

NIDDK

# Kidney Research National Dialogue Archived Posts and Comments

---

This is a collection of all the Postings on the Kidney Research National Dialogue (KRND) from November 2010 to April 2013. The postings are in the order of the topic categories as selected by the author of original post. Comments and votes are also provided.

## Contents

Acute Kidney Injury .....	2
Normal Biology, Development, and Physiology of the Kidney .....	15
Chronic Kidney Disease .....	24
Diabetic Nephropathy .....	48
End Stage Renal Disease .....	80
Glomerulosclerosis/Inflammation .....	104
Hypertension.....	113
Translation/National Kidney Disease Education Program (NKDEP).....	117
Polycystic Kidney Disease .....	121
Training .....	131
Transplantation .....	142
Other .....	153

## Acute Kidney Injury

Postings and Comments

### **Title: Mechanisms of repair and regeneration in acute kidney injury**

Author: Anupam Agarwal

Votes: 85

This is an important area for mechanistic insights to further elucidate understanding of how the kidney elicits repair and regenerative processes in response to injury.

*Comments:*

*Rick Schnellmann—I agree with Anupam in that more effort should be devoted to the repair and regenerative processes following AKI and that drug-able targets may be in this area.*

*Benjamin Lee—We need better methods and assays to quantitate acute renal injury to help assess damage to the kidney.*

*Bruce Molitoris—Having methods to rapidly quantify function such as GFR or RBF or tubular function, would allow for establishing the severity of injury and extent of recovery with acute or chronic therapy.*

*James Tumlin—I agree with Bruce and Mark's comments, but would like to add that we ultimately need a system of organized trialists to apply these approaches to the bedside. I fear nephrology is sorely behind in this area and getting worse. I also believe that if we were to reduplicate the success of the ARDSnetwork in AKI, it would lead to more funding in this area. My two cents. J. Tumlin.*

*Vinod Bansal—I agree with Dr. Lee's comment that we do need better methods to assess true renal injury as opposed to transient hypo perfusion. The severity of renal injury needs to be more quantitative something like burn injury. That would help to better understanding of mechanism of regeneration and subsequent the extent of renal recovery in terms of function.*

*Mark Okusa—It would be best with methods that are noninvasive and provide information in real time. Contrast enhanced ultrasound is one tool that might be more effectively used.*

### **Title: Can biomarkers be utilized to guide the therapy of AKI?**

Author: Paul Palevsky

Votes: 59

Several candidate biomarkers have been proposed for the early diagnosis of forms of AKI. Are these biomarkers sufficiently sensitive and specific to guide therapeutic interventions? Do they provide robust prognostic information?

*Comments:*

*Vinai Modem—I think ideally biomarkers should be able to do the following to be useful:*

*1. Identify early in the course, the presence of injury to the kidney and be specific and sensitive.*

2. Reliably identify early in the course, the severity of renal dysfunction.
3. Be able to mark the progression of AKI into different stages.
4. And finally, be able to identify renal recovery.

*Paul Kimmel—Thanks -- good points -- we should add predict response to therapy as well*

*Paul Palevsky—I would agree that we have little data at this point. What are the criteria for biomarkers that would need to be fulfilled in order to be useful in either the research or clinical arenas? Validation of biomarkers may need to go hand-in-hand with testing of potential therapeutic agents*

*Paul Kimmel—There are little data to guide use of biomarkers to gauge response to therapy -- a key characteristic of biomarkers -- since we have few therapeutics to provide -- except fluid administration / hemodynamic stabilization in patients with pre-renal azotemia*

*Ganesan Ramesh—These are good points. I think we need do more research on sublethal/subclinical injury and how kidney recovery from it without any problem. If we have knowledge on this, we can enhance recovery process and also we may able to suppress injury.*

*Oana Schiller—It is also very important that the biomarker could help to identify etiology. It is very challenging to treat an AKI with multiple pathogenic mechanisms. Sometimes the only therapy is to interrupt a nephrotoxic agent (and I am not talking about a well-known agent). Especially when you have also another mechanism that triggers AKI, i.e. an acute coronary syndrome. So, you have to do a panel of biomarkers for each patient in order to identify the correct injury in order to help us to guide the exact therapy, in an individualized manner.*

*Sarah Faubel—Treatment of patient with AKI is different from patients without AKI. So, although no specific pharmacologic intervention for patients with AKI is available, data and logic suggest that appropriate care of patients with AKI will improve outcomes. Thus a trial combining biomarkers for early diagnosis and then "excellent supportive care" with the following interventions 1) avoidance of nephrotoxins (including IV contrast), 2) conservative fluid strategy, 3) appropriate medication dosing, and/or 4) low tidal volume mechanical ventilation would likely be a strategy that would validate biomarkers and develop a best practice strategy in AKI. (I suggest low tidal volume ventilation as a strategy as it is well known that mortality drastically increases in the setting of AKI and mechanical ventilation and low tidal ventilation may be a way to affect improve outcomes in this setting). This is where we should start and could be the start of a clinical trials network which needs to be developed and then maintained.*

**Title: IS AKI Modifiable by dialysis**

Author: Emil Paganini

Votes: 30

What is the true value of dialytic support? There seems to be a fixed outcome regardless of dialysis dose/technique. Thus what is the true value of dialytic support in AKI outcome OR is AKI merely an indicator of poor outcome overall, and dialysis impact is merely at the 4-5% level?

Comments:

*Vinai Modem—I would hypothesize that early dialytic support for AKI, especially in critically ill, would improve outcome. The uremic environment and fluid overload associated with AKI worsen the dysfunction of other organ systems which in turn have a major impact on outcome. Hence, early dialytic therapy may potentially minimize the worsening of other organ dysfunction and thus improve outcome.*

**Title: New strategies to prevent ischemic AKI based on pathophysiology**

Author: Ken Hallows

Votes: 27

Ischemic AKI is a familiar and often anticipated occurrence in our hospitalized patients. A better understanding of the underlying pathophysiology of ischemia and ischemia-reperfusion injury to the kidney at the molecular and cellular signaling level may afford the identification of new potential drug gable targets and therapeutic avenues that could be exploited in clinical settings where ischemic kidney injury is predictable (e.g., abdominal aortic aneurysm repair surgery) or ongoing. Particular effects in epithelial, endothelial, and other cell types need to be better characterized. There has been much research along these lines in the areas of cardiovascular disease and stroke prevention, but as the underlying physiology of the kidney differs, identification of different and additional renal-specific strategies may prove useful in helping prevent or ameliorate ischemic AKI.

*Comments:*

*Zheng Dong—Talking about the pathophysiology, we tend to think about the tissue injury and regeneration. But the cells also respond with sometimes robust self-protective mechanisms such as autophagy. These endogenous protective mechanisms may be activated or augmented to combat AKI and other related renal diseases.*

*James Tumlin—I agree with Dr. Hallows. I also believe that there is a great disparity between the marvelous advances in the understanding of the pathophysiology of AKI and studies designed to exploit and apply new basic science knowledge. For example, the reduction in blood flow to the outer medulla in AKI is well described, but attempts to exploit this potentially critical point in the pathophysiologic sequence of AKI has been more or less dismissed within the academic community because of a very small number of clinical trials: namely the Anaritide study and the IGF-1 study. The Anaritide study was full of design error most notably excessive drug dose, while the IGF-1 study had a total of 70 patients. I believe it is as important for the NIDDK to circle back and fund clinical studies that are designed to determine whether existing drugs; —products currently available to us---have the potential to treat AKI. A number of thought leaders in AKI including Ravi Mehta and Bruce Molitoris have called for the creation of an AKIN clinical trials network. I believe this should be given strong consideration. To not address this issue will only add to the growing chasm between what we know and what we can do.*

**Title: Early versus late dialysis?**

Author: Kathleen Liu

Votes: 25

For patients with AKI, should dialysis be started early versus late? How should early and late be defined - based on novel biomarkers, volume status, or "conventional" parameters (eg, BUN/Cr)?

*Comments:*

*Paul Kimmel—What do you mean by "conventional parameters?"*

*William Fissell—Seems to me this could be expanded? Now that we have a strong sense of a few things:*

*1- ARF predisposes to subsequent CKD and probably results in permanently changed renal architecture*

*2- ARF is a highly complex event that involves all "compartments" of the kidney*

*3- Efforts to improve outcomes by adjusting delivered dose and mode of therapy have proved frustratingly limited in visible impact on survival and recovery*

*perhaps we need to broaden this a little to ask two questions:*

*'what constitutes adequate supportive care after support becomes necessary' and, separately ask,*

*'what can be done to abort the chain of events in ARF before support is necessary'.*

*The former is sort of a superset of Kathleen's excellent suggestion, and the latter closely tied to Paul Palevsky's suggestions regarding biomarkers.*

*How could we distill the broad brush strokes I painted with those two questions into defined research programs?*

*Harold Feldman—To address this question, we will need to address the difficult challenge of identifying the time of onset of AKI to avoid bias from only studying patients who ultimately undergo renal replacement therapy.*

**Title: Contrast Agents**

Author: James Hainfeld

Votes: 22

Develop non-nephrotoxic CT or MRI contrast agents.

**Title: miRNAs and Renal Disease**

Author: Ben Humphreys

Votes: 17

It is becoming clear that miRNAs regulate all aspects of renal disease, and they are 'druggable' targets: the first antagomir human trial is underway in heart. We need to understand which miRNAs are specific to kidney, in what to kidney cell type they are expressed and how they regulate renal disease. This effort should be systematic - with data made available publicly to avoid duplicative effort and funding.

*Comments:*

*Zheng Dong—Agree, emerging important field. Investigation of miRNAs in renal pathophysiology may identify novel strategies for the prevention, diagnosis, and treatment of major renal diseases. In addition, delineation of specific miRNA expression and targets will advance the fundamental aspects of cell biology.*

*Rama Natarajan—Discovery of disease specific microRNAs (in urine, exosomes, plasma and biopsies) can be very useful for early detection of various kinds of kidney diseases.*

*Rama Natarajan—Agree those studies of the Epigenome and its component factors will give us a much needed window of opportunity to uncover newer druggable targets. They will also help determine the important role of the environment in kidney diseases. Such studies can be aided by the rapid advances in epigenome profiling technologies.*

*Vallabh (Raj) Shah—The science of Epigenome now includes histone modifications, methylations, telomere attrition along with profiling miRNAs and many studies have come out with results suggesting importance of epigenomic events which are reversible and thus target for interventions. Raj Shah*

*Rama Natarajan—Clearly miRNAs are an important area for investigation in the kidney since there are several miRNAs that are either kidney specific or kidney-enriched. Moreover, antagomirs can be modified to specifically target the kidney. The recent discovery of miRNAs in the urine is exciting and suggests that they could be novel biomarkers for kidney disease. Given that they are "modulators" of gene expression, miRNA targeting could be combined with other therapies for improved efficacy*

**Title: Acute on Chronic Kidney Disease**

Author: KJ Kelly

Votes: 16

Clinical studies and basic models of CKD, the influence of AKI on progression and potential therapies

*Comments:*

*Zheng Dong—This is indeed an interesting and important area of research and again it is clinical significant and has actually been led by epidemiology studies. However, little is known why CKD patients are so sensitive to AKI.*

**Title: What are Determinants of Recovery of Kidney Function after AKI?**

Author: Paul Palevsky

Votes: 12

Many patients who sustain an episode of AKI either have no recovery of kidney function and remain dialysis dependent or have only partial recovery of kidney function. Epidemiologic studies have demonstrated that patients who survive an episode of AKI are at increased risk for development of progressive CKD or ESRD.

What factors determine recovery of kidney function after an episode of AKI?

Are any of these factors modifiable?

