



U.S. Food and Drug Administration

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Agenda

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

A Public Workshop

Sponsored by the Food and Drug Administration (FDA)

September 8 and 9, 2011
Crowne Plaza Hotel
8777 Georgia Avenue
Silver Spring, MD 20910

Goals: To identify and discuss scientific, clinical, and regulatory issues pertaining to ischemia reperfusion injury and downstream effect on long term outcome in kidney transplant recipients to facilitate and encourage the development of therapeutic modalities for the management of this condition and related indications

Day 1	September 8, 2011
9:00am 5 minutes	Welcome and Introductions: Renata Albrecht, MD (FDA)
5 minutes	Session 1: Pathophysiology and Contributing Factors of Ischemia Reperfusion Injury (IRI) and DGF in Kidney Transplantation Moderators: Christopher Lu, MD and Ergun Velidedeoglu, MD (FDA)
15 min	Topic #1: Cellular and Molecular Mechanisms of IRI Speaker #1: Christopher Lu, MD
15 min	Topic #2: Role of Immune Cells and Complement System in IRI (Innate and Adaptive Immunity) Speaker #2: Peter Lobo, MD
15 min	Topic #3: Donor Factors Influencing IRI/DGF Speaker #3: Sandy Feng, MD, PhD
15 min	Topic #4: Effect of Recipient Factors in IRI/DGF Speaker #4: Mona Doshi, MD
45 minutes	<i>Question and Answer Period (Panel and Audience)</i> <i>Suggested Questions for Discussion</i> <ol style="list-style-type: none"> 1. Discuss pathophysiological mechanisms that may serve as potential targets for treatment/ intervention. 2. Discuss important donor characteristics that influence recipient outcome (important to consider in clinical trial design, inclusion/exclusion criteria) 3. Discuss important recipient characteristics that influence outcome (important to consider in clinical trial design, inclusion/exclusion criteria)
10:55am	Break

11:15 am 5 minutes	Session 2: Downstream Measures of Response to IRI in Kidney Transplantation Moderators: Marc Lorber, MD and Patrick Archdeacon, MD (FDA)
15 min	Topic #1: The Utility of Biomarkers for Early Identification of IRI and their Correlation with Long-term Outcomes Speaker #1: Chirag Parikh, MD, PhD, FACP
15 min	Topic #2: Early and Late Histopathologic Findings Associated with IRI Speaker #2: Lorraine Racusen, MD, FASN
15 min	Topic #3: Role of the Transcriptome – extra renal compartments Speaker #3: Philip Halloran, MD, PhD, OC
15 min	Topic #4: Role of the Transcriptome – in the kidney Speaker #4: Philip Halloran MD, PhD, OC
15 min	Topic #5: Early and Late Clinical Findings Associated with IRI Speaker #5: Arthur Matas, MD
45 minutes	<i>Question and Answer Period (Panel and Audience) /Public Comment</i> <i>Suggested Discussion Questions</i> <ol style="list-style-type: none"> 1. Discuss biomarkers that may be ready to incorporate in clinical trials <ol style="list-style-type: none"> a. Histology b. Transcriptome c. Other biomarker 2. Discuss factors important to short-term outcome and factors important to long-term outcome 3. Discuss concordance between short- term outcome and long-term outcome.
1:20 pm – 2:20 pm	LUNCH on your own

2:20 pm 5 minutes	Session 3: Current Management Strategies and Outcomes Moderators: Michael Abecassis, MD, MBA and Joette Meyer, Pharm.D. (FDA)
15 min	Topic #1: Treatment of the Donor, including ischemic preconditioning Speaker #1: Michael Abecassis, MD, MBA
15 min	Topic #2: Natural History, Management and Clinical Outcomes of DGF in the Early Post-Transplantation Period Speaker #2: Jimmy Light, MD, FACS
15 min	Topic #3: Review of Previously Studied Therapeutic Agents (including immunosuppressant and non-immunosuppressant drugs/biologics which have been studied in randomized, controlled trials in patients) Speaker #3: Marcello Cantarovich, MD
45 minutes	<i>Question and Answer Period (Panel and Audience Suggested Questions for Discussion)</i> <ol style="list-style-type: none"> 1. Discuss the natural history of IRI and whether the course is “typical” and can serve as a historical control for clinical trials. 2. Discuss the type of information on donor and recipient that would be needed to interpret the results of clinical trials evaluating products intended to prevent or treat IRI and early allograft function dysfunction and should be systematically collected in the protocol. 3. What lessons may be learned from past clinical trials evaluating products intended to prevent or treat IRI and early allograft dysfunction? 4. Are there additional published or unpublished experiences from clinical trials of such products that should be brought to our attention?
3:55 pm	Break

4:10pm	Session 4: Industry Perspective and Public Comment
	Device Industry
10 min	Robert Warren, Waters Medical Systems
10 min	Organ Recovery Systems, Inc (LifePort TM)
	Drug Industry
10 min	M. Roy First, MD, Astellas
10 min	Evan Unger, MD, DDFPe (NVX-108) as potential treatment for IRI, NuvOx Pharma, LLC
	Patient/ Public Session
10 min	Patient Perspective, Donna Cryer, JD, CEO of CryerHealth
5:00 PM	Summary Day 1, overview Day 2
	Adjourn Day 1

