for kidney transplantation story, and they looked at
19 their blood sugar level before transplant on day 3, day
20 7, day 14 and day 21. The top table up here shows that
21 the patients with delayed graft function were more
22 likely to be diabetic, newly diagnosed diabetic, than

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1 those without delayed graft function. On the table in
2 the bottom down, shows that numerically the blood sugar
3 levels were much higher in the delayed graft function
4 group than those who did not develop delayed graft
5 function. Although only data on day 7 was
6 statistically significantly different between the two
7 groups, but this data suggests that patients with
8 delayed graft function were more likely to have higher
9 blood sugars.

10 What are the possible mechanisms for why
11 should diabetics have more delayed graft function?
12 Perhaps there is lower threshold for the providers to
13 dialyze diabetics, as they are more likely to have
14 cardiovascular disease, atherosclerotic heart disease.
15 Perhaps as Crystallent (ph) et al has shown, that
16 diabetics are more likely to have perioperative cardiac
17 events. As a result they may have cardiac instability,
18 which further decreases the blood flow during -- around
19 the perioperative time, leading to more delayed graft
20 function. Also, diabetics are known to have calcific
21 vessels, more atherosclerotic diseases in the iliac
22 vessels, perhaps leading to increasing sewing time,

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1 increasing warm time, leading to more ischemia. And
2 lastly, probably diabetics have a generalized pro-
3 inflammatory state, potentiating ischemic reperfusion
4 injury.

5 Now, what I'm going to allude to next paper
6 is a paper that was an experiment that was done in
7 rats. So what these investigators did is they took a
8 rat, they did the right nephrectomy. On the left
9 kidney, they clipped the renal artery for 25 minutes
10 and then released it. One group of animals were given
11 IV saline before ischemia, during ischemia and during
12 reperfusion. The second group of rats were given
13 dextrose before ischemia and during reperfusion, and
14 that's how they manifested high blood sugars during
15 ischemia reperfusion injury.

16 On the left side is the rats that received
17 saline perfusion. On the right-hand side are the rats
18 that received dextrose perfusion during ischemia
19 reperfusion injury. As you see here, that rats who
20 received dextrose were more likely to have ATN after
21 the injury than those who received saline. So blood
22 sugars around the time of ischemia reperfusion play an

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1 important role as to how the kidney is going to
2 manifest their injury.

3 Moving along, what about dialysis modality?

4 So this paper and this group, the investigators looked
5 again at UNOS database and compared the modality PD
6 versus hemo in occurrence of patients who had any
7 urine output during the first 24 hours, those who
8 required dialysis. As expected, hemodialysis patients
9 were more likely to require dialysis within the first
10 week after transplant, and they did not make any urine
11 within the first 24 hours after transplant in the first
12 two rows. However, the incidence of acute rejection
13 rate and primary non-function were no different between
14 the two groups.

15 So what are the possible mechanisms that
16 patients with hemodialysis are more likely to develop
17 DGF? One could speculate that patients with peritoneal
18 dialysis are more likely to have residual kidney
19 output, and therefore maybe they don't need dialysis.
20 Maybe volume -- they don't run into problems with
21 volume. They also generally -- they are generally
22 hypokalemic and therefore don't run into problems with

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1 hypokalemia. So to dissect this further, the same
2 group of investigators looked at patients who were on
3 dialysis for more than two years and prior studies have
4 shown that by two years being on dialysis, even the PD
5 patients, are more likely to lose their native kidney
6 function. So even after looking at a cohort that had
7 been on dialysis for more than two years, they found
8 that patients who were on hemodialysis were more likely
9 to develop DGF than those who were on peritoneal
10 dialysis, suggesting that only residual kidney function
11 does not play a role in occurrence of delayed graft
12 function. And there is something about different
13 immune response, depending on the modality type, and
14 this is just speculation -- there's no evidence about
15 this.

16 Lastly, what about duration of dialysis as an
17 indication for, or as a risk factor for occurrence of
18 delayed graft function? Now, Dakin (ph) et al., looked
19 at UNOS database and looked at the duration of
20 dialysis. On the extreme left is no dialysis and then
21 progressively as each year of dialysis goes by from one
22 year to more than 72 months or more than six years.

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1 And these solid bars are the need for dialysis within
2 first week of transplant, and in the open bars are the
3 failure for drop in serum creatinine by 25 percent
4 within the first post-operative date; that is if you
5 would say slow graft function.

6 What we see here is as the duration of
7 dialysis increases, the occurrence of delayed graft
8 function and slow graft function increased with time.
9 However, there was a plateauing effect. After three to
10 four years, there was not much differences between the
11 incidences between occurrence of delayed graft function
12 and slow graft function based on duration of dialysis.
13 So what are the possible mechanisms that explain these
14 differences? Again, maybe after two, three years as
15 the patients lose their native kidney function perhaps
16 the correlation between duration of dialysis and DGF
17 fades away. It's unclear whether the uremia per se is
18 a friend or a foe. There are some studies that suggest
19 that when patients who had any residual kidney
20 function, they are less likely to have delayed graft
21 function and have more reparative processes in action,
22 versus those who have lost native kidney function are

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1 more likely to manifest delayed graft function.

2 Lastly, we cannot tease out the association between
3 increased duration of dialysis and other risk factors,
4 such as African Americans, more HLA mismatching, high
5 PRA. As we know more sensitized patients are more
6 likely to wait longer for a kidney transplant.

7 Lastly, another thing I wanted to bring up is
8 the volume status of the patient when we call in for
9 transplant. This study looked at a hundred patients
10 and measured their CVP, and the amount of fluid that
11 the recipient received during this kidney
12 transplantation. What they found is right after the
13 transplant that if the CVP was less than 8, if they
14 received less than two liters of fluid during the
15 surgery, they were more likely to develop delayed graft
16 function.

17 So I would like to summarize as follows.
18 Recipient risk factors leading to DGF, some of them are
19 truly pathogenic, such as diabetics getting more
20 delayed graft function, African Americans having more
21 delayed graft function. Whereas there are some that
22 may not truly be pathogenic, such as hemodialysis,

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1 maybe prolonged wait time. On the other hand, there
2 are some other processes that may not even reflect
3 ischemia reperfusion injury but still lead to need for
4 dialysis within the first week, such as recurring
5 disease such as FSGS or acute rejection.

6 And lastly, there are some factors which we
7 have no idea how they play a role in ischemia
8 reperfusion injury such as warm time, size mismatch,
9 and it is hard to tease out which factor plays how much
10 of a role. Also, I want to bring home two more points
11 before I leave. Changing paradigm of recipient risk
12 factors and Dr. Feng already alluded to that when she
13 talked about the prediction model for DGF. Early on, a
14 decade ago, peak PRA, HLA mismatches, repeat
15 transplant, had a greater impact on occurrence of
16 delayed graft function. However, over time, as we have
17 better immunosuppressive agents, antibodies for
18 induction, better assays to detect antibody, HLA
19 antibodies, these players are no longer as important as
20 they used to be a decade ago. However, now, terminal
21 donor creatinine, donor quality, et cetera, are playing
22 a bigger role in occurrence of delayed graft function.

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1 And thank you very much.

2 DR. VELIDEDEOGLU: We thank all the speakers
3 for very nice presentations. Unfortunately, we are
4 running out of time and we have very little time left
5 for the Q&A section and probably we won't have time to
6 discuss all the questions. So I will try to summarize
7 and reshape the first question to include a little bit
8 of the second and third questions, and the discussion
9 obviously will be carried on in the upcoming sessions,
10 so every session is tied to each other.

11 First I want to direct my question to Dr.
12 Hamid Rabb, and I will let Dr. Lu to comment on that if
13 he wants to add a few things more to that. You want to
14 say something?

15 DR. RABB: Thank you. Regarding Dr. Lu's
16 presentation and Dr. Lobo's, and I think directly
17 related to the theme of the meeting in terms of future
18 therapies for DGF/IRI, and tomorrow's topic,
19 limitations of animal models over strengths, I feel
20 compelled to address the slide that Dr. Lobo showed.

21 So in 2003 we published a paper that showed
22 in the Journal of Immunology that B cells are playing a

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1 role in ischemic injury using the mu MT models, and
2 then subsequently Thurman (ph), et al. could not
3 reproduce that. And it is very difficult at times from
4 lab to lab to sometimes reproduce these complex models,
5 but I can tell you, when we did that experiment I had
6 three different people doing that, because I couldn't
7 believe it myself. And what we found is in a mu MT,
8 when we put back in a soluble product, we took normal
9 serum from mice that had B cells we could change the
10 outcome to, but when we put in B cells we could not,
11 but we did the serum.

12 Now, more recently, we ordered the same mice
13 from the same supplier, and I tried to do those same
14 studies though with a different postdoc, and we had
15 some funny results. And this is from the same lab.
16 What we did find, very surprisingly, was that the B
17 cells were having a little bit of effect in early
18 injury, but they were having an effect on repair. And
19 we started to look at that more. And we found -- and
20 this was published in Journal of American Study of
21 Nephrology last year -- Jang (ph) is the first author -
22 - that the B cells were actually limiting repair. So

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1 what we're finding from some of these experimental
2 models, though they're somewhat difficult to fully
3 interpret, is that the immune system, the lymphocytes
4 and the B cells, are playing a role. It's very
5 important what stage you're looking at early in injury,
6 maybe a little bit later or during repair. And
7 sometimes it could be subsets of these immune cells are
8 playing different roles in different times, which make
9 it more difficult to tease out. But I think this opens
10 up the possibility for lymphocyte-mediated
11 therapeutics, either in early injury or I think more
12 practically, in repair.

13 DR. VELIDEDEOGLU: Thank you for your
14 clarification. So I want to come back to the question.
15 Now, first I want to make a point. Even without the
16 long-term consequences, probably DGF is an undesirable
17 occurrence. We have listened to the speakers and then
18 in certain donor recipient combinations, they have
19 clearly stated that there may not be too many long-term
20 consequences in terms of graft and patient survival and
21 graft function despite the occurrence of DGF. But just
22 by and of itself, DGF is probably an unpleasant

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1 occurrence. It has a certain level of morbidity
2 associated with it, and it's a period of uncertainty
3 and apprehension, and that's also up for discussion.

4 And after stating this, and coming back to
5 the pathophysiology and the mechanisms involved in the
6 occurrence of DGF, I would like to ask, what are
7 possible points of intervention? Probably we have
8 dozens or even more of them, but without going into too
9 much detail, and in which certain donor recipient
10 combinations or which donor populations such as
11 expanded criteria donors, we have room for improvement,
12 and how can we intervene and what are possible points
13 of intervention in the light of the pathophysiology
14 that has just been discussed? And I don't know if Dr.
15 Lu has anything to add to this before directing my
16 question to Dr. Rabb first?

17 DR. LU: I think that this is a -- that's a
18 huge question -- Dr. Rabb, Dr. Bobentry (ph) and a
19 number -- Dr. Lobo and a number of us are working in
20 this area. I think one of the things to keep in mind
21 is that you can -- I think all of us are addressing the
22 issue of how injuries translate into inflammation, and

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1 then what are the results of the inflammation. So you
2 can say in about 20 words what the question is. The
3 problem is that the nature of the inflammatory response
4 is incredibly complex and sophisticated, and there are
5 number of players. The B cells, and T cells, maybe
6 various things at various points in time. So I think
7 one of the key things here is to try to understand the
8 processes better through fundamental research in the
9 hope of identifying pathways which are important in
10 mice and that are also important in our patients and
11 then try to dissect out which of these are going to be
12 appropriate targets for therapy. I guess I said
13 nothing in a lot of words. Maybe Hamid can do better
14 job than I can.

15 DR. RABB: I totally agree with Chris. I
16 would like to make a comment. Particularly, I think
17 it's appropriate for this audience, that those of us
18 who are pathophysiologists can find our molecule or
19 pathway of interest, but I think for clinical
20 therapeutics, just as we're not going to give
21 Prednisone alone or CellCept alone, I think for
22 therapeutics towards DGF and ischemia we need

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1 cocktails. We need combinations. And somehow we'll
2 have to -- between industry and academia or federal
3 government, we have to find a way that we can -- if
4 we're really going to help the patient to bring in
5 targeting; let's say for example that Dr. Lu mentioned,
6 something targeting free radicals, maybe something on
7 another inflammatory pathway, something on apoptosis,
8 and we're going to have to put them together. And I
9 would give it back to the feds and to industry to say
10 how can we do this in a way that will benefit
11 everybody, but particularly the patient, rather than
12 one pathway or one key process.

13 DR. VELIDEDEOGLU: Thank you. Anybody else
14 who wants to comment on this? Dr. Halloran?

15 DR. HALLORAN: I really wonder whether
16 inflammation is injurious -- I don't use the word
17 maladaptive; that's really a term from evolutionary
18 biology but injurious. If you had a wound at time
19 zero, it looks perfectly clean. By day six hours it
20 starts to get inflamed; it peaks around day five. It
21 resolves. The inflammation is really part of healing.
22 You can manipulate that in animals, but it's very

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1 difficult to make it any better, especially by
2 manipulating the inflammatory signal in wound healing.

3 I really think that this inflammation that we
4 see makes the organ look worse, makes the wound look
5 worse, but it's actually part of a beneficial effect of
6 the overall wound healing response.

7 DR. LU: Maybe I can carry on that
8 conversation a little further. I think one of the ways
9 that the question has been posed is we discover
10 pathways which are shared by the response to pathogens,
11 so by response to the PAMPs, the pathogen activated
12 molecular patterns. And they're shared in the
13 inflammatory response to injury. But as you say,
14 common sense says, these responses are different; they
15 have a different outcome. I mean there's a very
16 aggressive response which limits a pathogen, but the
17 inflammation response to injury is very limited, and it
18 actually culminates in wound repair if everything goes
19 well.

20 So I think one of the challenges that we have
21 is to understand the complexity and the sophistication
22 which the -- what one might call the innate immune

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1 system brings to the stimuli. On the one hand you have
2 a set of responses which is very aggressive and
3 eliminates pathogen and some collateral damage is
4 acceptable, because you have to eliminate the pathogen.
5 On the other hand, one has an inflammatory response
6 which is actually minimal. I mean I was taught that
7 acute kidney injury didn't have an inflammatory
8 response, and in truth, in order to look for it, you
9 have to look very hard. And the culmination of that
10 response is different. As you said, inflammation is
11 very important for repair.

12 So the question is how does one take these
13 same molecules, these same ligands and receptors and
14 ultimately get a different response? And I think this
15 is the kind of challenge that we have. I mean I agree
16 with you that wound repair, if everything goes well, is
17 the ultimate culmination of the response to injury, and
18 how can similar pathways but clearly quite arrive at
19 very different responses, and I think that's one of the
20 biggest things to understand.

21 DR. ABECASSIS: I'm going to politely
22 disagree with Bill. Wounds result in scars. That's

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1 what we're dealing with. It's not exactly what we want
2 in a kidney, I don't think. I'm a surgeon; I like
3 scars, because they mean that what I cut open is healed
4 up, but I wouldn't call a scar a good thing. So I
5 think that to say these are not maladaptive is to be a
6 little bit naive.

7 So I'm going to disagree with the fact that
8 all these responses, whether they be adaptive or innate
9 or inflammatory or whatever they are, are a good thing
10 in the kidney. The best thing in the kidney is, A, not
11 to have the stimulus to have a response; i.e. the
12 injury, and B, not to have a response, because you
13 didn't have the injury in the first place. And that's
14 what a normal kidney is that hasn't gone through the
15 injury. So I understand this holistic view, but I
16 think we need to really get down to, how do we do a
17 transplant and not have that injury or minimize or
18 mitigate that injury so that we minimize a response to
19 it, instead of saying, well response is good because
20 it's part of healing. Healing in a wound which you've
21 chosen to use as an example, is a big ugly scar, and
22 that's not what we want, so I'm just applying to

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1 disagree.

2 MR. PHILIP HALLORN: Does anyone in the room
3 think that wounding is good? So if you can prevent
4 wounding, that would be great. I agree with you. But
5 once you're wounded, you want it to heal. And that's
6 really what we're talking about, and inflammation is
7 intimately related to wound healing.

8 MR. BOVENTRE: Just to follow up on that a
9 little bit, so what we're basically saying is that what
10 determines the healing process as an adaptive one
11 versus a maladaptive one. In fact, that's I think one
12 of the key elements I'll touch on that potentially
13 tomorrow a bit.

14 The other thing I would mention is that -- I
15 think Chris you mentioned the importance of the
16 endothelium, and I think it clearly is coupled however,
17 to something that you didn't have time to get into, and
18 that is the anatomy of the kidney, which is really part
19 of this whole story, I think. Because the vascular
20 supply in the outer medulla -- and I'll also show a
21 picture of this tomorrow -- is very susceptible in ways
22 that I think has been significantly underappreciated,

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1 very susceptible to things like a little bit of tissue
2 edema, which we all sort of think about as part of the
3 inflammatory response, but I don't think we give enough
4 credence to it as really a fundamental part of the
5 pathophysiology, which can get markedly affected by our
6 therapeutic approaches, because we have trouble
7 measuring that or looking at it.

8 And in that context, one of the additional
9 components that's becoming appreciated more and more,
10 is what role the glycocalyx plays in the endothelium,
11 because now we realize that that's an element of the
12 endothelium that we haven't been able to see because of
13 our fixation approaches. And as we look more and more
14 to that, I think the glycolipids and components of the
15 glycocalyx might also be an interesting target for
16 therapeutics in terms of protecting the endothelium.

17 DR. ALBRECHT: Ergun, you had Patrick and
18 Marc -- I'm sorry, Patrick Archdeacon and Marc Lorber
19 wanted to make some comments?

20 DR. ARCHDEACON: Actually, I just wanted to
21 ask a different question, or redirect a question. I
22 was real interested in Dr. Feng's presentation when you

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1 talked about sort of the disparate outcomes with DCD
2 patients who experienced DGF compared to other patients
3 who experienced DGF. And I think in some of these
4 questions we're getting the idea of, if we know that
5 there are patient populations who experienced DGF at
6 higher rates, that might suggest the possibility of
7 enrichment designs. But the issue that you raised sort
8 of suggests that perhaps this is the more heterogeneous
9 disease process than a homogeneous disease process.

10 And so I just was hoping maybe the group
11 could sort of talk to how we can leverage this
12 information we've heard about donor factors with
13 regards to the pros and cons about different approaches
14 to enrichment designs.

15 MS. FENG: I'll just add one comment to that,
16 and I think that - there are some apples and oranges in
17 the basket, but they're also fruits of different sizes.
18 And I think that there's some inherent limitations if
19 you're studying very old kidneys, because of their
20 incredible vulnerability to injury and therefore the
21 severity. And I think when we look at agents to try to
22 intervene in the DGF process, it would be naive to

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1 think that these agents would attenuate entire range of
2 injury. Perhaps it would be effective in the milder
3 injury zones and less effective in the more severe
4 injury zones, and that that inherent donor kidney
5 quality can place a lot of limitations as to what can
6 be accomplished.

7 So I do think that when designing trials, we
8 need to -- there are going to be a lot of
9 stratification issues unless we do create a more
10 homogeneous sort of population. And it may actually be
11 easier to affect the ischemic injury versus that
12 vulnerability to the ischemic injury because of an
13 intrinsic quality issued, but perhaps that can be
14 teased out more in the animal models.

15 DR. VELIDEDEOGLU: Thank you. Dr., Lorber,
16 you've been waiting for some time.

17 DR. LORBER: Just a brief comment, that may
18 also be something that we can think about as we go
19 through the next day and a half. And that's, I'm
20 hearing -- it hasn't been said, but I'm hearing a
21 proposal that maybe what one might want to do is stop
22 inflammation or reduce inflammation as a consequence,

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1 or to address the IRI or the DGF issues. And if that's
2 the case, I guess I'd be interested in thoughts around
3 what might be the consequences of how one might address
4 those consequences. And again, we can have a little
5 bit of a discussion now but I think this is something
6 that it might be nice to think through as the rest of
7 the presentations come through over the next day and a
8 half.

9 DR. WOODLE: Yeah, just one point of
10 clarification. By enrichment do you mean an apriori
11 selection in terms of inclusion, exclusion criteria, or
12 do you mean in the context of an adaptive trial zone?

13 DR. ARCHDEACON: Yes, I was actually really
14 thinking particularly about inclusion exclusion
15 criteria, so that if -- I think in previous trials that
16 have attempted to look at DGF there's been a concern
17 that maybe you didn't get as many DGF patients as you'd
18 want. And so perhaps -- and if some other trial going
19 forward, people might try to recruit patient
20 populations that they thought would have very high
21 rates of DGF. And certainly, prior to hearing these
22 talks I would have thought DCD might be an interesting

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1 place to look, and now I sort of have a concern about
2 that. And we've heard about other groups, so males,
3 African Americans, diabetics, people with high body
4 mass index, and you start to wonder, well would it be a
5 good or a bad idea to try to recruit patients who have
6 these risk factors?

7 DR. ARCHDEACON: So I think when you're --
8 this is to me when you look at -- let's say for example
9 when we had an AMR meeting, we were dealing largely
10 with the recipient issue. The difference between --
11 when I see about these types of studies is the thing
12 that you need, because you've got the factor of the
13 donor kidney. And that adds a layer of heterogeneity,
14 on top of the recipient heterogeneity that makes this
15 particular issue very complex. And we have a new agent
16 and you're starting to go into clinical trials. I
17 think this is an ideal situation for enrichment via
18 adaptive trial design.

19 The simple example is if you take a DCD, the
20 lesion there is warm ischemia but no brain death. When
21 you take an ECD, it's brain death plus underlying
22 chronic changes in the kidney. When you have a

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1 standard criteria donor it's an underlying normal
2 kidney, and the lesion may impose as a cold ischemia
3 time lesion with long storage times. And so I think
4 that being able to sort out the populations in which
5 your drug has an effect via enrichment and adaptive
6 trial design is something that's very conducive to
7 sponsor.

8 DR. VELIDEDEOGLU: I think Dr. Lu has a
9 comment.

10 DR. LU: I just wanted to make one comment.
11 I think what Dr. -- maybe if I could restate what Dr.
12 Halloran, Bonventre, and Bob and I are saying is
13 that there may be a good and a bad result from
14 inflammation. And I think from a therapeutic's point
15 of view one needs to be very careful, because if one
16 gives the therapy which eliminates the bad, one might
17 end up also preventing the good; that is to say some of
18 the healing that occurs after the therapeutic is given.

19 MR. DOUGLAS HANTO: I was going to respond to
20 the point that Patrick made and maybe the point that
21 Sandy made. I'll show the data tomorrow, but the best
22 data does show if you want to enrich -- for example, if

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1 you want to study some intervention that's going to
2 reduce DGF, I mean the data shows pretty clearly that
3 the incidence of DGF progressively increases when you
4 go from SCD to ECD to DCD and then to DCD, ECD going
5 from 20 percent to over 50 percent on the SRTR data.
6 And the effect on long-term graft function is similar.
7 It varies by group, so if you want to study a group
8 that has the highest impact of DGF on graft function,
9 it turns out that it's the DCD group, and so I think
10 that if you are interested in simple endpoint of DGF
11 and graft survival, there certainly are groups that you
12 would want to accentuate, and we'll talk a little bit
13 about this carbon monoxide tomorrow.

14 Some of these interventions become a problem
15 in the DCD if you want to treat a donor, because
16 they're not dead and so you've got all kinds of issues
17 regarding consent and IRB and et cetera.

18 DR. VELIDEDEOGLU: Dr. Lobo?

19 DR. LOBO: One quick comment. One small loop
20 is ischemic reperfusion injury and a big role of
21 inflammation. I'm wondering if that might apply to
22 delayed renal function, especially when you're using

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1 optimal donors. Before this presentation I tried to
2 look and find out if anyone had done an investigation
3 on human kidneys, human and animal kidneys after
4 transplantation, to look at whether inflammation plays
5 a big role and four hours during transplantation rather
6 there are a lot of inflammation in the kidney. At
7 least I could not find it. I was wondering if that is
8 indeed the case.

9 And the second thing is that I guess the cold
10 temperature also has a role to play when warm blood
11 goes into a cold kidney. And before we contemplate on
12 trials, I think, which is important for us to better
13 understand what we're dealing with delayed renal
14 function.

15 DR. VELIDEDEOGLU: I think Dr. Rabb wants to
16 answer this question, and then afterwards I believe we
17 need to stop in the interest of time; we are running
18 behind schedule. Dr. Rabb, please?

19 DR. RABB: From my understanding, one of the
20 first descriptions in the human kidney in terms of
21 ischemic injury and inflammation, inflammatory cells,
22 was Kim Soles, who identified mononuclear cells.

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1 But the level of cellular inflammation as you
2 have demonstrated in your studies and as we all know,
3 and Dr. Racusen and others can attest, is in ATN or
4 ischemic injury, is minimal. So one is not going to,
5 as you know, see the robust changes like the cellular
6 rejection. So my understanding is that there's a
7 disconnection between seeing cells in the kidney in ATN
8 and having a pathophysiological and injury and repair,
9 which has impeded or delayed discovery of many things
10 in the field.

11 So I think it's a little bit more -- we
12 should think of it a little bit more like AMR. I mean,
13 you don't see many B cells during an AMR infiltrating
14 in the kidney, but we know they're vital. So I think
15 the histology is crucial; as you say, better
16 understanding, but I would be very careful about either
17 in terms of studies, in terms of diagnosis and
18 therapeutic outcomes to quantify the number of
19 inflammatory cells in IRI. I think it's a very
20 different disease in that connection between, let's
21 say, acute cellular rejection.

22 DR. LOBO: I was looking at somebody's paper,

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1 and most of the studies were done after seven days, but
2 the delayed function we see four hours like animal
3 model, no one has really done, looked for leukocytes in
4 the first four hours.

5 DR. VELIDEDEOGLU: Thank you for all the
6 comments. I think we will have a short break, and I
7 suggest we start our meeting at 11:25 to start the next
8 session. Thank you.

9 (Whereupon, a recess was had.)

10 Session 2: Downstream Measured of Response to IRI in
11 Kidney Transplantation

12 DR. ALBRECHT: If everyone could take their
13 seats again so we can start with the next session. So
14 as soon as everyone is able to take their seats in
15 anticipation of the next session, we'll ask that some
16 of the panel members who've been able to join us since
17 the morning introduction session introduce themselves.
18 So as soon as we're able to get everyone seated, I will
19 ask that Dr. Neuland from DCRH and then Dr. Parikh
20 introduce themselves, state their positions and any
21 conflicts.

22 DR. NEULAND: Good morning. My name is

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1 Carolyn Neuland. I am the Chief of the
2 Gastroenterology and Renal Devices Branch in the Center
3 of Devices and Radiological Health, and we're the part
4 of the FDA that regulate medical devices. As an FDA
5 employee I have no conflicts to report.

6 DR. PARIKH: Good morning. I'm Chirag Parikh
7 from Yale School of Medicine. I'm director of the
8 Transitional Research Program for the Department of
9 Medicine and my interest is kidney injury biomarkers.

10 DR. ARCHDEACON: Great. Dr. Parikh, I think
11 you might as well turn your microphone on when you're
12 ready to give your talk.

13 DR. PARIKH: Okay.

14 DR. ARCHDEACON: I'll give just a very brief
15 introduction. So we're very excited about this next
16 section. We'll be talking about different tools that
17 we have or that we're trying to develop, and of
18 measure, ischemia reperfusion injury. In terms of the
19 structure of this next session, we're very interested
20 in the question-and-answer session afterwards, so we're
21 going to ask that our speakers stick strictly to the
22 time limits given. And in keeping with that, I'll just

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1 go ahead and move forward. Great. So Dr. Parikh?

2 DR. PARIKH: Okay. That given to me is
3 utility of biomarkers for earlier identification of
4 ischemia and infusion injury and correlation of long-
5 term outcomes. There is paramount literature about
6 kidney and biomarkers in native kidneys, but there is
7 enough evidence that has accumulated over the time in
8 the transplant setting. And I am going to focus my
9 talk mainly with the transplant literature. Disclosing
10 of the (inaudible) event around eyelet pattern which is
11 one of the diagnostics for acute injury, (inaudible),
12 and I have several (inaudible) biomarkers discovered in
13 validation.

14 Ischemia reperfusion injury plays a central
15 role in short-term and long-term graft prognosis.
16 Diagnosis of ischemia reperfusion injury by traditional
17 parameters of serum creatinine, and urine output is
18 inadequate and there are significant efforts for early
19 biomarker discovery and development in the transplant
20 setting. And this is the out turn of my talk but this
21 is also the theme that will emerge at the end of my
22 presentation.

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1 So the differential diagnosis for delayed
2 graft function are several, but the main key cause in
3 the modern transplant at setting are ischemia
4 reperfusion injury. And there's always been a debate
5 where the (inaudible) matters or injury matters in the
6 setting of kidney transplantation is the advent of new
7 immune suppressives. I think the tackling injury has
8 become a major problem. But the concept that injury
9 matters was -- came out in this paper in 1995 from
10 Terasaki (phonetic) that it showed that the spousal
11 donors who have ALMS match but do not have kidney
12 injury because of no cold ischemia do much better than
13 six antigen matched kidneys. At the same time, the six
14 antigen matched kidneys which make urine do better than
15 the six antigen matched kidneys that do not make urine
16 on the first day after transplant. And if we just
17 think about this concept it shows the immense
18 importance of injury in the setting of long-term
19 outcomes.

20 So this leads to the injury hypothesis that
21 we have been working on from the human patient-oriented
22 (inaudible) point of view. Ischemia reperfusion injury

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1 leads to adaptive immune response which can lead to
2 acute rejection and chronic (inaudible) property but
3 that is not an intervention that happens in this party.
4 But the bigger problem which is unfactored is ischemia
5 reperfusion injury can lead to incompletely cover your
6 maladaptive repair which leads to graft failure.