*Comments:*

*Vinai Modem—Slightly off the point, I wonder if biomarkers also have a role in identifying renal recovery. In the ideal world, biomarkers should be able to tell us when to start renal support and when to stop it and identify how irreversible the kidney injury is.*

*Paul Palevsky—Although we can identify risk-factors for non-recovery or progression, the clinical course of patients with these risk-factors remains variable. What are the factors that allow one patient to recover while a second patient with similar risk factors does not recover? Are any of these factors amenable to therapeutic intervention?*

*Paul Kimmel—Mink, Carlos Palant and I presented data on this question at the ASN -- not surprisingly -- the usual culprits were associated with progression to CKD stage 4 -- in patients without preexisting kidney disease. Peak Cr, DM and preexisting CKD were associated with poor outcome*

**Title: Regulation of immune cell activation by renal epithelial cells**

Author: Ganesan Ramesh

Votes: 10

Renal epithelial cells may possess inherent immuno suppressive properties. If we can understand how epithelial cells and/or product keep immune cells under inactive state, we could use this knowledge to develop effective therapy.

**Title: Monoclonal Antibody Targeted Delivery of Therapeutics**

Author: Lauren Brasile

Votes: 7

The development of humanized, chimeric or FAB' monoclonal antibodies with specificity for specific differentiated cells in the kidney could provide a targeted delivery system for treating diseased kidneys. For example monoclonal antibodies conjugated with growth factor(s) that target the proximal tubule segments would theoretically deliver requisite signal transduction for accelerated cellular repair. Local growth factor therapy would be clinically relevant because FGF, EGF, etc. have been shown to play an important role in wound healing and regenerative responses. Targeted delivery of growth factor may be beneficial since there is a reduction in local endogenous growth factor mRNA once inflammatory cytokines is up-regulated. Similarly, the inflammatory processes associated with ATN could be modulated to address the up-regulation of specific cytokines following injury.

**Title: Portable Imaging Technologies to Diagnose AKI**

Author: Joseph Bonventre

Votes: 7

Portable bed-side technologies will potentially provide imaging biomarkers as well as provide insight into pathophysiology

*Comments:*



*William Fissell—I think Joe is on the right track in expanding our sense of biomarker to include bedside diagnostics, although imaging may not be the only modality needed.*

*Charles Edelstein—How about urine output as a bedside marker of GFR. Anuria means no GFR !!*

*Osun Kwon—I absolutely agree on the need of bedside tools monitoring change in renal function (solute clearance) and ongoing pathophysiology. Dynamic monitoring of each parameter in relation to each other may lead to development of therapeutic intervention.*

*Bruce Molitoris—Bedside determinations of functional parameters, as well as structural makers of injury, will allow for a more complete evaluation of injury, potential recovery, effect of therapy and resolution.*

**Title: Physiologic analysis of AKI**

Author: Osun Kwon

Votes: 7

Most of AKI research studies have been done to assess if one factor or some factors are related to kidney function and damage and try to speculate the pathogenetic mechanism. Serum creatinine is used as an only marker of kidney function in those studies. However, solute clearance is carried out through different routes in the kidney. It is determined by 1) glomerular filtration, factored by transglomerular filtration pressure 2) tubular secretion 3) transtubular backleak. I think we need to have mechanistic explanation of how renal solute clearance decreases in different types and stages of AKI. I suggest that the physiologic study should be paralleled in any research study on pathogenesis of AKI and recovery from it. In that way, we would be able to find out intervening means by which renal solute clearance is improved and uremic state is relieved, leading to lower morbidity and mortality in patients with AKI. Such a physiologic study may also give us an insight after recovery from AKI as well as in acute phases.

**Title: Cardioresenal Syndrome: is it all about volume?**

Author: Mark Unruh

Votes: 7

Heart failure accounts for over 1 million hospital admissions annually in the United States, and is a leading cause of disability and healthcare costs. Cardioresenal syndrome occurs when cardiac and kidney dysfunction coexists, with each accelerating the progression of the other through a combination of renal hypoperfusion, venous congestion, and neurohormonal dysregulation. In patients with cardioresenal syndrome, attempts at diuresis often exacerbate underlying renal dysfunction. Venous congestion may play an important role in worsening renal function due to increased renal interstitial pressure. Therefore, volume removal may potentially prevent or abolish the development of worsening renal function in cardioresenal syndrome. Clinicians caring for cardioresenal failure patients are limited in medical therapies to effectively remove fluid. When medical therapies fail to alleviate congestion, ultrafiltration may be used for mechanical fluid removal and is endorsed by current heart failure treatment guidelines. What is the timing, type and mode of volume removal? Is volume overload the bad actor or is it simply these are patients with multiple organ failure. Can we prevent CHF patients from developing renal dysfunction? What is the mechanism of renal dysfunction in cardioresenal?

Comments:

*Osun Kwon—I think this is an important area of research since we are often involved in the care of the patients, yet we do not have clear understanding and parameters for optimal management.*

**Title: AKI in postoperative cardiac surgery (the effect of the pump)**

Author: Fernando Clau-Terré

Votes: 5

How the cardiopulmonary pump effect on renal function (on-pump vs. off-pump differences)

**Title: Chronic kidney disease as risk for AKI**

Author: Roland Blantz

Votes: 4

A high percentage of patients in the ICU and CCU have been found to have chronic kidney disease and therefore have abundant opportunities for AKI events. However, is this a direct result of risk factors associate with CKD physiology? There are recent studies that suggest that the phenotype of CKD exhibits certain elements that should increase the frequency or severity of AKI. These include studies suggesting increased oxygen consumption by the CKD kidney. However, other factors, including expression of molecules like HIF-1 or HO-1 that may confer protection. Feedback systems may also be suppressed in the CKD kidney. Both basic and clinical research is required to determine whether treatments can be applied in the setting of CKD that will diminish the likelihood of AKI events in the hospitalized patient. Also, are their molecules expressed in the CKD kidney that could provide beneficial therapy to any patients at risk for AKI in particular in the ICU setting?

**Title: Clinical correlates of experimental AKI**

Author: Richard Zager

Votes: 3

Because there has been very little progress in treating clinical acute renal failure, one must start to question the relevance of the experimental models that are being used to address it. New insights into clinical AKI are needed; particularly to test whether correlates to widely used experimental models exist. One example of this from our laboratory has been to correlate histone modifications in urine samples from AKI patients with changes that are observed in renal tissues obtained from rodent models of experimental AKI. This type of information permits both clinical - experimental correlations as well as the ability to probe pathogenic mechanisms in patients with acute renal failure.

**Title: What is the optimum serum Na level for AKI patients on CRRT?**

Author: John Daugirdas

Votes: 3

The acceptable serum Na level for ICU patients with AKI ranges from 133-148 mM. Administration of low Na fluids tends to keep serum Na ~135, whereas a higher serum Na of ~145 may help mobilize interstitial fluid and help lung compliance. An RCT is proposed for

patients receiving CRRT where attempts would be made to keep serum Na close to either 136 vs. 144 mM, with the hypothesis that edema mobilization and lung compliance would be enhanced at the higher serum Na level.

**Title: ATN: not too specific a term**

Author: Ladan Golestaneh

Votes: 2

To determine the difference between ischemic ATN, septic ATN, toxic ATN and renal angina from decreased perfusion states. Can microarray analyses and urinary biomarkers be used to differentiate between these pathologic states? If so: what are the implications for outcome?

**Title: Drug Discovery**

Author: Rick Schnellmann

Votes: 2

This is a critical area if we wish to decrease the mortality of AKI. While measuring AKI in humans provides some limitations in this area, animal studies provide evidence that renal epithelial, endothelial and immunological contain drug-able targets. Drug discovery is a long process and animal studies are needed now.

**Title: Pericytes in repair or fibrosis**

Author: Jeremy Duffield

Votes: 2

Kidney pericytes have recently been described as the major source of myofibroblast precursors in the kidney. However in health they are attached to peritubular capillaries and emerging evidence indicates that they function normally to stabilize the peritubular capillaries. Pericyte detachment which occurs in AKI and other kidney diseases not only leads to fibrosis but leads to capillary rarefaction as a result of pericyte detachment. This is a new area of research in the kidney and requires directed funding to support the study of understanding the role of pericyte in development, organ homeostasis and understanding the mechanisms of pericyte detachment and molecular programs that govern myofibroblast functions vs. pericyte functions.

**Title: Neonatal/pediatric AKI**

Author: Patrick Brophy

Votes: 2

The underpinnings of AKI in the smallest patients are not well elucidated. Indeed even the diagnosis of AKI is difficult. The potential to reduce morbidity and mortality as well as cost in this patient group depends on our ability to have a focused effort for appropriate size device development, diagnosis, patient characteristics and general epidemiologic understanding. Pediatric/Neonatal cohorts require center collaboration given the patient volumes. Developing a Pediatric/Neonatal strategy to define, understand the epidemiology, and develop interventions for AKI would be a monumental health service for American (and other) children. This in

combination with the "omics" analysis would help develop risk factors, drug based strategies and outcome predictors for this significant health care problem.

**Title: Is there a role for inflammatory inhibitors in AKI?**

Author: Rolando Claire

Votes: 1

Inflammation plays an important role in the pathophysiology of AKI. Inflammation can result in reduction in local blood flow with adverse consequences on tubule function and viability. Both the innate and adaptive immune responses are important contributors of kidney injury especially during the extension phase. Recent studies have shown that T lymphocytes have a role in the early pathogenesis of renal ischemic reperfusion injury. Tipping the balance in favor of regulatory cells or reducing the pool of inflammatory cells may shorten extension phase of AKI or may prevent long term outcomes like post AKI-CKD.

**Title: Immunologic mechanisms of kidney injury**

Author: James George

Votes: 1

A large part of the mechanisms of kidney injury involves the development of inflammatory processes that are dependent on the resident hematopoietic cells within the renal parenchyma as well as cells that immigrate to the kidney after injury. There are also feedback mechanisms, positive and negative, between the kidney parenchymal cells and elements of the immune system that can strongly affect the outcome of kidney injury.

**Title: Dialysis method for ARF caused by renal artery embolism or throm**

Author: Yu Ling Chen

Votes: 1

In patients who have acute renal failure caused by renal artery embolism or thrombosis are undergoing dialysis, it is not known whether the hemodialysis or peritoneal dialysis offer a better chance of survival. Continued use of heparin and other anticoagulants in hemodialysis patients can promote the dislodgement of emboli into the renal and peripheral circulation. Whether peritoneal dialysis, which does not require the use of anticoagulants and usually is not associated with hemodynamic instability, may lead to better outcomes remains to be studied.

*Comments:*

*Richard Solomon-This does not appear to be an adequate test of the hypothesis. Why not randomize patients to systemic heparinization or not. A clear outcome (primary) needs to be stated and defined.*

**Title: Screening atheromatous plaque before performing the invasive vas**

Author: Yu Ling Chen

Votes: 1

Arteriographic procedures constitute the most common intervention to incite atheroembolic renal disease (AERD). The most common of these is coronary angiography, which has a rate of

cholesterol embolism of 0.1% to 1.4%. Whether there is any potential benefit of screening the thoracoabdominal aorta for the presence of atheromatous plaque before performing the invasive vascular procedure should be studied in a prospective manner.

**Title: Fenofibrate effect on renal function**

Author: Yu Ling Chen

Votes: 1

Fenofibrate is a potent lipid-lowering agent that was found to increase serum creatinine and the underlying mechanism remains controversial. We believe that the underlying mechanism of fenofibrate-induced creatininemia needs further studies to elucidate. Although the effect of a shorter course of treatment seems reversible, but longer duration of treatment may have not completely reversible and detrimental effects on renal function.