Day 2	September 9, 2011
8:00 am	Welcome and Introduction Renata Albrecht, MD (FDA)
5 minutes	Session 5: Animal Models of IRI and DGF/SGF Moderators: Stefan Tullius, MD, PhD and Shukal Bala, PhD (FDA)
15 min	Topic #1: Models of Brain Death Speaker #1: Stefan Tullius, MD, PhD
15 min.	Topic #2: Models of Cold and Warm Ischemia Injury Speaker #2: Joseph Bonventre, MD, PhD
15 min	Topic #3: Experience with carbon monoxide - from animals to humans Speaker #3: Douglas Hanto, MD, PhD
15 min	Topic #4 : Activated Protein C (aPC) in IRI in kidney transplant, Speaker #4: John H Griffin, PhD
15 min	Topic #5: Strengths and Limitations of Current Animals Models Speaker #5: Hamid Rabb, MD
35 minutes	<i>Question and Answer Period (Panel and Audience Suggested Questions for Discussion</i> Discuss the value/utility of proof of concept studies in an animal model of ischemia reperfusion injury and/or early allograft dysfunction for new molecular entities. Some examples of discussion point are listed below: <ul style="list-style-type: none"> •The type of proof of concept studies •Timing--before initiation of clinical investigations in kidney transplant recipients? •The pros and cons of testing in small and large animals. •The appropriate models for testing of small molecules and large molecules such as monoclonal antibodies or fusion proteins. •The appropriate endpoints to be used in animal models. • Any potential biomarkers that could be incorporated in animal model studies for these indications.

	<ul style="list-style-type: none"> •Additional studies that would be helpful in improving the utility of animal models. <ol style="list-style-type: none"> 2. If a therapeutic agent is already approved for an indication other than transplant indications (such as psoriasis or rheumatoid arthritis) what type of studies should be done in animal models, if any, prior to initiation of clinical investigations in human kidney transplant recipients in the treatment or prevention of ischemia reperfusion injury and/or early allograft dysfunction. 3. Discuss examples where studies in animal models of transplantation were predictive of findings in humans and where they were not; if not, it will be valuable to discuss the reasons. 4. Discuss the possibility of evaluating potential safety or toxicity signals in animal models of transplantation that ordinary preclinical safety studies would not detect.
9:55 am	Break

10:05am 5 minutes	Session 6: Device Issues in IRI/DGF Moderators: Jimmy Light, MD, FACS and Arturo Hernandez, MD, FACS (FDA)
10 min.	Topic #1: The Approval Process for Devices in Kidney Preservation. Speaker: Carolyn Y. Neuland, PhD (CDRH)
10 min	Topic #2: 510K and PMA Applications Speaker: Gema Gonzalez, MS (CDRH)
10 min	Topic #3: Preservation Solutions and Pumps for Organ Preservation Speaker: Arturo Hernandez, MD, FACS (CDRH)
20 min	Topic #4: Long Term Outcomes with Cold Storage Solutions Speaker: Dorry Segev, MD, PhD
20 min	Topic #5: Cold Machine Perfusion versus Static Cold Storage for SCD, ECD, and DCD Kidneys. Speaker: William Irish, PhD

20 min	Topic #6: Innovative Methods of Kidney Preservation Speaker: Sarah A Hosgood, B.Sc.
35 minutes	<i>Question and Answer Period (Panel and Audience)</i> <i>Suggested Questions for Discussion</i> <ol style="list-style-type: none"> 1. Discuss the measures of effectiveness, endpoints and potential surrogate markers for the evaluation of devices in organ preservation 2. Discuss target study population in clinical trials for the evaluation of new devices in kidney preservation (SCD, ECD, DCD, UNOS current mix) 3. Discuss the target population that would benefit most from pump perfusion vs. cold storage 4. Discuss the appropriate follow- up for the evaluation of new devices for kidney preservation.
12:30pm	LUNCH

1:00 pm	
5 minutes	Session 7: Clinical Trials Issues Related to the Recipient Moderators: Marcelo Cantarovich, MD, Mary Beth Harler, MD, and Marc Cavaillé-Coll MD, PhD (FDA)
15 minutes	Topic #1: Indications (prevention/treatment) and Populations (inclusion/exclusion) Speaker #1: Dorry Segev, MD, PhD
15 minutes	Topic#2: Clinical Pharmacology Issues (PK/PD, Phase 2b and getting the dose right) Speaker #2: Rita Alloway, Pharm D, BCPS, FCCP
15 minutes	Topic #3: Statistical Issues (including blinding, enrichment and adaptive design, etc) Speaker #3: Hongling Zhou, PhD (FDA)

15 minutes	Topic #4: Clinical trial design issues Speaker #4: E. Steve Woodle, MD, FACS
15 minutes	Topic #5: Endpoints: Short term and Long-term (graft survival) Speaker #5: Bruce Kaplan, MD
30 minutes	<p><i>Question and Answer Period (Panel and Audience Suggested Questions for Discussion)</i></p> <p>1. Discuss characteristics of kidney transplant recipients (or donor recipient combinations) at high risk for IRI/DGF that may warrant separate trials or stratification in randomized controlled trials.</p> <ul style="list-style-type: none"> • What endpoints should define clinical benefit in high-risk recipient/donor combinations (same or different from patients not considered high-risk)? • In your discussion, please consider what potential concerns would there be about products which are developed for prevention and/or treatment of IRI and/or early allograft dysfunction in high risk kidney transplant recipients subsequently being used much more broadly in all kidney transplant recipients? <p>2. Discuss what would be some of the more desirable features of a Phase II (or III) study in of products intended to prevent or treat IRI/DGF?</p> <ul style="list-style-type: none"> • What populations should be studied in Phase II versus Phase III? • Should different endpoints be evaluated (explored) in Phase II versus Phase III? • Regarding Phase II study - discuss important design and data collection considerations • Regarding Phase III – discuss important design and data collection considerations
2:50 pm	Summary
3:00 pm	Adjourn