7 And when does kidney injury occur in
8 transplantation and there are at least five artificial
9 stages that we have broken down in the setting of
10 kidney transplantation where intervention trials need
11 to happen as Sandy was telling on where potential
12 agents can be done, so it's at the time of bridement
13 during organ procurement, during transfer, during
14 reperfusion when the kidney is sown back, and following
15 transplantation the way the (inaudible) treats this
16 kidney.

17 And the importance of injury to kidney
18 transplantation is very long over time there is 40
19 percent increase risk of graft loss, if you get DGF,
20 there is long hospital stay, increase of rejection and
21 graft fibrosis. However, the Achilles' heel of the
22 whole process is we cannot measure injury well, and

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1 this has lead to identification and discovery of better
2 tools for capturing or quantifying the amount of injury
3 that is happening during inflammation.

4 So when we started this in the kidney
5 transplantation we wanted to see what people have been
6 done in the literature and we did a systematic review
7 of biomarker studies in kidney transplantation. If you
8 use the term DGF ATN in transplanted kidney or ischemia
9 reperfusion, we found 47 unit studies and 93 separate
10 biomarkers that have been proposed in the setting of
11 transplantation where people have done some work. And
12 this is the laundry list. The slide is not there.
13 I'd be happy to pass it along. And people have
14 identified markers in blood serum and plasma, in urine,
15 gene expression or immuno-chemistry. I think the most
16 promising ones are the urine biomarkers which is IL-18,
17 NGAL in Kidney injury molecule where a significant
18 model of epidemiologic work and these biomarkers show
19 promise in kidney transplantation.

20 So why do we have 93 biomarkers but very few
21 that are for clinical use? And the reason for this is
22 the biomarker to be successfully available for clinical

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1 transplant has to go through the phases of validation.
2 And there are five phases: Phase 1, which is promising
3 directions identified; Phase 2 is the phase of
4 translation; Phase 3, where you start doing lab
5 studies; and Phase 4, population studies. And for
6 these three urine biomarkers I am going to tell you the
7 studies based on the phases. So the Phase 1 and 2
8 studies for kidney biomarkers. This is the immunized
9 chemistry staining of NGAL in the transplanted kidneys
10 and the top is the positive control, the top right is a
11 negative control. But if you take several kidneys
12 immediately cover the DGF, you can see intense staining
13 for NGAL which is strong staining on the left side, the
14 weak staining on the right side. And same thing with
15 IL-18. You see strong staining and weak staining in
16 various biopsies when you compare it with positive
17 controls. All of these biomarkers have very good
18 animals studies which show that these biomarkers are
19 mediators of ischemic reperfusion injury but when we
20 saw the staining in the level of human tissue, we were
21 very happy that there is a possibility that these can
22 be used as biomarkers. Similarly there are the studies

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1 on KIM-1 where the biopsies -- where it is present in
2 kidney biopsy.

3 Following that, we embarked on to the Phase 2
4 study, and this was now several years ago, where we
5 tried to see if IL-18 can be captured and measured in
6 the urine and can be used as a novel biomarker of
7 delayed graft functions. And, again, this was the
8 proof of concept study where the grafts to the
9 biodiagram to the left -- or the box score to the left
10 is the living donor where there is very little injury.
11 The middle box is the deceased kidney with problem
12 graft function and the highest level, where in a
13 deceased kidney with delayed graft function once again
14 giving a proof of concept that injury can be captured
15 in the urine with various -- in a dose response fashion
16 in kidney transplantation.

17 Similarly, couple of tiers following that, we
18 saw similar phenomenon with NGAL where we saw those
19 response with increased injury in the setting of kidney
20 transplantation. And this is a study on KIM-1 where
21 they demonstrated that in patients who bring that --
22 the levels of KIM-1 were much higher compared to

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1 patients who are living kidney donation.

2 So since the Phase 2 studies were promising,
3 we moved on to the Phase 3 studies, and the goal of the
4 Phase 3 studies to see if biomarker detects disease
5 early before it becomes clinically obvious and to
6 determine the performance of the biomarker in large
7 patient cohorts. So this was published last year in
8 JASN. It was a prospective translation of multi-
9 center observation of cohort study of adult patients
10 undergoing nonpreemptive deceased donor kidney
11 transplant.

12 DGF was defined as dialysis at least once
13 within one week of transplant. Slow graft function
14 with serum creatinine introduction issue of less than
15 70 percent. And immediate graft function of serum
16 creatinines reduction ratio of better than 70 percent
17 in non-DGF patients.

18 We collected CDL urine samples every six
19 hours for the first 24 hours and then on post-operative
20 they went into -- they were processed and stored at
21 minus 80 and blinded samples were analyzed for NGAL,
22 IL-18 and KIM-1 and for (inaudible) by iso-

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1 nepholometry and prospective data and events confirmed
2 with chart review.

3 So we enrolled 92 patients over the 18
4 months. We had to explode one for graft failure due to
5 epidemiologic occlusion, but we got a good distribution
6 of events: 34 are DGF, 33 are slow graft function, and
7 24 are the immediate graft function. And these are the
8 results for delayed graft function. I just make one --
9 one thing we learned is the indications of dialysis
10 change from setting to setting and surgeon to surgeon
11 so a difficult outcome for clinical trials if you're
12 trying to use that.

13 So these are the biomarker results for NGAL.
14 We see a nice separation of the three codes. The black
15 line is the delayed graft function; the red line is the
16 slow graft function and the dotted line is immediate
17 graft function over time. Same thing with urine IL-18.
18 The patients who have delayed graft function have much
19 higher levels than slow graft function and immediate
20 graft function. And in urine KIM-1, we were surprised
21 to see that the levels, the three types of graft
22 function did not separate out with KIM-1. The levels

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1 were very high as we have seen with histology in all
2 the three groups of patients irrespective of the graft
3 function.

4 If you look at the performance of the
5 biomarker for predicting DGF on the first post-
6 operative day, so I after the surgery, next morning
7 when the surgeon comes back around can he predict the
8 first week of graft function. We see that NGAL and IL-
9 18 have 82 percent of accuracy compared to absolute
10 change in creatinine, relative change in creatinine,
11 KIM-1 start to see which are around .5 to .7. So once
12 again, two out of three biomarkers giving us good
13 information in the short-term setting. If we do the
14 traditional statistics and determine the odds at issue
15 for predicting kidney graft function, we see that the
16 urine output and serum creatinine were not significant,
17 but first post-operative they often in NGAL and IL-18
18 had five-fold and 6.8-fold odds are adjusted odds
19 initially respectively for predicting delayed graft
20 function.

21 We followed this cohort for three months and
22 tried to see if we can predict the biomarkers at the

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1 time of transplantation can predict three-month graft
2 function, and we were delighted to see that third times
3 of NGAL and IL-18 were predict -- showed again that
4 those response patterned with graft function by DGF
5 found all serum creatinine demonstrating that this
6 injury biomarkers predicting terminal graft function of
7 -- the graft function at three months.

8 Around the same time, another study came out
9 from Mt. Sinai where they demonstrated that due to the
10 expression of KIM-1 does not predict DGF, and they
11 quantified staining of KIM-1 on various biopsies, and
12 we looked at KIM-1 score, but when unblinding was done,
13 the biopsy staining and the graft function were not
14 significant demonstrating that urine biomarker studies
15 and histology are showing similar results in terms of
16 (inaudible) expression and not good separation with
17 graft function.

18 So whenever I presented the results to my
19 surgeons they said, oh, this is nothing, I can look at
20 the patient and look at the urine output and say who
21 will have delayed graft function. So we have taken
22 these studies forward and followed the patients for the

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1 one year, and this is -- this data is their review and
2 hopefully will come out soon.

3 So we -- the well done cohort we continued
4 enrollment and we had 177 patients out of which we were
5 to exclude some for preemptive transplants and primary
6 nonfunction, but the final cohort is 153. So the
7 primary outcome now we are trying to associate the
8 biomarkers to graft function at one year, and we have
9 decide -- the findings of the composite of return to
10 dialysis or GFR is at 30 ml per minute. And eventually
11 it was 24 of the 153, so 16 percent of patients had
12 very poor graft function in this cohort.

13 And I think this is the key slide, which
14 tells us the relationship between biomarkers, shortened
15 graft function which is -- let's see if my add-on can
16 come up -- so this is every transplant kidney injury
17 where we are using biomarkers as a surrogate tool.
18 This leads to delayed graft function, and delayed graft
19 function is related to poor one-year allograft
20 function. We have hypothesized that there's a lot of
21 injury which happens outside DGF which can be captured
22 to biomarkers which will predict poor one-year

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1 allograft function and this way we can show that
2 biomarkers are mediators of one-year allograft
3 function. And then there are other factors which we
4 have adjusted for, which is donor in the (inaudible),
5 cold ischemia time and HLA match. So I demonstrated
6 all the results which are different adults.

7 So urine injury biomarkers in the first
8 postoperative date corresponding with occurrence for
9 composite outcome and we see that on the first post-
10 operative date if you take the biomarker values less
11 than median or greater than median you can see that the
12 patient -- the recipients with -- patients with lower
13 biomarker values had 5 percent incidence of event
14 (inaudible) as opposed to 20 percent with patients who
15 had very high injury score. This is for both NGAL and
16 IL-18.

17 We start to find the results by delayed graft
18 function and in patients with DGF we still got a
19 separation with biomarkers showing that within DGF we
20 can stratify high and low injury groups, but the most
21 exciting thing was in patients without DGF once again
22 we were to start (inaudible) the kidneys which had very

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1 low biomarker values and correspondingly had very low
2 one-year graft outcomes as opposed to patients who did
3 not have DGF but had high biomarker values.

4 If you put this in a material equation we get
5 an odds ratio of around 4 for both and NGAL and IL-18.
6 If you adjust it actually the association gets better.
7 To be total, we have made sure that the traditional
8 biomarkers do not give the same information, so we have
9 taken first post-operative serum creatinines,
10 discharge serum creatinines or discharge GFR and they
11 were not associated with this cohort with one-year
12 graft outcomes.

13 So the key limitations as far as the
14 biomarker field as studies are concerned is this is
15 observational data and there's lack of formal peri-
16 transplant, surgical or medical protocols across sites.
17 There is lack of formal indication of post-transplant
18 dialysis indication. However, I think the results are
19 consistent when we look at short-term, intermediate and
20 long-term outcomes. And therefore I would like to
21 conclude by saying that urine levels of NGAL and IL-18
22 on the first post-operative date after kidney

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1 transplant that are associated with early and late
2 allograft function, these novel biomarkers perform
3 better than traditional biomarkers, serum creatinines
4 or urine output and urine KIM-1 levels do not
5 differentiate between DGFs, SGF and IGF.

6 In terms of future directions, confirmation
7 is needed in larger independent cohorts than in other
8 transplant settings and incorporate -- I think in
9 future we have to incorporate biomarkers into clinical
10 trials which are looking to mitigating ischemia
11 reperfusion injury and improve long-term outputs after
12 transplant. This is the research team and the sites
13 who have contributed to all this (inaudible). And
14 thank you.

15 DR. LORBER: Questions? Comments? Okay.
16 The next presenter -- sorry about that -- will be Dr.
17 Lorraine Racusen from Johns Hopkins, who's going to
18 talk just a little bit about the histopathology of this
19 situation. Lorraine?

20 DR. RACUSEN: Great. Well, thank you very
21 much for the invitation. I will try and be very pithy.
22 I have way too many slides, of course. Okay. So I'm

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1 talking today about histopathologic findings in
2 ischemic reperfusion injury. I'm going to make some
3 important points I think building on some things that
4 have been discussed already and some things that are
5 discussed tomorrow.

6 Okay. No relevant. So basically there are
7 limitations in the use of rodent models in
8 extrapolating to human clinical biopsies, although
9 clearly there are strengths, particularly with genetic
10 studies and knockouts, et cetera. Primate models are
11 rare and native kidney IRI is hard to study because
12 usually these folks are not biopsied. So actually,
13 human allograft biopsies have become really the model
14 system for studying human ischemia reperfusion injury
15 and so there is some information out there.

16 And an important point that I think needs to
17 be made that has been alluded to is the fact that there
18 are different areas of vulnerability to ischemic
19 injury, and here in the pale blue we see that in the
20 medullary rays and particularly in the outer medulla,
21 and I think this is the point Joe made earlier, this is
22 where the vulnerability really lies, and the difficulty

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1 of course becomes if you're doing a subcapsular wedge
2 biopsy up here somewhere, you may not be looking at
3 where the action is either in terms of tubular injury,
4 microvascular injury or even inflammatory infiltrates.

5 So and the other point to be made is that
6 although this is often referred to as acute tubular
7 necrosis or ATN really we don't see true necrosis very
8 often. What we're looking at actually are these
9 subtler features, loss of differentiated features like
10 the apical brush border and basolateral in-foldings,
11 bleeding of the apical cytoplasm, cell swelling and
12 vacuolization, cell exfoliation and loss into the
13 lumen. And so these are the sorts of things that
14 really need to be looked at and not necessarily lethal
15 injury, per se. And so you have a state of tubular
16 unrest. The tubular cells are unhappy looking, but
17 they are clearly quite viable.

18 We may be able to appreciate accumulation of
19 some inflammatory cells here, and as we look here, we
20 can see again, tubular unrest, lack of the nice tall
21 differentiated-looking epithelium, loss of brush
22 border, and actually some regenerative changes which

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1 we'll allude to here. Here we see an exfoliated cell.
2 And here we do see some inflammation and edema. We can
3 see exfoliated cells in the lumen, and even in the
4 urine, speaking of urine biomarkers.

5 There can be lethal injury and there may be,
6 particularly if you look at the more vulnerable
7 regions, and this can take the form of either
8 coagulative necrosis or apoptosis. And here we see an
9 extreme example of coagulative necrosis in which all of
10 the tubular cross-sections are showing necrosis in this
11 area. This is a very rare phenomena, but you can see
12 even in here severe injuries, we can see some of the
13 regeneration that is already taking place and we'll
14 make the argument that it's really the regenerative
15 phase of balance of injury and repair that are
16 important.

17 We can also occasionally see apoptotic cells.
18 Here we can see these highly condensed nuclei and
19 cells, parameter shape, sort of extruding out of the
20 epithelium, but the best way to look for that of
21 course, is to look for apoptosis-associated proteins,
22 use tunnel and make end labeling, et cetera. And that

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1 has been done in the context of transplantation. For
2 example, here is actually an older article, and they
3 were able to show the tubular epithelial cells but also
4 endothelial cells undergo apoptosis at the early
5 reperfusion phase in human biopsies and kidneys with
6 early graft dysfunction had more apoptotic cells.

7 Repair or regeneration I think is a very
8 important phase. I mean, we all admit that even in
9 live donor kidneys there is some injury, and it's
10 really how the tubules respond to that and whether or
11 not they're able to regenerate and repair. There are a
12 variety of phases that we can recognize histologically,
13 alterations and adhesion with exfoliation, spreading,
14 flattening of the epithelium and migration or
15 premitotic phenomena, and then as those cells recover
16 they look de-differentiated, they're flatter, they
17 express things like Vimenten, NCAM, there are growth
18 factors around, et cetera, paralleling really
19 organogenesis. And so it's only later that the cells
20 resume their definitive differentiated phenotype. And
21 again, an example of the very, very hyperchromatic
22 nuclei, it's very easy to see that these cells are

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1 regenerating, but of course you can use markers of
2 this phenomenon as well.

3 So Kim Solez, and Steen Olsen and I looked at
4 acute tubular injury and ischemia reperfusion injury in
5 allografts and these are the features, and I've already
6 alluded to many of these, but there is more
7 interstitial inflammation than we typically see; for
8 example, in native kidneys. True necrosis is seen in
9 this context, although at that time most of these
10 patients were on cyclosporine and that of course has
11 hemodynamic effects. Regeneration was also a prominent
12 feature. Interstitial edema, I think testify to the
13 presence of microvascular injury. Tubular dilation is
14 a feature that I think reflects functional capability
15 in that the dilated tubules are probably obstructed and
16 the tubule is not functioning, per se, some oxylate and
17 then some shed cells in the tubular lumina.

18 How do you quantify tubular injury? Well,
19 you can do it for high-power field, number of injured
20 cells for high-power field. You can do it number of
21 injured tubules for high-power field. You can look at
22 the balance of injury and repair, although I have to

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1 say the repair and regeneration phase is usually not
2 looked at very carefully and of course is not as
3 relevant in the immediate post-transplant period.
4 Severity scores, of course, if you want to quantitate
5 these phenomena, are enhanced by morphometric
6 techniques, and there hasn't been a lot of application
7 of this to the transplant setting. And then apoptosis
8 and regenerative changes again, not usually assessed
9 very completely.

10 This is a nice article actually from AJT a
11 number of years ago now, in which they found that
12 tubular dilatation was present initially at increase in
13 the first week post-transplant in those recovering
14 function but remain, the dilatation remained constant
15 in those who sustained dysfunction, which I think again
16 is a morphologic marker of what is actually happening
17 functionally. Adhesion molecules have been looked at
18 and again, this is vis-a-vis amplification of the
19 inflammatory process that we have heard allusion to.
20 And indeed when you look in transplantation in this
21 article, for example, ICAM-1 and VCAM-1 expression were
22 higher in deceased donor kidneys than in live donor

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1 kidneys, and as a matter of fact expression of ICAM on
2 the tubular cells was actually a predictor for delayed
3 graft function.

4 And there are other interesting morphologic
5 markers. The literature is beginning to get into this
6 area. There have been studies of KIM-1 in the tissue
7 as well as a urinary biomarker, as you've heard, and on
8 pre-perfusion biopsy from deceased donors, the final
9 donor creatinine was negatively correlated with KIM-1.
10 So clearly, there is this injury marker present,
11 although interestingly in this small study, DCD kidneys
12 have lower scores per injury than -- and perhaps not,
13 surprisingly. There was no correlation, however, with
14 tissue injury or delayed graft function, but the
15 authors pointed out that they did not sample the outer
16 medulla well and they thought that this might be an
17 explanation for that.

18 Hypoxia induce were factored, lower
19 expression and post-perfusion biopsies with early
20 oliguria. We've already heard about the toll-like
21 receptor and they're living more abundant in tubules
22 and deceased donor kidneys, and proliferated progenitor

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1 cells are of interest, and there's been some
2 interesting studies recently. And these cells are
3 decreased in donor acute tubular injury underlying
4 delayed graft function and increased during the
5 recovery phase. So again, the idea that this repair
6 process is going on in the background and getting a
7 handle on that may actually be critical.

8 The microvasculature I think has also been
9 understudied and underappreciated and Hamid alluded to
10 this earlier. There's a lot happening in the
11 microvasculature, but particularly but not exclusively
12 in the outer medulla, and here we see an example of
13 dilated basal recta with very, very congested
14 capillaries with lipid biostasis, in addition to the
15 accumulation of cells, including mononuclear cells and
16 a few neutrophils in this area, presumably responding
17 to endothelial injury in this particularly vulnerable
18 zone. And this has been studied.

19 Now, this is an article for example, from AJT
20 looking at peritubular capillary damage. And they
21 looked at the disappearance of von Willebrand factor
22 from endothelial cells and found that it was more

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1 severe in sustained acute renal failure than those with
2 rapid recovery. And the peritubular parasites and
3 myofibroblasts were more pronounced in those that
4 recovered rapidly.

5 And interestingly, all seven subjects with
6 mild to moderate tubular damage recovered, but only a
7 subset of the cohort was severe damage recovered
8 function. And there's a lot of experimental evidence,
9 of course, indicating that microvascular loss underlies
10 the progression to chronic changes in ischemic
11 reperfusion. The story about inflammation and ischemic
12 injury is a fairly extended one, and there are people
13 here who have worked in this area. This is sort of
14 innate or adaptive immunity in the context of the
15 native kidney, but of course can trigger alloimmunity
16 as well. And this has also been looked at in the
17 transplant setting. And this study actually showed P-
18 selectin and neutrophil inflammation and infiltration
19 were more abundant in reperfusion biopsies and deceased
20 donor grafts -- and here we see the numbers -- than
21 live donor grafts, for P-selectin and neutrophils. And
22 P-selectin was expressed on activated platelets,

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1 interestingly enough, of endothelial, at least in the
2 co-labeling studies that are shown in that article.
3 Neutrophils of glomerular were associated with a long
4 cold ischemia time and delayed graft function, and
5 neutrophils and platelets after reperfusion were
6 associated with elevated creatinine at three to six
7 months. So again, I think the inflammatory cells are
8 there if you look for them carefully. The platelets
9 are there, reflecting endothelial injury and
10 microvascular changes and can be predictive. Of
11 course, sometimes the immunostaining -- and I'm always
12 amazed when I do immunostaining and how many more cells
13 pop out at these sections than you can actually see
14 without that aid.

15 Early graft fibrosis certainly can occur, and
16 this is an interesting article actually from Clinical
17 Transplant in which they had a donor after cardiac
18 death, a 63-year-old female with subarachnoid
19 hemorrhage and preterminal problems. Biopsies revealed
20 of one of her two kidneys relieved progressive early
21 fibrosis, not in the other, and they speculated that
22 perhaps anemia in the recipient, which was quite

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1 severe, played a role in sort of an early progression
2 of fibrosis. But it is certainly true that creeping
3 fibrosis is a typical morphology of chronic ischemic
4 injury and capillary loss is often associated with
5 this. And the capillaries actually have much poorer
6 regenerative capacity than the tubules do. So I really
7 think that a lot of focus should be on the
8 microvasculature. And of course, failure of tubular
9 regeneration may also play a role, and Joe Bonventre's
10 group, for example, had suggested that G2 arrest may
11 actually underlie a progression of fibrosis. But there
12 are many potential exacerbating factors between point
13 zero and early post-transplant period, and fibrosis
14 that you might see later on, a lot of supervening
15 processes like drug toxicities rejection, et cetera.

16 This was an interesting study from the
17 Edmonton group in which they have a large center for
18 cohort protocol and indication biopsies, and did focus
19 appropriately on sub-lethal injury and did some semi-
20 quantitation of that. And you can see here there's
21 quite a high prevalence on protocol biopsies at six
22 weeks, three, and six months. Quite a high percentage

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1 of cases have some level of acute tubular injury. This
2 was associated with delayed graft function and long
3 cold ischemia times, and they found that the GFR at one
4 to two years correlated inversely with the frequency of
5 biopsies from an individual patient that showed tubular
6 injury. And the prevalence of chronic changes -- I
7 seem to have lost -- the prevalence of chronic changes
8 at six months was also higher in the group with
9 multiple biopsies with acute tubular injury, although
10 this was not statistically significant, I don't
11 believe. So this whole concept of lack of recovery or
12 ongoing injury with failure to recover completely I
13 think is an important one, and here we see creeping
14 fibrosis.

15 So biopsy findings. When we look at these
16 things, it depends on the severity of the injury.
17 We've heard about donor factors, recipient factors.
18 The localization of the injury is important. There are
19 zones that are susceptible to this and sampling issues
20 arise anytime you try and get a small tissue specimen
21 to represent an entire organ. And the time of the
22 biopsies vis-a-vis injury of course, is critical,

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1 depending on how much injury versus how much repair you
2 can find.

3 So how could we optimize assessment of
4 pathological assessment? I think we need broader
5 morphological observations, including increasingly
6 subtle observations, tubular dilatation, platelet
7 aggravation, using immunostaining to highlight the
8 inflammatory infiltrates, the accumulation of
9 platelets, differentiation markers, occlusion
10 molecules, et cetera, which can amplify an ongoing
11 injury response. We need deeper biopsies, resampling
12 of outer medulla. We need assessment of endothelial
13 and microvascular injury, which I think we don't really
14 look for carefully, and we need serial biopsies,
15 because frankly I think everybody agrees that there's
16 some injury at zero time, but what happens, how quickly
17 that repairs, how completely it repairs, I think is an
18 important factor and if you don't get some sense of the
19 kinetics of this, you're going to miss a lot of
20 valuable information.

21 And of course, the peritransplant biopsies do
22 provide other observations that are extremely relevant

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1 to outcomes in addition to a ischemia reperfusion
2 injury. Donor disease and all of those terrible things
3 that I show you there are things that we've seen in the
4 past couple of years, and donor biopsies. We've
5 already heard how fibrosis atrophy, atherosclerosis,
6 but particularly the chronic vascular changes can be
7 predicted for both short and long-term prognosis, and
8 there's a nice recent review of that.

9 You can find hyper acute rejection processes
10 beginning. You can see early drug toxicities. So
11 there's certainly value added to the zero time biopsy,
12 but I think that we need to sort of refine how we
13 approach these, and in particular I think serial
14 biopsies would be very useful. Thank you.

15 DR. ARCHDEACON: Thanks very much, Dr.
16 Racusen. I think we're just going to save our
17 questions for the end. So Dr. Halloran has been kind
18 enough to agree to do double duty because Dr. Dan
19 Salomon was unable to join us today as originally
20 planned. So he'll be talking about genomic approaches
21 to measuring ischemia reperfusion injury both within
22 the renal compartment and outside the renal

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1 compartment. Since he'll be doing two lectures, he'll
2 essentially have twice the time.

3 DR. HALLORAN: Thank you very much and thank
4 you very much to the organizers for inviting me and
5 giving the privilege of talking to this wonderful
6 group. Okay. So we'll talk about the transcript
7 changes in acute kidney injury and I'll be expounding
8 on this idea that this is wound repair and it's a
9 symphonic process. These are my disclosures. We've
10 gone over those.

11 Christina Roseetti, who is the sister of
12 Dante Gabriel Roseetti, the father of pre-Raphaelism,
13 the pre-Raphaelite movement, and he painted her picture
14 here. She had said, "Who has seen the wind? Neither
15 you nor I, but when the trees bow down their heads the
16 wind is passing by." That's what it is with injury. We
17 see the response to injury and the response to injury
18 is an integrated, orchestrated, highly evolutionarily-
19 evolved process, in which every molecule is intimately
20 tied with every other molecule and as you'll see, tens
21 of thousands of molecules are involved.

22 So this is undetectable by histology, really;

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1 you'll see that. Differentiation involves de-
2 differentiation because the units of their injury are
3 taking out of service, just as you would with a large
4 industrial facility when some of your robots aren't
5 working. You take it out of service for repair. So
6 they de-differentiate and they lose their solutaries,
7 end up having massive changes in metabolism. And then
8 they undergo active repair, and we can see that. And
9 this is really a parenchymal process. And then there's
10 mild inflammation which is intimately tied to this.
11 There's some residual atrophy fibrosis because repair
12 cannot be complete. Just check your latest surgical
13 scar. And then in some cases you can't repair the
14 parenchyma and then you revert to healing by second
15 intention, which is the best alternative as opposed to
16 leaving giant holes in your body.

17 So we will go over some recent insights, why
18 kidney transplants fail. We'll look at the
19 definitions, some historical lessons. So the
20 transcript changes in acute kidney injury. And then
21 we'll look at the changes in three sets of human
22 biopsies, and we have now many, many -- maybe a

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1 thousand human kidney affymetrix microarray results.
2 We'll look at indication biopsies, one-hour biopsies
3 and protocol biopsies, and then we'll go back to our
4 messages. And we'll try to incorporate the messages
5 that we got from Dan Solomon's slide set.

6 So we'll be looking at why kidney transplants
7 fail, and we've been doing this after biopsies for
8 cause and we've been doing this in the DeKAF study with
9 Arthur Matas and the Genome Canada study that we have
10 in Edmonton. And the picture we get is something like
11 this. Kidney comes to us with a certain number of
12 nephrons that have a certain gender age and mass, a
13 certain function. In order to transplant it in any
14 way, we have to damage it. It undergoes a variety of
15 types of damage, including early acute mediated
16 rejection episodes. And the result is an injury repair
17 response, which we can measure in every single kidney,
18 isografts in mice. And at the end of this, the process
19 is resolved to the point where you now have baseline
20 function. And this is probably the key parameter
21 coming out of these studies is the baseline function
22 that you will get at six months. Now, that baseline

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1 function may not be ideal, but it's stable. And we'll
2 -- there's no evidence that this early injury actually
3 programs delayed events. I'll show you that. So now
4 you even have the capacity for hypertrophy over time in
5 the best kidneys and you have a little atrophy
6 fibrosis, because remember, this is wound repair.

7 Now, when we look at the causes of failure,
8 and this paper has just been accepted pending revision
9 in AJT, we see that in the 60 failures we've seen so
10 far after indication biopsies in this study -- so we've
11 had initiation biopsies from day 7 to year 34 in the
12 kidney transplant population. And then as we follow
13 those patients, 60 of them have failed so far and the
14 failures have been due to antibody mediated
15 rejection, mixed rejection, and that accounts for 65
16 percent of the failures, and 48 percent of them were
17 recorded as non-adhered by their clinicians. So that
18 seems to be the problem with late graft loss now based
19 on the observations in the Genome Canada study and the
20 DeKAF study. There's not mysterious creeping fibrosis.
21 There are some people that have recurrence of their
22 primary disease. There are some -- this is where --

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1 this is what -- this could be relevant. If you have a
2 major medical surgical event, you end up in the
3 intensive care unit. The kidney transplants often fail
4 during that context, but that is a complex event. Some
5 of those kidneys have underlying medical disease and so
6 there may be an interaction there. Polyoma virus
7 nephropathy. There are some that are missing.

8 But the main thing is, The Mayo Clinic, the
9 DeKAF study and Genome Canada study all say that the
10 failures can now be given a disease explanation in most
11 cases. It's not mysterious creeping fibrosis of some
12 kind. It's not mysterious inflammation; it's a
13 disease. If there's a disease there will be
14 inflammation because the tissue is try to remodel and
15 repair.