**Title: Nanotherapy for Kidney Injury**

Author: Farhad Danesh

Votes: 1

Nanofibers are defined as fibers with diameters less than 100 nanometers. Several groups, including our own, have utilized biodegradable peptides to create biocompatible nanofibers. Nanofibers have been most recently popularized as drug delivery agents and as scaffolds to support cell proliferation and differentiation. Nanofibers are also playing a major role in providing new types of therapy for cancer and heart disease. For instance, it has been recently shown that delivery of platelet-derived growth factor (PDGF) by nanofibers decreases infarct size and improves cardiac function following myocardial infarction. Likewise, tethering of insulin-like growth factor-1 to peptide nanofibers increases survival of neonatal rat cardiomyocytes following myocardial infarction. We have recently used nanofibers as a platform for the local and systemic delivery of cytokines, chemokines, and growth factors secreted from embryonic stem cell (ESCs) to the kidneys. Our data indicate that preconditioned nanofibers deliver secretome from ESCs both in vitro and in vivo, and exhibit cytoprotective and anti-inflammatory properties. We think that this novel approach will harness beneficial effects of stem cells in the repair and remodeling of damaged organs, while addressing many limitations associated with the use of ESCs in vivo, including issues with limited cell engraftment, cell viability, immune tolerance, and formation of teratomas. However, additional preclinical and clinical observations are needed to establish the role of preconditioned nanofibers in both acute as well as chronic kidney diseases.

*Comments:*

*Andrew Wang-It is worth to try nanotherapy approach. However, some critical issues of the nanotherapy approach have to be considered, such as size of nanodrug and efficiency of the delivery of the nanodrug.*

*Kelvin Brockbank-This suggestion links into two later suggestions; autologous kidney production Idea #71 and treatments to rescue allograft kidneys that may be damaged, idea #101. Delivery of therapeutic agents to existing cells in kidneys for inhibition or repair of damage or to influence cells that are perfused into kidneys.*

**Title: Transcriptome Analysis in Kidney Injury Models**

Author: Ben Humphreys

Votes: 1

Gene array technologies are mature and have been successfully used to catalog cell-specific transcriptomes during renal and urogenital development (GudMap). It would be very useful to extend this effort to include adult models of kidney disease (AKI, fibrosis, GN, PKD) for the major kidney cell types.

**Title: Increasing AV fistula maturation**

Author: Surendra Shenoy

Votes: 0

Significant differences in fistula maturation (range:>90% to <15%) between surgical practices indicate that patient evaluation and technique play a major role in AVF maturation. A study of work flow - including patient evaluation, pre- and post- operative management including surgical technique, to fistula maturation - and correlation with outcomes would provide data to help develop a protocol that would universally help to increase fistula maturation rates.

**Title: Haemofiltration could aid recovery after cardiac arrest**

Author: Vijay Karnad

Votes: 0

CRRT is known to remove free radicals, stabilize haemodynamic status and improve microcirculation, remove accumulated cardiac drugs like betablockers, Ca<sup>2+</sup> channel blockers etc., correct electrolyte imbalance, off load the cardiac burden when it is in a stunned state, decongest the lungs, which could preclude a smooth recovery and induce hypothermia to. Over the past 40 years the mortality after arrest has not changed and we need a device to induce haemodynamic stability.

*Comments:*

*Vijay Karnad—There is an urgent need for assessing this logical modality in the salvageable cardiac arrests.*

**Title: Third generation sequencing for pathogen detection**

Author: Joseph Bonventre

Votes: 0

Given the power of third generation sequencing technologies allowing for rapid characterization of pathogen genomes one could imagine very effective use of this in the context of transplantation or for surveillance in dialysis

**Title: EARLY VERSUS LATE**

Author: Steven Rosansky

Votes: 0

## HOW MANY OF THE EARLY VERSUS LATE STARTERS OF CHRONIC DIALYSIS HAVE AKI PRIOR TO START

### **Title: Prescribing of known nephrotoxins by non-renal physicians**

Author: Janice Cobb

Votes: 0

Despite myriad advances, particularly in pharmacology, throughout the medical disciplines, apparently misguided non-renal physicians continue to prescribe known nephrotoxins -- e.g. lithium -- despite the existence of viable alternatives. Can we unite to stop this insidious practice?

### **Title: Sodium retention in cirrhosis and respiratory cardiac filling**

Author: John Daugirdas

Votes: 0

Inspiratory augmentation of filling of the right heart is a normal physiologic process that allows increase of right-sided cardiac output to the inspiration-expanded lungs. In early cirrhosis, due to hepatic changes, loss or reduction of this augmentation may lead to activation of low-pressure baroreceptors and increased sympathetic nerve activity. A study is proposed to determine if inspiratory augmentation of right heart filling is reduced in early cirrhosis, and if this correlates with sympathetic activation and renal sodium retention.

## Normal Biology, Development, and Physiology of the Kidney

Postings and Comments

### **Title: Development and Regeneration**

Author: Greg Dressler

Votes: 24

Before we can think about stem cells or iPS cell based therapies, we need to understand how renal epithelial cells are programmed. Basic studies in development and differentiation will help to identify factors that could be used for reprogramming. We may find that it is easier to reprogram a renal fibroblast or myofibroblast into an epithelial cell if we introduce the right combination of factors. These ideas are being pursued in the pancreas and other tissues. Pushing forward with stem cell based therapies without a basic understanding of development is potentially dangerous. Of course this is a biased view from a basic scientist.

*Comments:*

*Sanjay Jain—I agree with this view, and believe it is necessary to understand this to be able to manipulate the cellular and anatomical architecture already laid out to make kidneys more resistant to damage or repair and regenerate.*

*Samir El-Dahr—I agree with Greg and Sanjay. Both genetic and epigenetic factors must be delineated since it likely that one will not work without the other.*

*Angela Wandinger-Ness—Indeed there is still significant disagreement about the characteristics, location and functions of adult renal stem cells relative to other organs. While this may in part reflect the complexity to the kidney, I feel strongly that this is an under-explored area that would benefit from greater investment of research energy from developmental, cell biological, biochemical as well as genetic perspectives.*

*Hila Barak—I agree with this idea and believe that understanding what is the molecular mechanism that regulate cell to be committed to a specific fate within the developing kidney will help us to understand both approaches- reprogramming of adult cells in the adult kidney and also will give support to research of iPS and stem cells.*

*Feng Chen—I also agree that the successful implementation of any renal regeneration/repair therapy requires better understanding of kidney development. There is sufficient evidence in other organ systems and in the kidney itself that similar molecular circuits are governing development and regeneration/repair. In addition to proliferation, growth, and differentiation during the formation of functional structures, normal development also provides us an important lesson on maturation/termination that prevents potential overcompensation in regeneration and the risk of tumorigenesis.*

### **Title: Mouse Tool Development**

Author: Ben Humphreys

Votes: 18



Do we need a set of validated tools for mouse models of kidney disease (and development), available to all, for example Cre/CreER drivers for the major relevant differentiated cell types in adult kidney (endothelial, nephron epithelia by segment, fibroblast, macrophage etc...)?

*Comments:*

*Youi—This Idea is also highly relevant to Normal Biology/Development.*

*Mohammed Razzaque—Agree, developing genetically engineered mouse models are key to gain in vivo mechanistic insights!*

*Michelle Southard-Smith—Such Cre drivers are critical to almost every type of developmental analysis, however they also need to be well-characterized BEFORE they are distributed to investigators in the field. Knowing that the tools that are generated have been tested and fully validated for temporal, spatial, and cell-type specific expression is essential. If this is not done BAC transgenics that harbor internal deletions or knock-in drivers that have removed essential gene regulatory elements could be driving expression in patterns that does not accurately reflect the endogenous gene. In addition to Cre drivers, floxed alleles that result in haplo insufficiency or amino acid changes are needed concurrently so that temporal effects on disruptions in development or post-natal maturation can be examined. Simply being able to fate map a particular cell lineage without being able to investigate the effects of discrete mutations won't get us very far.*

*Ben Humphreys—Couldn't agree more that Cre drivers need thorough characterization ahead of time. I would add that in regard to floxed alleles, efforts might be coordinated with the Int'l Knockout Mouse Consortium (<http://www.knockoutmouse.org/>) with 15,500 alleles targeted so far and the majority as conditionals.*

**Title: In vitro Models for Kidney Disease**

Author: Sundararajan Madihally

Votes: 15

Currently disease analyses studies use 2D cell culture studies. Recent advances have shown that they do not mimic physiological conditions. Developing models using tissue engineering technologies allows better understanding of diseases while reducing time and money invested in animal models. These efforts could ultimately lead to regeneration of kidney.

**Title: Big and small science**

Author: Dennis Brown

Votes: 15

Many younger investigators are drawn to big science labs where large scale GWAS, genomic, proteomic and other omic studies are performed. The expertise for teasing out defined physiological mechanisms is slowly but surely being lost. We need to ensure that funding is distributed in such a way that precious resources are not consumed generating mountains of data that may never be appropriately analyzed - we don't even know what CFTR and PKD proteins really do, despite their discovery years go!

Comments:

*Chris Mullins—I feel this is an important observation and relevant to many fields. Perhaps it may be useful to in time (perhaps in Phase II of the KRND) outline some approaches to addressing how best this data may be assessed for true in vivo relevance - e.g., is there a analogous "large scale" approach that may be taken to move the analysis of candidates forward?*

*Robert Hurst—Perhaps we should concern ourselves more with how to analyze these "mountains of data" in clinically meaningful ways as well as how to efficiently integrate small and big science. These are not mutually exclusive and ideally should work together much more efficiently than is the case currently.*

*Jeremy Duffield—I agree with the sentiments of Dennis Brown. Part of the problem I think is that basic sciences require another level of commitment from people compared with joining a group who mine datasets that are already established. The dwindling number of US trained fellows combined with training grants that exclude people without citizenship is not helping this issue, and the lack of longer-term commitment to talented fellows who travel down the basic science path combined with the increasing salary gap between basic science fellows compared with those taking other Nephrology career avenues serves to undermine the base of talent that wants to enroll in basic sciences.*

*Pablo Ortiz—I totally agree. While it is great to have mountains of data suggesting "possible" pathways that may be the product or the cause of hypertension, CKD, or other renal disease, translating these data into meaningful renal function is a lot harder. The "small science" or targeted discovery pathway is time consuming and requires the development of new techniques and refinement of existing ones. Few young scientists are being appropriately trained in these techniques and even fewer are pursuing new avenues to monitor renal function at the cellular and molecular level. Without these, I find it hard to effectively translate the mountains of data into RENAL FUNCTION.*

*Hsiao Lai—As one of those young scientists, I would agree with all of the above comments.*

*Sumant Chugh—I agree with Dennis. Generation of mountains of data is not helpful if resources to mine the data are not available. Generating a large dataset may only require 3-4 million dollars in funding, but mining it requires additional investigators who will need another 200 million dollars of funding, which is next to impossible in the current environment. Most investigators anyway would independently confirm any data obtained from a large data base by conducting their own limited study before embarking on a project that may last upwards of 5 years.*

*Pierre Ronco—I think that omics and targeted discovery pathways are neither mutually exclusive nor antagonistic provided that the population of patients is very well phenotype. Recent advances in the pathophysiology of membranous nephropathy nicely illustrate the complementarity of these approaches. I fully agree with Dennis that omics applied to large cohorts of heterogeneous patients are loss of money and waste of time, particularly for young investigators.*

*James George—I also agree with the above sentiments. It is important to remember that the majority of innovations come from small laboratories working on problems that may or may not be "in fashion" at the time. In addition, to divert large proportions of funding to a few large enterprises will, in my opinion, result in a diminution of the overall research base.*

**Title: Ageing of the kidney**

Author: Melissa Little

Votes: 12

What does happen to the normal kidney across the lifetime of a human (i.e. what usually happens with aging? Is this simply a result of accumulated insults or not? How does the kidney maintain function across time)? How is this informed by the pathways involved in kidney development?