16 So transplants fail due to diseases. We
17 don't see any late effects of transplant survival from
18 early acute kidney injury other than what might be due
19 to lower baseline GFR and to the co-variance, like
20 donor age. So that later on we say that this is what
21 happens. The kidney remains stable until it gets a
22 disease; then it deteriorates, develops fibrosis and

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1 atrophy, and at that point it develops another wound
2 healing response, develops injury repair response, and
3 that is what we showed in this paper in JCI last year.
4 But basically in chronic kidney disease the signal in
5 the tissue that tells you that you're progressing is
6 the injury repair response. So the disease is one
7 thing; the degree of progression is the extent of
8 response of the nephrons to injury, attempted repair.

9 So acute kidney injury is not delayed graft
10 function, and we have to try to get this distinction
11 right. Acute kidney injury is an insult that induces
12 the injury repair response, and the de-differentiation
13 is why the creatinine goes up. It's intrinsically
14 reversible. It does not include particle nephrosis,
15 nephritic syndrome and acidosis failures obstruction,
16 and that's an important distinction that is not made in
17 the registry data. So delayed graft function is any
18 observed impairment in kidney function, including
19 kidneys that have disasters.

20 So acute kidney injury causes transient
21 dysfunction that recovers; however, there is -- and
22 Sandy outlined this very well, and I won't beat this

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1 point up -- the real problem is that in old kidneys,
2 old nephrons are not just fewer, they're old. And
3 probably this is an somatic cells senescence issue, and
4 they don't deal with injury as well. Whether this is
5 additive or synergistic, acute kidney injury can cause
6 some of these kidneys that had creatinine, which is
7 really quite decent in the original owner, to be really
8 absolutely miserable in the new recipient, and that's
9 what we're trying to predict. Delayed graft function
10 includes AKI plus many unmodifiable factors that we've
11 been over, including in the past sensitization, and we
12 think that this is playing a less, a lower and lower
13 role, and this is exclusively due to antibody mediate
14 rejection which was undetectable before. And so
15 increasingly we think we're able to sort that out.

16 So strategies to reduce or fix acute kidney
17 injury can impact early function but are unlikely to
18 have an impact on the diseases causing late graft loss;
19 at least we can't find any so far. So this is a slide
20 adapted from Larry Hunsicker (ph), from the 2000
21 meeting. Basically we have the phenomenon, the
22 phenotype, of unacceptably poor initial function, which

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1 we'd like to improve. And we can define it in a number
2 of ways, but don't dichotomize this. The
3 dichotomization of data misses some of the data. This
4 is a continuous phenomena. So then we have feeding
5 into this recipient factors, donor factors, HLA
6 antibody sensitization causing early antibody-mediated
7 rejection, and acute kidney injury. And the AKI signal
8 can be due to a number of factors -- ischemia, brain
9 death, possibly cold itself.

10 So we integrate that with this phenotype, and
11 then the consequences associated with this phenotype
12 can be death of the patient because this is bad for
13 you, primary graft failure, incomplete recovery of
14 function, complete recovery of function, and there's an
15 increased diagnosis of T cell mediated rejection.
16 That's probably due to biopsies. More biopsies you'll
17 find are inflammation; some of it you'll call T cell
18 mediated rejection. There's no robust evidence that
19 the degree of acute kidney injury determines whether or
20 not you get rejection. That's a myth.

21 So let me put it together this way. We have
22 the biological variables -- kidney quality, patient

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1 quality; incidentally, that's not pejorative. At my
2 age I'm not the same quality I was at age 30. That's
3 the way it is. Acute kidney injury and donor specific
4 antibody, we think this may be dropping out. All of
5 these have a major effect on the phenotype. And then
6 on the late phenotypes, they play it like this. Kidney
7 quality plays a role on the baseline GFR that you'll
8 get at the outcome of the resolution of the wound
9 response. Patient quality continues always to play a
10 role, including creation of these major medical
11 illnesses in which the kidney may fail.

12 Acute kidney injury plays mainly as a
13 variable which determines the six-month GFR perhaps,
14 maybe a little residual fibrosis, but it doesn't affect
15 the delayed slope of the GFR and donor-specific
16 antibody, obviously, has a catastrophic effects if you
17 miss it. We can deal with these in a number of ways,
18 but mainly selection and allocation. We are limited in
19 what we can do with selection and allocation because
20 you have to give good kidneys to good people and you
21 have to -- therefore, the bad kidneys have to go
22 somewhere. So the allocation, there's not a lot of

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1 leverage in allocation. We're doing the best we can.
2 And the fixes here, the fixes, we would like to be able
3 to fix this element, the acute kidney injury element.
4 We'd like to reduce it, yes, Professor Abecassis. We
5 would like not to injure kidneys, and if you can find a
6 way we would not injure them, that would be good.
7 Fixing it, that would be good, and good luck on that.
8 At any rate, we're doing what we can.

9 Now, the historical lessons are assimilated
10 in this meeting from 2000. It pretty much covers
11 everything we've said so far this morning. So a new
12 generation of associate professors are presenting the
13 data, but that's okay. That's the way academic medicine
14 works. Old kidneys have fewer nephrons, but the
15 remaining nephrons are old and somatic cells senescence
16 issue is one that you did a lot of work on, and I'm
17 very interested in seeing Joe Bonventre's work on this.
18 We have to understand how the rules of somatic cells
19 senescence play a role in determining whether a nephron
20 can recover. Because a nephron has a circle mechanism
21 that says whether or not it can operate. A circle
22 mechanism has so far cost most of us .75 percent of our

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1 nephrons every year, and that will continue every year.
2 That circle mechanism will cause dropping out, and we
3 think that acute kidney injury may trigger that circle
4 mechanism as well, which causes nephrons to drop out.

5 Michael Cecka did an analysis where he loaded
6 all the covariates that he could into the model and
7 then looked at the effect of an element of acute kidney
8 injury. The element of acute kidney injury was, what's
9 the cold ischemic time influence? And then he looked
10 at long-term outcomes. Now, cold ischemic time
11 definitely plays a role in determining how much acute
12 kidney injury you see in terms of delayed graft
13 function. So it's an element of pure acute kidney
14 injury, and when he asked how much does that influence
15 long-term outcomes, he came up with this slide.

16 (Slide says: "zero, non, zip!, Zielch,
17 nada.)

18 So most of the effect on long-term outcomes is due to
19 the covariates associated delayed graft function, not
20 to the acute kidney injury elements, and that's
21 relevant to this issue of the way acute kidney injury
22 plays out in the donation after cardiac death versus

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1 the conventional donor.

2 So in mouse kidney transplants, we look at
3 mouse kidney isografts, and we published this. The
4 isograft is the most reliable model for acute kidney
5 injury in our hands. You get -- the cross-clamping
6 models have very, very high degrees of variability --
7 operator dependent in the same laboratory. Don't even
8 talk about the variation between laboratories. And
9 this creates a literature which is very difficult to
10 interpret and very misleading if it's being used as a
11 basis for human interventions.

12 So what we did was we looked at mouse kidney
13 isografts. These had no rejection, obviously, and they
14 had essentially no histologic abnormality, except to
15 very subtle interstitial inflammation, which is below
16 the threshold that pathologists usually call
17 inflammation. We also studied native kidney ATNs and
18 we compare that. And so what we see is basically
19 there's an acute phase response in the kidney that also
20 is seen in the other host tissues, and this is the
21 response to the surgical procedure to the anesthetic
22 and that shouldn't be mistaken for injury. And then

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1 there's also injury in the tissue. So when we -- this
2 is the pathology of these kidneys. They basically look
3 very good. Actually if you do confocal microscopy on
4 them, they don't look so good. They have lost some of
5 their solute carriers on the brush border but you need
6 confocal microscopy to see it.

7 So these are functioning and life-supporting
8 kidneys, and then if we look at the transcripts in
9 these -- and these are affymetrix chip results -- and
10 we take the injury genes, so we subtract in this case T
11 cell genes and macrophage genes, gamma interferon
12 regulated genes. Again, we're looking at the injury
13 genes, injury up. We find that there are really --
14 this dichotomous clustering. We identified three
15 classes of genes. They are those that are introduced
16 on day one and then regress. They were never re-
17 induced. These are the isografts. They're never re-
18 induced in the allografts, as the allografts reject.
19 So this is really the systemic response of kidney cells
20 to injury. It's the systemic acute phase response as
21 seen in the kidney. And it's seen in the host kidneys,
22 if we need a host kidney and don't manipulate it.

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1 However, the injury genes really are these
2 that play out in -- they're called -- we call them
3 IRIT-3 and IRIT-5. They play with a plateau at around
4 day 3 and then regress in the isograft, but they take
5 off in the allograft with T-cell mediated rejection or
6 they peak at day 5 which is like the healing of a wound
7 and they really take off in the allograft. They
8 regress in the isograft. However, the isograft by day
9 21, against still histologically normal and functioning
10 still retain the signal from the injury genes.

11 So we've taken the genes and created gene
12 sets, and I won't go through them, but we can basically
13 dissect injury, inflammation up and differentiation,
14 loss of kidney genes. So now, we look at the isografts
15 day by day, and each of these has about 10 or 15
16 kidneys at each point. And we start off with a normal
17 kidneys and we see signals at day 1, and basically
18 you're seeing ramping up of the orchestrated symphonic
19 response to injury, which includes inflammation,
20 repair, and this includes many acute kidney injury
21 biomarkers, and I'll show you that, and de-
22 differentiation maximizing at day 5 in the isograft.

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1 If you then look in the ATN model, you get simply an
2 exaggeration of the same orchestrated response, and if
3 you look at T-cell mediated rejection it's just an
4 amplification of the same response. It's actually just
5 using the same language as the injury response. T-cell
6 mediated rejection is a cognate T-cell process in the
7 tissue that triggers the injury repair response in the
8 nephron.

9 What about indication biopsies in the human?
10 Indication biopsies in the human. Now, we've submitted
11 this paper, and so this is the only part which is not
12 actually published. Okay. There are three elements
13 that we see in the transcripts in indication biopsies
14 with acute kidney injury the first six weeks post-
15 transplant in which we've taken out all of the
16 rejection biopsies or even suspected rejection. We've
17 taken out all recurrent disease, so now we're looking
18 at human kidneys with acute kidney injury. Now, we see
19 they have a range of GFRs. So what we find is we see
20 features of aging. We've got a signature for human
21 aging, has basically in the hemoglobin transcripts
22 because plasma cells go into scarred areas. Acute

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1 phase response, so this is like the mice, but we can
2 neutralize that, and then the injury repair response.
3 We can see this in biopsies at the time of surgery, in
4 early indication biopsies in the six weeks protocol
5 biopsies, and it's basically the same and it's the same
6 as it is in the mice.

7 We can compare these to normal kidneys, but
8 in fact if I had a piece of your kidney, it's not
9 normal. You would have an operation or you had a
10 biopsy, so there is no such thing as normal human
11 tissue we looked like in the transcripts, so what we
12 see is when we look at normal human kidneys, which
13 we've received from surgery at the time of hyper
14 nephroma removal, they have the effects of ischemia and
15 we're into -- imagine this is a cancer operation. They
16 clamp it before they give us any of the tissue, so that
17 these -- there's no such thing as normal human tissue,
18 but we put these into the algorithms.

19 So when we take these acute kidney injury,
20 what we get is a signature of genes which is very
21 rewarding for those of you that look at biomarkers.
22 And I'd love to eke out and go through these one by one

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1 for you and explain what I think it all means. The top
2 one is integrin beta 6, which the epithelium uses to
3 locally activate TGF beta, so that the epithelium talks
4 to TGF beta. You also get a few inflammatory markers.
5 There's superoxide dismutase 2. There's Webuclaion-2,
6 which some of you know as NGAL. There's
7 lactostransferin. Anyway, this is a very rewarding set
8 of genes because it basically validates the things that
9 people have been seeing with biomarkers in urine. So
10 it's essentially the same signal as is seen in most
11 isografts, most ATN human, acute kidney injury human
12 protocol biopsies in human one-hour biopsies. That's
13 basically a stereotype response.

14 So when we look at this signal and we say,
15 how much of the signal do you have in your indication
16 biopsies and from the first six weeks, it correlates
17 very nicely with a degree of depression of the GFR in
18 the kidney at the time of biopsy. It does not
19 correlate with anything the pathologist calls acute
20 tubular injury. So acute tubular injury has nothing to
21 do with the GFR and does not correlate with the
22 molecular changes. However, interestingly, it does

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1 correlate, if you've got continuous inflammation scores
2 and mild interstitial inflammation does correlate. So
3 the only thing in histology that does correlate in the
4 injury signal is actually the mild interstitial
5 inflammation, which is below the threshold of the I
6 score in DAMPH. It also correlates with whether or not
7 you had delayed graft function, so everyone with
8 delayed graft function had a high injury repair
9 associated transcript score. We looked at pathways,
10 and the pathways say, this is like cancer, because
11 cancer is the wound that doesn't heal. It says it's
12 associated with cellular movement because you've lost
13 your tight junctions, your adherence junctions. You
14 become mobile, you've liquidated the basal membrane.
15 It's associated with reexpression developmental genes,
16 and that's why you're getting apoptosis, because this
17 is a worm redeveloping, and the developing worm uses
18 apoptosis. It's like the tadpole's tail. And there's
19 a little bit of acute phase response, but basically the
20 acute phase response is virtually absent.

21 So now, the answer to your question: How
22 many genes are there that are changed and have acute

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1 kidney injury? How many would you like, as your
2 accountant says when you ask what's two and two and
3 four. What would you like it to be? Well, we can show
4 you as many as you'd like. So if you take the
5 phenotype on this axis and say, what genes predict the
6 lower third of GFRs in acute kidney injury biopsies,
7 you could have 10,000. You could have 30. But all the
8 ones we've been saying are the acute kidney injury
9 genes in the top 30 are in this part of the tail, and
10 if you look at those in more detail, that includes --
11 there's KIM-1, here's onset gamma receptor, you have
12 lipocalin-2 in here, NGAL. IL-18 doesn't perform
13 particularly well, but there is, so it's not different
14 from the others.

15 So the reason that these are biomarkers is
16 that they're part of the injury response of the
17 epithelium and including some inflammatory markers
18 which are tied into the injury response. So you can
19 set the FDR wherever you want it. You can get whatever
20 answer you want, but it is interesting that there are
21 many other genes of equal value which are missed by the
22 statistical filtering down in this end and then -- oh,

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1 these are all the downers. Many of the downers are
2 also highly informative and have high correlations as
3 well.

4 So then we see the same thing in the one-hour
5 biopsies, the signal for the acute kidney injury that
6 we see across the indication biopsies is there at a
7 lower level in the one-hour biopsies. So we took one-
8 hour biopsies from live donors or deceased donors and
9 we did a principal component analysis and this is the
10 first hundred or so that we published. So when we do
11 principal component analysis across the IQR filter
12 genes which come out of the microarrays, what you see
13 is the live donor kidneys are quite separate from all
14 the deceased donor kidneys, and there are two groups of
15 deceased donor kidneys. There are good ones and bad
16 ones. And the good ones are sort of like the live
17 donors and the bad ones are distant from them. And
18 this principal component is basically the injury repair
19 response. The more of it you have, the worse you have,
20 the worse outcomes. These are the kidneys that have
21 delayed graft function. Delayed graft function is a
22 very poor way of taking out genes, because there are

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1 some other kidneys that have what Arthur would call
2 slow graft function, which are biologically just about
3 the same but they put out a little bit more urine and
4 you don't have to dialyze them but they're just as
5 injured. So if you use delayed graft function as your
6 tag you get no molecules. You have to do it this way,
7 because many of the slow graft function molecules are
8 biologically the same as the delayed graft function
9 molecules.

10 So then we end up with good deceased donors
11 here, live donors and bad deceased donors and delayed
12 graft function occurs in the bad deceased donors, but
13 some of the bad deceased donors have the phenotype
14 where we arbitrarily dichotomize as delayed graft
15 function. And when we look at the genes here, we see
16 several things. First of all, there's injury response
17 gene. There's integrin beta 6, there's KIM-1, but
18 there's also this signal, antibody globulin genes.
19 That's because they're old. The older the kidney is,
20 the more likely is that delayed graft function. But if
21 you've got two kidneys 67 years old and one has delayed
22 graft function, it will give you a signal that it's

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1 biologically old because it is, because chronological
2 age is not biological age. So the biological age
3 signal comes out in scarring and atrophy information,
4 so that also comes out when you're looking at delayed
5 graft function.

6 Let's look at the six-week protocol biopsies.
7 So we have six-week protocol biopsies from Hanover, and
8 we looked at the signal there, and what we found was
9 that the inflammation in protocol biopsies is primarily
10 due to the injury of the kidney, not due to rejection.
11 And if we take a very small number of rejection
12 biopsies out, we end up with-- well, whether we leave
13 them in or take them out or not, we look at the
14 transcript changes that are abnormal in these protocol
15 biopsies at six weeks. Protocol biopsy means you did
16 not have an indication for biopsy, so if you actually
17 were rejecting at that time it's not a protocol biopsy.
18 And we find that the genes which most abnormal are the
19 injury repair genes, the injury up and injury down
20 genes, and that correlates with the history of delayed
21 graft function number of dialysis. So the driver of
22 abnormalities in protocol biopsy is actually the injury

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1 history of the biopsy, just as what Dr. Racusen was
2 saying.

3 So I guess the key messages would be that
4 acute kidney injury evokes an injury response. This is
5 an orchestrated stereotype of response, and it's seen
6 in the mouse and seen in the human. No treatment seems
7 to accelerate the resolution of these changes, but it
8 would very nice at least to be able to reduce the
9 injury that this kidney -- and if you reduce the injury
10 you'll be able to tell that you'll get a reduction in
11 the injury repair response.

12 We'd also like to be able to make it heal
13 better, but we don't have anything that works in wound
14 repair to actually make wound repair better. It's very
15 dangerous, though, to take any one point in a curve
16 like the one that I showed to you in the isografts,
17 that the orchestra goes up to a crescendo and comes
18 back down over months because you could shift that
19 curve and at any one point and say, I made a benefit,
20 but actually you may not have made a benefit if you
21 looked at another point on the curve.

22 So the ATN AKI part recovers with little

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1 sequelae except that the kidneys with ATN and AKI may
2 have impaired GFR and some fibrosis as a result. But
3 that can be seen in the six months and subsequent
4 baselines serum creatinine and GFR measurements.

5 Delayed graft failure is mainly due to issues
6 such as recipient death and morbidity, and then the
7 occurrence of diseases, and there doesn't seem to be
8 any phenotype associated with the kidney remembering it
9 had delayed graft function other than baseline GFR.
10 DGF and registries is a very complex variable, which is
11 loaded with biological information which is hard to
12 tease out with factors such as donor age. Just putting
13 donor age in does not account for biological age, which
14 is what we're seeing in the biopsies. And the
15 biomarkers in the urine, we can say with confidence,
16 are very reliably representative in the biology of the
17 kidney. Thanks very much.

18 Just to summarize Dr. Salomon's presentation,
19 there are no genomic studies on fluids, which address
20 this question in the kidney, but he sent along some
21 slides on other issues, which we can go over.

22 DR. LORBER: Thank you. The final speaker in

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1 this session will be Dr. Arthur Matas from University
2 of Minnesota, who's going to tie this all together.

3 DR. MATAS: Thank you. I'm going to try and
4 follow all of this science with a bit of a clinical
5 perspective. My conflict of interest is shown on the
6 slide. Basically I have no conflict of interest in
7 relation to this talk. And in some ways they should
8 have followed Chirag because he says that is surgeons
9 tell him they don't need all these studies. I think
10 from a clinician's perspective, we do know delayed
11 graft function when we see it, but what I'm going to
12 try to talk about is how you then translate that into
13 something you would study. Obviously when we have low
14 urine output and no fall or even a rise in serum
15 creatinine we know that's not a kidney that's working
16 as well as a kidney with immediate good urine and
17 output and a rapid fall in serum creatinine.

18 But the literature on delayed graft function
19 or early post-transplant graft dysfunction is limited
20 by a few measurement tools, poor definitions, multiple
21 causes and differences in clinical evolution. I would
22 add one more to that in that some of that literature,

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1 including some of the slides I'm going to present to
2 you today, were from a time before we knew about
3 antibody mediated rejection. And in fact some of the
4 long-term effects may in part have been related to that
5 phenomenon. What's totally confusing to me as a reader
6 of the literature is that people group all sorts of
7 reasons under the concept of delayed graft function.
8 We'll look at that definition in a minute, but you can
9 have a poor -- and poorly graft function from hyper
10 acute rejection, from early acute cellular or antibody
11 mediator rejection, from technical problems, such as
12 vascular, urethral or other injury such as a
13 compartment syndrome, from ischemia reperfusion injury,
14 which is really what you want to be talking about
15 today, or from donor injury. All of these are
16 clinically manifest by the same clinical phenomenon as
17 poor early function and yet these studies or most of
18 these studies have not controlled for these factors.

19 So what we do know and some of this has been
20 alluded to already -- there's data showing that along
21 with the inflammatory response there's up regulation of
22 HLA antigens. There is an associated increase in acute

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1 rejection episodes in kidneys with early dysfunction
2 and there is worse long-term graft survival, although
3 we can argue about what that is.

4 So bringing it back to the meeting today,
5 what are really looking at this for or why do we need
6 better definitions? Well, are we looking for a guide
7 for intervention because if we're looking for
8 intervention clinically we know what delayed graft
9 function is, and we know at least we've developed
10 protocols for taking care of the patients with delayed
11 graft function. But if we're looking for the
12 phenomenon as an endpoint for clinical trials or a way
13 to measure the success of clinical trials, I think
14 we've got some real problems.

15 So let me just try and define delayed graft
16 function as it's been used in the literature because
17 here are just some of the definitions that I found in
18 various papers. Now we ourselves have usually used
19 dialysis in the first post-transplant week. As I
20 showed you in an earlier slide, there are many reasons
21 besides ischemia reperfusion injury that can result in
22 a patient being dialyzed in the first post-transplant

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1 week. But at the same time look at these other
2 definitions: urine output less than 1,200 a day, no
3 fall in creatinine, less than ten percent fall in
4 creatinine within 48 hours or the time for the kidney
5 to achieve creatinine clearance of greater than ten
6 mils per minute. They're all from a variety of papers
7 in the literature and you can't compare apples and
8 oranges, and if we're going to be thinking of it by the
9 endpoints for clinical trials, we need to try and come
10 to grips with this specific problem. In addition, slow
11 graft function, which is something we originally
12 defined as a patient who does not need dialysis but has
13 a creatinine level of a greater than 3 on post-
14 operative day 5, has been recorded by others as having
15 -- being defined as less than 20 percent creatinine
16 following the first 24 hours, serum creatinine
17 increased remain unchanged or decreased less than ten
18 percent a day for 3 consecutive days. And again, if we
19 can't have common definitions, how are we going to have
20 endpoints for clinical trials or be able to compare one
21 trial to another?

22 And so this was our original paper. And I'm

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1 just going to use some of these definitions in terms of
2 looking at what they do mean clinically. Now,
3 remember, this paper was written before the concept of
4 antibody mediated rejection was well-defined. But
5 again, looking at immediate graft function as a fall in
6 serum creatinine it's less than 3 on post-operative day
7 5, slow graft function is no dialysis but a creatinine
8 greater than 3 on post-operative day 5, and then
9 dialysis, need for dialysis in the first post
10 transplant week. Well, we showed that there was an
11 increase of rejection rates. This is the rejection
12 rate with immediate graft function. Both slow graft
13 function and delayed graft function had an increased
14 associated rejection and it is still noted that the
15 signal was not much different between slow and delayed
16 graft function.

17 But what we also showed was that if you
18 didn't have rejection, neither slow nor delayed graft
19 function had an impact of survival. And in the red you
20 see immediate graft function, no rejection; in the
21 white, slow graft function, no rejection and a slight
22 impact in delayed graft function with no rejection.

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1 But where the big impact was in slow or delayed graft
2 function either associated with or subsequent with
3 rejection episodes and that's clearly consistent with
4 the message that Dr. Halloran was giving that it's the
5 initial injury that's important in looking at outcome.

6 A recent paper was looking at the same
7 phenomenon, 5-year graft survival now, 85 percent with
8 immediate graft function. This is one of the papers I
9 showed you that had a different definition of slow
10 graft function, with 76 percent five-year graft
11 survivor, 54 percent with delayed graft function. But
12 again, they notice clinically now that those with
13 delayed graft function and slow graft function who
14 recovered to within 90 percent of the expected
15 creatinine clearance in the first three months did well
16 so that the slow and delayed graft function alone had
17 no real long-term impact on five-year graft survival I
18 think consistent with the message that you've already
19 heard from others. A paper just recently published did
20 notice decrease graft survival with slow graft
21 function, but again not controlled for the other
22 variables.

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1 So what are the problems with the current
2 definition besides the fact that people use different
3 definitions? Well, first of all, as a clinician, when
4 I see poor output in urine output in the first few
5 hours, it doesn't necessarily tell me what's going to
6 happen to the patient, because we can see poor urine
7 output in the first few hours followed by the kidney
8 essentially -- we call it waking up when we're talking
9 to the patient -- good urine output in a fall in the
10 creatinine or good urine output in the second day
11 without a fall in the creatinine or continuing poor
12 output. So what you see in the first few hours or even
13 the first day isn't necessarily representative at least
14 from a clinical perspective and coming to grips with
15 definitions what you're going to see subsequently.
16 Similarly, what you see in the first 24 hours can be
17 followed by a variety of clinical pictures. And again,
18 it makes it hard to come to any definitions in terms of
19 endpoints for clinical trials.

20 So I think this study quite makes the point,
21 and this is a study that Bert Kasiske did, and Bert's
22 at Hennepin County, which is a mile away from us. And

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1 it just points out when you're coming to try to define
2 these endpoints how different centers approach patients
3 affects what we might be using for our endpoints. So
4 the study was published in AJT in 2009 and compared
5 delayed and slow graft function in Hennepin County and
6 delayed slow graft function at our center at the
7 University of Minnesota and then the subsequent
8 outcome. And looking at 5,000 patients at the two
9 centers over a long period of time, the rate of delayed
10 graft function as defined by dialysis in the first
11 post-transplant week was significantly higher at
12 Hennepin County than at the University of Minnesota.
13 And yet, the relative rate of graft function -- of
14 graft loss in patients with delayed -- in patients was
15 equivalent. What was noted, and this just looks at the
16 delayed graft function at the University of Minnesota,
17 14 percent; 33 percent in Hennepin County, but what was
18 noticed was that 14 percent at the University had slow
19 graft function; only six percent in Hennepin County.
20 And again, the adjusted rate of delayed graft function
21 was higher at Hennepin County but absolutely no
22 difference in graft survival between the two centers,

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1 and a greater risk of slow graft function in Hennepin
2 County. And slow graft function at Hennepin County was
3 not a risk factor in graft loss, but at the University
4 of Minnesota it was, and it was similar to that with
5 delayed graft function.

6 And really what you get when you try to sort
7 it all out is, they were just quick to dialyze at
8 Hennepin County; that's the bottom line. They took
9 patients to -- you know, out of the OR and if they were
10 worried about urine output or potassium, they dialyzed
11 it. We had a philosophical belief that dialysis hurts
12 the kidney and prolonged the delayed graft function,
13 and we were really resistant to dialysis. Well, if you
14 are trying to do a study looking at these two centers,
15 the center approach would have a marked impact on your
16 -- at least the definition being delayed graft function
17 or slow graft function, and so I think as the FDA
18 thinks about future clinical studies, these kinds of
19 studies at least inform trying to think about what
20 endpoints they should be, so this just summarized the
21 same thing again.

22 Then there was a similar study and again it's

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1 looking at the USRDS database and was by Luvardal (ph)
2 and Jason in 2009 and Kasiske was one of the co-authors
3 of this paper as well, looking at 7,000 transplants at
4 the same center, paired kidneys now, versus 11,000
5 paired kidneys transplanted at different centers, and
6 in this particular study there was a 24 percent of
7 incidence of delayed graft function. The odds ratio
8 for delayed graft function in the contra-lat -- if one
9 kidney had delayed graft function the odds ratio for
10 DGF in the contra-lateral kidney at the same center was
11 3.2; whereas if this contra-lateral kidney was
12 transplanted at another center, the odds ratio was
13 2.05, suggesting that the center effect again had a big
14 role to play in the rate of DGF. In fact, if they were
15 at the same center there was a 42 percent increase in
16 risk for DGF compared to being transplanted at
17 different centers.

18 So there was a significant correlation within
19 pairs for the occurrence of DGF and allograft failure.
20 And, again, just a conclusion from the paper,
21 suggesting that unmeasured donor factors contribute to
22 outcome, but transplant center effect was on DGF but

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1 not on allograft failure. And the bottom line was that
2 the data suggested both unmeasured donor
3 characteristics and transplant center care
4 characteristics contribute to the risk for, again, DGF
5 as defined by dialysis in the first post-transplant
6 week.

7 So as this all came up, one of the questions
8 that -- or as this meeting was being discussed, one the
9 questions that arose was what about using GFR? Well,
10 I've just told you quickly that the kidney function can
11 change in the first 24 or 48 hours following it, a
12 kidney transplant, and yet here are calc -- here's a
13 study on calculations of GFR in stable transplant
14 patients, and looking at 500 consecutive inulin
15 clearances -- I'm sorry -- in 294 patients, and
16 concluding that none of these formulas in stable
17 patients substituted for inulin clearance. So if
18 you're starting to thinking about using these formulas
19 in patients who have such a change in clinical course
20 in the first 24 hours to 48 hours after a kidney
21 transplant, I'd suggest that this is an endpoint is not
22 going to be useful.