*Comments:*

*S. Stevan Potter—Important questions!*

*Matthias Kretzler—and I like it being posed by developmental biologists. Integrating efforts with the aging community and developing model systems and integrating a renal element in the ongoing human cohort studies will steps which need to be taken now to take advantage of biological insights.*

**Title: Targeted research or targeted training?**

Author: Doris Herzlinger

Votes: 11

Over the past 20 years, the developing kidney has received recognition as a powerful model system to investigate the molecular regulation of several developmental programs including mesenchymal-to-epithelial conversions, branching morphogenesis, and segmentation of tubular structures into functional domains. This is due, in large part, to the generous support of the NIH in funding fundamental scientific research. This research justified the use of several model organisms to study kidney development and generated the large number of mutant mouse lines with kidney defects that are now available for analysis. Most importantly it has provided novel insight into the development of kidney structure. It is now timely to address the development of renal function. Although there is a rich literature on adult renal function, it is a complex subject and may be intimidating to young investigators lacking a strong physiology background. I propose that the NIDDK organize a course on renal physiology for these investigators and encourage them to expand their thoughts and studies towards the acquisition of renal function during embryogenesis. This paradigm shift towards physiology would bring adult kidney disease into the field of developmental biology. It is likely to be more effective, in the long run, than targeting research towards a specific diseased state, which may or may not be due to primary defects in kidney function.

*Comments:*

*Martin Pollak - The MDI Biological Laboratory Course for Renal Fellows is perhaps a start:  
[http://www.mdibl.org/courses/The\\_Origins\\_of\\_Renal\\_Physiology/114/](http://www.mdibl.org/courses/The_Origins_of_Renal_Physiology/114/)*

**Title: Role of epigenetics in normal development and its dysregulation**

Author: Frederick Kaskel

Votes: 11

Investigate the role of epigenome disruptors that change gene activity and alter stem cell activity resulting in gene dysregulation. (Science 29 Oct 2010 330) “Epimutations” can pass through germ line to the gametes and affect heredity. Stem cells display developmental plasticity and offer opportunity to examine epigenetic perturbations during normal development such as DNA methylation as well as their response to injurious agents (epigenetic reprogramming?) Identify mechanisms responsible for the plasticity of epigenetic states that may be operative in dysregulation in disease.

**Title: Kidney regeneration via reprogramming**

Author: Melissa Little

Votes: 10

If we were able to generate nephron progenitors (e.g. from ES/iPS cells or via reprogramming), what could we do with them? Can you re-induce an existing collecting duct network to fuse with a neo-nephron?

*Comments:*

*Sanjay Jain—Yes this is the big question. In the current state I would not think so as the major hurdles include:*

- 1) Normal anatomical connection between the proximal and the distal nephron*
- 2) Prove it is functional and efficient. This is important as kidney as a whole has a huge dynamic range but it is not a very efficient machine as it takes back most of what it filters.*
- 3) The iPS cell safety will be a concern as it is being learnt that these cells may harbor new deleterious mutations due to going through processing etc.*

*In some respects kidney problem is little more challenging than brain as direct physical connections are needed as opposed to interneurons that can function through synapses, still a difficult problem. So, it may be worth looking at alternative ways to replenish non-functioning kidney.*

*Jeffrey Kopp—Another approach is to study how we might increase the production of stem cells in vivo, e.g. podocyte stem cells or tubular epithelial stem cells, as these cells are already located in niches from which they can emerge to repopulate depleted cell zones."*

**Title: Coordination of development**

Author: Melissa Little

Votes: 10

How is the development of neural, vascular and lymphatic elements of the kidney coordinated with the development of the nephron epithelia? This must occur as the pattern of, for example, the arterial plexus within the organ is very highly regulated.

*Comments:*

*Lauren Brasile—During the 1990's the major reason why tissue engineering attempts to develop bio hybrid organs failed can be attributed to the lack of vascularity. This problem remains an obstacle to current efforts in regenerative medicine based upon stem and progenitor cell constructs using scaffolds and matrices. In vivo cells are never more than a few microns away from a blood vessel. The*

*development of technology that can substitute for vascular function in delivering nutrients, oxygen, etc. to the cells within 3-dimensional, differentiated structures would solve a major barrier in creating tissue and organ replacements.*

*William Fissell—I think this is an insightful comment, as a major barrier remains blood flow distribution, both within artificial and bio artificial devices. The transition from macroscopic vessels to capillary networks remains extremely challenging.*

**Title: From knock-out models to role of important gene regions in vivo**

Author: Sanjay Jain

Votes: 9

Considerable effort and studies have been done on total gene knock-outs to understand physiological roles. While these are necessary, we need to transition to Phase 2 where models of alterations in individual regions of genes are made in vivo. For example, an important domain such as point mutation of a protein interaction domain, or DNA binding site or phosphorylation site. These will give more relevant mechanistic insights into development and diseases and are more relevant to diseases as you are more likely to see a single base alteration or a small deletion of an important region than a complete null. Further, the phenotypic outcome may be totally different than what the null studies may have pointed to, In this regard mutational screens or development of animal models based on identification of deleterious variants in human diseases may be helpful.

**Title: Coordination of development**

Author: Melissa Little

Votes: 10

How is the development of neural, vascular and lymphatic elements of the kidney coordinated with the development of the nephron epithelia? This must occur as the pattern of, for example, the arterial plexus within the organ is very highly regulated.

*Comments:*

*Lauren Brasile—During the 1990's the major reason why tissue engineering attempts to develop biohybrid organs failed can be attributed to the lack of vascularity. This problem remains an obstacle to current efforts in regenerative medicine based upon stem and progenitor cell constructs using scaffolds and matrices. In vivo cells are never more than a few microns away from a blood vessel. The development of technology that can substitute for vascular function in delivering nutrients, oxygen, etc. to the cells within 3-dimensional, differentiated structures would solve a major barrier in creating tissue and organ replacements.*

*William Fissell—I think this is an insightful comment, as a major barrier remains blood flow distribution, both within artificial and bioartificial devices. The transition from macroscopic vessels or capillary networks remains extremely challenging.*

**Title: Linking development and disease**

Author: Melissa Little

Votes: 5

To what degree is the hypothesis that an understanding of developmental mechanisms underpins our understanding of renal repair correct? What pertinence does this have to i) normal kidney repair and regeneration strategies or ii) structural maintenance of function across the postnatal period?

*Comments:*

*Samir El-Dahr—One area that is understudied is how reprogramming occurs whether in response to fetal or postnatal injury. The epigenetic component in my opinion should be explored with novel and new technologies and in collaboration among several interested labs.*

*Hila Barak—I agree with this idea and therefore believe that characterization of the molecular mechanisms of normal kidney repair will give insight to a big question that is still open- Do adult stem cells re-use developmental gene expression pathways to repair nephrons? Also characterization of molecular mechanisms of repair of different segments of the kidney will help our understanding in support repair or regeneration of an injured kidney.*

**Title: Variation in development**

Author: Melissa Little

Votes: 4

While we know that there is considerable variation in nephron number, less attention has been paid to other likely variations between individuals that may result from environmental or genetic effects during development. Given the association between loop of Henle length and concentrating capacity, what level of variation exists in the human population, how is this developmental regulated and what are the clinical consequences?

**Title: Model systems for studying kidney development**

Author: Melissa Little

Votes: 4

*Comments:*

*Chris Mullins—This is a very interesting issue. Has a side-by-side comparison been made between different model systems to outline the advantages/disadvantages of various mammalian systems for studying kidney development - with a focus on relevance to mimicking human development? This might stimulate a criterion for assessing relevant models and aid in selection.*

**Title: Regulation of nephron number**

Author: Melissa Little

Votes: 4

How the number of nephrons regulated and what causes cessation of nephrogenesis? It is now widely appreciated that the number of nephrons varies considerably between individuals. It is also generally accepted that there is an inverse relationship between nephron number and renal

disease in adult life. While nephron number is determined during development, we do not fully understand what regulates the rate at which this occurs or what triggers the process to end. It does appear that the cap mesenchyme nephron progenitor population eventually fully commits to differentiation, exhausting that population. However, is this triggered as an active signal or via passive exhaustion of the stem cell population? If we could understand this better, and indeed understand how intrauterine stresses can affect these processes, we may be able to extend or reinitiate the process to ensure a better outcome.

**Title: The value of cloning disease genes...**

Author: Iain Drummond

Votes: 3

Cloning human disease genes is clearly a strong priority but one could ask: How often does knowing sequence lead to therapy? I would argue that knowing disease gene sequence does not lead to cures; it leads to building models of disease that can be used in large scale screens for cures. So disease gene cloning without model building leaves our large investment in genomics and sequencing "stranded" as a diagnostic tool at best. I echo Bob's point below that integration of human genetics with experimental systems will be the key to translating genetic research. The task at hand is to identify the strengths of each model organism (i.e. the broadly relevant and translatable features of their cell biology) and prioritize specific types of studies using model organisms that best exploit their advantages. My experience has been that collaboration between zebra fish and human genetics labs can be a highly efficient way not only to validate candidate disease genes but to build models that bridge the gap of genes to cell biology. Ideally a screenable (large scale chemical library screen for instance) model can be generated. I think currently the impressive advances in human disease gene cloning are rightfully taking center stage however the full value of the approach is not realized unless we can integrate genetic information with organ cell biology and ultimately organ function.

*Comments:*

*Michelle Southard-Smith—Certainly collaboration between fish and human genetics researchers has been productive. However Doris' comment that we need to better understand normal physiological processes is well taken and relevant to this discussion point. Better understanding of how renal physiological parameters develop and mature will facilitate our ability to take advantage of large mutant resources that have been and already are being in the most relevant model organism (mice). We are only going to be able to appreciate so many mutants by looking to see whether they have polycystic or absent kidneys! That said NIDDK should continue to support genetic association and linkage studies - these type of fundamental genetic studies offer the opportunity to identify the genes that are relevant to clinical phenotypes. The biggest challenge to human genetic studies right now is clearly defining the phenotypes.*

*Iain Drummond—"The biggest challenge to human genetic studies right now is clearly defining the phenotypes"*

*This raises a useful point that the field of kidney development/function might benefit from supplementing the training of M.D.'s to better recognize genetic disease. Implicit here is the idea that if you can't accurately group patients then all bets are off when it comes to analysis of genetic associations.*

*How can the pipeline for patient disease recognition/DNA acquisition be improved? Is it an issue of broader M.D. training or is it primarily a regulatory/IRB bottleneck?*

**Title: Discovery Work Flow**

Author: Robert Bacallo

Votes: 3

One fundamental problem in our field is the lack of an integrated work flow to address clinical issues. For example, developmental models (zebra fish, xenopus, mouse, chicken), lack some genetic power (xenopus, chicken). Cell biology model systems utilize cells from dog, monkey, human, rat, mouse, possum, pig and are frequently used but findings seldom transfer to developmental systems or physiological systems (rat, mouse, dog, pig, rabbit). So from a standpoint of efficiency important findings are not being translated as rapidly as possible from genetic models, cell culture, physiology and eventually to the patient. An NIDDK sponsored meeting on translational medicine should be held with all stakeholders to work on how we can become more efficient in bringing fundamental science findings to therapy.

**Title: Vasopressin action**

Author: Dennis Brown

Votes: 3

We need to understand why the antidiuretic hormone vasopressin functions at picomolar levels in vivo, with low receptor occupancy, but not in any in vitro system in which much higher levels are needed to elicit a response.