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1 So I think DGF and SGF have clinical
2 consequences certainly in terms of costs and how we
3 take care of the patient. There may be more long-term
4 consequences that suggest from some of the studies that
5 we've heard of from today and from what I've shown you,
6 but current clinical endpoints certainly do in the
7 first 24 hours and I would argue perhaps the first 48
8 hours don't predict the course of DGF or SGF and this
9 variable course requires identification of better trial
10 endpoints and/or enrollment of a large number of
11 patients. And certainly the transplant center effect
12 suggests the need for stratified multi-centered trials.
13 Thank you.

14 DR. ARCHDEACON: Great, thanks. It looks
15 like we have at least a half-hour for discussion, which
16 is very encouraging, and expect we will use at least
17 that much time. I guess I would open by just referring
18 to the provided question, although I'd rephrase it a
19 little bit. So it in essence discussed which
20 biomarkers may be ready to incorporate clinical trials.
21 I guess I would actually rephrase it after listening to
22 the talk as which biomarkers if any, would any trial be

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1 deficient to not have. And I think we sort of heard
2 from Dr. Matas the story now of what some of the
3 limitations are with regards to clinical definitions
4 which rely on GFR or on a diagnosis of DGF or SGF.
5 Have we heard sufficient evidence that some of these
6 other biomarkers definitively have added value such
7 that people believe or don't believe that it would be
8 deficient not to include them at this time? I guess
9 I'll just open with that.

10 DR. HALLORAN: So my response would be that
11 the truth is in the kidney and that I would submit that
12 if you're going to do a study right now you'd be remiss
13 if you didn't have a kidney biopsy and the kidney
14 biopsy should be read molecularly. And then the
15 biomarker has to be validated against the truth in the
16 kidney. And right now we're not quite sure about the
17 relationship between biomarker as a quantitative
18 measurement and the truth in the kidney as a
19 quantitative measurement. So that would be -- my take
20 would be right now that the biomarkers look like
21 they're wonderful, but they need to be related
22 quantitatively to the truth by some gold standard and

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1 the gold standard to me would be in the kidney.

2 DR. LORBER: Phil, could you expand on that
3 by defining how you propose that a kidney biopsy should
4 be done? Is it protocol biopsy at some predefined time
5 interval? Is it for cause? Is it something else that
6 you're thinking of?

7 DR. HALLORAN: Well, I think from some of the
8 things you've been hearing I think the -- if you're
9 looking at acute kidney injury as a phenomenon in
10 transplantation and you're trying to understand it, you
11 would probably do a protocol biopsy on a certain day,
12 and clinicians -- and I've looked after these people
13 for more decades than I'd like to remember -- and what
14 we usually do would be we'd look at them at the end of
15 the first week, and that would be clinically. Whether
16 you call that an indication biopsy or not, but of the
17 kidney isn't working and the want to know how to manage
18 it and the management would usually require a biopsy.
19 In many centers that would be standard of care, do a
20 biopsy around the end of the first week. And whether
21 you call that a critical biopsy or an indication
22 biopsy, I would call it an indication biopsy.

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1 But then the other measure, which is very
2 important as an outcome, would be can you take the
3 kidneys that we're transplanting right now and give us
4 better function at six months, better baseline output.
5 And that baseline output is really -- the reason that a
6 lot of kidneys aren't transplanted is that the
7 clinician who has to make the decision doesn't think
8 that the kidneys are going to ever establish good
9 function. And if you could change that for us, that
10 would be another important outcome measurement is six-
11 month serum creatinine and GFR measurements when the
12 kidneys are stable, what kind of baseline do you get?
13 Because a lot of the kidneys, as you've heard from the
14 presentation this morning, a lot of kidneys that we're
15 taken that are from very old donors, those nephrons
16 never seem to open up properly and that's the disaster.
17 That's usually an older person who's received an old
18 kidney and now they've got an inferior result and
19 that's what clinicians are afraid of. And if you could
20 change that, that would be really meaningful. So that
21 would be an important outcome measure.

22 DR. LORBER: Doctor Matas again, and then after

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1 that Dr. Bonventre.

2 DR. MATAS: So quick comment for Phil and
3 then a separate comment. I mean, the problem with the
4 biopsy at one week, as Philip described, is we only
5 biopsy those patients whose kidneys haven't opened up.
6 So that sort of gives you a limited sample size and
7 really the worst kidneys, at least the way we do it
8 clinically, those kidneys that have and may have had
9 dialysis but have opened up and working fine -- and are
10 working fine tend not to get biopsies. Tomorrow I'm
11 going to -- because Bruce Kaplan (ph) is not here, I'm
12 going to be presenting his talk. He sent the slides
13 and he makes Phil's point actually. It's his talk that
14 does sort of overlap with mine, but he makes the point
15 that Phil made that he really believes that it's the
16 six and twelve-month end result that we wanted looking
17 at and the DGF in and of itself, as the speakers this
18 morning have alluded to, may not have any long-term
19 consequences. But what we're really trying to look at
20 is whether we can use more kidneys and how to have good
21 function at six and twelve months in those kidneys, and
22 so we can at least go over that a bit tomorrow.

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1 DR. BONVENTRE: Yeah, I would just like to
2 ask or follow-up to Phil's comment. The problem with
3 using the kidney as the final arbiter is the selection
4 bias. So the question of, you know, how you think we
5 can deal with that. In the PSTC Consortium, looking at
6 biomarkers and pre-clinical, they had the advantage of
7 having the whole rat kidney, and the pathologists
8 graded injury in nine different parts of the nephron,
9 you know, and moving from cortex to medulla and were
10 able to then correlate urinary biomarkers and temporal
11 characteristics of urinary biomarkers in a variety of
12 nephrotoxic situations and also ischemic situations,
13 correlate that with the urinary biomarkers. But in the
14 (inaudible) situation where we've got the -- you know,
15 the sample bias and that sample bias cortical versus
16 auto-medullary which has already been talked about,
17 different regions of the cortex that may be affected
18 differentially.

19 So I'm not sure we're going to answer this in
20 as quantitative a way as you could if you had the whole
21 -- access the whole animal. And, you know, one could
22 say that, you know, if you're a proponent of biomarkers

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1 as I tend to be as you might imagine, you know, the
2 biomarker is giving you a more integral parameter.

3 Now, it's not that simple, though, because
4 the biomarkers are also telling you different things,
5 which hasn't really come out. I mean, biomarkers are
6 not -- you know, some of them are telling you more
7 about more specific areas of the nephron than others.
8 Some of them are telling you more about inflammation
9 and to some extent we know about systemic factors.
10 Some of them are telling you about systemic injury as
11 well as kidney injury.

12 And so -- and in some cases, as we published,
13 sometimes it's better to have an injury biomarker
14 because that's telling you that the underlying kidney
15 parenchyma is able to produce the biomarker; whereas in
16 a situation where you've got very little functioning
17 underlying kidney, you're not going to be able to
18 produce as much of a biomarker.

19 DR. ARCHDEACON: So I think I've been
20 signaled by Dr. Parikh and then Dr. Cantarovich and
21 then Dr. Rabb and we'll come back to Dr. Halloran.

22 DR. PARIKH: Yeah. Going on first talk like

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1 if injuries are like wind we are never going to capture
2 it in biopsy. And I second what Joe is saying that if
3 there is an opportunity to collect biopsy it's great,
4 but in this modern clinical trials we would be remiss
5 if we don't collect blood and urine while the clinical
6 trial is ongoing. Observational data demonstrating
7 very good correlation or association between biomarkers
8 and short-term and long-term outcomes, but what we need
9 now is something to jump- start the field. So like is
10 there's a clinical trial which had a six-month or a
11 one-year outcome where the intervention improved
12 outcome and if you had collected urine samples which
13 demonstrated that the biomarkers moved in the same
14 direction that the changing biomarkers explained the
15 change in six-months creatinine, we would certainly
16 have a biomarker that would be available to all other
17 trials that we can use as a surrogate or as an
18 endpoint. So if on all the ongoing trials we showed
19 collect the samples, if possibly we should collect the
20 biopsy, but biopsy may only tell you part of the story
21 as opposed to the biomarker.

22 DR. CANTAROVICH: So I think Art may have

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1 said it all. We probably really need to redefine DGF
2 and is dialysis bad? We all think that dialysis is
3 bad, but as (inaudible) published, there was no
4 difference with your institution. So as Dr. Halloran
5 said, it's probably in the kidney. So is there any
6 marker, biomarker that will tell us about the good and
7 the bad kidneys in the long run because we all have in
8 mind patients who were dialyzed at 3:00 in the morning
9 because high potassium who had normal creatinines in
10 the long term. So I think that we need to redefine
11 DGF.

12 DR. PARIKH: But these are the injury markers
13 which are telling you about the clinical phenotype is
14 the DGF which tells you the severest severe injury.
15 The biomarkers are molecular signatures which are
16 giving you continuous measure of mild, moderate, severe
17 injury that is ongoing. So we need to make this leap
18 gradually with more evidence and move away from
19 clinical phenotype to molecular phenotype of injury.

20 DR. ARCHDEACON: Dr. Rabb and then Dr.
21 Halloran?

22 DR. RABB: Thank you. I'd like to make two

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1 points for a future trial design on this and justify
2 why I'm saying that. I really support the importance
3 of, in addition to blood and urine, to get the tissue -
4 - the kidney tissue samples for ischemic injury. And
5 we were involved in the Y's study. We were sent
6 samples in a blinded fashion, and we assessed 70
7 kidneys that were studied. And there were pre- and
8 post-reperfusion biopsies performed. And what happened
9 is even though that study with be selected ligand
10 antagonists was negative in the 10 or 12 different
11 studies in terms of delayed graft function, the primary
12 outcome, when we looked at the biomarkers there was a
13 protection in the group that were treated.

14 And so what we did is after the data was
15 analyzed and the biomarker results were positive, and
16 we found that a major problem was dialysis, as exact as
17 our dimension, dialysis was done very differently in
18 different sites which affected the primary endpoint, we
19 then suggested that the next study was done in one
20 large site. And so liver ischemia was studied, and it
21 was all done in UCLA by Ron Busuttil (ph), and
22 everything was controlled at the endpoints, and then

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1 there as a positive outcome found.

2 So the two points again, the biomarker
3 analysis of the tissue helped us to understand things,
4 and helped guide a larger study. And number two, again
5 emphasizing the need for a consistency in how dialysis
6 is done. When we participated, our center did the VA
7 ATN dialysis study that was published in The New
8 England Journal about two years ago, and similarly
9 there's a chaotic indication in nephrology when we
10 start dialysis for native kidney, but we standardized
11 it among all the different centers, and it was done
12 successfully, so it can be done.

13 DR. HALLORAN: I would make the point that
14 the quantitative relationship of the biomarkers to the
15 phenotype has to be established. The phenotype really
16 is in the kidney. So I would submit that probably in
17 trial design one would consider the one-hour biopsy at
18 the time of surgery and probably for those kidneys not
19 working that had an indication, but even in the trial
20 one could make it, these are presumably kidneys which
21 are going to be at high risk. A seven-day protocol
22 biopsy would be reasonable and then include the

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1 biomarkers, but then you'd have a chance to establish
2 the relationship of the biomarkers to the renal
3 phenotype in a quantitative sense. And right now that
4 has to be done because there's really no quantitative
5 relationship right now.

6 As qualitative tests they're performing very
7 well, and I think what we've found is that the rationale
8 for using them looks like it's excellent, but the
9 quantitative relationship -- and then at that point,
10 one could stop dropping biopsies out of the studies.

11 Strangely, some of them don't work as well as
12 others. Like, KIM-1 does not have as high a
13 statistical correlation to the phenotypes as some of
14 the other molecules and yet it's there in the data when
15 you go back and look retrospectively at the data. And
16 this is the kind of thing that you'll find when looking
17 at the renal phenotype versus individual biomarkers.

18 DR. ARCHDEACON: Dr. Lobo?

19 DR. LOBO: Yeah, I would like to add support
20 what Dr. Halloran is -- has supposed to do the biopsy
21 because in addition, if somebody is having a rejection
22 or some other reason for degenerative function, the

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1 biopsy would pick it up. It would also add specificity
2 to the biomarker.

3 I would also try to propose something else,
4 and that is in a kind of study that we do biomarkers it
5 would be best if you got the studies from both kidneys
6 because in that way we would be better able to define
7 recipient factors that might be contributing to the
8 factors rather than doing it all in one center where we
9 compare one kidney with another kidney from a totally
10 different donor.

11 DR. ARCHDEACON: So I had sort of follow up
12 question about the biopsy and the analysis of the
13 biopsy and this ties specifically to Dr. Halloran's
14 presentation. So I noticed that you showed the IRIT
15 (ph) score, and that correlated nicely with the
16 diagnosis of acute kidney injury, if I understood it
17 correctly. The one question I had, though, is you also
18 emphasized repeatedly and there's probably most notably
19 with the slide from Dr. Cecka, that acute kidney injury
20 by itself did not necessarily have any clinical
21 implication. So I guess in that context, if we were to
22 get biopsies as a biomarker, what is the tool which we

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1 should be using to evaluate those, and maybe Dr.
2 Racusen, I can invite her to join in as well. Should
3 it be the IRAT score; should it be a diagnosis of the
4 histology? And I'll stop there.

5 DR. HALLORAN: What was the question again?

6 DR. ARCHDEACON: Well, I guess I'm wondering
7 which tool is the appropriate tool to be looking at
8 ischemia reperfusion injury as -- and I guess
9 particularly if you could comment on the use of the
10 IRIT score, if that correlates with acute injury, but
11 your suggestion as I understood it was that an acute
12 kidney injury by itself has no clinical significance or
13 it's difficult to know whether it has any clinical
14 significance.

15 DR. HALLORAN: So think of this as a signal
16 and the signal is that the nephrons are remodeling and
17 they are -- this is an orchestral symphonic movement.
18 And if you grab what the third violin is doing and then
19 at a certain point in the Ninth Symphony, you know
20 exactly what all the other instruments are doing at
21 that point in the Ninth Symphony. And so as a
22 biomarker, the third violin, if you know the program,

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1 you know the whole program from what the third violin
2 is doing or it has predictive value.

3 So what I say is the symphonic movement in
4 the organ is the basic information you're going after.
5 Now, the fact is that in a good organ that regresses to
6 basically close to zero over months and then this will
7 not have long-term consequences. But in a really bad
8 organ, it's probably going to have a lot of difficulty.
9 This is what we're trying to understand, what happens
10 to the injury response in the face of near senescence
11 nephrons and that's what the clinician has to make.
12 Thousands of times, that decision every year, thousands
13 of people are trying to make this decision across the
14 kidney transplant world. And tragically, many of the
15 kidneys are thrown out because we can't answer that
16 question. So I would move it forward.

17 I don't think acute injury is benign when
18 you've got seriously damaged kidneys, but in ideal
19 kidneys acute injury is relatively benign in terms of
20 long-term outcome. We've been unable to make a link
21 between acute kidney injury and actual immunogenicity.

22 DR. RACUSEN: I actually was invited to

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1 comment so I will. I think a combination of histology
2 and immunohistology, is very powerful. And I think for
3 example the microvascular injury I think it's very
4 difficult to get at when you're just looking at
5 molecular signals. You can't really see -- I mean,
6 what you're going to get mostly is the signals from the
7 tubules. And so it's difficult I think, to -- I mean,
8 you're getting different kind of information. You're
9 obviously getting a lot of metabolic information.
10 You're getting a lot of very specific molecular
11 information, but I think that histology gives some form
12 and substance to that.

13 And I think -- Phil and I have always agreed
14 on this point. I think that you combine the
15 histological observations and the molecular
16 observations, and I think you use a combined report
17 form. As a matter of fact, the University of Alberta,
18 where you take histologic variables, the most relevant
19 molecular variables and put them together in a report
20 that is integrated. And I think so to just focus on
21 the molecules perhaps you lose some information.
22 Certainly the histology can't give you the information

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1 that the molecular signals can, but I think combining
2 the two, you end up with a very powerful and relatively
3 complete picture. That said, though, I also am a
4 believer in biomarkers, I think. But I think people
5 who would advocate biomarkers would agree that you need
6 to see the tissue as well.

7 So I think the three approaches, I'm hoping
8 that we're not going to develop the philosophical
9 approach of eliminating any of these approaches because
10 I think they all have value.

11 DR. HALLORAN: Just as a point of
12 clarification, one of the gene sets I showed you were
13 the endothelia genes, so the endothelial genes are
14 remodeled. The endothelium is remodeled during the
15 injury response, so very predictably.

16 DR. ARCHDEACON: Dr. Abecassis?

17 DR. ABECASSIS: All right, I hate to say this
18 in a room full of nephrologists and renal pathologists,
19 but there is -- there are other spaces other than the
20 kidney. I really think that -- you know, if you think
21 you're going to keep biopsying a kidney whether it's to
22 look at histology, as to pathology, kidney biomarkers,

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1 you know, you're going to have a lot of patients who
2 are unhappy with that and complications of biopsy.

3 So, yeah, you need to know what's going on in
4 the kidney, and I'm sorry I missed the later part of
5 Phil's talk, but I think you really have to identify
6 biomarkers in the urine, biomarkers in the plasma,
7 biomarkers in the peripheral blood cell compartment,
8 that tell you what's going on in the kidney. And I
9 know Phil's view on this. I've heard it for several
10 years now. It's whatever is going on -- it's the
11 kidney, stupid, is Phil's view on this. But, you know,
12 at the end of the day, there's only so many times you
13 can biopsy a kidney, especially in the early post-
14 operative period. So I think the focus really does
15 need to be on peripheral and blood and plasma and urine
16 biomarkers.

17 DR. ARCHDEACON: Thanks. Dr. Bonventre, I
18 apologize.

19 DR. BONVENTRE: I just to want to actually,
20 we're in an FDA meeting and we're giving signals to the
21 FDA, and I think we ought to call the question. What
22 I'm hearing is that delayed graft function is not an

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1 endpoint for looking at pharmaceutical agents or other
2 things that are given early on fairly on peri-
3 transplant. Is that the signal we want to be giving?
4 You know, it's something. It's -- and I think we ought
5 to just clarify it. Is it okay to give -- is that the
6 signal in standard kidneys that are transplanted but
7 not the signal -- in other words, if we're looking at
8 aged kidneys that potentially delay graft function is
9 something that we might be able to use as a surrogate
10 in the short-term, as an indicator of long-term
11 efficacy of an intervention? I just think it's -- from
12 what I'm hearing, I could imagine that our FDA
13 colleagues are getting a signal and I just want to,
14 from the experts here, sort of just make sure that
15 we're clear about that signal.

16 DR. MATAS: So delayed graft function,
17 without an impact on 1, 3 and 5-year graft survival, is
18 not an endpoint, right? And you'd agree to that. I
19 mean, that's the problem so I would argue that even
20 though there are bad things about delayed graft
21 function other one through 5-year graft survival, like
22 the cost and all those things, but what we're really

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1 trying to do is achieve long-term graft survival and
2 perhaps as Bruce Kaplan would argue find a way to use
3 some of the kidneys that we're currently not using,
4 which may be a different kind of an endpoint. So I
5 think we have to sort that out, and that would be the -
6 - I think that's part of the message.

7 DR. BONVENTRE: So that's what I'm hearing in
8 some sense, but I -- from Phil I hear maybe if you
9 segment the group in the context of the age of the
10 kidney maybe that's -- maybe we could use delayed graft
11 function.

12 DR. ARCHDEACON: Dr. Woodle, Dr. Halloran and
13 then Dr. Albrecht.

14 DR. WOODLE: I think what I'm hearing is that
15 the traditional definition of DGF, such as dialysis in
16 the first week, has some very serious problems with it.
17 It includes renal dysfunction from a number of
18 different causes, some of which can be addressed with
19 inclusion/exclusion criteria so that it's better
20 reflected, but the problem is that it is subjective and
21 that's a fundamental problem with it. It's also a
22 binary component. It's been used binary. It's either

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1 there or it's not there and that doesn't really reflect
2 the fuller spectrum of renal function that we see there
3 are spectrums in between. So I think that's the
4 message that I'm hearing.

5 DR. HALLORAN: I'd like to be very
6 encouraging to those that want to give us some new
7 tools to intervene, to reduce kidney injury, to manage
8 kidney injury in relationship to the problem of
9 transplanting the available kidney pool. Three
10 thousand kidneys were thrown out last year after being
11 harvested because the clinician was so uncertain about
12 whether it was good enough for the patient. Those
13 kidneys could be transplanted. I think almost all of
14 them could be transplanted, if we could give the
15 clinician a number. We could say, this kidney has a
16 number below 42; therefore, you can transplant it. But
17 you've got to have some quantitative assessment of the
18 tissue.

19 And so I would say that delayed graft
20 function is not suitable as an endpoint, for the
21 reasons that Arthur outlined, but acute kidney injury
22 in its interaction with the organs that we have to

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1 transplant is a very serious problem and if you win in
2 that space, you would win in the intensive care unit,
3 too. You win in a much bigger space.

4 DR. ARCHDEACON: Dr. Parikh had a comment and
5 I think Dr. Albrecht wanted to wrap up perhaps after
6 that. I'm sorry, you had a different question?

7 DR. PARIKH: So I think this is an ongoing
8 debate in the field is DGF a good surrogate outcome.
9 Clearly, it's not a good outcome for case for Phase 3,
10 Phase 4 trials. But if you are a trialist trying to
11 make a decision at the level of Phase 2, should you
12 carry it forward. Currently we do not have anything
13 else except DGF. It's equivalent to mortality in
14 cardiovascular field. There are people who die outside
15 heart disease.

16 So if DGF is used as an outcome, it should be
17 used with some caution and maybe adjudicated diagnoses
18 of DGF, but protocol indications of DGF would have to
19 be qualified so it can become a viable outcome, and you
20 don't make a false negative decision for a drug and
21 throw it out. But you need a short-term outcome for
22 Phase 2 trials otherwise you cannot do one-year

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1 studies.

2 DR. ALBRECHT: So actually the speakers,
3 between Dr. Bonventre's comment and my comment have
4 talked about some of the -- some of what I wanted to
5 mention, which is I think you were asking the question
6 about what signal are you sending and I think and what
7 we'd like to do is ask -- that's actually exactly the
8 question that we're trying to ask this panel to
9 discuss. And although the question has been focused
10 primarily on the first question in this panel
11 discussion, we did raise the questions in the other --
12 or we did ask that the group discuss short-term and
13 long-term outcomes in correlation. So I think that is
14 exactly part of the discussion we'd like to have about
15 DGF, what is it, how valuable is it, is it useful, how
16 is it useful, and how does it relate to the more long-
17 term outcome which, again, as I said, the panel has
18 been discussing. I think we can do five or ten more
19 minutes.

20 DR. LORBER: So could I throw out just a
21 little bit more? What I thought I heard was that maybe
22 it's not just DGF, but is it something about injury in

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1 the setting of, for example, how many nephrons were
2 transplanted or how many nephrons are surviving, and is
3 that a way to maybe focus this a little bit more?

4 DR. BONVENTRE: I mean, my feeling, from what
5 I heard from Dr. Halloran and my own bias from the
6 animal studies that we've done little bit that I'll
7 talk about tomorrow, is that, you know, as he's pointed
8 out a number of years ago is that the aged kidney,
9 whether it's senescence or some other things, certainly
10 related to the number of nephrons but there may be
11 other aspects that make one kidney more aged than
12 another that's different than chronological age clearly
13 could have a difference. Maybe an acute kidney injury
14 in the setting of that subgroup of kidneys may be
15 different than acute kidney injury in the setting of,
16 you know, a 25-year-old donor kidney.

17 DR. ARCHDEACON: I apologize for my left-
18 sided hemi-neglect here, but I think Dr. Lundberg had a
19 question or comment and then Dr. Hanto and Dr. Feng?

20 DR. LUNDBERG: Bill Lundberg from Alexion
21 Pharmaceuticals. I think this is a very important
22 conversation from us in the industry. We're trying to

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1 developing drugs in the States, and it's very important
2 for me to hear that DGF in and of itself is not
3 potentially a clinical benefit endpoint when we think
4 about developing drugs here. In the mandate to either
5 have kidney survive longer or be able to increase the
6 donor pool I wanted to ask if a DGF trial in early
7 development in a population of patients with high-risk
8 kidneys demonstrating a reduction in the rate of DGF in
9 that population would be predictive or perhaps more
10 supportive of this concept of being able to expand the
11 donor pool and how would we go about thinking about
12 that in the context of biomarkers and the discussion
13 that's been going on.

14 DR. ARCHDEACON: So before we move to Dr.
15 Hanto, I just wanted to provide one comment which is as
16 I understood it, I think we were talking about DGF as a
17 measure of ischemia reperfusion injury within this
18 session. I think there is a separate question about
19 whether DGF has clinical consequences which make it
20 significant that it would be justifiable as an
21 endpoint, but your point may be correct, but I just
22 want to leave that a little bit open. Dr. Hanto?

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1 DR. HANTO: I guess what I was hearing was
2 that DGF is not necessarily terrific as currently
3 defined but we need a better, tighter definition
4 because there certainly are studies where they used,
5 and this is to Arthur's point on some of their studies
6 where a very tight definition of DGF has been used.
7 It's demonstrated an impact on six-month creatinine and
8 the GFR, which may relate to the number of nephron
9 concept that Phil talks about, which that may have an
10 effect on long-term outcomes. So I think if we throw
11 out DGF as an endpoint, I think we may have some
12 difficulty in finding other good, easy measurable
13 endpoints, and I would like to see us look very
14 carefully at that.

15 And to echo Phil's comments about the time
16 zero biopsies, Terry Strom published a paper in JC 2005
17 looking at time zero biopsies and looking at pro-
18 inflammatory genes, anti-apoptotic genes, protective
19 genes that did predict in fact, delayed graft function
20 in kidney patients. And if we have something like that
21 that is reproducible as Phil says, a number, I think
22 that will be very useful to clinicians that want to

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1 extend the boundaries of the kinds of kidneys that we
2 use, whether the types of donors that we use or even
3 kidneys that are frequently getting turned down now
4 because they had 18, 20 hours of cold ischemia, which
5 might work fine.

6 DR. FENG: I was just going to add that I
7 think, as I talked about in the donor talk, there's --
8 the kidney has an incredible ability to tolerate the
9 injury if the basic substrate is high quality. And so
10 I think we've heard that that's probably a big reason
11 why DGF in the broadest sense may not have an impact on
12 long-term outcomes because a large majority of the
13 kidneys that we use are still standard types of donors.
14 And I think we see that from both the using kidneys and
15 acute renal failure, which I think we all are using
16 more and more. These kidneys work fine in the long
17 term, and in that DCD group where, again, the DGF
18 doesn't seem to translate into as much of a hit.

19 So I think in order to help clinicians make
20 decisions about that do we use a kidney or not that has
21 to do with some assessment of the protoplasm before we
22 even put the kidney in. And I think that is also going

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1 to be potentially a very important way to stratify any
2 intervention trials we do because I think it's that
3 baseline protoplasm quality that sets that
4 vulnerability to the injury that then can translate
5 into whether the DGF and the insult leads to a
6 detriment in outcomes.

7 And so I think we have to focus on this
8 instead of just suggesting on that time zero or time
9 minus in order to be able to get that information and
10 that may actually help us interpret the information
11 that is to follow.

12 DR. ARCHDEACON: So if we could just go back
13 to the microphone, and I think that may be the last
14 question, unless anyone else has any pressing comment.

15 DR. SILVERSTEIN: Thank you. Doug
16 Silverstein. I'm a medical officer at the FDA. My
17 problem with DGF have always been twofold. Number one,
18 it's an all or none phenomenon; either you have it or
19 you don't. And the second problem that I have with it
20 is how is it assessed over time. My proposal would be,
21 we have LIFO criteria for AKI and I'm wondering if
22 there has been any effort, if there is any effort

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1 undergoing to develop a similar criteria to look at
2 graft function in the first week of life as opposed to
3 the same, go on dialysis or you don't go on dialysis.
4 So is there a way to parse this out a little bit to get
5 a better assessment tool as opposed to just looking at
6 an all or none phenomenon and you either go on dialysis
7 or you don't?

8 DR. MATAS: So remember, you can go on
9 dialysis for various reasons. I think as Doug
10 suggested and as Doug reiterated, you know, there's no
11 reason why they can't go back and try and come up with
12 a better definition especially in terms of study
13 design, but it has to be consistent and it has to be
14 consistent amongst the study centers in terms of how
15 they take care of the patients. But DGF as it's
16 currently defined, is the issue, and it leaves out some
17 of the other issues as Steve pointed out. So I think
18 your point is well taken.

19 DR. ARCHDEACON: So Dr. Halloran had one
20 comment and then we'll wrap up after that.

21 DR. HALLORAN: Whatever we use has to be
22 quantitative. This idea of dichotomizing DGF or TGF,

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1 that is not working, and as I showed you in the
2 molecular studies, if there's no signal if you just use
3 DGF versus no DGF, because Arthur's slow kidneys are
4 just about as bad and that's the problem, so it has to
5 become quantitative.

6 And the other thing is that in order to
7 quantitate it you have to normalize it against another
8 -- a whole population to get the numbers. So to say
9 Mrs. Jones has 42 in her kidney, then that has to be
10 compared to a stat -- normalized across a population.

11 DR. ARCHDEACON: So I'll just make one
12 summary comment and then I'll turn it over to Dr.
13 Albrecht to get some instructions. So it does sound,
14 in this section we heard from Dr. Matas definite
15 deficiencies when just relying strictly on clinical
16 measures. And I think across both biopsy and serum and
17 urine biomarkers we definitely saw some room for added
18 value. I think we opened this session by having a sort
19 of provocative question about whether it be deficient
20 to not include certain things, but certainly it was
21 meant to be sort of just provocative and I think that
22 the conversation has been very helpful and that it

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1 illustrated the value of each of these different
2 approaches all through.

3 DR. ALBRECHT: Thank you. So just a couple
4 of practical comments. Today we have an hour allocated
5 for lunch and lunch is on your own. And for those who
6 do not wish to leave the hotel, I've been told that the
7 hotel does have a lunch buffet special and you can take
8 that up as an opportunity.

9 I wanted to speak more about tomorrow.
10 Tomorrow's agenda is really full. We start at 8:00 in
11 the morning promptly and we will finish at 3 o'clock
12 promptly, and as a result we have an extremely short
13 lunch break, if you will. And so my next comments are
14 more directed to the audience because for the panel
15 your arrangements have been finalized. So for the
16 audience, up at the registration desk there is a sheet
17 where you do have the option if you'd like to to
18 purchase a box lunch and bring it back to the room so
19 that tomorrow we can pretty much continue from morning
20 through the afternoon with just about a half-hour for
21 the lunch break. So again, the sheet is up at the
22 registration desk if you're interested and the plan

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1 tomorrow is that we will take a short break at lunch to
2 get through it and then we'll promptly continue so that
3 we can finish it at 3:00 o'clock so people can make
4 their flight.

5 So that's all I wanted to say. Today what
6 I'd like to do is ask that at 2:30 promptly we're back
7 here so we can reconvene. Thank you.

8 (Recess taken.)

9 Session 3: Current Management Strategies and Outcomes

10 DR. ALBRECHT: Okay. If I could ask everyone
11 to take their seats, we're going to be starting with
12 the first afternoon session, which is Session No. 3,
13 and our co-moderators are Dr. Michael Abecassis and Dr.
14 Joette Meyer.

15 Dr. Meyer.

16 DR. MEYER: So welcome back after lunch. The
17 Session 3 is titled "Current Management Strategies and
18 Outcomes." It's a short session. We have three
19 speakers. The first is going to be my co-moderator,
20 Dr. Abecassis, and he's going to focus on treatment of
21 the donor.

22 Dr. Light will follow and speak about

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1 natural history, management and clinical outcomes in
2 the recipient.

3 And Dr. Cantarovich will finish out the
4 session by talking about previously studied therapeutic
5 agents that were evaluated in randomized controlled
6 trials.

7 So just one note before Dr. Abecassis starts,
8 and then I just wanted to acknowledge that the focus of
9 the workshop is understanding ischemia reperfusion
10 injury for the purposes of developing therapeutics for
11 use in the recipient and also for devices for organ
12 preservation. And in planning the workshop, we
13 acknowledged the importance of treating the donor as
14 well.

15 But since treatment of the donor requires
16 legal and ethical considerations, we really decided
17 that it was a much broader topic and that we wouldn't
18 be able to give it adequate discussion during these two
19 days. But we are noticing the interest of the audience
20 and the panel members in speaking about treatment of
21 the donor, and we will consider this for a future
22 workshop topic.

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1 So with that, Dr. Abecassis.

2 DR. ABECASSIS: Thank you very much.

3 I apologize for being late. It was Phil
4 Halloran's fault.

5 (Laughter.)

6 DR. ABECASSIS: So this is a session that is
7 supposed to talk about current management strategies
8 and outcomes. So we're going to switch gears a little
9 bit from this morning, and my talk is specific to
10 treatments of the donor, including ischemic
11 preconditioning.

12 And I could tell you this talk could be very,
13 very short. I scoured the literature looking for
14 exciting clinical trials to tell you about, and it was
15 a lot of scouring and not a lot of finding. In fact,
16 I'm glad Babu is here because the only study that I
17 could find was his after looking at NIH.gov in an act
18 of desperation.

19 So first I wanted to go over the logistics of
20 treating a donor, and I think some of this has been
21 alluded to this morning, but I wanted to maybe drill
22 down a little bit more. So you can treat an organ

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1 donor pre-donation, but only once donor consent is
2 obtained, but really this only applies to DBD, or
3 donation after brain death donors, who have the lowest
4 risk of DGF, and you know, we're going to call DGF the
5 three-letter word, because for DCD donors even after
6 you have consent for donation after cardiac death, you
7 really can't do anything to them in most hospitals, and
8 it's important to understand that for DCD donors most
9 of the time you're relying on what the particular
10 hospital policy is. It's not an OPO policy or state
11 policy. It gets down to what the hospital's policy is
12 whether you can do this in the ICU or in the operating
13 room, whether, you know, you can't heparin and there's
14 all these rules.

15 So essentially, and I don't know if most of
16 you know this, but a transplant surgeon either went to
17 jail or came close to going to jail a couple of years
18 ago because he suggested that this DCD get some
19 morphine.

20 So you can't touch; you can't go anywhere
21 near the donor for a DCD until five to ten minutes
22 after the heart has stopped. So to try to do a trial,

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1 and this is the group with the highest DGF ratio.

2 And, by the way, I want to make sure that we
3 clarify something that Sandy Feng said earlier. I
4 think when Sandy was talking about outcome of DCD
5 versus DBD she was talking about the six and one and
6 three year outcome, not the DGF rate because the DGF
7 rate is definitely higher. It's about twice time
8 period by time period, DCD versus DBD. So I wanted to
9 clarify that it's the DGF rate that's important.

10 But if you wanted to pretreat a DCD donor,
11 you can't. So there's no sense even thinking about it.

12 Now, you could potentially treat a DCD donor,
13 but you'd have to have special dispensation like the
14 recent big thing in New York where they got vans
15 driving around, and they can get the legislation to
16 allow for interventions. And maybe Jimmy wants to talk
17 about in #Washington, you know, putting in these
18 cannulas and precooling and stuff like that, but that
19 requires very specific changes in the law, and so in
20 most states, in most jurisdictions, you're not allowed
21 to go near a DCD donor until five or ten minutes after
22 cessation of heartbeat.

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1 Now, if you're talking about brain death,
2 well, we know that the brain death factors are already
3 released in the DBD by the time consent is obtained.
4 So you can't really pretreat a DBD donor before they
5 become brain dead because they're not consented to be a
6 donor. So if you're going to treat a DBD donor, you
7 have to do it after establishment and confirmation of
8 brain death, which, again, is different for every
9 hospital and every OPO, every hospital within an OPO.

10 Now, the other issue is that if you're going
11 to treat any donor, any deceased donor, it really
12 requires a wide approval from not only all the
13 transplant programs in the OPO, but all of the
14 different organ groups.

15 So there are some organ people that are more
16 finicky than others. The lung people tend to be prima
17 donnas. So I hope there's a bunch of lung people here.
18 They're all my friends, but they're real prima donnas
19 because they worry about too much lung water and all
20 this kind of stuff. So you've got to keep them dry as
21 a chip, and that's bad for the kidneys, and the liver
22 people don't really care, and the pancreas people don't

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1 want edema. So even how much fluid to give becomes an
2 issue.

3 So any time that you are considering doing
4 something interventional to a deceased donor, not only
5 do you have to get buy-in from all of your competitors,
6 which are the other transplant programs in your OPO,
7 which by itself is a big deal, but you have to get
8 approval from all the other organ people. So what may
9 be good for the kidney may not be good for the lungs.
10 So you have to take that into consideration.

11 And of course, you can treat a live donor.
12 That's easy. They're not brain dead. They can
13 consent, not a problem. But then you get into all
14 kinds of ethical and issues, all kinds of ethical and
15 moral issues that need to be considered, and it's
16 usually not a good idea to do something to a live donor
17 where you don't really know what the result might be,
18 not just tomorrow, but in five years and ten years, et
19 cetera.

20 So treating living donors is a big deal.
21 Plus they don't have a high rate of DGF anyway. So
22 it's not like this is your prime population, and so the

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1 most logical donor treatment may be treating the organ
2 post removal and pre-implantation because then you're
3 not affecting the other organs. You can consent the
4 recipient, but the problem is that delivery of a drug
5 or an agent or a molecule is problematic, and the
6 kinetics of delivery and the kinetics of everything
7 that needs to go on are extremely unpredictable. It
8 has to be done in the cold, and you have to kind of
9 assume that things that happened at 37 degrees also
10 happened in the cold, and we don't have, as everybody
11 knows, great ways to deliver things into cells. So
12 this is an issue.

13 But theoretically, that would be the best
14 time to actually try to get to an organ. But then the
15 things that have happened have already happened.
16 You've already cross-clamped. You've already had a
17 brain dead donor. So, you know, you've already had a
18 lot of the things happen that you're trying to avoid.
19 To my earlier point with Phil, you know, you want to
20 avoid injury, and the way to do that would be to take
21 the organ before the donor even becomes brain dead and
22 be able to do something to it, and we've gone over all

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1 of the difficulties with that.

2 Therefore, but if you were going to treat an
3 organ, probably the best way to do that would be to put
4 the organ on a pump under good, stable conditions and
5 be able to treat an organ on a pump, and that would
6 allow you to study kinetics, to study what's going in,
7 what's coming out, what the flows are, what the
8 pressures, et cetera, et cetera.

9 So, in summary, most applicable treatments
10 may be organ treatments post implantation-reperfusion,
11 but that's somebody else's topic. So I'm good. So
12 everything that I'm supposed to talk about I can't
13 because it doesn't make a lot of sense and so you see
14 the difficulty.

15 Now, I tried to look. So this is not my area
16 of expertise. My area, I happen to be interested in
17 ischemia reperfusion injury in the kidney of mice only
18 because I'm interested in reactivation of CMV, which
19 has absolutely nothing to do with anything that anybody
20 is thinking about today.

21 So I thought I'd sort of refresh my memory of
22 what's important, and I found this article not because

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1 it's in a great journal and not because, you know, I
2 even know the people, but it actually read very nicely,
3 and I thought it was a very good summary. And what I
4 learned from this, and I think it was Doug who brought
5 this up earlier or somebody from that side -- I think
6 it was Doug -- there are definitions of AKI, but
7 there's really no definition of AKI in a kidney
8 transplant.

9 And I think, if nothing else, we should be
10 working really hard at trying to standardize what we
11 now call DGF because DGF, the definition may be that
12 the weekend is coming up and you don't want to bring in
13 the dialysis people on the weekend. So you're going to
14 dialyze on Friday because, you know, who knows what
15 might happen on the weekend, or it might be a fight
16 between the surgeon and the nephrologist, and as Phil
17 was saying, surgeons don't like to dialyze because by
18 definition it's a failure. It's a DGF. Nephrologists
19 love to dialyze. So it depends on who wins that week.

20 If the nephrologist wins, it's DGF. If the
21 surgeon wins, it's not DGF. So we need a better
22 definition of acute kidney injury in the post

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1 transplant period.

2 But reading this review, there were things
3 that came up that I thought were interesting, and the
4 reason I made this slide so busy is hopefully you won't
5 read it, and you know, I put the references and
6 everything, but you know, so HIF seems to be something
7 that people are excited about, and it has to do with
8 the fact that the HIF's alpha subunit escapes
9 degradation. So anything that you can do to stabilize
10 that molecule is important, and I thought it was kind
11 of cool that xenon anesthesia in rodents does that.

12 I know Doug is going to talk about carbon
13 monoxide, and my summary of reading the literature on
14 this is there's a lot of talk. There's a lot of talk
15 about a lot of molecules and a lot of potential
16 targets, but I have yet to see anybody do anything in
17 the clinical arena other than carbon monoxide and maybe
18 a couple of other ideas, but I think it really does
19 have to do with the fact that I mentioned earlier.
20 It's really hard to pre-treat a donor and try to
21 achieve a benefit to it.

22 So that brings me to ischemic

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1 preconditioning, which is sort of the most attractive
2 hypothesis that's out there right now, and before I go
3 any further in this, lock into that. So why is this
4 important?

5 And then this xenon paper kind of caught my
6 attention because this is not ischemic preconditioning
7 but it's preconditioning using something that hopefully
8 will stabilize the right molecules. So now we're on to
9 ischemic preconditions. So I was a little ahead of
10 myself.

11 So why is ischemic preconditioning important?
12 Because presumably by -- so what is ischemic
13 preconditioning for people that are not familiar with
14 this? You basically make an organ ischemic for a very
15 short -- relatively short period of time, and then let
16 the clamp go so that the organ gets a drink again, and
17 presumably you've set off all of these repair
18 mechanisms that Dr. Halloran was talking about that are
19 good so that when you clamp it for real you've got all
20 of these things going already that are supposed to be
21 healing the organ or trying to heal the organ, and
22 that's sort of the easy way to try to understand this.

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1 And there's all kinds of studies that have
2 been done, and I just put a few. People are all
3 excited. This may actually affect Tregs and
4 macrophages and all this kind of stuff. There's a lot
5 of very exciting rodent experience in this, and you
6 know, I could probably fill several slides with all the
7 different molecules that have been brought up a
8 possibilities.

9 The sad news about this is there was a period
10 of about three or four years where there was a lot of
11 excitement about this in liver resection. So I'm a
12 liver surgeon, and I've been paying a lot of attention
13 to this because it turns out if you're going to cut
14 half of somebody's liver, it turns out that if you
15 clamp the hilum for ten minutes and made the liver
16 ischemic and then let it go for another ten minutes and
17 then clamped it again and did the liver resection under
18 total vascular exclusion, there were people that were
19 very excited because they thought that the results were
20 better on the piece of liver that was stained.

21 So if you looked at liver enzymes or you
22 looked at all of these molecules, it was some very good

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1 way to prevent ischemic damage to the part of the liver
2 that you're not taking out.

3 So there was a randomized controlled study
4 that came out that showed all of this benefit, and
5 recently there's a randomized controlled study that
6 shows that there's absolutely no benefit. So you have
7 two randomized controlled trials that are in complete
8 conflict with each other.

9 And by the way, I don't know what surgeon is
10 going to be happy with saying, "Do you know what? Why
11 don't we put a clamp on this kidney for ten minutes
12 before we take it out and transplant it into somebody
13 else?" You know, that's causing ischemia to an organ
14 that you're going to transplant. So I'm not sure that
15 you'd get a lot of sell on that.

16 However, this idea of remote ischemic
17 preconditioning is one that seems attractive. So just
18 like the title says, so this means that you make some
19 other part of the body ischemic. You get all of these
20 nice molecules going systemically and hopefully they'll
21 have that beneficial effect on the organ of interest so
22 that when you clamp to take it out, it's already kind

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1 of protected.

2 So the idea is you don't have to put a clamp
3 on that organ. You can put a clamp on something else
4 or interrupt blood flow to something else or you can
5 get the same systemic effect, and this is all good. So
6 theoretically this would be something very interesting.

7 And there's a whole bunch of papers on this
8 having absolutely nothing to do with transplant, mostly
9 in the cardiac, in the CABG area and a lot of very
10 vascular kind of oriented areas.

11 So I was preparing for this talk, and I'm
12 really scrounging. I'm saying I'm not going to have
13 anything to say, and so I went there and I found this
14 announcement of a grant or of a study, and I thought,
15 "Oh, I haven't heard anything about this," and I
16 checked it out and it was 2009. So I said, "Well, I
17 wonder who's doing this."

18 So Dr. Koneru was sitting here. So I saw his
19 name. He was the PI. I said, "I know Babu. I'll call
20 him and see what's going on with this," and he was very
21 kind and has given me the slides that I'm going to show
22 you, which are the results of this study, which are not

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1 published. I don't know if it's even been -- has it
2 been presented, Babu anywhere?

3 It hasn't been presented. So thank you for
4 allowing us to have these data, and by the way, he just
5 found out that this was funded by HRSA. HRSA is here.
6 Thank you for funding this kind of work.

7 And the bottom line is the question that they
8 had that they wanted to answer is: does remote
9 ischemic preconditioning in abdominal organ
10 transplantation affect the outcome? And this was
11 actually not just for kidneys. Kidneys and livers and
12 I don't know what other organs, but it was more than
13 just one organ, and the amazing thing is they got
14 approval from the OPO and from all the organ people,
15 and they did all the things that I said would be very
16 difficult to do.

17 And so let me go back. And these slides are
18 all courtesy of Dr. Koneru.

19 So the hypothesis is that lower limb ischemia
20 induce remote preconditioning prior to organ recovery
21 in deceased donors, and that this will improve early
22 and late outcomes after kidney transplantation. And

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1 so, again, this picture was provided to me by Babu, and
2 so you can see they put these blood pressure cuffs in
3 the mid-thigh, and the idea was for this to be
4 prospective, stratified, SCD versus ECD, randomized one
5 to one.

6 By the way, if I'm saying anything wrong,
7 please correct me.

8 No remote ischemia versus remote ischemia.
9 All five New Jersey kidney transplant centers agreed to
10 this. Presumably all the different organ groups agreed
11 to this, and their protocol was ten minutes of
12 sequential inflation of the tourniquets, both lower
13 extremities, 30 to 60 minutes before cross-clamp.

14 And you know, as I'm going through this in my
15 head, having been in more donors than I care to admit,
16 you know, timing cross-clamping with all different
17 teams is not a minor feat because you never know when
18 the heart guys are going to want to clamp, and they
19 want to know what the recipient is doing, and the lung
20 guys, of course, they're always prima donnas, and then
21 the kidney guys, they really don't care, and the liver
22 guys, who are the most important guys in the room, you

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1 know, they're telling you what's going to go on.

2 So this by itself is not a minor feat, and
3 then the rest of procurement and everything else is
4 standard of practice. So all that they did was they --
5 well, not all that they did. The intervention here is
6 that they applied tourniquets to both thighs, and they
7 inflated them presumably to make both legs ischemic,
8 and then this was 30 to 60 minutes of time allowed for
9 the systemic reaction to this, to theoretically or
10 hypothetically have an effect on the organs.

11 And there were early and late outcomes. The
12 early outcomes, the primary endpoint was initial poor
13 function, and they defined DGF as hemodialysis during
14 the first week, and we talked about that. And then
15 slow graft function; no dialysis, but CRR2 less than 30
16 percent, and they defined CRR2 as a creatinine
17 reduction by post-op day two, serum creatinine day one
18 minus day two divided by serum creatinine and multiply
19 it by 100 with a percent.

20 And then a secondary endpoint had to do with
21 resource utilization. We talked about that earlier,
22 the need for dialysis and the cost of DGF, and duration

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1 of dialysis id DGF occurred, and the complications in
2 the first month, and these were graded using the
3 Clavien classification of surgical complications.

4 And the late outcomes were primary non-
5 function, and the variable was eGFR at six months and a
6 year, and then the secondary was acute rejection, graft
7 survival, patient survival, and the reason I'm going
8 into a lot of detail is I know that one of the purposes
9 of this meeting over the next couple of days is to try
10 to identify what are the right endpoints and what are
11 people using and what's important and what's not
12 important. There's a lot of controversy about
13 rejection. So variables was treated; biopsy proven
14 acute rejection during the first year; graft loss at
15 one and two years; patient death at one and two years.

16 And this is the update that I got about a
17 week ago from Dr. Koneru. So from February 2009 to
18 November 2010, after stratification of ECD, SCD, 85
19 deceased donors were prospectively randomized one to
20 one, RIPC versus no RIPC. Informed consent was waived,
21 which answers questions about how do you do this in
22 terms of the informed consent, but a simple permission

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1 was obtained in the form of a check box under the
2 nation consent, and the recipient consent was also
3 waived.

4 The intervention consisted of a single
5 application in the operating room. We've talked about
6 inflated to 250 millimeters of mercury for ten minutes
7 on each side. The deflation of the second cuff was
8 timed to be 30/60 minutes, and all other care was
9 standard.

10 And kidney recipient data were obtained with
11 the cooperation of all the centers. So there was a lot
12 of collaboration and the trial was registered, which
13 how I found out about it.

14 And I took the data that Dr. Koneru sent me,
15 and I made a table of things that I thought were
16 relevant, and you can see in the null RITC group 64 and
17 in the RITC group 66. There were some patients that
18 were excluded for various reasons, and you can see if
19 -- and, by the way, I'm told that the statistics on
20 this have not been done, right? So they're in the
21 process of being done. So I don't have any statistics.
22 So all we can do at this point is eyeball the data.

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1 So it looks like there was no difference in
2 terms of initial poor function. DGF may be a little
3 higher with the remote ischemic, but who knows if this
4 is statistically significant or not? And a little
5 higher SGF in the group. So when you take them
6 together, which I think is the right way to do this,
7 there's no difference.

8 In terms of hospital days at first month, no
9 difference. Biopsy confirmed rejection, no difference,
10 and you can just go all the way. Chronic allograft
11 nephropathy, maybe a trend towards more in the no RITC
12 group. Six-month creatinine may be a little higher
13 than the RITC group. Six-month eGFR, essentially
14 identical. Twelve-month creatinine, again, if
15 anything, a little higher on this group. Twelve
16 months, a little lower in this group.

17 So, I mean, eyeballing the data I would say,
18 you know, we have to wait for the statistics, but
19 there's certainly nothing major jumping out at us.

20 Now, there was a very interesting finding
21 that had to do with pump parameters on these kidneys.
22 So of these 64 kidneys, 18 were pumped, and of these

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1 66, 16 kidneys were pumped. And, again, this was very
2 preliminary, and they did do some statistics on this,
3 and they looked at flow and resistance, which are the
4 two parameters that we tend to look at in pumped
5 kidneys to make decisions about whether we use them or
6 not, and there's certainly a difference in both the
7 flow and the resistance.

8 So for those of you that don't do this on a
9 daily basis, high flow is good; high pressure is bad.
10 So you want high flow with low pressure, which tells
11 you that the resistance in the vascular bed of the
12 kidney is low, and that's good. That's good perfusion.

13 So, again, this is very preliminary data. It
14 is unpublished. It is unrepresented except for here.
15 The randomized controlled trial suggests no difference
16 in early or late primary or secondary kidney endpoints
17 following remote ischemia reperfusion. Again, the
18 statistical analyses have not been completed. However,
19 there appears to be a benefit to kidney perfusion in
20 pumped kidneys from donors that were subjected to
21 remote induced preconditioning. And, again, I make a
22 note that this has recently been funded by HRSA.

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1 So in conclusion, in terms of donor
2 treatment, what does donor treatment really mean? Is
3 it the donor? Is it the organ? Is it pre-perfusion?
4 Is it post perfusion? I think, you know, you have to
5 answer the question at what point does that organ stop
6 being a donor organ and become a recipient organ, which
7 means that you can treat the recipient, and I think the
8 answer to that is probably right before you unclamp in
9 the recipient, but you know, you could split hairs
10 about what donor treatment really means.

11 The logistics of donor treatment per se are
12 very difficult, and I went through a lot of the reasons
13 as to why that is. You need multi-center OPOs. The
14 centers will fight it out. You need multi-organ
15 donors. The organ teams will fight it out, and for
16 living donors you have all kinds of ethical
17 considerations of giving a living donor anything that
18 they don't need.

19 There are lots of cellular molecular targets
20 that I could find. There seems to be a focus on HIF,
21 but I think a lot of this at this point we can call
22 hype more than hope because I don't see any evidence

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1 that any of these great molecules or targets have been
2 taken to the preclinical or certainly the clinical
3 arena.

4 Ischemic preconditioning may not be
5 applicable for the reasons that I suggested. I think
6 it would take a lot of courage for a surgeon to put a
7 clamp on an organ for ten minutes, risk of clots and
8 risk of all kinds of things that they're then going to
9 unclamp and then they're going to clamp again to take
10 out. I can't see myself doing it. I certainly can't
11 see myself agreeing to have any organs that I
12 transplant at this point going through this, especially
13 since the best data that we had on the liver resections
14 is now not confirmed.

15 And I think that the idea of remote ischemic
16 preconditioning is certainly applicable easily. I
17 think the group in New Jersey has just demonstrated
18 that. It holds some promise, but its effectiveness in
19 donor treatment remains to be proven. Are we looking
20 at the right endpoints?

21 I think we will await the final results of
22 this study, and I think that we really need to go back

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1 to what we talked about earlier in that the primary and
2 secondary endpoints need to be clinically relevant, but
3 we may do some studies and then learn something from
4 other measures. In this case I think what was learned
5 or what is being learned from the pump kidneys and the
6 pump parameters, I think, could be something that in my
7 opinion should at least be pursued.

8 I think that's it. So I'm going to sit down,
9 right? Okay.

10 (Applause.)

11 DR. MEYER: Our second speaker is Dr. Jimmy
12 Light from the Washington Hospital Center, and the
13 title of his talk is "Natural History, Management and
14 Clinical Outcomes of DGF in the Early Post-
15 Transplantation Period."

16 DR. LIGHT: So good afternoon, everyone.
17 This, you see the title, and my co-author, Dr. Africa,
18 one of my colleagues at the Washington Hospital Center.

19 So what I'm going to talk to you about is
20 essentially kind of how we do it, let's say. So
21 nothing here to disclose, and if you reduce it to the
22 ultimate simplicity, what you really want is the kidney

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1 to work to make your end, to eliminate the need for
2 dialysis, restore normal metabolism for the patient,
3 and thereby improve their quality of life. So that's
4 the overall objective of preservation.

5 And then when we think about kidney quality,
6 well, then you think about there being a hierarchy with
7 immediate graft function, slow graft function delayed
8 graft function, and some primary non-function,
9 hopefully very little, if any.

10 The objective of all the preservation is
11 actually to move everything up and have everything work
12 immediately if possible, and to shift all the
13 categories in that direction. But if you start with
14 this as the basic premise that all deceased donor
15 kidneys have a spectrum of injury created by donor
16 factors, recovery techniques, preservation solutions,
17 storage time, those all preexist and are not under
18 control of the transplant team at all, and so as the
19 surgeon, you go to the OR and you have your recipient
20 there, and you've got a box, and so the question is:
21 what's in the box? What's in the box? Because you
22 don't ever truly know exactly what you're getting

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1 unless you take it out of the box.

2 And you'll hear more about this trial from
3 another speaker, but that's in essence what they did in
4 this trial published just recently, was to take one
5 kidney out of the box and put it on a machine and leave
6 the other one in the box and then compare the outcomes.

7 And quite quickly, here are the outcomes, and
8 as you can see, the machine preservation arm has a
9 significantly lower DGF rate than the cold storage arm,
10 and that translated to improved graft survival, and
11 that improvement actually was quite remarkable in the
12 comparison group where there's machine preservation in
13 DGF versus the group cold storage in DGF. So you'll
14 hear more about that, I think, from another speaker.

15 So in summary, machine preservation reduced
16 the risk of delayed graft function compared to cold
17 storage regardless of the donor type. It reduced the
18 duration of DGF as well, and in recipients who
19 developed DGF, the graft survival was improved 12
20 percent in one year and better in all categories with
21 machine preservation versus cold storage.

22 So I guess the question is why don't we all

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1 do it all the time. So this trial shows -- I don't
2 know how I got these sequentially, but it's kind of
3 neat -- at any rate, machine preservation reduces
4 delayed graft function and reduces the deleterious
5 impact and improves graft survival, and this is a
6 really kind of good study.

7 Now, the second premise then is that the
8 things that are under control of the transplant surgeon
9 are the recipient management and the medications and
10 the decisions you make in the operating room. These
11 all strongly influence whether there is immediate
12 function or not, in essence, how the kidney functions.
13 The goal is always immediate graft function, and that's
14 the most desirable outcome.

15 Some things that can be done are to use
16 lymphocyte depletion, thymoglobulin or perhaps campath
17 pre-reperfusion to improve immediate function, and it
18 turns out to be good evidence for this, although I
19 think the mechanism is not fully explained, but the
20 evidence is here, and it's from a New England Journal
21 article by Goggins looking at the new England Organ
22 Bank data.

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1 And what you see here is that there's
2 significant improvement in early function -- this is a
3 tricky deal -- early function with machine
4 preservation, along with significant decrease in length
5 of stay, and the next slide, I think, amplifies that
6 just a bit more.

7 I believe you could see this for your own,
8 and the take-home line is that patients who received
9 thymoglobulin intraoperatively did significantly better
10 than those who received it post reperfusion or
11 postoperatively.

12 So other things you can do to promote
13 immediate function or to de-grease delayed graft
14 function are to avoid preoperative dialysis if at all
15 possible. There's a strange dynamic that goes on that
16 seems to transcend just volume reduction. That's not
17 adequately explained in my opinion, but it may very
18 well reflect cytokines or other things that are
19 released and are circulating as a result of blood
20 volume changes.

21 Obviously you should keep cold ischemia time
22 as short as possible, and there are plenty of studies

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1 looking at cold paired kidneys with cold storage versus
2 longer storage, and cold short always wins.

3 Interoperative hypotension and basal pressors
4 kind of go without much elaboration. If you want the
5 kidney to work, you have to give it stuff to work with.
6 Hypotension is definitely not a salutary event, and in
7 addition to, again, releasing catecholamines, and so
8 on.

9 You want to promote renal blood flow. The
10 best quick study on this, I think, was by Brennan from
11 some numbers of years ago where he gave all recipients
12 five liters of fluid. At the time we thought that was
13 really, hum, crazy, but what it turned out was that the
14 DGF rate was extremely low in his hands compared to
15 others in that same area.

16 Dopamine may or may not be helpful. It
17 doesn't seem to be hurtful. I think protecting the
18 tubules by decreasing their work and by increasing the
19 intraluminal volume seems very reasonable. So a little
20 Mannitol is good. I think more is better, and we're
21 kind of the big Mannitol guys, usually upwards of 100
22 grams per patient, which seems kind of ridiculous, I

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1 think, on the face of it, but over the years I've just
2 kept increasing the dose, and it seems to be well
3 tolerated and most all the time I think we have just
4 eight percent DGF perhaps as that result.

5 Lasix bolus, I think there's a paper in the
6 session that may contravene my opinion that Lasix does
7 decrease tubular work and does improve immediate
8 function. So we use it and use an infusion for the
9 first 24 hours or so.

10 And I think one of the more important things
11 is that we have no interest in extubating the recipient
12 in the operating room. We just take the patient to our
13 recovery area, leave them intubated, make sure the X-
14 ray is wet and then diurese, diurese, diurese, and
15 after a couple of liters of urine they seem to extubate
16 just fine. If they aren't making urine, well, then
17 they stay intubated until dialyzed usually 12 hours or
18 24 hours later.