*Comments:*

*Jia Zhuo—I agree with Dr. Dennis Brown's idea on vasopressin action in the kidney. The key is the better understanding the V2 receptor pharmacology and its downstream signaling mechanisms, and what regulates V2 receptor sensitivity and what contributes to its resistance in rodents and humans. This issue is highly relevant to renal physiology and kidney diseases with urine concentration defects.*



## Chronic Kidney Disease

### Post and Comments

#### **Title: Alkali therapy to slow down progression of CKD**

Author: Daniel Batlle

Votes: 272

Recent studies in experimental animals and clinical studies suggest that alkali therapy may be a powerful suppressor of CKD progression. There is a need for well controlled studies and using alkali formulations that are more palatable than existing ones to enhance patient compliance.

#### *Comments:*

*Kristina Paquette—I was aware that citrate salts had shown promise in delaying CKD progression in PKD rats. I guess I was thrown off by use of the word "alkali" in the title. Potassium and sodium citrate are not alkaline salts as citrate is the conjugate base of citric acid, a weak acid. A citrate buffer is used to maintain pH 3-6, well in the acid range. Sodium bicarbonate and calcium carbonate, however, are alkaline salts.*

*Bruce Carter—Yes, PKD community has been studying this, (more often potassium citrate, sodium citrate.) Promising animal (PKD rats) results since around 2000 (Tanner). Also for prevention of kidney stones in PKD.*

*Kristina Paquette—Has this therapy been shown to have any benefit for genetically-based CKD such as PKD?*

*Bruce Carter—These citrates are metabolized to corresponding bicarbonates, so act as systemic alkalinizers. Potassium salts advocated by some due to excess sodium "concerns" (despite surprisingly few reported problems in these recent studies - a finding contrary to expectations) Total amounts of actual sodium arguably modest regardless.*

*Bruce Carter—Based on Wesson and others' hypothesis that this involves endothelin-1 and other inflammatory mechanisms (results are disproportionate to what can be explained just in terms of acid-base), I concur there seems reasonable probability of equal or greater relevance to diabetic nephropathy. However, I would not recommend diluting this topic as a separate post. Diabetics should definitely be included within future research cohorts, which would expand, rather than limit our knowledge of relevant patient populations. However, it does not seem that diabetic nephropathies' response to alkali therapy would arise through fundamentally \*unrelated\* mechanisms. (Therefore, it seems that they represent one aspect of the alkali question, rather than comprising a truly separate question.) Sub-analysis should be relatively straightforward. Phase II of KRND will provide opportunity to refine research strategies.*

*Daniel Batlle—Thank you for your support of this concept and kind words, Dr. Carter. As you are probably aware, most of the recent work in this area comes from studies led by Dr. Don Wesson. Both in the rat model of renal ablation and in patients with CKD associated with hypertensive nephropathy, there has been a remarkable effect in terms of disease progression. I concur with your sense of urgency to undertake such studies in CKD patients, but I would propose including patients with diabetic nephropathy*

*or even study them separately as this population was not included in Dr. Wesson's clinical studies. Given the importance of diabetic nephropathy, it seems that studies in such patients are warranted and perhaps this should be a separate proposal altogether. Before I propose it as a separate idea on this website, I will wait to see if there are any comments in this regard.*

*Daniel Batlle—Thanks again for your comment and support Dr. Carter. Since our last communication of about 2-3 weeks ago, no one has offered comments regarding the need of a separate study in diabetic nephropathy. Therefore, I agree with you that for now, the focus should be on prevention of CKD progression in general using alkali-based therapies and that in phase II of the KRND, the issue of diabetic nephropathy can then be addressed.*

*Bruce Carter—For such powerful reported effects (through such a simple intervention) to have gone this long with so few human trials is a research oversight clearly needing correction. NIH and other governmental direct funding will be crucial, since industry will not pay for this particular avenue of research. Without \*substantially\* more direct support, studies will continue to be small and isolated, and definitive answers to the alkali question will continue to languish.*

*Bruce Carter—Perspective: For the first time in nearly a generation, it looks like we might have found a truly "new" weapon against CKD. Not just refinement of upon previous strategies--something different. If this effect is confirmed and sustainable (plausible), CKD becomes a far more "manageable" disease for many, or even most patients. ESRD or dialysis delayed not by a few years, but perhaps a decade or more. ("Powerful suppressor" as described by Daniel Batlle refers to recent studies showing relative impacts ranging from 30%-80%, even for early CKD). The alkali question MATTERS, not just for the sake of scientific curiosity, but for today's patients--not just future generations. We can't let the alkali question languish yet another 25 years. Thank you very much Dr. Batlle for posting on this highly important topic.*

### **Title: Disease self-management and health care transition**

Author: Maria Ferris

Votes: 235

To improve the health outcomes of adolescents and emerging adults with CKD/ESKD as they transfer to adult-focused providers, a successful health care transition (HCT) process needs to take place. This preparation from parent-directed care to disease self-management should be planned and monitored longitudinally. Tools to measure and monitor the HCT process need to be developed and validated.

#### *Comments:*

*Maria Ferris—This idea could also include treatment adherence and patient education curriculums*

*Kenar Jhaveri—The adolescent group of patients is usually non-compliant and a cross talk with pediatric nephrologist and adult is very important. Educating the adult nephrologist of these topics is essential as well.*

*Mike Steiner—I think transition research and care planning is intensely important through all of medicine, but this is particularly acute for chronic diseases whose course is "managed" like CKD. I fully*

*support this as a primary research focus of the NIDDK.*

*Ted Ferris—As someone who ended up having two kidney rejection episodes due to never getting the opportunity of going through a transition program, I can attest to the vast importance and need for transition programs across the country and for various chronic conditions.*

*Santi Bhagat—The planned process of health care transition is absolutely critical for emerging adults with chronic health conditions. Unless these young people master management of their health, it is unlikely they will succeed in other life areas. Developing tools that can be used by all emerging adults with CMCD will help physicians who do not practice in transition centers to embark on the transition process.*

**Title: Causes and Prognosis of Decreased GFR by Race and Ethnicity**

Author: Andrew Levey

Votes: 117

Chronic kidney disease disproportionately affects racial and ethnic minorities, but little is known about the determinants and consequences of decreased GFR (45-75 ml/min/1.73 m<sup>2</sup>) in these populations. Current studies are limited by non-representative populations, and gaps in knowledge about normal levels of measured GFR, appropriate methods to estimate GFR, associations of decreased GFR with development and progression of CKD and CVD, and effect modification by other biomarkers. Measurement of GFR in an ongoing longitudinal study of a representative, multi-racial and multi-ethnic population, with utilization of stored serum and urine for investigation of emerging biomarkers, is required to address these questions.

*Comments:*

*Bruce Carter—Rather than just another "associational" study--useful perhaps for prediction/prognosis (some groups do better worse than others is not by itself as useful), such efforts should be used to better identify specific genetic differences that might someday yield more targeted therapies, (and specific molecules worthy of targeting.) Recent work such APOL1/MYH9 indicates potential mis-steps, but also new targets on the horizon. No "magic bullet"--but perhaps better aim.*

*Helen Nickerson—DNA would also be useful if these measurements and samples were to be collected*

*Harold Feldman—The study of racial and ethnic minorities with CKD is a very important goal. Adequate assessment of kidney function is likely to require more than GFR estimation. In addition to protein excretion, other metabolic parameters may be needed to provide a panel of measures that capture various aspects of renal function.*

*Bruce Molitoris—Excellent idea but will have to have reliable measured GFR. Also, why not quantify additional kidney functions such as serum erythropoietin and 1, 25-D3 levels?*

*Vallabh (Raj) Shah—Given the complexity of stages of CKD along with CVD, a multi-marker approach will be needed to add incremental value to clinical and imaging variables for prediction of progression of CKD. That a single molecule can unambiguously specify disease is a dangerous and unrealistic expectation. The development of 'signatures (profiling)' of bio-markers in etiologic pathways as opposed*

*to measuring individual markers will facilitate identification of perturbed pathways and the development of new diagnostic and therapeutic interventions. We've to focus on signatures through high throughput metabolomics and or epigenomics now that GWAS didn't give us a magic bullet.*

**Title: Intensive vs. Standard Therapy for slowing CKD**

Author: Bruce Carter

Votes: 110

Researchers affiliated with the Mario Negri Institute and other institutions in Italy have developed a "Remission Clinic" intervention protocol and have reported achieving substantial (on the order of 90%) reductions in GFR decline, observed ESRD, and projected ESRD, with delays ranging from 12 (all subjects) to 21 years (nondiabetics).

<http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2396935/>

<http://clinicalweb.marionegri.it/remission/letteratura.php>

A more recent randomized trial again found substantial slowing (greater than 50%) of CKD progression:

<http://www.ncbi.nlm.nih.gov/pubmed/20097461>

Such findings warrant validation through larger multi-center trials, as such remarkable results would represent a significant improvement in prognosis.

**Title: Targeting phosphate metabolism in CKD to improve survival**

Author: M Wolf

Votes: 61

Disordered phosphate metabolism is associated with increased risk of death in ESRD, CKD, following kidney transplantation, and in the general population. FGF23 is an early marker of disordered phosphate metabolism that could be used to identify participants for an RCT in which one or a combination of phosphate binders, dietary manipulation or niacin could be used versus placebo to examine impact on CKD progression and mortality.

*Comments:*

*Gary Striker—Both calcium and phosphate metabolism are reasonable targets, as well as the multiple factors which control them. The VDR should also be included, and I quite agree that CKD at any stage should be evaluated, since many, of not most CKD patients succumb prior to ESRD.*

*Frederick Kaskel—The role of disorders of the vitamin D, PTH and FGF23 interaction during CKD progression in children and adolescents remains unknown. The opportunity to examine these critical factors and their implications in bone and cardiovascular health and disease will provide new and useful information on the etiology of the pathophysiology of CKD.*

*Bruce Carter—Also to be included, more aggressive interventions to normalize 25(OH)D levels, which at least one recent study has shown to be very unlikely to ever be achieved using current KDOQI vitamin D recommendations. Dietary studies have not cleanly untangled protein vs. acid-base vs. phosphate, since all tend trend together. Whether or not early and aggressive phosphate control will slow the course of CKD is very uncertain, although some recent studies showing clinically significant (40%) mortality reductions compared with placebo, suggest it is worth pursuing regardless of CKD course. Survival is*

*survival is survival to a patient.*

*Bruce Carter—And magnesium . . . perhaps not just a reflection of D, PTH, Phosphorus, but a potential direct clinical target in its own right:*

*<http://content.karger.com/ProdukteDB/produkte.asp?Aktion=ShowFulltext&ArtikelNr=321837&ProduktNr=223997>*

*Augusto Cesar S S Jr—Studies are needed to evaluate whether lowering serum phosphorus levels improve coronary artery calcification, intima-media thickness of large arteries and arterial elasticity indices. FGF23 could help to predict mineral disturbances in individuals where phosphorus, calcium and PTH are still normal and enable early associations with possible modifiable risk factors.*

*Bruce Carter—Why limit just to ESRD rather than earlier? With CV risk factors, likely the earlier the better. Vit. D (and active D) has previously been shown to be anti-proteinuric, so possible is also therefore reno-protective in addition to plausible (but unproven) CV risk reductions. Again, earlier likely "better", needing validation in controlled settings.*

*Zohreh Soltani—Studies are needed to evaluate direct effect of active vitamin D on PO4 in ESRD patients.*

*Daniel Batlle—I agree that the earlier the better. There is a need, however, to define what is normal phosphorus level in early CKD. Bad outcomes may occur at levels which are near or slightly above normal as shown in recent studies from England. Also plasma phosphorus level should be measured in a more standardized fashion to avoid fluctuation with food intake.*