19 So we think that if you hydrate adequately to
20 distend the left atrium, that's a good thing, and
21 atrial natriuretic factor, while it can't be measured
22 in standard clinical practice, does improve renal blood

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1 flow in the animal.

2 So here's a recent case. It's not showing up
3 so red hot. There's two patients. One is FR. The
4 other is CC. They got the same donor kidneys, 52 year
5 old female, hypertension, smoking history, CVA, bad
6 kidney on biopsy or not biopsy, but occlusive renal
7 artery disease at the aorta turnoff, but any rate,
8 there was good renal function, and the two recipients
9 are here. They're about the same, hypertension as
10 their history, some diabetes in both, dialysis for four
11 years, dialysis for six years, so on.

12 The main difference pre-transplant was that
13 FR had dialysis the day before. CC had not had
14 dialysis for a couple of days, and so he was dialyzed
15 immediately pre-transplant for good reasons; made
16 surgery safer.

17 Induction used depleting agents in both
18 cases, Thymo in this one; Campath in this one, and the
19 kidneys were relatively similar in terms of
20 atherosclerosis, and they had amputated. So we had
21 direct renal artery implants rather than patches like
22 you normally would.

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1 So some more details of the surgery, and the
2 main difference here is that CC had hypotensive
3 episodes in the operating room despite a lot of fluid.
4 I think this probably directly relates to pre-op
5 dialysis. Here's the fluids, significantly less in
6 this guy; the same amount of Mannitol, albumin, Lasix,
7 et cetera. Blood loss is relatively the same. OR
8 times are about the same.

9 Here's the ischemia times. First patient,
10 things went quite smoothly; made urine in the operating
11 room. Creatinine came down each day; no dialysis, and
12 by the 16th post-op day creatinine is pretty normal.

13 Here's this one with minimal function; needed
14 dialysis two days later, and by day 16 creatinine and
15 23. Creatinine is still significantly higher.

16 So this is a little kind of busy, I think,
17 more than anything, but FR is in blue. You just saw
18 all of that, and that's here. This is the creatinine
19 coming down to this value about three weeks later.
20 Here's the urine output for their SCC; creatinine
21 dialysis coming down. It's kind of a neat picture once
22 you get your hands around it.

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1 So here's the X-rays, pre and post, and I
2 don't know that they're a whole lot different, although
3 you could say that this patient, the one with immediate
4 function, went to the OR a little wetter, came out a
5 little wetter, and that was kind of consistent with our
6 hypothesis that expansion is a good thing in terms of
7 creating immediate renal function.

8 So what if you don't get immediate function?
9 Well, then here's the impact of a delayed graft
10 function according to SRTR data. You can see for
11 yourself graft survival on the ordinate and time on the
12 x-axis, and then the ten to 15 percent impact of DGF on
13 graft survival. That essentially never goes away.

14 And it's a little more marked, maybe only two
15 or three percent in the extended donor kidney, but in
16 any case DGF is a bad thing.

17 So what if there is? Well, then you have to
18 be sure that technical aspects of surgery are okay. We
19 have tools for that. We usually recheck the cross-
20 match and check donor specific antibody as well against
21 a different kind of panel to make sure there's no
22 antibody.

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1 If some are found, well, then you're obliged
2 to do something about it, pherese it to remove it;
3 immunoglobulin to interfere with it perhaps. Rituxan
4 and Velcade, or bortezomib, to try to get in the way of
5 more formation, and the T-cell depletion, those are all
6 somewhat draconian measures compared to what happens if
7 the kidney works immediately, but I think you need to
8 remove the immune component and hope the kidney will
9 recover, and you have to start immunosuppression, of
10 course, with regards to whether the kidney works or
11 not. That's a little counterintuitive because of the
12 Prograf or cyclosporine having a nephrotoxic sort of
13 component, but if you don't give it, well, then there
14 are T-cell factors that get elaborated that are not
15 taken care of by T-cell depletion.

16 So this kind of brings me to the end, and the
17 conclusions are here. I guess they're my final
18 thoughts, if you will. So what we would do is avoid
19 pre-dialysis at all costs, if possible. If the patient
20 hasn't been dialyzed for two days or three days but the
21 chemistries are reasonable, we wouldn't dialyze simply
22 because of the time. We would dialyze only to make

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1 anesthesia safer, if that was necessary.

2 We would use lymphocyte depleting antibodies
3 in everybody, and they're begun shortly after
4 anesthesia is begun so that they're on board at the
5 time of reperfusion.

6 We delay calcineurin inhibitor start until
7 usually three days post-op, but some time in the post-
8 op period. If the kidney is working, then we would use
9 our standard dose. If it's not working, we would use a
10 lower dose and sort of creep up on it, if you will.

11 And we always recheck immune parameters
12 within the first several days in case something was
13 missed during case or some kind of accelerated recall
14 that we weren't expecting so that you could use
15 measures to prevent or treat antibody mediated
16 rejection.

17 And I think that's kind of it. Thank you.

18 (Applause.)

19 DR. MEYER: Our next speaker is Marcello
20 Cantarovich from McGill University, and his talk is on
21 review of previously studied therapeutic agents,
22 including immunosuppressant and non-immunosuppressant

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1 drugs and biologics, and he's going to be looking at
2 randomized controlled trials.

3 DR. CANTAROVICH: Thank you. I would like to
4 thank the FDA and TTS for our invitation to attend this
5 meeting.

6 And this is my conflict of interest. That
7 was shown earlier.

8 And we reviewed the literature, the English
9 literature, and the key words were ischemia reperfusion
10 injury, DGF, ATN, and renal and kidney transplantation.
11 So there were ten papers dealing with randomized
12 controlled trials between 1985 and 2010, furosemide
13 versus controls; cyclosporine versus ALG; multivitamin
14 infusion versus controls; Anti-ICAM-1 monoclonal
15 antibody versus placebo; then pentoxifylline versus
16 placebo; intra-op versus post-op ATG; insulin growth
17 factor 1 versus placebo; Dopamine renal dose versus
18 Dopamine 1 receptor agonist; and the recent Cochrane
19 review on calcium channel blockers; and finally, EPO
20 versus controls.

21 So coming back to furosemide, this is a study
22 published as you can see in '85. Fifty renal

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1 transplant recipients received anywhere between 200 and
2 400 milligrams IV prior to reperfusion, and all the
3 patients received Mannitol. Controls received no
4 furosemide.

5 So what were the results? There was no
6 difference in the cold ischemia time, 33 versus 36
7 hours, and there was no difference in the need for
8 dialysis, about three quarters in both groups, and
9 again, no difference in one month serum creatinine.
10 There was no data on longer follow-up.

11 What about the use of cyclosporine versus ALG
12 in patients with DGF? You will see a variety of
13 definitions of DGF in this paper. It was defined as
14 diuresis of 700 cc's on day one and no fall in serum
15 creatinine.

16 In patients presenting with DGF, cyclosporine
17 is given at 12 milligrams per kilo or four milligrams
18 per kilo, and it was compared to ALG. All the patients
19 received prednisone.

20 A resolution of DGF was defined as no need
21 for dialysis, and 25 decline in serum creatinine.

22 So what were the results? The main result

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1 was the time to recovery of DGF from DGF, and as you
2 can see, patients who received cyclosporine recovered
3 at about 14 days compared to about ten days in patients
4 who received ALG.

5 In this slide you can see perhaps not that
6 well from far. Renal function parameters in this case,
7 in this case serum creatinine, that was not different
8 compared to what -- I'm sorry. It was higher in
9 cyclosporine treated patients at one month, at three
10 months, and at six months, but there was no difference
11 at one year.

12 There was no difference in graft survival
13 comparing patients receiving ALG or cyclosporine who
14 experienced DGF.

15 So in conclusion, cyclosporine compared to
16 ALG, we saw that a slightly increased duration of DGF,
17 four days; no effect on one year serum creatinine; and
18 no effect on graft survival.

19 This is a very interesting trial published in
20 Kidney International from 1993 about the use of
21 multivitamins. So the hypothesis was that ischemia
22 reperfusion injury in kidney transplantation is

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1 associated with lipid peroxidation and intubation of
2 lipid peroxidation with antioxidants would improve
3 kidney function. So how was lipid peroxidation
4 assessed?

5 It was assessed by measuring monoaldehyde
6 content by HPLC, and renal function was assessed using
7 serum creatinine and creatinine clearance. Fourteen
8 controls were compared to 16 patients who received this
9 compound, two vials of Omnibonia. This was a
10 European study.

11 So patients who received the multivitamin
12 infusion had lower levels of monoaldehyde as you can
13 see by the lower curve compared to controls, and serum
14 creatinine was lower in patients receiving
15 multivitamins up to six days post-transplant compared
16 to controls.

17 This slide summarizes the previous two,
18 showing that renal function was better by serum
19 creatinine the first two days, and creatinine clearance
20 was better in patients receiving multivitamins up to
21 five days post transplant.

22 So in conclusion, antioxidant treatment with

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1 multivitamins could be an important regimen in the
2 reduction of reperfusion damage.

3 Then there was another trial in 1997 about
4 the use of Pentoxifylline compared to placebo. So
5 Pentoxifylline suppresses TNF alpha released by
6 activated macrophages and inhibits subsequent Superoxide
7 anion release from neutrophil activation. As
8 well, the Pentoxifylline decreases cyclosporine induced
9 renal endothelial release and vasoconstriction.

10 So this was a double blinded randomized
11 controlled trial, including 140 kidney transplant
12 recipients from deceased donors, and the final result
13 was the Pentoxifylline had no impact on the instance of
14 DGF compared to placebo.

15 This was a study published in '99 about the
16 use of Anti-ICAM-1, and this compound was a murine,
17 non-humanized monoclonal antibody against ICAM-1 with a
18 half-life of 21 to 31 hours. This was a large, multi-
19 center trial including 130 patients per arm, and the
20 compound was given three hours prior to reperfusion and
21 40 milligrams per day for five days. All of the
22 patients who received cyclosporine got Pentoxifylline

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1 and prednisone, and again, another definition of DGF:
2 serum creatinine greater than 500 micromoles per liter
3 throughout the first week, more than one dialysis in
4 the first week, and delay more than two days to urine
5 output of one liter in 24 hours.

6 The baseline correct diuresis were similar in
7 both groups as well as patient and graft survival at
8 six and 12 months, and there was no difference in the
9 instance of acute rejection.

10 When it comes to the delayed graft function,
11 there was no difference between groups. As well, there
12 was no difference in adverse events, in this case
13 infections.

14 So in conclusion, short term Anti-A Chem 1
15 monoclonal antibody induction therapy after renal
16 transplantation did not reduce the rate of acute
17 rejection or DGF.

18 So we're moving on to 2002, if I read well,
19 and this was a randomized controlled trial using ATG
20 control versus post-op, and Jimmy Light mentioned this.
21 So I'll pass on the slides. So the majority of the
22 patients received tacrolimus, and that's a dose of

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1 ATG, one milligram per kilo, three to six doses. So no
2 difference in baseline demographics.

3 And then the most important result was that
4 there was a reduction in the incidence of DGF, 14.8
5 percent in patients receiving ATG intra-op, compared to
6 35.5 percent in patients receiving ATG post-op. And,
7 as well, there was a shorter length of stay of 7.5
8 versus 11 days.

9 This slide was shown by Jimmy. So I will
10 pass on.

11 And in conclusion, intra-op ATG in adult
12 recipients of deceased renal transplantation resulted
13 in a lower incidence of DGF, better renal function the
14 first month, and decreased length of stay.

15 There was a study, a randomized controlled
16 trial using insulin growth factor 1, and in this study
17 patients were randomized within five hour post renal
18 transplantation into the compound, 100 milligrams per
19 kilo sub Q twice a day for six days, 19 patients,
20 versus 24 patients who received placebo. The primary
21 outcome was the insulin clearance on day seven. As you
22 can see, there was no difference between groups. As

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1 well, there was no difference in serum creatinine at
2 six weeks and the need for dialysis.

3 This slide shows to your left the insulin
4 growth factor levels, and to your right, the insulin
5 clearance that did not defer in both groups.

6 More recently, a trial using Dopamine renal
7 dose versus Dopamine receptor agonist, again, this is a
8 very small study including 14, 12 patients, 14 in group
9 one, 12 in group two, and you can see the doses of
10 Dopamine and the agonists in group two. And the main
11 result was that there was no difference in urine output
12 and serum creatinine in postoperative day one.

13 Again, this study was a very small study, and
14 there was no data in the intermediate term, I would
15 say.

16 This is a Cochrane review looking into
17 calcium channel blockers to prevent ATN post kidney
18 transplantation. There were 13 randomized controlled
19 trials, including 724 patients, looking in to the use
20 of calcium channel blockers during the perioperative
21 period by any route, to the donor, to the recipient or
22 within the purview site.

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1 This is a little bit of a busy slide looking
2 at outcomes. Immediate graft function defined as fall
3 in serum creatinine more than ten percent within 24
4 hours, close to what we use now. Poor graft function,
5 no full insulin creatinine within 24 hours, but no need
6 for dialysis, no immediate graft function, no fall in
7 creatinine more than ten percent and need for dialysis
8 within 72 hours.

9 They look at serum creatinine and GFR at one
10 week and one month, at the adverse events and at biopsy
11 proven ATN. So what were the main results?

12 First, the use of calcium channel blockers
13 decreased the risk of post-operative ATN with a
14 relative risk of 0-62. It decreased the risk of DGF,
15 relative risk of 0-55. However, there was no
16 difference in GFR graft lost and mortality.

17 This slide shows all the studies looking into
18 calcium channel blockers versus placebo or no treatment
19 on the impact on the impact of an ATN post kidney
20 transplant, and this one looks at the impact on DGF.

21 This is the last study that was found in this
22 search, and it's about the use of high dose of

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1 ethropoietin in renal transplant patients. This was a
2 multi-center, randomized controlled trial including 13
3 centers in France. The DGF risk index of DGF was
4 greater than seven, and what is this risk, this DGF
5 risk?

6 It includes the donor age, CVA, age, younger
7 or older than 50 or not, and the receipt in ethnicity
8 and previous transplant. As an example, a DGF risk of
9 three to six is associated with a 61 percent risk of
10 DGF post transplant and a risk of seven to 18 with 100
11 percent. So all of these patients were considered at
12 high risk of DGF. They used EPO 30,000 units on day
13 zero, one, seven and 14. So what were the results?

14 I mean, the baseline correct statistics would
15 be not different, and I will pass on this slide, and the
16 main results are shown in this slide. There was no
17 difference in the eGFR between groups. There was no
18 difference in DGF. There was no difference in graft
19 loss, in slow graft function, on biopsy proven acute
20 rejection on day 90.

21 This slide shows the GFR, no difference, and
22 to the right, hemoglobin levels that were slightly

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1 higher in patients receiving EPO.

2 The important thing is that there was no
3 serious adverse event, most importantly thromboembolic
4 events.

5 So in conclusion of this study, the high dose
6 of EPO during the first two weeks post kidney
7 transplant did not reduce the risk of DGF or slow graft
8 function; did not have an impact on the eGFR; did not
9 decrease the risk of acute rejection. It was
10 associated though with higher hemoglobin levels, and it
11 did not increase the risk of vascular thrombosis.

12 The next two slides will talk about the
13 overall conclusions. There are few randomized
14 controlled trials; a variety of definitions of DGF.
15 Several studies showed no beneficial effect on DGF,
16 furosemide versus no furosemide at least at the dose
17 that was used, 200 to 400. They didn't use a gram or
18 above a gram per day.

19 Anti-ICAM-1 versus placebo; Pentoxifylline
20 versus placebo; Dopamine versus Dopamine receptor
21 agonist; insulin growth factor 1 versus placebo; EPO
22 versus controls. So none of these studies showed any

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1 benefit.

2 What about the study that shows a beneficial effect
3 on DGF? These are the following: ALG versus
4 cyclosporine; ALG resulted in a shorter duration of
5 DGF. However, there was no impact on the one-year
6 serum creatinine end graft survival. Multivitamin was
7 associated with a lower serum creatinine up to five
8 days. Intra-op ATG resulted in less DGF and lower
9 serum creatinine up to about 30 days post renal
10 transplant compared to ATG and a shorter length of
11 stay, but no difference in creatinine at one year, and
12 calcium channel blockers versus placebo resulted in a
13 decreased incidence of ATN and DGF, and I believe that
14 future studies will need longer follow-up.

15 Thank you.

16 (Applause.)

17 DR. MEYER: So we can open up this session
18 for discussion. Maybe the first thing that I'll ask is
19 if there's anyone in the room that wants to discuss any
20 other published or unpublished data looking at
21 interventions that were in clinical trials, if there's
22 anything to add to what Dr. Cantarovich has already

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1 summarized for us.

2 (No response.)

3 DR. MEYER: If not, we can open it up for
4 general discussion. It would be interesting to hear
5 from the group. You know, unfortunately the studies
6 were not very positive. So if anything, can we learn
7 some lessons from how these clinical trials were done
8 in the past so that we go forward and don't make the
9 same mistakes in the future?

10 DR. ABECASSIS: So maybe I can just add to
11 the question. I mean, this whole pumping thing becomes
12 a hot topic and then it kind of goes away and then it
13 becomes a hot topic again. I mean, if pumped kidneys
14 do better at least in terms of DGF, why aren't we
15 pumping all the kidneys?

16 I'm not a big pump person, but we do pump
17 kidneys in our OPO that are deemed to be marginal or
18 older, and part of the reason we do that is because we
19 use the pumping parameters to make a decision about
20 whether to use the kidneys or not.

21 But I'd be interested in at least people in
22 the audience that deal with this on a day-to-day basis

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1 what your thoughts are in terms of pumping kidneys.

2 Steve, I saw you, yeah.

3 DR. WOODLE: So Ploeg's trial is an
4 instructive trial. I think that if you're looking at
5 doing these types of studies, I think there's a number
6 of aspects about that trial that are interesting and
7 have important implications for a lot of the questions
8 we're asking. I'm planning on using that trial as a
9 bit of an example in the talk that I'm going to do
10 tomorrow.

11 In answer to your question, clinically it's
12 expensive. It adds an expense. So I think that doing
13 it for all kidneys and all donors doesn't make sense.
14 Certainly for an SCD donor with short storage time, it
15 doesn't do anything for you I don't think.

16 But we use it like you do to help us
17 discriminate with an ECD and particularly a DCD donor
18 whether or not to transplant and particularly when the
19 frozen section biopsy findings are equivocal. In our
20 experience, we have a real problem with frozen
21 sections. I just don't think they help you at all.
22 They're wrong about as often as they're right.

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1 So there's expense. The cassettes are
2 actually pretty expensive with the LifePort machine.
3 The Waters machine is cheaper. You've got to have
4 people trained in your OPO that are available 24-7/365
5 to be able to do this, and so I think those are the
6 major reasons why there's not a universal application
7 of machine perfusion.

8 DR. SEGEV: Yeah, we used to be sort of
9 universal pumpers, and then we were selective pumpers,
10 and now we're non-pumpers. So I think part of it
11 depends on what information, what the reliability is of
12 the information you get. So we used to use a pump
13 system with a dedicated technician, and we could give
14 very reliable information and we had a sense of what
15 those numbers meant. That person left. Those numbers
16 started to not mean the same thing. They started to
17 not correlate with the biopsies we were getting. We
18 happened to get really, really good biopsy reads, and
19 so we had very reliable biopsy reads, and oftentimes we
20 go look at them ourselves or, you know, Dr. Racusen
21 or one of her colleagues is looking at them for
22 us.

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1 So we have a lot of faith in the biopsy reads
2 and so we didn't find that we were using the numbers as
3 much to help us, and then while a randomized trial in a
4 controlled setting with a handful of technologists
5 working in an organized way with, you know, sort of
6 homogeneous pumping and homogeneous protocols showed an
7 advantage, there is still some retrospective data that
8 suggests that there may be no advantage, and there is
9 even some retrospective data that suggests that there
10 may be a disadvantage to pumping with the suggestion of
11 sheer injury, sheer force injury, particularly in the
12 DCD kidneys, which are the ones that you would want to
13 pump to being with, and so that combination has sort of
14 taken that out of our radar.

15 DR. HOLLORAN: Over the years there have been
16 two interventions to actually reduce acute kidney
17 injury from the point of view that we don't want the
18 organ to be wounded. We don't want to have to try to
19 fix it, but we don't want it wounded.

20 One is to reduce cold ischemic times, and
21 that reduces observed DGF measurements, but doesn't
22 really change long-term outcomes, and the other is

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1 pulsatile perfusion. It does the same thing.

2 Now, the Ploeg study, and it's regrettable
3 that Dr. Ploeg couldn't be here. I talked to him in the
4 Netherlands, and I guess he wasn't able to get support
5 to come here, but I think it was just an accident of
6 getting organs of different biological quality in the
7 two arms. It's just a statistical accident that they
8 got a difference in long-term outcomes.

9 They got the usual thing that had been
10 observed previously. You can change short-term
11 measurements of dialysis dependency by perfusion, but I
12 think it's an accident in clinical trials that you get
13 differences in long-term outcome because other trials
14 have not shown that.

15 DR. ABECASSIS: Bill.

16 DR. IRISH: Yeah, I was just going to add
17 that there's really limited data on the cost
18 effectiveness of machine perfusion. As Dr. Woodle
19 said, you've got an expense, the logistics. You've got
20 a decrease in incidence of DGF in a highly controlled
21 environment with what is an apparent increase in one-
22 year graft survival, but the long-term sort of impact

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1 and sort of the cost component is very limited.

2 DR. ABECASSIS: Yes. Another thought. So
3 how many people here have used a kidney that had
4 terrible pump parameters, but everything else looked
5 really good?

6 Do you want to comment? Because I have, too.
7 What's been your experience with that? In the back,
8 I'm sorry. You raised your hand?

9 Because what I'm going to allude to is one of
10 the down sides is you reject a perfectly good kidney
11 that, you know, has terrible pump parameters.

12 AUDIENCE PARTICIPANT: So Dorry alluded to a
13 study we were doing while I was at Hopkins where we
14 were pumping pretty much every kidney, including
15 kidneys that we would not have traditionally pumped.
16 So sometimes we had patients or donors who were young
17 and healthy but may have poor pump numbers. So in that
18 scenario if the pump numbers were poor but otherwise
19 the donor was young and healthy, we would still use the
20 kidney and invariably those kidneys did fine.

21 So if it was a young kidney, then you would
22 go ahead and use it. Now, if it was an older donor,

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1 someone that you would be more worried about and you
2 had poor pump numbers, then that was a different
3 scenario.

4 DR. ABECASSIS: And just one more comment.
5 And how many times have you had two kidneys from the
6 same donor that both pumped and you get terrible
7 pumping parameters on one and good on the other, and
8 there's no dissection? There's nothing you can see,
9 but you have to kind of live with the fact that the
10 numbers are completely irrational between the two
11 kidneys.

12 AUDIENCE PARTICIPANT: Yeah, we get offered
13 those. They say the first one is used locally. It
14 worked immediately. The pump numbers were terrible on
15 the second one, and we are offered those kidneys.

16 DR. WOODLE: So, Mike, I think that there's
17 an issue --

18 DR. ABECASSIS: I'm sorry. One second. I
19 think Marcello may have been first and then, Steve,
20 coming back to you, or you guys, whoever. It doesn't
21 matter.

22 DR. WOODLE: So I think that gets to the

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1 pump. They've got to be calibrated. They've got to be
2 tested. You know, we've had poor numbers and just said
3 we don't believe them, went ahead and transplanted the
4 kidney. We got the machine calibrated the next day
5 and found it was way off.

6 So you have to have a technician there,
7 somebody that really knows what they're doing and
8 they've got experience.

9 The other thing is those tips, if they get up
10 against the sidewall, you know, you're going to get
11 some funky numbers. You're going to get high
12 resistances, and so you've got to pay attention to the
13 technical aspects of pumping the kidney. It's really
14 critical.

15 And I think that's what Dorry and them were
16 probably seeing, is that they were just getting some
17 really high resistances. It was probably a technical
18 issue either with the machine or with the tips, and
19 you've always got to enter that in your equation.

20 The best thing for us, I think, that we've
21 ever seen is that we can get a rapid permanent section,
22 and if that looks good, we'll go with that, but we've

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1 been burned countless times on frozen.

2 Marcello.

3 DR. CANTAROVICH: Just to echo the comment
4 from Johns Hopkins, we do exactly the same. The
5 surgeons design an algorithm. We pump all the
6 kidneys, not the living donors, but we pump all the
7 kidneys and if the kidneys from a standard criteria
8 donor and resistances are increased, we do use them and
9 we do run into trouble. We are analyzing the data, but
10 do use them.

11 However, if the resistances are elevated in
12 the deceased criteria donors, we may not use those kidneys
13 irrespective of amount of sclerosis.

14 DR. ABECASSIS: Well, so I think this has
15 been a very helpful discussion because, again, this is
16 the thing that just won't go away, and it keeps coming
17 back, and now you've got a randomized controlled trial,
18 and even if you don't care about whether the effect on
19 long-term function is reflective of reality or not,
20 there's no question that when you pump kidneys,
21 especially if you pump the kidneys that are, you know,
22 a little longer on the cold ischemic time, they're

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1 going to pee better.

2 But then you have all these caveats. My
3 biggest concern, and I do use the kidneys with bad --
4 and, you know, you get burned every once in a while,
5 but for the most part those are very good kidneys if
6 you just go by everything else. So my concern about,
7 you know, pumping kidneys and using the data is that
8 you might toss out some very good kidneys.

9 So I think pumping is certainly one thing
10 that I don't think we can put to bed. I'm afraid we'll
11 probably never put to bed, but it's one of these things
12 if you're designing a trial, I think I'm kind of
13 interested in knowing if Dr. Koneru is still here, but
14 what was the thought process?

15 You pumped some of the kidneys and he didn't
16 pump others, but in the pumped kidneys, there seems to
17 be some at least preliminary beneficial effect to
18 remote ischemic. Do you think that's real or what are
19 your thoughts on that and any other thoughts you have
20 on this trial, which again is the only randomized
21 clinical trial out there?

22 DR. KONERU: The standard of practice --

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1 DR. ABECASSIS: Can everybody hear? Because
2 his mic is not working.

3 DR. KONERU: Thank you.

4 The standard of practice in our OPO is that
5 the standard criteria donor kidneys are not pumped and
6 the ECD kidneys are pumped. However, what we noticed
7 during data collection on this is a few standard
8 criteria kidneys are pumped at the discretion of the
9 recipient team that gets it. So that was the practice
10 basis upon which this data was collected.

11 As the numbers showed, the number of kidneys
12 that were pumped were like 16 and 18 in each group.
13 Again, the perfusion parameters that we collected, it
14 was after the study design was completed, and we said,
15 you know, this data is available. Could we look into
16 it? We certainly didn't project that as an initial
17 outcome we were going to look at.

18 I think it's fair to say it's interesting,
19 but I'm not really sure what to make of it. I think
20 additional data is required, and you know, based on
21 what some of the kidney surgeons said, if the perfusion
22 parameters are good, we would use them and if the

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1 perfusion parameters are not good, especially in ECD
2 kidneys, we would not use them.

3 I mean, one could speculate in a bigger
4 trial, and if such data were to hold up, it might lead
5 to increased use of kidneys, but that's purely
6 speculation.

7 Thank you.

8 DR. ABECASSIS: Great. Patrick, you had one?

9 DR. ARCHDEACON: If I could ask one question
10 about the calcium channel blocker issue, I'm curious.
11 You know, it appears that we've seen some studies here.
12 I understand none of them are particularly powered, but
13 that shows the calcium channel blockers could
14 potentially prevent delayed graft function, but to the
15 best of my knowledge, it's not standard use that
16 they're used.

17 I guess I'm just wondering if you could sort
18 of poll the room as to that. Is that because people's
19 impressions of the quality of those trials or is that
20 because we can as FDA take this as some insight into
21 the community's value of this endpoint of DGF?

22 DR. ABECASSIS: So let me add one more kink

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1 to this calcium channel blocker deal. We use calcium
2 channel blockers in the perfusate when we perfuse the
3 kidney on the back table right before we implant it.
4 There's absolutely no real data to support.

5 You know, a lot of this stuff, and I think
6 the surgeons in the room will probably agree with me,
7 even if they're embarrassed by it, you know, a lot of
8 this is just voodoo and, you know, what you've been
9 doing for a long time. You don't want to rock the boat
10 and change anything because your results are pretty
11 decent, and the only time you ever change something is
12 when you've got a bad run and then you blame it
13 something that you stopped doing and you go back to
14 doing it.

15 We had, you know, a pretty good DGF rate, and
16 then it got higher, and then we realized that they
17 weren't making Collins solution anymore and we were
18 using something else, and you know, we were always
19 adding this calcium blocker. So we decided to add
20 verapamil back in the mix, and our DGF rate went down.

21 Is that scientific? Not by a long shot, but
22 it's not just the calcium blocker systemically, but I'm

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1 curious. How many people add calcium blockers to the
2 whatever it is they're perfusing the kidneys with?

3 DR. CANTAROVICH: Actually, in the early
4 1980s actually, mid-1980s, Neumayer from Germany
5 where I was a Fellow in Paris then, they published on
6 the use of calcium channel blocker in Euro Collins
7 solution. A few years ago, maybe a decade ago I
8 remember reviewing a paper that was finally published,
9 I believe, in Transplantation, and patients who were on
10 calcium channel blockers on dialysis had better
11 outcomes early post transplant than those who did not.