*Bruce Carter—"Optimal" phosphorus for the CKD population may not be identical to "normal" as defined for the general population. Although the recent encouraging studies on phosphate binders/reduced mortality were associational rather than randomized trials, reductions on the order of 39% (Kovesdy's VA study), or Tsuneo Konta's Japanese study (use of phosphate binders combined with Vitamin D - 3.5 times mortality reduction) seem dramatic enough to warrant more rapid investigation. Newer binders have emerged with potentially better tolerance and safety, all the more reason to accelerate the pace. Gerald Appel recently presented some reasons why sevelamer binders could still be justified economically over calcium-based binders, including reduced hospitalizations and other possible benefits on FGF23, improved serum bicarbonate (using Renvela), and reduced lipids/  
<http://blog.ecu.edu/sites/nephrologyondemand/?p=5831>*

*Too often in CKD management it seems the proverbial barn doors get closed long after the horses have already gotten out--but there may be several doors which ALL need to be closed.*

*Bruce Carter—Extending the use of such strategies for "primary prevention" in CKD has gotten far less attention--even though the greatest good for the greatest number ("patient-life-years") comes by saving lives earlier, rather treating (only the survivors) later. Perhaps this historical attention bias on "later" contributes to an impression that more aggressive primary prevention efforts for CKD are either unnecessary, or hopeless—even though most (if not all) of the same mechanisms would seem relevant and beneficial through a greater portion CKD spectrum. The mortality and CV complications don't just suddenly "show up" with ESRD, yet care standards have only recently (and begrudgingly) begun to suggest that earlier phosphate interventions are warranted. Rather than an incremental approach for each population separately and in sequence, CKD should be evaluated simultaneously, as one needs to also consider the disproportionate number of patients represented. Such an approach might generate the risk/reward curves needed to settle the unanswered question of when "risk onset" begins to matter.*

**Title: Endocrine regulation of mineral ion metabolism**

Author: Mohammed Razzaque

Votes: 49

Study endocrine (bone-kidney axis) regulation of calcium and phosphate metabolism by FGF23-klotho system. Explore how FGF23-klotho system influences PTH and vitamin D in CKD to induce phosphate toxicity and associated complications, including vascular calcification.

*Comments:*

*Beate Lanske—Also, examine the direct role of FGF23 on bone mineralization, a process that seems to be independent of serum phosphate levels, and probably also independent of Klotho.*

*Bruce Carter—Perhaps this idea should be combined with #223?*

*Bruce Carter—BMP-7 or related mechanisms should also be considered as a potential direct therapy, as it has been shown to reverse CKD in animal models (2003), and more recently shown promise in CKD-BMD, including actual \*reversal\* of vascular calcification:  
<http://jasn.asnjournals.org/content/18/1/122.full>*

**Title: Imaging Biomarkers of CKD Progression**

Author: Chris Flask

Votes: 48

Development and validation of noninvasive imaging techniques to study microstructural and/or physiologic changes associated with chronic kidney disease progression.

*Comments:*

*Daniel Battle—Bold MRI should be considered as a key tool to assess renal hypoxia in vivo. Hypoxia may be importantly involved in the progression of CKD.*

**Title: CKD: genetics vs. environment-epigenomic**

Author: Vallabh (Raj) Shah

Votes: 39

In early CKD progressing to ESRD with/without complications, accompanying oxidative / inflammatory stress, triggers a persistent, self-reinforcing reprogramming of cellular function and gene expression that culminates in progression to a pathological state. Recent studies suggest that gene-environment interactions relevant for CKD are at least partly regulated by epigenomic mechanisms and may contribute to the progression of CKD. Aberrant expression patterns that develop in response to diet, increased body weight and environmental factors in CKD are likely to become “locked” by DNA methylation if they occur over a longer period of time. In this model, production of ROS by mitochondria is central to the change in DNA methylation patterns that contribute to the progression of CKD / CVD.

*Comments:*

*Janice Cobb—I am intrigued by your comments that the etiology of some of the metabolic processes, acknowledged as potentially deleterious to renal function, that have been induced and perpetuated by exogenous stressors, will, eventually, if permitted to continue, actually become locked with that patient's genetic structure! Apropos of a 2007 ASN article, concerning the undermining effects of chronic sympathetic activation, might not your concepts be applicable, also, to stressors of an emotional nature?"*

**Title: Pain management in CKD**

Author: Witty Kidney

Votes: 38

Pain is common and is under recognized and under-treated in chronic kidney disease (CKD). Often these patients with various co-morbidities undergo operative procedures and require analgesics. The most-responsible physician providing the care to these individuals during their hospitalization is often a non-nephrologist. Opioids are commonly used in the management of both acute and chronic pain, and often a standard dose is used by the health-care providers without taking into consideration the kidney function. Prolonged narcotic effects and ventilatory depression due to morphine and other opioids have been known for over a century in patients with kidney failure. The exact incidence is not known but it occurs in over half of the patients with chronic kidney disease. Despite the increased potential for respiratory depression, especially in patients with chronic kidney disease, life-threatening cases of opiate toxicity continue to occur not only in patients with kidney disease but also in patients without kidney disease. It is important to evaluate and highlight the issue of central nervous system (CNS) and respiratory depression with opioid analgesics in patients with chronic kidney disease and then formulate strategies to prevent these complications, while providing effective pain relief.

**Title: Progression of CKD from Stage II/IIIa**

Author: Harold Feldman

Votes: 34

Studies of large cohorts of CKD (AASK, CRIC, MDRD) have shown that some individuals seem not to progress while others follow an inexorable path toward ESRD (or earlier cardiovascular demise). More research on the prediction and determinants of progression within the population with early stages of kidney disease will potentially provide greater opportunity to intervene before advanced and irreversible complications of CKD have occurred.

**Title: Develop therapies to reverse deterioration in renal function**

Author: John Stokes

Author: 33

Progressive decline of function in CKD is common and for some/many patients inevitable. We need to develop therapies that will improve GFR and tubular function, not just slow the deterioration.

*Comments:*

*Daniel Batlle—I couldn't agree more.*

*Patrick Brophy—Genetically targeted therapies may well offer potential in this regard. We may be able to alter fibrosis, AKI and other factors that impact progressive decline*

*Bruce Carter—This is a VERY worthy goal, but perhaps too broadly worded to convert into a specifically funded research program. Therapies which stop or even reverse CKD progression, appear to realistically achievable goal in the relatively near future, hence should be a TOP priority. Years, NOT decades.*

**Title: The care needs of young and emerging adults with CKD**

Author: Maya Doyle

Votes: 32

Transitioning from pediatric to adult care is talked about at every peds-related conference. We need to move beyond struggling with institutional transitioning programs and focus on the needs, outcomes, and experience of young adults who have grown up and survived with kidney disease. Adult-oriented nephrology and primary care practices needs to be ready to provide developmentally appropriate care to young and emerging adults. While understanding outcomes for patients is vital, new initiatives in training adult nephrology fellows (along with primary care and family medicine) to care for those with congenital and childhood-acquired kidney disease are equally so.

*Comments:*

*Frederick Kaskel—This important progression of care from pediatric to adult transitioning is critical to the success of novel efforts to improve outcomes. Innovative approaches are needed to characterize specific population and gender-based challenges to implementing effective transitioning of adolescents to adult care. Collaborative designs from pediatric and adult care-takers, including the families, are needed.*

*Hsiao Lai—I get to see the spectrum Peds-Adult. Unfortunately many of these patients come into the adult setting as ESRD considered untransplantable. I am often faced with attitudes of defeatism/persistent noncompliance/avoidant interaction or mistrust. They are not prepared in many cases to deal with adult reality and very difficult to re-engage in the busy adult setting. From the adult nephrology standpoint we do not have a good mechanism to help these patients who may comprise only 1-2% of our population. Tools/Resources for young adults definitely needed along with a unifying organization that both young adult patients and adult nephrologists seeking resources can easily access-eg a guideline on KDOQI for transition/tools would be great! As Pediatric Nephrologists we also need better methods to redirect our expectations of the patient and family prior to adolescence-again I suggest we ask for a focus to address this through KDOQI.*

**Title: Sequella of chronic renal disease**

Author: Ken Bernstein

Votes: 31



I think the future of renal research will be to broadly define our areas of interest as a community. Chronic renal disease touches hypertension, cardiovascular disease, metabolic diseases etc. I believe NIDDK has to support cutting edge research in all these areas, whether or not the work strictly focuses on the kidney

*Comments:*

*Isak Prohovnik—In particular, I would emphasize that recent literature strongly suggests a dramatic effect of CKD on the brain, and a massive risk to the development of a dementing illness, which greatly impacts on the quality of life and the cost of caring for CKD patients.*

**Title: Obesity and CKD**

Author: Richard Johnson

Votes: 31

The mechanisms by which obesity and metabolic syndrome influence kidney function have not been well elucidated. Studies to investigate potential pathways are needed

*Comments:*

*Karen Moulton—Is insulin resistance an underlying mechanism for endothelial dysfunction in the kidney and other microcirculatory beds?*

*Srini Beddhu—I agree. The prevalence of obesity has substantially increased in the past decade. There is likely non-diabetes and non-hypertension mediated mechanisms of kidney injury in obesity. Interventional studies that target these mechanisms are warranted.*

*Andrew Rule—A lot might be learned from studying the implantation biopsies of living kidney donors. Obesity is not uncommon in this population.*

**Title: Diastolic heart failure**

Author: Flora Sam

Votes: 29

Diastolic heart failure comprises up to 50% of heart failure presentations. The majority of these patients have abnormal renal function. Despite the incidence increasing there are no therapies and an unclear understanding of the mechanisms involved. What is the role of increasing renal blood flow in diastolic HF? Is there more to this than "volume" or is this congestive "renal" failure?

**Title: What is the optimum dietary sodium intake in CKD?**

Author: John Daugirdas

Votes: 25

A lower Na diet has been suggested for CKD patients, and may help reduce proteinuria, but impact on progression has not been proven, and in heart failure, the role of a low sodium diet is being questioned (see Rothberg et al, J Gen Intern Med 25(10):1136–7, 2010).

Proposed would be a randomized study in proteinuric diabetic CKD patients with target dietary Na of 1.5 vs. 3.0 g/day, with endpoints being 50% reduction in estimated cystatin GFR or dialysis/transplantation.

**Title: Non-CVD Morbidity in CKD**

Author: Harold Feldman

Votes: 23

Increasingly, studies like the Chronic Renal Insufficiency Cohort (CRIC) Study are making us aware of the large burden of morbidity associated with chronic kidney disease that appears in forms other than classical CVD morbidity or progressive reductions of GFR. Research initiatives are needed to characterize and quantify this morbidity, seeking better primary and secondary preventive strategies. Failing to do so may represent missed opportunities to reduce cost and morbidity if we continue to focus principally on the CKD-CVD relationship.

**Title: Reducing uric acid levels to slow CKD progression.**

Author: Bruce Carter

Votes: 22

Recent single-center randomized trials suggest reducing uric acid levels to be simultaneously renoprotective and cardioprotective, even without the presence of gout. Risk reductions on the order of 50% have been reported. These results need validation in larger, multi-center trials, as well as determining optimal targets and treatment guidelines.

*Comments:*

*Bruce Carter—Untangling whether the antioxidant effects of these drugs vs. whether uric acid itself is the actual "trigger" is a riddle worth solving. However, even without such understanding, this could become useful therapy much sooner. Poorly understood drugs can be beneficial regardless and "imperfect" drugs which are available today trump "better" (future) drugs which are not. The recently reported CKD and cardio-vascular effects of urate-lowering were dramatic, not marginal, including endpoints that \*should\* translate into saving lives--using drugs which are currently and widely available, even inexpensive. All the more reason to investigate.*

*KUH Moderator—Suggest that investigators also monitor oxidative stress endpoints in such trials of xanthine oxidase inhibitors (allopurinol, febuxostat) to try to begin to differentiate the effects of reducing uric acid per se vs. effects of reducing superoxide production (oxidative stress endpoints, e.g., erythrocyte GSSG/GSH). Both of these endpoints can change as consequences of this drug class.*

*Bruce Carter—A more recent review of the observational studies, rationale for a multi-center trial:[http://www.nature.com/nrneph/journal/v7/n5/full/nrneph.2010.186.html?WT.ec\\_id=NRNEPH-201105](http://www.nature.com/nrneph/journal/v7/n5/full/nrneph.2010.186.html?WT.ec_id=NRNEPH-201105)*

**Title: Survival and Cardiovascular Paradoxes in Chronic Kidney Disease**

Author: Kamyar Kalantar-Zadeh

Votes: 22

Most of the 20 million Americans with chronic kidney disease (CKD) die before commencing dialysis. One of every five dialysis patients dies each year in the United States. Although cardiovascular disease is the most common cause of death in CKD, conventional cardiovascular risk factors such as hypercholesterolemia, hypertension and obesity are paradoxically associated with better survival at least consistently in hemodialysis patients. Emerging data indicate the existence of this ‘reverse epidemiology’ even in earlier stages of CKD. These survival paradoxes might evolve progressively over the natural course of CKD as a result of time differential of the competing risk factors and the overwhelming contribution of malnutrition, inflammation and wasting. Reversal of the reverse epidemiology upon successful kidney transplantation underscores the role of nutritional status and kidney function in engendering these paradoxes. These observations, if indicative of biologically plausible and causal associations, may lead to emergence of new paradigms and potential management strategies to improve survival in CKD patients. Such movement away from use of targets derived from general populations (e.g. Framingham) would represent a major paradigm shift in clinical medicine and public health.

*Comments:*

*Manish Ponda—Understanding the mechanisms of accelerated cardiovascular disease in kidney disease could also benefit non-CKD patients. Partnerships with NHLBI to explore this interface should be encouraged.*

### **Title: Chronic Infections and CKD**

Author: Adeel Butt

Votes: 19

What is the association of hepatitis C virus with CKD?

How does HCV and its treatment modify CKD

How do HIV and its treatment modify CKD?

*Comments:*

*Adeel Butt—There is a lot of controversy on the association of HCV and CKD. With such high prevalence of HCV and increasing epidemic of CKD, I think it is time to conduct some large scale epidemiologic studies.*

### **Title: Environmental Factors**

Author: Richard Johnson

Votes: 16

Role of diet and environment in CKD is important. Most studies have focused on genetics and specific mediators. Less is known on the role of diet, environmental factors, etc.

*Comments:*

*Vincent Gattone—Environmental factors may play an important role in CKD progression, i.e. dietary fructose in diabetes. However dietary fructose contribution to AGEs may also play a role in many forms of CKD. The kidney is a major organ involved in eliminating toxic agents and toxicants, but environmental, i.e. water-borne agents, may be okay for those with normal kidneys, but may contribute to the progression of various forms of CKD. These factors may be manageable and controllable without adding to the healthcare cost burden.*

*Anastasia Kalea—The role of dietary factors and food behaviors is extremely critical for the disease progression but stands poorly explored. Levels of a few macro and micro minerals are carefully regulated in dialysate, however many of them are measured infrequently, if ever, despite the accumulation of scientific knowledge on their important biological functions. In our highly polluted societies, toxic trace elements present in water but not in blood may accumulate and cause toxicity. The role of trace elements on immunological defenses, oxidation and infection, requires special consideration and study of their role in CKD.*

**Title: CKD and Cognitive Decline**

Author: Harold Feldman

Votes: 15

Early findings from the CRIC Study indicate an important relationship between level of kidney function and cognitive function. Additional study is needed understand the mechanisms for these associations as well as the subpopulations at greatest risk.

*Comments:*

*Anne Murray—This is a critical area that needs further understanding from the molecular to organ level to understand the renal- brain connection. The role of stroke especially needs further assessment.*

*Isak Prohovnik—Dementia substantially adds to the financial and emotional burden of CKD, to the patients, their families, and society. This is an important issue.*

**Title: BURNT-OUT DIABETES IN CKD**

Author: Kamyar Kalantar-Zadeh

Votes: 14

Treatment of early diabetes mellitus, the most common cause of chronic kidney disease (CKD), may prevent or slow the progression of diabetic nephropathy and lower mortality and the incidence of cardiovascular disease in the general population and in patients with early stages of CKD. It is unclear if glycemic control in patients with advanced CKD, including those with end-stage renal disease (ESRD) who undergoes maintenance dialysis treatment is beneficial. Aside from the uncertain benefits of treatment in ESRD, hypoglycemic interventions in this population are also complicated by the complex changes in glucose homeostasis related to decreased kidney function and to dialytic therapies, which may occasionally lead to spontaneous resolution of hyperglycemia and normalization of hemoglobin A1c levels, with a resultant picture of “burnt-out diabetes”. Further difficulties in ESRD are posed by the complicated pharmacokinetics of antidiabetic medications and the serious flaws in our available diagnostic tools used for monitoring long term glycemic control. Studies are needed to examine the physiology and

pathophysiology of glucose homeostasis in advanced CKD and ESRD, the available antidiabetic medications and their specifics related to kidney function, and the diagnostic tools used to monitor the severity of hyperglycemia and the therapeutic effects of available treatments, along with their deficiencies in ESRD. Studies need to investigate the concept of burnt-out diabetes and summarize the findings of studies that examined outcomes related to glycemic control in diabetic ESRD patients.

**Title: All deleterious CKD mutations: Find, model, screen for new drugs**

Author: Friedhelm Hildebrandt

Votes: 12

Chronic kidney disease (CKD) is frequently caused by a mutation of a single gene. In children >25% of FSGS, cystic kidney diseases, and (likely) congenital abnormalities of the kidney and urinary tract (CAKUT) are due to a multitude of single-gene causes.

Very likely, these RARE, HIGH-PENETRANCE VARIANTS will be the same that contribute as MODIFIER genes to loss of kidney function, premature ageing of the kidney, and lack of renal repair in adults.

Every individual carries >20 deleterious (recessive or dominant) mutations, which as of this year, can be identified for \$1,000-\$3,000 per individual by whole exome capture (WEC) and NextGen sequencing.

I think we owe to the community of nephrology patients that these full-penetrance mutations/CNVs are now identified (starting with severe early-onset phenotypes), then rapidly transferred into animal models (mice, zebrafish, c. elegans), in which the disease mechanisms will be studied, and in which small molecule (drug) libraries will rapidly be screened (high-throughput screening performed in lower organisms).

This will reap by far the most important genetic DIAGNOSTIC, MECHANISTIC, and THERAPEUTIC information the genome projects can offer TODAY.

**Title: How does diet affect progression of CKD?**

Author: John Daugirdas

Votes: 10

Diets may impact CKD progression in several ways. A vegetarian diet lowers colon-derived uremic toxins such as indoxyl sulfate and p-cresol (Patel, J Am Soc Nephrol (Nov) 19:488A 2008). Diets high in advanced glycosylated end products are associated with evidence of glycation of body tissues. Phosphate restriction in CKD lowers serum FGF levels. A study is proposed using a 2 x 2 factorial design to study progression of CKD in patients eating a vegetarian vs. meat-based diet, with or without restriction of phosphate and high-AGE foods. Outcomes would be 50% reduction of cystatin-estimated GFR or progression to dialysis/transplantation.

*Comments:*

*Janice Cobb---Do you consider strict adherence to an ""anti-inflammatory"" diet, consisting of raw vegetables -- e.g. broccoli, tomatoes, spinach and kale (as serum K values permit) -- and steamed wild salmon effective in maximizing GFR among CKD patients?"*

*Anastasia Kalea---Efficient studies on the dietary effect of high-AGE foods on CKD progression can cover many existing gaps in scientific knowledge. The bioavailability of the highly glycosylated forms in diet needs to be evaluated in order to reach a valid conclusion.*

*Kristina Paquette---How would people on peritoneal dialysis get enough protein on a vegetarian or alkaline diet as nuts and beans are extremely high in phosphorus? The phosphorus restrictions (and potassium in hemodialysis patients) are difficult enough for patients to follow. By adding the vegetarian/alkaline diet restrictions, I think patients would rebel and reject dietary restrictions altogether.*

*Note: The sodium and potassium citrate salts that have been shown to slow progression of CKD are ACID salts. How does that fact fit in with theories about an alkaline diet?*

*Bruce Carter---"Renal" diets place emphasis on "limits" (protein, sodium, potassium, phosphorus.) Alkalinizing diets place emphasis on "balance" (But you still need limits to get balance!) It's not what you eat, rather what are the \*results\* of what you eat, (often not measured in the past research, focused on input.) Without going into detail, it appears hopeful that CKD diets can be made more reliable and effective. The title of this post suggests a "yes/no" question when we really have a "how/details" question, but only the original poster or moderator can revise.*

*Kristina Paquette---Thank you very much for your comment. I noticed that part of it was omitted in the web post: "Alkaline foods in raw form may not be 'alkalinizing' and vice-versa for acidic foods." I have repeated it here because I think that this concept is very important in designing a diet that is intended to achieve a particular acid-base balance.*

*Bruce Carter---These citrates are metabolized to corresponding bicarbonates, so wind up acting as systemic alkalinizers. Regarding alkalinizing diet: yes, compliance challenging for any dietary intervention, especially if complicated and unenjoyably. Foods themselves need not be particularly "alkaline"--key is net \*result\* of foods as metabolized. Perhaps the latest diet fad but some nephrologists are recommending it.*

*Bruce Carter---Add-on research question: Renal vs. "alkalinizing" diets. Is one better than the other or are they really one and the same (renal diet as a subset of alkalinizing, since has net alkalinizing tendency.)*

### **Title: CKD-low turnover mineral bone disease**

Author: Deepak Sharma

Votes: 9

Low turnover bone disease is quite common in CKD population and does not have a satisfactory management protocol so far. A multipronged protocol including a customized combination of PTH and Bisphosphonates is the need of the day

### **Title: More Skepticism**

Author: Greg Dressler

Votes: 8

As a community, we need to be more critical of the science being done in our field. There is much confusion, debate, and disagreement when it comes to disease mechanisms in the kidney. Issues like whether EMT occurs or whether stem cells exist are not at all clear. Much of the prevailing views are based on scant evidence. We are doing a disservice to young PIs who may base their fledgling research programs on poorly substantiated dogma.

*Comments:*

*Andrew McMahon—The kidney field is no exception, one should be mindful of officially sanctioned views and one should expect and encourage the young PI to weigh up the evidence and come to their own conclusion. In general, biologists seem less able to abandon a theory they have invested in than our physics colleagues when the weight of evidence moves away from a previously held view. Messy as it is, it is hard to replace "confusion, debate and disagreement" in resolving difficult issues such as disease generating and disease remedying processes.*

*Jeffrey Miner—Terry Watnick brings up an interesting skepticism regarding cilia and the role of PKD1 and PKD2 in the PKD section of this website.*

*Martin Pollak—See an interesting article on truth in science in this week's New Yorker!*

*Bruce Carter—"Confusion, debate and disagreement" is necessary in any scientific process in order to overcome dogma which has achieved a level of unquestioning acceptance solely by virtue of its longevity. In terms of creating new tools resulting in improved clinical outcomes, the field of nephrology research has arguably stagnated in recent years. Some of the most provocative recent results have come from the margins rather than the mainstream, with results (and non-results) challenging deeply cherished beliefs. Perhaps though, the current confusion and debate is cause for optimism,--suggesting a period of more rapid discovery may be imminent. Yes, young PI's may pursue false leads, but blazing new trails is sometimes also the only way out of a rut. The recent New Yorker article is a sobering reminder that scientific advancement is largely a socio-political process of competing belief systems and personal biases --no matter how much we may wish otherwise. It raises serious questions regarding the reliability of the very process by which we document the paradigms everyone "agrees" upon. Not a simple process of "survival of the fittest" or empirical Darwinism.*

*Definitely worth a read:*

*[http://www.newyorker.com/reporting/2010/12/13/101213fa\\_fact\\_lehrer?currentPage=1](http://www.newyorker.com/reporting/2010/12/13/101213fa_fact_lehrer?currentPage=1)*

**Title: Cell therapy**

Author: Richard Gilbert

Votes: 8

Adult progenitor cells reduce proteinuria and improve GFR in animal models of CKD. Results from human studies in cardiac disease are looking cautiously optimistic. Time to start planning early phase studies in patients with CKD.