12 So it seems to me that's the recent area that
13 we can look at, it's not expensive, as well as
14 multivitamins. There are a couple of little things
15 over there that I think we should look at, and those
16 that didn't work perhaps didn't work because of the
17 sample size. I believe that there was not much of a
18 sample size calculation if you had 14 patients in one
19 group and 14 in the other.

20 But the ones comparing ICAM, Anti-ICAM-1,
21 et cetera, with 100 patients, that was pretty robust as
22 a sample size. So I think there was a sample size

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1 effect. So I wouldn't dismiss Lasix, for instance, up
2 front, and I would pay attention to cheap things like
3 calcium channel blockers and multivitamins, for
4 instance.

5 DR. ABECASSIS: Steve, I think you had your
6 hand up and then Sandy.

7 DR. WOODLE: I just wanted to comment on
8 Phil's comment about the survival benefit that was seen
9 in the Ploeg study. The difference was 94 percent in
10 machine perfused versus 90 percent in the cold stored
11 kidney. So it's a small difference.

12 The reason that was statistically significant
13 was that there were 672 patients in the trial. So it
14 was very large numbers, and that was death censored
15 graft survival. There are actually two more deaths in
16 machine perfused group. So if you looked at overall
17 graft survival and not death censored, you didn't have
18 statistical analysis.

19 The other point was that this was an
20 interesting trial in that they used logistic regression
21 and odds ratios for the primary endpoint determination,
22 and that's another important issue, I think, for

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1 clinical trial design because it helps to
2 counterbalance all of these variable heterogeneities
3 and risk factors.

4 DR. ABECASSIS: Sandy. Last comment. I
5 think we're running short on time, right? This will be
6 the -- I'm sorry. Sandy and then one more comment.

7 DR. FENG: I am aware of another randomized
8 trial in donors, and that's actually happening in our
9 OPO. Claus Niemann who was the author of the rat study
10 looking at hyperglycemia in the recipient has finished
11 a randomized controlled trial where he's doing tight
12 insulin control in the donor versus standard insulin
13 management in the donor, and he's undergoing data
14 analysis right now, but there are some hints that this
15 may be promising at least in the liver because, you
16 know, we do the livers, but we don't know yet for the
17 kidneys. But that is a randomized controlled trial in
18 donors.

19 DR. ABECASSIS: Great. Thank you. We'll be
20 looking forward to that.

21 No?

22 DR. LIGHT: I was just going to say I'm a

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1 calcium channel believer.

2 DR. ABECASSIS: Do you put it in the
3 perfusate?

4 DR. LIGHT: We don't control the perfusate.
5 So I don't use it on the back table, and it's not added
6 to the machine, but I give it to all the recipients.

7 DR. ABECASSIS: Who perfuses kidney on the
8 back table if it's not the surgeon before implantation?

9 DR. LIGHT: When it's in the box, we don't
10 reperfuse.

11 DR. ABECASSIS: Oh, okay. We do. That's
12 when we give it.

13 DR. LIGHT: That's probably why.

14 DR. ABECASSIS: Okay. I'm sorry. One more
15 comment.

16 DR. BONVENTURE: Well, just to the extent
17 that animal studies might be informative in that
18 context, back around '93 or so we published a paper in
19 rats where if you infused norepinephrine you can
20 completely shut down renal blood flow just locally and
21 if you pretreat with verapamil what happens is when you
22 stop the perfusion of norepinephrine, you get a much

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1 more rapid return to normalcy in regard to renal blood
2 flow.

3 So to the extent that the things that we're
4 doing are equivalent in humans to infusing
5 norepinephrine or some other vasoconstrictors, it has
6 always made a lot of sense physiologically to me that
7 verapamil might be useful.

8 DR. ABECASSIS: Okay. I guess we're closing
9 this session. Are we moving right along to the next
10 one?

11 DR. ALBRECHT: A ten-minute break.

12 DR. ABECASSIS: Ten minutes. Okay.

13 (A short recess was taken.)

14 Session 4: Industry Perspective and Public Comment

15 DR. ALBRECHT: ...that we have basically what
16 we've provided in this session is an opportunity for
17 members of industry and from the public to make any
18 comments that are of relevance to the area of ischemic
19 reperfusion injury and kidney transplantation, and we
20 have a number of people who have asked to make
21 presentations. The format is going to be a little bit
22 different in that after each presentation if there are

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1 any questions for the speakers I would just ask the
2 audience or the panel members to ask those questions
3 directly of the speakers. And at the end of the public
4 and industry presentations, we are not planning on
5 having a discussion period as we have in the others.

6 So with that as a brief introduction, the
7 first presentation is from Waters Medical Systems and
8 Dr. Robert Warren will introduce the speaker.

9 MR. WARREN: Not doctor in this lifetime.
10 I'm Bob Warren. I'd like to thank you for letting us
11 be a part of this workshop. Today our presenter will
12 be Kevin Darnell of Lifebanc in Ohio, so I'll turn it
13 over to Kevin.

14 MR. DARNELL: I have no conflicts. Neither
15 does Bob. What we are asked to demonstrate today to
16 demonstrate Waters' Medical Systems history of machine
17 perfusion and illustrate the RM3 unit in perfusion
18 circuit and comment on U.S. data; to provide a brief
19 overview of preservation theory; insights into why the
20 industry used machine perfusion; review machine
21 perfusion parameter and monitoring techniques; and
22 review example of important scientific literature.

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1 Some terms we'll use in this presentation
2 which we've been hearing all day, but it seems like a
3 lot of them haven't been well-defined, is we'll use
4 SCD for standard criteria donors. Those are typically
5 our younger, healthier donors under 50-years old. ECDs
6 are expanded criteria donors. Those tend to be our
7 donors over 50-years old with certain medical
8 conditions. DCD donors are donation after cardiac
9 death. They're declared by cardiac death and brain
10 death. And then delayed graft function in the
11 presentation is represented the recipient needing
12 dialysis within one week post transplant.

13 Waters Medical Systems has 40 years
14 experience with machine perfusion. Waters introduced
15 the first commercial perfusion device in the 1970s, and
16 they introduced the first computer-controlled
17 monitoring device. Waters' machines are used in over
18 10 different countries. The most common Waters
19 perfusion pump currently in use is the RM3 and in
20 addition have a new pump which is awaiting FDA
21 approval.

22 As seen in this slide, the total number of

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1 kidneys being perfused in the U.S. is steadily
2 increasing. The data for 2010 is not yet available but
3 is expected that over 5,000 kidneys were perfused in
4 the U.S. in 2010.

5 This slide shows the percent of kidneys
6 perfused by donor type. As you see, the most common
7 type of kidneys perfused are DCD kidneys. This
8 information is surprising because as you'll see the
9 literature all supports the pumping of ECD kidneys.
10 Also note that the total number of kidneys being
11 perfused is increasing with three out of every 10
12 kidneys being recovered is currently being machine
13 perfused.

14 I'll discuss the preservation theory and the
15 basic concepts of preservation. The Waters' system is
16 based on preservation theory established by Drs. Belzer
17 and Southard. The basic concepts are to exanguinate
18 the organ while core cooling and provide effective
19 washout of the organs; to decrease the temperature,
20 which decreased the cellular metabolism; to control the
21 physical environment with the preservation solution;
22 and to prevent cellular swelling. In addition, we can

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1 add pharmacological agents to the kidney while it is
2 being perfused. With all this, we still need to
3 establish better methods to assess kidney viability
4 such as kidney markers to assess the kidney volume
5 pump.

6 This slide just further illustrates the
7 perfusion theory that's being used.

8 Next we'll discuss the clinical realities.
9 The quality of organ donors is decreasing. This is
10 seen in the rise of ECD and DCD donors. Due to this
11 increase, transplant centers are expanding their
12 acceptance criteria of organs. The literature supports
13 the benefits of machine preservation over static cold
14 storage. The data show a decrease in DGF rate and is
15 showing a lower cost of transplant.

16 Transplant centers are also being monitored
17 more closely and in response need to find ways to
18 increase positive outcomes of transplants while
19 decreasing transplant cost.

20 The Waters' RM3 is a portable computerized
21 monitoring unit that uses disposable kidney cassettes.
22 While the machine is portable, it is most often used in

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1 preservation lab. The perfusion circuit has a pulse
2 pump which pumps the solution through a heat exchanger
3 to cool the solution and then is pumped into the organ,
4 and the cycle repeats itself. The RM3 is a physiology-
5 based pulsatile perfusion machine. The machine allows
6 us to measure the temperature of the perfusion solution
7 directly prior to entering the organ. We can also
8 measure the systolic, mean, and diastolic pressure and
9 the flow of perfusion solution through the organ. Then
10 the machine will calculate a renal resistance.

11 The knowledge or lack thereof of a
12 perfusionist has on the machine, the perfusion
13 parameter, and experience in the field can greatly
14 impact the result of perfusion. It is important for
15 the perfusion of organs to be done in a similar manner
16 so a transplant surgeon can have comparable data to
17 evaluate a kidney.

18 The next few slides will show how the
19 perfusion parameters are used along with biopsy and
20 donor information to determine a kidney's suitability
21 for transplant.

22 General perfusion parameters may differ by

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1 device. A perfusionist's lack of knowledge of devices
2 and how they operate can affect the outcome of the
3 perfusion event. Temperatures are generally preset by
4 the manufacturer with a typical temperature range of
5 two to seven degrees Celsius. The RM3 displays a true
6 perfusion temperature of the solution prior to entering
7 the organ. Pressures will be different based on the
8 type of machine and pump being used. There have been
9 discussions on which types of pump or wave form is
10 best, but there is little data to suggest the right
11 answer.

12 The RM3 uses pulsatile pump with a full
13 systolic and diastolic phase. The average perfusion
14 pressure of the RM3 is 40 mm of mercury. The
15 perfusionist can impact the perfusion of the kidney by
16 manually adjusting the perfusion pressure.

17 The flow is the volume of solution flowing
18 through the kidney at any given time. An ideal flow is
19 .5 to 1 cc/g of kidney weight. Flow may take as much
20 as 4 to 6 hrs to optimize. Higher flow rates may be
21 reported on other machines. This could be due to
22 different pumping mechanisms.

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1 The renal resistance is a ratio of mean
2 pressure to flow. Optimal renal resistance is thought
3 to be .25. A lower renal resistance shows a likelihood
4 of a lower rate of DGF but is not a good indicator of
5 kidney viability.

6 This slide just shows the pressure change
7 over time and where a perfusionist can have a direct
8 impact on perfusion outcome by manually adjusting
9 perfusion pressures.

10 The next slide shows how flow is increased
11 over time while the renal resistance will decrease and
12 the temperature will remain the same.

13 We'll now review some of the literature.
14 While early studies did not show an advantage to
15 machine preservation, newer studies have started
16 showing an advantage over cold storage. This is an early
17 study showing a lower relative risk of DGF with machine
18 preservation at all time intervals especially at long
19 preservation times over cold storage.

20 This study from the University of Alabama
21 again shows a lower rate of DGF with machine
22 preservation over cold storage.

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1 Next is a study from Ohio State which showed
2 a significant cost savings associated with the median
3 function of a kidney versus a kidney with delayed graft
4 function.

5 Here is a study that shows a better long-term
6 graft survival of machine perfused kidneys versus cold
7 storage although as far we know this study has not been
8 replicated.

9 A review of data from UNOS showed an increase in
10 use of ECD kidneys when machine perfused versus cold
11 storage. In addition, the perfused kidney is at a
12 lower rate of DGF.

13 A study by Dr. Stratta showed that despite
14 longer cold ischemia time recipients of ECD kidneys
15 managed with machine preservation have similar survival
16 and functional outcomes but experienced a marked
17 reduction in DGF rate.

18 A study by the University of Miami showed that
19 even with longer preservation times DGF remained low.
20 Through the study, Miami continues to pump all kidneys
21 in their local OPO.

22 To summarize, the rate of machine perfusion

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1 is increasing as donor-mix demographics change. This is
2 due to the prevalence of ECD kidneys and increase in
3 DCD donors. Our current understanding of perfusion
4 theory supports the use of machine preservation.
5 Various machine preservation devices could have an
6 impact on the outcomes of kidney perfusion, but there
7 is little or no data to support that at this time. A
8 perfusionist can have an impact on the outcomes of
9 machine preservation based on their understanding of
10 the perfusion machine and their experience in the
11 field.

12 Research suggests centers may control or
13 decrease overall transplant cost with machine
14 preservation. This is due to the length of stay in the
15 hospital decreasing and not having the cost of
16 dialysis. Most recent machine preservation data show
17 beneficial trends for all kidneys but clinically
18 significance differences for ECD donors.

19 Are there any questions?

20 (Pause)

21 MR. DARNELL: Okay.

22 DR. ALBRECHT: Thank you. The next

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1 presentation is by Organ Recovery Systems, and I'd like
2 to call David Kravitz to the podium.

3 MR. KRAVITZ: First, I'd like to thank you
4 for inviting me to speak today. I'm David Kravitz.
5 I'm CEO of Organ Recovery Systems, and I'm also a
6 founder of the company. But before I get started, I'd
7 like to actually thank the FDA and the organizers of
8 this workshop for inviting a deeper collaboration
9 between academia and industry to help drive forward
10 thought and to help solve some of the key problems that
11 are facing us today in transplant.

12 Today, I'm just going to give you a very
13 brief intro to the company Organ Recovery Systems.
14 Some of you have asked for that. The LifePort Kidney
15 Transporter, which is one of our core products, its
16 history, its adoption, and outcomes in recent studies
17 and some new product pipeline information.

18 We were founded in 1998. Our mission is to
19 help improve patient outcomes in transplantation by
20 scientifically proven innovations, focusing on
21 preservation transport and evaluation of organs and
22 tissues. We're headquartered in Chicago. We have

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1 European headquarters in Brussels, Belgium. We just
2 opened up an office in Sao Paulo, Brazil, and we have 44
3 employees.

4 We have invested over \$70 million to date in
5 research, development, and engineering and continue to
6 invest heavily in developing new technologies. Since
7 those 2006, we have become the global market leader in
8 machines and solutions for organ preservation, emphasis
9 on kidney, and the biggest driver has been the LifePort
10 Kidney Transporter's adoption.

11 The research and development pipeline for us
12 today includes devices and solutions for improved
13 outcomes with extrarenal organs and adherence, perhaps
14 the next frontiers, which we'll talk a little bit about
15 later.

16 The first step for us in developing the
17 LifePort Kidney Transporter was to get a grounded
18 understanding of clinical needs. And what the
19 marketplace told us was there was a need for lower
20 incidences of DGF, fewer incidences of discards, fewer
21 days of in-patient dialysis, few retransplants. And it
22 was suggested that improved preservation methods could

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1 help make a difference and that machine preservation
2 could be and should be further evaluated.

3 So we immersed ourselves into the space for a
4 couple of years, first observing, listening, learning,
5 before we ever designed our product. We learned that
6 MP must meet the following challenges to be routinely
7 adopted in clinical practice, so this is what the
8 industry taught us. Robust clinical evidence was
9 sorely needed as available data was then anecdotal and
10 retrospective. Some used the term religion or
11 witchcraft.

12 Easy to use as the box of ice was another
13 common call that we heard. Conveniently portable while
14 operational even as unattended freight in the cargo hold
15 of an aircraft. And this is for sharing organs on
16 pump. Provide maximum physical protection for the
17 kidney; diminish potential for organ injury; work
18 smoothly within an existing allocation scheme; and
19 automated precision calculation of renal resistance and
20 other key organ and machine performance parameters. So
21 this is what we heard from industry.

22 What we designed into the machine in response

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1 were several features. We won't go into all of them,
2 but I do want to say, for example, one of the pieces we
3 put in -- and this was beginning in 2004 when we
4 introduced the product -- pressure transducer built
5 into the disposable set to ensure consistent calibrated
6 performance with every perfusion and to provide
7 consistent results from machine to machine and from
8 location to location, so eliminating taking away the
9 potential for user error or user interface through
10 manual manipulation.

11 We also designed a pressure control system
12 that safely pumps at all pressures, allowing the flows
13 to be determined by the kidney, so a gentler, natural
14 method of perfusion whereby the organ acts as its own
15 control.

16 Upon LifePort's clinical availability and
17 driven by the lack of strong scientific clinical data
18 regarding MP versus cold storage, we began working with
19 the transplant community to design a rigorous clinical
20 study. The trial was designed to address key medical
21 and economic questions around DGF, PNF -- primary
22 nonfunction days of post-transplant dialysis -- and

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1 logistics of MP in a complex international organ
2 allocation scheme, all in a properly controlled,
3 prospective randomized trial. So this is what we
4 sponsored.

5 We retained Eurotransplant Foundation to act
6 as CRO to conduct the study. And to manage the day-to-
7 day affairs of the study, they selected a nine-member,
8 independent, multinational scientific steering
9 committee comprised of prominent surgeons/scientists
10 from Germany, The Netherland, and Belgium.

11 Study design was a multicenter, multinational
12 trial enrolling 336 matched pairs of kidneys as they
13 naturally presented in the course of donation
14 throughout the seven-member Eurotransplant region. In
15 the study, one kidney went into the box of ice; the
16 other kidney into the LifePort; then off to transplant
17 with no selection bias on the part of the transplanting
18 surgeons. Kidney transplant patients being enrolled in the
19 2005, and they were enrolled through the end of 2006.

20 In January of 2009, the first study results
21 were published in The New England Journal of Medicine,
22 and I'm just going to for the sake of time just show

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1 some of the key conclusions that the authors reported.
2 First, hypothermic machine perfusion reduces incidences
3 of DGF in the kidneys obtained from the most common
4 types of deceased donors. Machine-perfused renal
5 allografts had a lower risk of graft failure in the
6 first year after transplant, and as a result, showed an
7 improved one-year graft survival as compared with
8 kidneys preserved by cold static storage.

9 In a subanalysis of the machine preservation
10 trial recently published in Transplant International,
11 Treckmann et al. thought that -- and these are among
12 their several conclusions -- "We believe that every ECD
13 kidney should be machine perfused because in the first
14 year after transplant alone 12 percent more grafts
15 could be saved as a result of machine perfusion. And
16 the number of recipients receiving an ECD kidney with
17 PNF was four-fold higher in the cold storage group
18 compared with the MP group. Such early graft failure
19 in addition to the subsequent graft failures puts a
20 severe burden on patients in waiting list for kidney
21 transplantation."

22 And then most recently -- I think this was

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1 just delivered yesterday -- in Glasgow at ESOT, the
2 European Society of Transplantation, this was the 3-
3 year outcomes data. These results further validated
4 the 1-year data, and the steering committee concluded
5 that -- meaning the scientific steering committee of
6 the machine preservation trial -- that 3 years
7 posttransplant graft survival of kidneys donated after
8 brain death remains significantly better after machine
9 perfusion compared to cold storage especially in
10 kidneys recovered from expanded-criteria donors. DGF
11 was associated with a notable lower graft survival of
12 kidneys donated after brain death. So this was just
13 presented yesterday, and we expect to see it in
14 publication shortly.

15 Just to give you some sense of scope for the
16 LifePort, we have over 120 leading transplant programs
17 using LifePort in 22 countries across the world today.
18 There were over 5,000 clinical perfusions worldwide in
19 2010 with LifePort, and to date, we've recorded over
20 25,000 clinical procedures with LifePort.

21 Here is some data that graphically kinds of
22 ties to what was presented prior by the folks from

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1 Waters. On the top, this is UNOS 2008 data. UNOS
2 data kind of lags behind Current affairs as we all
3 know. And you see 30 percent machine perfusion, 70
4 percent not machine perfused in the ECD category; 15/85
5 in the SCD category; 50/50 in DCD. And this slide was
6 actually prepared by Bob Stratta and presented in
7 Glasgow. Bob's at Wake Forest, and his center is
8 trending as you see here reported in these graphs, and
9 we see this trend happening worldwide really. It's
10 kind of migration towards an increased use of pumping
11 as the folks at Waters noticed as well. So in Bob's
12 shop, we have 17 percent of the ECDs were not machine
13 perfused versus 83 percent that were machine perfused;
14 56/44 for SCDs, and 4 percent versus 96 percent for
15 DCDs.

16 And here's looking at the data another way,
17 all deceased donors UNOS's data reported in 2008 80
18 percent of the kidneys recovered were not perfused and
19 20 percent were. And Wake Forest reported during their
20 2010-2011 period 36 percent not machine perfused versus
21 64 percent. And again, we just put the Wake Forest
22 data up because it does seem to be a trend that we're

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1 experiencing around the world.

2 And lastly for us, this is our future. We've
3 got some new products coming out for extrarenal organs.
4 We're working in warm perfusion. We're studying
5 oxygenation. There's quite a debate right now as to
6 whether oxygen is needed or not. We're looking at
7 biomarkers and, again, adherence. We want to know the
8 impact of posttransplant therapeutic regimes as it
9 applies to pretransplant interventions. I think that
10 needs to be studied as well.

11 So thank you very much.

12 (Applause)

13 DR. ALBRECHT: Are there any questions for
14 Mr. Kravitz?

15 (Pause)

16 DR. ALBRECHT: Dr. Woodle.

17 DR. WOODLE: I have some questions about the
18 Eurotransplant study. In The New England Journal of
19 Medicine paper, it noted that you provided support for
20 that study. Can you tell us a little bit more about
21 the support?

22 MR. KRAVITZ: And by support?

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1 DR. WOODLE: Yes. Did you provide all of the
2 perfusionists? Did you provide all the training? Did
3 you provide the LifePort devices? Did you provide the
4 cassettes? Just --

5 MR. KRAVITZ: Yes --

6 DR. WOODLE: -- the nature of the support
7 that you gave to the study?

8 MR. KRAVITZ: Sure. Thank you very much for
9 the question. We provided first and foremost financial
10 support. We underwrote the study, but beyond that, we
11 were involved primarily with setting up the perfusion
12 centers, so we supplied machines. We supplied of all
13 of the disposables. We had our top perfusion manager
14 train in each perfusion center the local staff on how
15 to use the LifePort, etcetera. We were available
16 through our 24/7 help desk, which we have to this day,
17 to answer questions that might arise during the course
18 of the study, and of course our normal day-to-day
19 maintenance and service capabilities were available to
20 the study participants. And that was about it really.
21 DR. WOODLE: So thanks. And how were the
22 data collected and who collected them and who analyzed

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1 them?

2 MR. KRAVITZ: The data was collected by
3 Eurotransplant. They acted as CRO. They were largely
4 the same folks that did the study for DuPont that put
5 VIASPAN on the map. In fact that's why we went to them
6 because they had done a successful job there.

7 DR. WOODLE: Can you give us a little
8 information about how much the LifePort device itself
9 costs and how much each disposable cassette costs?

10 MR. KRAVITZ: Sure. I can tell you what
11 LifePort is priced at in the market on a list basis,
12 but depending on volumes center by center, we have
13 different tiers of pricing, all of which is available
14 on our Web site and through our literature if anybody
15 in the room would like to follow up on this. LifePort
16 generally is priced in the \$20,000 range, but, again,
17 depending on the nature of usage, the volumes,
18 etcetera, it is often discounted. And then the
19 disposables range in price. We priced them on a bundle
20 basis. We price them individually. It's actually a
21 very difficult question to answer because it's really
22 all over the board in terms of how we price. So much

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1 as to do with the individual relationship we have with
2 the client. Yes, sir.

3 DR. HALLORAN: So the interesting result
4 would be that this can prevent primary nonfunction in
5 kidneys at very high risk. Would that question be
6 supported by the data of the European study that the
7 way that this could change graft survival is by
8 preventing primary nonfunction in that group of kidneys
9 we were talking about this morning, which are old going
10 in and the damage causes them to not recover?

11 MR. KRAVITZ: Are you referring to the
12 expanded criteria subgroup?

13 DR. HALLORAN: Yes.

14 MR. KRAVITZ: Yes, I think that's one of the
15 findings certainly. I think one of the other things we
16 hear quite a bit and it's rather logical is that
17 clinicians are not omniscient. They can't look at a
18 donor chart or hear about a donor or see a kidney and
19 determine whether it's going to have delayed graft
20 function by just looking at those items. So by putting
21 the organ on the machine based on the data that's
22 currently available, at least the kidney has got a

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1 fighting chance for having reduced DGF. We're not
2 suggesting it eliminates it --

3 DR. HALLORAN: So how many --

4 MR. KRAVITZ: -- and also reduced PNF.

5 DR. HOLLORAN: How many actual events were
6 there that would support what I just said that primary
7 nonfunction can be reduced by this across the
8 widespread use of this? How many primary nonfunctions
9 were there in each group?

10 MR. KRAVITZ: I don't have the data on the
11 tip of my tongue. I'm happy to get it for you though.

12 MR. IRISH: The rates are low.

13 MR. KRAVITZ: And if I may, the --

14 MR. IRISH: It's like 4 or 5 percent versus 3
15 percent or...

16 (Pause)

17 MR. IRISH: So, Phil, there were 336 kidneys
18 in each group. The rate of primary nonfunction was 4.8
19 percent in the cold stored and 2.1 percent in the
20 machine perfused at a P value of 0.08.

21 DR. WOODLE: So an absolute difference?

22 MR. IRISH: An absolute difference of 2.7

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1 percent and a relative reduction of about 50 percent.

2 DR. PARIKH: Yes. The number needed to treat
3 would be within 50.

4 DR. ALBRECHT: Yes.

5 DR. PARIKH: Yes.

6 DR. HALLORAN: Do we have a statistical
7 comment on that? How robust is that?

8 MR. IRISH: I can't give you a statistical
9 interpretation of the robustness, but that's a clinical
10 sort of decision rule, but a 3-percent reduction of
11 2.5-percent reduction is small, so how that translates
12 clinically...

13 DR. WOODLE: So in the logistic regression
14 analysis looking solely at graft failure within one
15 year after transplant machine perfusion versus cold
16 storage has a ratio of 0.52 with a confidence interval
17 of .29 to .93, p value of 0.03.

18 DR. MATAS: Steve, so you're presenting the
19 data, but do you know if machine perfused kidneys were
20 sometimes not used because of the machine parameters?

21 DR. WOODLE: Yes. So in the methods -- I'll
22 quote for you the methods. They actually did that

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1 right. In the methods, "To prevent bias in clinical
2 decisions about transplanting of discarding an organ,
3 intravascular resistance and flow readings were never
4 revealed to the transplantation team." So the
5 transplantation team was completely blinded to the pump
6 perfusion parameters during the study. They did it
7 right.

8 MS. HOSGOOD: Hi. I just wanted to see if
9 you've got any comments about the U.K. trial which
10 showed no difference in the machine perfusion versus
11 cold storage for DCD kidneys.

12 MR. KRAVITZ: I'm going to leave that one to
13 Mr. Irish to deal with tomorrow. I think he's done
14 some interesting analysis there. I've heard so many
15 comments from the U.K. transplant community, and many
16 retorts to those comments by the machine preservation
17 trials scientific steering committee that my head is
18 spinning actually. So I'm going to leave it to you all
19 to go there. We just make the tools.

20 MR. IRISH: One of the sort of interesting
21 issues -- we've talked about it in sort of the past
22 session -- is the center effect. This in the DCD

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1 trials. This was a particular issue in terms of the
2 experience of the perfusionist, which was highly
3 controlled. The experience and the preservation trial
4 were sort of maximized. So there are similar designs,
5 similar definitions, similar study population. The
6 machine preservation trials was not designed to look at
7 DCD. This was sort of an exploratory analysis, but
8 there are inconsistent results.

9 DR. LOBO: I had a question. Why is the
10 delayed graft function rate in the European trial just
11 for cold storage very low like 4 percent? Because in
12 the United States we do not see such low percents.
13 Were they transplanting kidneys in less than 12 hours
14 or what's the story?

15 DR. WOODLE: That 4.8 is primary nonfunction.
16 It's not DGF.

17 DR. LOBO: And what's the DGF rate?

18 DR. WOODLE: The rate was on the order of
19 about 20 percent; 70 patients out of 362.

20 DR. LOBO: And did the perfusion --

21 DR. WOODLE: That was machine perfused versus
22 89 in a cold storage group.

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1 DR. LOBO: Eighty-nine percent?

2 DR. WOODLE: Eighty-nine patients out of 362.
3 It's about 25 percent. So the absolute difference is
4 on the order of about 5 to 6 percent. The relative
5 reduction is on the order of about 20 percent, and it
6 was statistically significant because there were 362
7 patient in each group.

8 DR. ALBRECHT: Just want to do a quick poll.
9 Is this something that Dr. Irish will be covering
10 tomorrow or should we spend a few more minutes
11 discussing it?

12 MR. IRISH: Yes, I'm going to present the
13 results of that particular trial as well as the DCD,
14 the one published by Watson in the AJT tomorrow.

15 DR. ALBRECHT: So would it be okay if we have
16 the discussion tomorrow after your presentation, Dr.
17 Irish, and then continue with the other presentation?
18 Dr. Abecassis, you had a comment?

19 DR. ABECASSIS: Yes. I have a question.
20 It's really a not a question. It seems to me there's two
21 different companies that make pumps, right? I don't
22 know anything about -- our OPO uses a pump. I don't

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1 even know what pump it is. I know that you can clip
2 the thing off, and it comes off, but --

3 (Laughter)

4 DR. ALBRECHT: Well, we have --

5 DR. ABECASSIS: -- so can I ask a question.
6 What is the difference between -- and I understanding
7 there's -- people have agendas here. I don't. I just
8 want to know, number one, what is the difference
9 between -- what are the fundamental differences in
10 terms of pumping between the two machines. Are they
11 the same concept?

12 And number two, since we're going after
13 disclosing everything under the sun in this speaker, I
14 would like to make sure that the disclosure statement
15 of the previous speaker is correct. You work for an
16 OPO. Who paid you to come here?

17 MR. KRAVITZ: Waters.

18 DR. ABECASSIS: Well, you should disclose
19 that when you present a paper. You can't say I got no
20 disclosures, and then the company you're presenting the
21 stuff -- just clarification, but since we're being so
22 hard on this other speaker --

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1 (Laughter)

2 DR. ABECASSIS: -- what is the difference,
3 what is the fundamental difference between the two
4 machines? That's what I'm interested in.

5 DR. ALBRECHT: Let me ask the same question.
6 Dr. Neuland, is this something that you group is
7 going to be covering tomorrow in the series of
8 presentations or should we go ahead and get that
9 clarification this afternoon?

10 DR. HERNANDEZ: We are going to cover some
11 details, but the question come here, and we have the
12 right people on the podium, so let's go ahead and --

13 DR. ABECASSIS: Are they essentially the same
14 thing? They pump; they show you the pressure and the
15 flow, and they're the same things? Or is there some
16 major difference that I as a consumer should know
17 about?

18 MR. KRAVITZ: I'm going to be here tomorrow,
19 and could we get into this -- Jimmy, you have -- I've
20 got -- I think --

21 DR. ABECASSIS: There's no difference.
22 They're pumps. Okay. Fine. Got it.

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1 (Crosstalk)

2 DR. ABECASSIS: Answer.

3 (Laughter)

4 MR. KRAVITZ: I mean in all fairness and all
5 due respect, they're dramatically different machines,
6 but it gets very technical, and we can spend a long
7 time talking about it. I would love, if anybody is
8 interested, I can do a sidebar and talk, or tomorrow I
9 know the topics are going to kind of bring us right
10 back to this point too, and we could come in and get
11 into a great deal of detail if the group would like to
12 hear it. But just in a few minutes, it wouldn't do
13 the subject justification.

14 DR. ABECASSIS: It's a very naand (ph) simple
15 question. Are they both pumps? They both have a
16 pressure and a flow and that's it, right? All the
17 bells and whistles --

18 MR. KRAVITZ: Right.

19 DR. ABECASSIS: -- being different, the color
20 and the shapes, but it's a pump right?

21 MR. KRAVITZ: Fundamentally.

22 DR. ABECASSIS: It's pulsatile, it's a pump,

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1 right? Got it. Okay.

2 MR. KRAVITZ: Very fundamentally, yes, but
3 many, many differences.

4 WATERS REPRESENTATIVE: I can state a couple
5 of the differences. On the Waters' pump, we do have an
6 oxygenator that oxygenates the fluid as it goes through
7 the cassette, and we've got a true pulsatile driver as
8 far as how we move the fluid through the cassette. We
9 pump two kidneys at once. We can pump and block. We
10 place our kidneys above the machine. There's is inside.
11 A couple of the differences.

12 DR. ALBRECHT: Thank you.

13 (Pause)

14 DR. ALBRECHT: Well, thank you very much I
15 think for that wonderful discussion. And now if we can
16 move to the next presentation, which will be by Dr. Roy
17 First of Astellas.

18 DR. FIRST: Dr. Albrecht, ladies and
19 gentlemen, good afternoon. I'd like to thank the FDA
20 and organization committee for inviting me to give this
21 presentation. By way of disclosure, I'm a full-time
22 employee at Astellas Pharma Global Development, for

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1 doctor (inaudible) they paid for trip, but they put me
2 up in the cheap hotel around the corner --

3 (Laughter)

4 DR. FIRST: -- but it includes breakfast.

5 (Laughter)

6 DR. FIRST: So what I want to talk about
7 today is our development program for Diannexin and talk
8 briefly about the mechanism of action, the Phase IIA
9 results, which were done by the developer of the drug,
10 Alavita; our Phase II/III study design; and some of
11 the challenges we face in developing such a program.

12 So by way of background, Astellas and Alavita
13 entered into an option agreement in October of last
14 year. We believe that Diannexin has the potential to
15 prevent DGF and improve long-term renal function. As
16 we all know, there are no drugs currently approved for
17 prevention of DGF. For Diannexin, orphan drug status
18 has been granted in the U.S. And if these new
19 therapies were successful, it could expand the organ
20 donor pool and help address organ donor shortages.

21 Turning to the mechanism of action of
22 Diannexin. Diannexin is a recombinant homodimer of the

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1 endogenous human Annexin V protein. With cell
2 ischemia, phosphatidylserines are exteriorized to the
3 surface of the cell where they have a proinflammatory
4 cascade that then develops. Diannexin binds to the
5 phosphatidylserine on the endothelial cell and
6 platelets, and this results in blockage of leukocytes
7 and platelet attachment and subsequent activation of
8 the inflammatory process. It inhibits the secretory
9 activity of phospholipase A2. There is inhibition of
10 prothrombinase and prevention of Factor XII activation
11 and thereby microvascular flow is maintained.

12 Whereby by blocking these early cellular
13 events in IRI, the initiation of the IRI cascade is
14 hopefully prevented.

15 This slides shows the mechanism of action in
16 diagrammatic form with the exteriorization of the
17 phosphatidylserine. The inflammatory and thrombotic
18 events that occur thereafter these result in tissue
19 destruction and edema, and hopefully, the addition of
20 Diannexin early on blocks this proinflammatory
21 thrombotic cascade.

22 So what do we have from the Phase IIA study?

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1 This Phase IIA study was completed by Alavita, who
2 owned this compound prior to our agreement, and they
3 did this trial. Here you see the incidences of delayed
4 graft function. In the study, delayed graft function,
5 the definition used was the need for dialysis in the
6 first week after transplant. Patients, you can see
7 here that in the placebo group in a group of recipients
8 receiving kidneys from ECDs and DCDs the rate of DGF
9 using this definition was 56 percent. There was a 200
10 mcg/kilo of Diannexin group. The rate was 55 percent,
11 and the highest dose used was 400 mcg/kg, and the rate
12 dropped to 32 percent. There were no significant
13 difference in the adverse event between the placebo
14 group and the two Diannexin groups.

15 If one looks at the eGFR in these three
16 populations of patients using the MDRD formulation, you
17 see the number of patients in each group; 9 in placebo;
18 20 and 21 in the 200 and 400 mcg/kg doses,
19 respectively. You see the month 1, the month 6, and
20 the month 12 eGFRs. And notice that at all time points
21 they are highest in the Diannexin group with this
22 difference being most notable at the 12 month time

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1 point.

2 Based on these results, we moved ahead our
3 planning of Phase II/III studies, which we hope to
4 start enrolling toward the end of this year or
5 certainly by the beginning of next year. This is a
6 double-blind placebo controlled study to assess the
7 safety and efficacy of a single intravenous dose of
8 Diannexin in kidney transplant recipient. The primary
9 end point in this study will be eGFR at 1 year.

10 Some of the key inclusion/exclusion criteria,
11 we will be using ECDs, DCDs, and the higher risk SCDs,
12 namely those with cold ischemia times greater than 25
13 hours and thermal serum creatines greater than 1.5.
14 The main exclusion criteria are cold ischemia times
15 greater 40 hours and donors over 66 years of age. All
16 patients will receive a single dose of Diannexin. In
17 the placebo controlled trial, we'll use two doses of
18 Diannexin. There will be an exploratory first part.
19 We'll definitely use the 400 mcg/kg dose, and depending
20 on the safety, we may go and also use the 600 or 800
21 mcg/kg dose.

22 All patients will receive 4 doses of

1 Thymoglobulin, and stratification of all subjects
2 entering the study will be done by ECD versus DCD
3 versus modified SCD, and the third level of
4 stratification will be cold storage versus machine
5 perfusion.

6 If we look at this from an industry
7 perspective and some of the challenges developing the
8 drug for DGF, some of the critical elements have come
9 out clearly during the discussions today. I think it
10 is clear that one needs to identify the appropriate
11 patient population. We need to achieve an agreement
12 between academia, industry, and the regulatory
13 authority on the importance of renal function as the
14 critical end point for such a trial. There needs to be
15 agreement going into these trials that 1 year renal
16 function is a valid point end that demonstrates the
17 long-term effect of a therapy that impacts on IRI-DGF.

18 And the superiority design of such a study
19 versus placebo plus what is the clinical relevant
20 difference in renal function will drive sample size
21 estimations in such a study.

22 So in summary, I think defining the at-risk

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1 population for inclusion in these trials allows for
2 applications of new therapies for IRI-DGF in the
3 targeted patient population, and Diannexin may be an
4 important treatment in addressing this unmet need with
5 a potential to provide a long-term benefit in renal
6 function. Thank you.

7 (Applause)

8 DR. FIRST: If there are any questions or
9 comments, I'll try and take them.

10 DR. ALBRECHT: Dr. Griffin.

11 MR. GRIFFIN: I have a question about the
12 mechanism and the rationale with which you or your
13 collaborators at Alavita proceeded. You indicated on the
14 mechanism slide, which is always important to
15 understand that it has an effect on Factor XII, but I
16 don't think I'm aware of anything relating
17 phosphatidylserine and Factor XII. I've studied this
18 for 30 years, and I'm not aware of that. On the other
19 hand, I'm well aware that phosphatidylserine on cells
20 that are activated could be blocked by Annexin V, and
21 it would inhibit coagulation, but I don't believe that
22 slide about mechanism is correct about Factor XII.

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1 DR. FIRST: I can only bow to your knowledge
2 on this. This is material --

3 MR. GRIFFIN: Got it.

4 DR. FIRST: -- inherited from them.

5 MR. GRIFFIN: Got it.

6 DR. FIRST: They have got a publication
7 coming out showing that it actually has minimal
8 anticoagulant effect.

9 MR. GRIFFIN: Yes. Right. And then the
10 second thing I was wonder perhaps your collaborators
11 had some studies, but one important, positive
12 beneficial effect of exposure to phosphatidylserine is
13 that it promotes clearance of apoptotic cells, and
14 therefore it minimizes the damages that apoptotic cells
15 and bodies provides. So I'm wondering if on the other
16 side if, again, the group -- and I'm talking about
17 mechanisms. I know everybody here is much more
18 concerned about what the 1-year survival is, and so am
19 I, but I am concerned about mechanism as well. Is
20 there any knowledge about how this compound effects
21 clearance of apoptotic bodies or cells?

22 DR. FIRST: Not that I'm aware of. Most of

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1 the basic science has been done in the past years by
2 Tony Allison who is still active in the company and
3 working with a number of basic scientists on these
4 mechanisms.

5 MR. GRIFFIN: Thank you.

6 DR. FIRST: One question -- yes?

7 DR. TULLIUS: Is there a particular reason to
8 exclude donors over the age of 66?

9 DR. FIRST: Not a particular good reason.
10 Certain -- no, really, certain things get handed down
11 from protocol to protocol, and trying to get rid of a
12 lot of these things is something we can consider.
13 We'll talk about and see whether it needs to be
14 retained. Sandy?

15 DR. FENG: Was the GFR benefit predominantly
16 in the non-DGF versus the -- was there a benefit across
17 the board? Or was the benefit -- was there anymore
18 analysis of that GFR benefit at 1 year?

19 DR. FIRST: I think if you examine the data
20 closely the numbers, first of all, are small, 20-odd
21 per group. So when you start getting into subgroups,
22 it's really difficult to do much analysis. It does

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1 appear to be a trend within both groups. But with 20
2 patients divided, I think a majority were DCDs, and
3 there were about half a dozen -- the majority were
4 ECDs, about a half a dozen DCDs. Both groups tended to
5 trend in a similar direction. There's no clear-cut
6 difference in this study.

7 DR. FENG: (off mic) When you compare the
8 treated versus the -- the 400 dose versus an
9 (inaudible) untreated and the 200 and you looked at the
10 patients who had DGF versus the patients who did not,
11 in the two groups and you sort them by DGF and by
12 treatment, not by (inaudible).

13 DR. FIRST: Right. If you look at that --
14 we've looked at that by individual treatments, and the
15 patients who meet this definition of DGF and you look
16 at those and the renal function, it tends to hold up in
17 the patients who received dialysis, those that the drug
18 works and the patients who've had dialysis as well as
19 in those who did not, and it doesn't appear to be clear
20 separation. Remember, again, you're looking at 13
21 patients versus 7 when you go to subgroups with such
22 small numbers.

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1 DR. PARIKH: Any plans of collecting
2 biomarkers of biopsies? Your Phase II data look so
3 promising, and if the Phase III is replicated, this
4 would be a good opportunity to test the biomarkers in
5 at trial setting.

6 DR. FIRST: We have plans to collect
7 biomarkers at multiple time points. Having heard talks
8 today and yours, we might be going back and rethinking
9 which ones. Currently, there's IP-10, which is a
10 carryover from what Alavita did in their study and KIM-
11 1. But it was one of the things we were talking about
12 for the group over lunchtime about rethinking that.

13 DR. PARIKH: Yes. As long as the samples are
14 collected stored, I think the menu of biomarkers can be
15 tested and designed later of course. Excellent.

16 DR. ARCHDEACON: So I can think of some
17 fairly attractive qualities of this type of trial
18 design, namely that it seems like it could be a
19 potentially easily blinded study, fully-blinded study
20 that these patients are only going to have a short
21 exposure to this medication so that 1 year out there's
22 not really any questions about a confounding factor

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1 that would make it inappropriate to compare GFRs. So
2 it does seem if there is a time to use GFRs and end
3 points, this is perhaps a candidate time.

4 I guess one question I have is it seems like
5 it would a straight superiority trial. Is there any
6 thought as to that there should be -- how would you --
7 would you also be looking at the difference between
8 mean GFRs in addition to a simple statistical
9 superiority? I guess what I'm saying is it seems that
10 the larger you make the trial that potentially the
11 smaller difference there could be between mean GFRs,
12 and have you thought at all about how you would
13 interpret what the average difference between GFRs were
14 in terms of establishing a benefit?

15 DR. FIRST: Patrick, this is a key question
16 obviously for this whole development: How much better
17 is clinically significant? And what we've done, we've
18 done a very thorough analysis of the different donor
19 types from the UNOS database out beyond 1 year. We've
20 also tried to reanalyze some of the Harry Haren (ph)
21 data looking at what impact this DGF might have not
22 only on the 1-year outcome but also in the long-term

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1 outcome.

2 We have actually set a margin of difference
3 in this study which may be a high hurdle of a
4 clinically meaningful difference in GFR of 7 ml/minute
5 between groups, but it's very difficult that 5 is not a
6 difference. If we get a difference of 5.5 is that
7 clinically significant or not.

8 DR. ARCHDEACON: And when you say that
9 though, that means that the point-estimate difference
10 would be 5.5 or 7; but when you calculate your p value,
11 it would simply be a -- is there a -- are these
12 statically different or not?

13 DR. FIRST: Correct.

14 DR. ARCHDEACON: I guess I would be sort of
15 interested in is it -- do people in the audience have
16 any thoughts about this that they would care to share
17 with us?

18 DR. FIRST: One quick comment I had. I
19 noticed on the data that Mike Abecassis presented
20 looking at the pre-ischemia model -- not model -- in
21 donors that at 1 year he had a 5.4 ml difference in
22 GFR. Is that clinically significant and meaningful for

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1 long-term survival would be my question? Dr. Lobo.

2 DR. ABECASSIS: The ideal way to do this
3 would be to -- and I don't know how you would do it
4 logistically, but you'd have to randomized two kidneys
5 from the same donor and try to then control for
6 variables of the recipient, but the problem is if you
7 have a center that is signed up for this who knows
8 where the other kidney is going to go. But the idea of
9 doing it in a small OPO let's say where there's only
10 one or two transplant centers where you can do that
11 would at least eliminate -- because I think if you're
12 looking at eGFR to a year, a lot of it is going to depend
13 on the quality.

14 I think your point is valid because if you're
15 comparing the means you're going to have a lot of
16 variability, and you may lose the effect to just the
17 variability of eGFRs at 1 year in a cohort of patients.
18 You might eliminate some of that by giving the left
19 kidney the drug and the right kidney a placebo and
20 having it blinded so it's not always a left and the
21 right kidney or something like that.

22 To me, you have to think of something like

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1 that to really decide if the 1-year GFR is meaningful
2 or not unless your primary end point is DGF versus no
3 DGF, which is probably more related to the kidney
4 itself than a lot of other factors. I'm just throwing
5 it out there because...

6 DR. FIRST: Yes. What you say, Mike, is
7 absolutely correct, and that would be the ideal world
8 that you could do that. But as you say, the logistics
9 are not impossible and nonexistent because you're
10 talking about a 600-patient trial here.

11 DR. ABECASSIS: Yes. But if you got -- I
12 don't know who's involved in this -- but if you got the
13 right OPOs with the right centers, you might be able to
14 pull it off depending on how long the enrollment was
15 going to be, if it was a strong commitment. I think if
16 the preliminary data were really exciting, and from
17 what we seen, it's certainly suggestive; but if you had
18 really exciting preliminary data and you could get
19 people to buy into this -- people meaning the
20 transplant centers -- you could potentially do a
21 multicenter study within OPOs. As we know, kidneys
22 tend to not leave OPOs as a rule, so you have sort of a

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1 -- 90 percent of kidneys would stay within the OPOs, so
2 you could potentially control at least for the quality
3 of the organ, which is I think what's going to give you
4 the variability that you're concerned about.

5 DR. ARCHDEACON: I appreciate what you're
6 saying, but it sounds like what you're saying is that
7 that suggestion could reduce variability and make it a
8 little bit cleaner. I guess even separate from that
9 though there is sort of the issue that let's say at the
10 end of the day the mean value of kidney function in the
11 treated group is 65, and it's 60 in the other group,
12 and the variability assures us that this is a true
13 difference. It's not clear that it's actually 5, but
14 it's greater than zero, and it's estimated around 5.
15 How then can we sort of estimate what the potential
16 benefit to the patient is so that we can weigh it
17 against whatever adverse event profile comes out of the
18 safety side of that? I guess that sort of -- is it
19 reasonable to infer that an average difference of 5
20 correlates to a true clinical benefit and how would we
21 approach that? And is it patently obvious? Is it
22 patently not obvious?

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1 I guess those are some of the thoughts of the
2 group that I was wanting to explore.

3 DR. ABECASSIS: My immediate answer would be
4 I would tie it to some biomarker data because if you
5 could show that there is a GFR difference of 7 or more
6 plus in the first few days whether it's in the urine or
7 plasma or, God forbid, the kidney itself there's a
8 difference in profile in terms of some of these kidney
9 injury biomarkers I think it would be exciting.

10 It would answer two questions. It would
11 answer the question about ischemia reperfusion injury,
12 and then it might answer a question about what's the
13 implication of that.

14 DR. FIRST: Dr. Lobo.

15 DR. LOBO: It's a very interesting study. I
16 was wondering whether there would be any advantage to
17 giving this Annexin while the kidney is still in cold
18 storage because hyperplasia occurs then, and as a
19 result, you would need to give less to the patient with
20 less side effects.

21 DR. FIRST: I think that's a great idea. The
22 Alavita group have done that in a very limited study,

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1 and it's something we certainly will be considering in
2 the future if this all turns out well. Bill

3 MR. IRISH: You made a comment about
4 targeting the right at-risk study population, and this
5 study is designed for ECDs and standard criteria donor
6 that meet a certain definition and DCDs. But I think
7 when we're discussing DGF we discuss the concept in
8 terms of a continuum, and I think the risk of DGF is
9 also on a continuum rather than sort of discrete sort
10 of buckets. So I just hope that that's another area
11 for sort of consideration or for discussion.

12 DR. FIRST: Thank you.

13 DR. HALLORAN: Could I just respond to that
14 question. Is a change in GFR of 7 a health benefit?
15 It absolutely is not a health benefit. You could not
16 make that case. The best way to get that in a
17 transplant population is take them off their ACE
18 inhibitors.

19 DR. PARIKH: On the other hand, just to see
20 how complicated the topic is. If you go into native
21 kidneys, improving GFR even by 3 ml/minute reduces your
22 cardiovascular event rate and improves mortality in

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1 large (inaudible) CKD population trials. So this is but
2 nontransplant setting. So there's a lot of variability
3 around ischemia GFR in transplant at the same time
4 other factors that play a role some --

5 DR. ALBRECHT: Okay. Thank you --

6 DR. PARIKH: -- complex.

7 DR. ALBRECHT: -- Dr. First, for the
8 presentation and for the discussion. Now let's go
9 ahead and hear the next presenter, who is Dr. Evan
10 Unger from NuvOx Pharma.

11 DR. UNGER: I'd like to thank the organizers
12 for the opportunity to speak here. I came at the
13 suggestion of Bruce Kaplan, who's a colleague at the
14 University of Arizona where I have an appointment as
15 professor of radiology and biomedical engineering. He
16 thought that there might be interest in our material
17 for applications related to transplantation. We're
18 beginning to have discussions with the transplant
19 surgeons. It's based upon the surprising discovery
20 that microbubbles transport gases far more efficiently
21 than other materials, and I cofounded the company that
22 is developing this technology.

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1 Here is an in vitro graft from in vitro data
2 showing the amount of oxygen absorbed for the different
3 emulsions. Dodecafluoropentane at two different
4 temperatures, physiologic temperature and room
5 temperature and then compared to perfluorooctyl bromide
6 and fluosol perfluorodecalin. The DDFPe, which has a
7 boiling point of 28.5 degrees Centigrade, absorbs more
8 oxygen at all temperatures but has this enhanced effect
9 when it's above the gaseous transition temperature.
10 And in vivo studies that I'll show you later suggest
11 that it could be over 100 times as effective in oxygen
12 delivery per unit weight than liquids.

13 The material that we are making is stored as
14 an emulsion, and here you can see the size of the
15 particles, around 300 nm, and we have citing data for
16 several years.

17 This is from a study published by a colleague
18 of ours, Dr. Lundgren at University of Buffalo funded by
19 Department of Defense where rats were bled and mature
20 animals were administer administered 0.7 cc/kg of a 2-
21 percent weight emulsion. And you can see they get down
22 here to a hemoglobin level of 2, and all of the rats

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1 receiving the DDFPe survived for over 240 minutes.
2 This is not a blood substitute. This is for this
3 application an oxygen therapeutic.

4 Here are results of studies, funded also by
5 Department of Defense, done by Tyssebotn and Lundgren.
6 And the Department of Defense wanted to have a model
7 relevant to polytrauma in a battlefield environment, so
8 here the animals are breathing room air, and the bleed
9 is done by exsanguination from the blood; but in
10 addition, they have a break of the femur. And the
11 amount of blood loss is greater than 50 percent, and
12 all of the controls die by about 160 minutes.

13 And here, the animals given the DDFPe, a dose
14 of 0.6 cc/kg all of them lived and have normal CO2
15 production and oxygen consumption, and then they are
16 administered fluids. Both groups received fluids. All
17 of these die. And then these animals then survive long
18 term and after 30 days are killed and shown to have
19 normal intestines, kidneys, and other organs.

20 Here is the most recent work that we've been
21 doing in collaboration with Dr. Culp at the University
22 of Arkansas, and this is an embolic model of stroke in

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1 rabbits. Rabbit is a very good model for stroke. It
2 was used to develop tissue plasminogen activator, and
3 Dr. Culp has currently done more than 750 rabbits and
4 gets a reproducible ipsilateral cerebral hemisphere
5 stroke, which can be quantitated the degree of damage
6 and also can be examined for hemorrhage.

7 And here is from animals administered DDFPe
8 at different time points either immediately, 30
9 minutes, 1 hour, 2 hours, or 3 hours following stroke
10 and the infarct volume measures compared to control.
11 And these animals were killed at 4 hours and the stroke
12 volume assessed.

13 And in all groups, it is significant, and
14 it's greater than an 80-percent reduction in the volume
15 of the stroke at 4 hours. All the animals are
16 breathing oxygen control and DDFPe.

17 So here are 7-hour rabbits, surviving 7
18 hours, administered the DDFPe either at 1 hour
19 following stroke or at 6 hours. And so we see that
20 giving the material that weight appears to make no
21 difference on the volume of the infarct, but
22 administering the material at 1 hour post infarct

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1 results in about an 80-percent reduction in the volume
2 of the infarct.

3 To point out how this seems to be quite
4 unique and to also acknowledge that these are not
5 prospective studies done in the same models but culled
6 from the literature, here is the dose of DDFPe used for
7 treating stroke, 1.2 ml/kg, 2 percent weight
8 fluorocarbon, total dose .028 g/kg. And this was the
9 real bane of the liquid fluorocarbons high doses,
10 translating to 4 g/kg over 5 g/kg, more than 100 times
11 the dose for the dodecafluoropentane.

12 We were recently funded by the NCI to look at
13 DDFPe as a radiation sensitizer, so we have a sealed
14 container here where we can instill Carbogen, and there
15 are eight mice positioned with the tail vein injections
16 infusion of DDFPe while they breathe Carbogen and the
17 tumors in a human tumor xenograft of prostate cancer,
18 which is a hypoxic tumor, is exposed then to the
19 radiation. And the animals treated with DDFPe plus
20 Carbogen and radiation have a significant increase in
21 survival compared to the other animals.

22 Radiation, as you may know, acts by creation

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1 of singlet oxygen by oxygen to hypoxic cancers tend to
2 be radiation resistant.

3 DDFPe increases the washout of other gases.

4 Here is a study in pigs of nitrogen elimination in
5 animal exposed to hyperbaric nitrogen, and
6 administering the DDFPe increases the washout rate of
7 the nitrogen compared to animals breathing oxygen
8 alone. So actually we are currently collaborating with
9 this as well. There is some data that it increases the
10 washout of carbon monoxide.

11 Now this agent was tested in 2,200 patients
12 as an ultrasound contrast agent and was not highly
13 effective as an ultrasound contrast agent because of
14 the tendency for the emulsion to want to stay
15 condensed. I actually invented an ultrasound contrast
16 agent that got to the market before this one and is
17 currently marked called Definity, so this may be partly
18 why this was not successful as an ultrasound contrast
19 agent, but there was 2,200 patients worth of data where
20 it was used at actually higher doses in some of the
21 studies than we envisioned for some of the ischemia
22 reperfusion application. But this is data from the

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1 DR. UNGER: Well, if you take stroke, for
2 example, there is a number around the core, and there
3 is some degree of blood flow, but it is inadequate to
4 meet the metabolic needs of the tissue. So that's what
5 we're seeing in our models of stroke.

6 And if you take other conditions where there
7 is decreased in blood flow, of course, myocardial
8 infarction is an area we want to look at, but the
9 hypothesis would be that if we can deliver more oxygen
10 during that acute period but without increasing the
11 oxidative stress or the free radical damage. And we
12 are conducting experiments now to try to really show
13 that we do not increase oxidative stress.

14 And if any of you are interested in making
15 suggestions, we of course are eager to learn and would
16 like to conduct appropriate studies.

17 DR. LOBO: With DCD kidneys, where there is
18 obvious ischemia at the time of death, how do you think
19 you would be able to use this?

20 DR. UNGER: I think if you wanted to have a
21 material that had very low doses might improve oxygen
22 delivery to the graft either before harvesting or during

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1 transit that might be an application or in the acute
2 peritransplantation period where there might be altered
3 blood flow and there might be ischemia this might be
4 useful.

5 Also, I should say there is some data that
6 these materials will increase the washout rate of
7 anesthetic. And so in small bowel, for example, after
8 abdominal surgery, there is some data that you give
9 this kind of material and the time at which the bowel
10 begins to function is shortened. So maybe the same
11 thing -- the kidney would function more quickly.

12 DR. TULLIUS: Just one quick question. How
13 close is this substance to a perfluorodecalin, which
14 was quite popular at one time? I don't know if it
15 still is. And there was a method called two-layer
16 preservation method, and one layer was the
17 perfluorodecalin, and the other layer was I believe the
18 UW solution, and the main characteristic of
19 perfluorodecalin being it can hold up to 10 times more
20 oxygen compared to water. And how close is this
21 substance to perfluorodecalin?

22 DR. UNGER: On the in vitro stuff that I

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1 showed you there where we actually compare it to
2 perfluorodecalin, it was more than a 7-fold greater
3 oxygen carrying capacity than perfluorodecalin on a per
4 weight basis. But on the in vivo studies that I've
5 been able to pull from the literature, the difference
6 appears to be more than 100.

7 And perfluorodecalin has a boiling point of
8 well over 100 degrees Centigrade, and it's a liquid,
9 and it's retained long term by the liver and spleen in
10 high doses. This material is cleared by the lungs
11 within minutes, and there is something we believe about
12 the bubbles -- this is near -- it's 28.5 degree
13 Centigrade because of LaPlace the loading and unloading
14 of the oxygen is probably much more efficient than
15 would be suggested by the in vitro studies.

16 Perfluorodecalin was promising, but we think
17 this may solve some of the issues that perfluorodecalin
18 was unable to solve.

19 DR. ALBRECHT: Thank you, Dr. Unger. Our
20 last presenter, Dr. Donna Cryer, actually called
21 earlier this afternoon to apologize that she will not
22 be able to join us because the roads which she travels

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1 are impassable with the excess rain. However, her
2 slides are in the handouts, so please go ahead and
3 review them at your leisure.

4 And with that actually, I'd like to say that
5 this concludes Session 4 today and also brings us to
6 the end of Day 1.

7 In summary, I just want to say thank you to
8 all the moderators, presenters, and discussions. And
9 as an overview of Day 2, I just want to mention again,
10 we are starting promptly at 8 o'clock tomorrow morning,
11 and we will conclude promptly at 3 o'clock, and we have
12 a very full agenda, so we look forward to presentations
13 and spirited discussions tomorrow and perhaps
14 identifying more questions and try to identify a few
15 answers to some of those questions.

16 So thank you very much for your attendance,
17 and tomorrow we look forward to seeing you bright and
18 early at 8 o'clock. Thank you.

19 (Applause)

20 (Whereupon, Day 1 was concluded.)

21

22

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1 CERTIFICATE OF NOTARY PUBLIC

2 I, Natalia Kornilova, the officer before whom the
3 foregoing meeting was taken, do hereby certify that the
4 proceedings were taken by me in audio recording and
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