*Comments:*

*Richard Gilbert—Adult progenitor cells reduce proteinuria and improve GFR in animal models of CKD. Results from human studies in cardiac disease are looking cautiously optimistic, including patients with diabetes. Time to start planning early phase studies in patients with DN.*

**Title: validation of eGFR formulae**

Author: Anupama Janardhana

Votes: 7

Various formulae for estimating GFR and defining CKD are available; but when it comes to screening for CKD in developing countries, it gets hampered due to lack of validation in native population. Large scaled multicentric studies need to be carried out to set up local correction factors to account for racial differences.

**Title: Cardio-renal Syndrome: management**

Author: Deepak Sharma

Votes: 6

Volume management being one of the most important deciding factor in the outcome of this syndrome, I feel that a concomitant multipronged approach involving a judicious combination of low dose aldosterone inhibition, hemodiafiltration, ACEI+/-ARB+DRI holds key for the future outcome of this syndrome & needs to be tried aggressively in a well-managed RCT.

**Title: Why is CKD associated with higher risk of cardiovascular disease?**

Author: Lawrence Fine

Votes: 6

Stage 3 and greater CKD is associated epidemiologically with higher CVD risk and associated with other types of vascular pathology, however do we really understand the causal pathways which lead to this increase CVD risk other types of vascular damage. There are some suggestions that at least for stage 4 and stage 5 CKD risk that pathways may to some extent be different because statins so far may be ineffective in patients with severe CKD. We also need to better understand the mechanisms that cause other types of vascular damage such as small vessel injury.

*Comments:*

*Dominic Raj—Completely, agree with the comment. It is important to explore novel pathways to explain the accelerated atherosclerosis in CKD. It is important to explore novel pathways as well as to validate established pathways known to be important in general population in CKD patients.*

*Brad Astor—Completely agree with both comments above, but I would expand it beyond atherosclerosis to include other CVD processes (e.g., smaller vessel disease, ventricular hypertrophy, etc.). I also think decreased GFR and increased urinary albumin excretion should be examined separately, as the pathways will likely differ between these, as well as across outcomes.*

*Dominic Raj—Two important pathways seem to over-ride other traditional risk factors for CVD in patients with CKD- Inflammation and malnutrition. In fact there is a close link between inflammation,*



malnutrition and CVD. While it is agreed that inflammation is increased in CKD, the etiology of the increase is unclear. Studies are underway to examine the inflammatory pathway genes and phenotype in CRIC cohort, but we have to go beyond that...

Bruce Carter—Recent studies on Allopurinol and Febuxostat are showing reductions in LVH and other cardiovascular complications. Notably these effects are even being seen without the presence of gout, and situations of relatively intact GFR. Will these agents help answer the above question, or even become the needed new weapon against the primary sources of CKD mortality?

**Title: Optimizing functioning and health through physical activity**

Author: Patricia Painter

Votes: 5

Patients with CKD, regardless of stage, have low functioning and physical activity. How can we effectively and efficiently incorporate physical activity into the routine care of these patients to optimize physical function, overall health and quality of life?

Comments:

Bruce Aronow—I agree with the importance of this point. I would like to see a clinical trial evaluate genetically defined CKDs/PKD's disease progression, with biomarkers and other OMICS measures as a function of improvements in sleep, exercise, diet, etc. All signs in the field of disease systems biology point to the importance of sleep exercise and decreased dietary load stress to improve cell differentiation, wound repair and organ function. How this translates to improve clinical outcomes needs to be evaluated! This study could be combined with a lot of the other submitted ideas such as those associated with improved diet and dietary modification.

Daniel Weiner—One of the other items that has arisen is that people have concern over exercise in this population, particularly diabetics - specifically regarding safety. I think that is totally overwrought, but it is nice to have evidence to support both safety and benefit of exercise, particularly in late stage CKD.

Janice Cobb—Although many, and perhaps most CKD patients eschew physical activity, might this tendency reflect, also etiology? I know of one CKD 3 (GFR 39) whose weekly regime includes four hour duration "high intensity" kickboxing classes.

Patricia Painter—Despite the fact that many, and perhaps most of the general population avoid regular exercise also, the benefits are clear. many, if not most dialysis patients really hate dialysis, but they go. I'm sure most diabetic patients hate their dietary and insulin regimens, but they must do it...the prevalence of functional decline and frailty in the CKD population is something that should not be minimized, at currently most are not given much of any recommendations to counteract it.

Janice Cobb—I apologize if my previous statement, concerning the possibly anomolous aforementioned CKD 3 patient (who participates in 4 x weekly "high intensity" cardio-kickboxing classes), seems, in any way, contradictory to the comments affirming the undeniable benefits of physical exercise.

Stephen Fadem—

1. I agree that there should be a clinical trial
2. All professional contacts with the CKD/ESRD patient should appropriately emphasize increasing

*activity and exercise - this includes PCPs, nephrologists, nurses, medical assistants, etc. We should lead by example!!*

*3. We should emphasize that strenuous exercise is not the ideal.*

*4. We once had exercise foot bikes in our dialysis facilities. The company providing this stopped because of a lack of funding. Perhaps we should pursue whether the cost/benefit of this warrants seeking funding opportunities.*

*5. I once published an article for AAKP on exercise that might be useful: <http://www.aakp.org/aakp-library/Dialysis-Patients--Exercise/>*

**Title: Management of Osteoporosis in CKD**

Author: Edgar Lerma

Votes: 5

What is the ideal regimen for managing osteoporosis in patients with CKD/ ESRD?

**Title: CKD in South Asian populations**

Author: Mahboob Rahman

Votes: 4

Several studies have shown that persons of South Asian descent are at high risk of cardiovascular disease. Less is known about the prevalence and progression of CKD in south asians. Studies that validate measurement of GFR, evaluate risk factors for progression of CKD, CVD and other outcomes will important in this growing segment of the population

**Title: Autoantibodies and Alport's**

Author: Patrick Donohue

Votes: 4

There was a recent paper that suggested that folks with Alport's have autoantibodies similar to those found in Goodpasture's. How is this possible given that the mutation in collagen that causes Alports's also makes the collagen "invisible" to any auto-antibodies that cause Goodpasture's?

**Title: CKD Genetics**

Author: Caroline Fox

Votes: 3

Should genetics research now focus on rare variants for common and rare diseases?

**Title: The pathogenesis of sickle cell nephropathy**

Author: Karl Nath

Votes: 2

Renal complications occur commonly in sickle cell disease and contribute to the morbidity and mortality that occur in this patient population. A better understanding of the pathogenesis of this major complication of this disease may offer new therapeutic insights.

**Title: New tools to reverse glomerular fibrosis and sclerosis**

Author: Maria Jose Soler

Votes: 2

The development of CKD and its progression may have few clinical symptoms, this will lead to delayed CKD diagnosis when kidney damage is advanced and glomerular fibrosis and sclerosis are already established. The development of new therapeutic tools aimed to reverse chronic kidney lesions as glomerular fibrosis and sclerosis may be very helpful.

**Title: Kidney function in aging**

Author: Gary Striker

Votes: 2

Renal function is thought to inevitably decline with chronological age, however the rate and even the existence of reduced renal function varies widely in the general public. Clearly more data is needed to dissect the underlying causes and consequences of declining renal function, and new thoughts about how to determine whether it represents a significant risk to the individual person. Finally, the means to interfere with the "inevitability" remains as an open question.

*Comments:*

*Augusto Cesar S S Jr—I believe this is a critical issue in CDK research. Aging is a worldwide phenomenon with direct impact on CKD prevalence. Decision on whether to consider reduced GFR a physiologic process in aging or not and how to treat this condition is an open question. Healthcare providers must design activities tailored to the individual with personalized interaction. However there must be also a comprehensive approach based scientific evidences.*

*Title: Bardoxolone*

Author: Edgar Lerma

Votes: 1

Bardoxolone methyl was associated with improvement in the estimated GFR in patients with advanced CKD and type 2 diabetes at 24 weeks. The improvement persisted at 52 weeks, suggesting that bardoxolone methyl may have promise for the treatment of CKD. (N Engl J Med. 2011 Jun 24) Is this GFR improvement due to hyperfiltration? Related to weight loss? Effect on degree of proteinuria/ microalbuminuria? As Phase III commences, what other measures of renal function should be evaluated?

*Comments:*

*James Tumlin—I was a part of the Phase II trial with Bardoxolone; very interesting drug. I agree with Bruce that the company should be encouraged to perform iothalamate clearance studies and determine the FF. I also agree with Alfred that we should be able to convince Reata to conduct some small ancillary studies to quantify markers of oxidant injury—e.g. F 2alpha isoprostanes. If the proposed mechanism is truly an upregulation of intra-cellular anti-oxidant pathways it would be helpful to document this at a clinical level. One more comment; we should continue to work with industry to refine their protocols*

keeping in mind their enormous financial and regulatory constraints.

*Mahmoud.Loghman-Adham—Before embarking on a long phase 3 trial, or as soon as possible, while still in early stages of a phase 3 trial, I suggest a dedicated study in 20-30 patients to definitively assess the hemodynamic effects as well as any possible interference with creatinine transport/secretion. Agree with Bruce Molitoris that iothalamate GFR and measurements of RBF (iodohippuran) should be performed in this group of patients.*

*deepak sharma—GFR should be measured by nuclear med based facility every 6 months to study the effects.*

*Matthew Breyer—Cimetidine also affects serum creatinine by blocking creatinine secretion. Is it possible that Bardoxolone affects tubular creatinine handling (e.g. stimulates active creatinine secretion)?*

*Bruce Molitoris—Would think iothalamate GFR and spot U P/Cr ratio would be more accurate and less patient specific. This would take into account muscle loss. To determine if there is hyperfiltration then RBF would allow FF calculation. However, this is not likely going to occur in a phase 3. Doing a subgroup for iothalamate would be my suggestion.*

*Alfred Cheung—Would the sponsor entertain ancillary studies? Mechanistic studies are interesting, but FDA approval is often primary consideration.*

*MACAULAY ONUIGBO—Baseline 24-hour creatinine clearance, repeated every 6 months throughout the duration of the trial. The trial duration should not be 3-5 years to ascertain the permanence and validity of any identified trends.*

**Title: Progression in Non-Diabetic, Non Hypertensive CKD**

Author: DR NARINDER PAL SINGH

Votes: 1

Once we calculate eGFR through any equation what is the progress in Non Diabetic non Hypertensive pts.?

**Title: Bone Disease in CKD**

Author: Emmy Bell

Votes: 1

Study toxins impeding bone integrity. One of more common exposures: Fluoride in CKD.

**Title: Does Niacin offer survival advantage in Pre ESRD?**

Author: Krishnsawamy Sampathkumar

Votes: 1

Niacin and analogs provide dual benefits in CKD by reducing serum phosphate and increasing HDL. The latter effect may translate in to reduction of high levels of CV events in stage 2-4 CKD population. A double blind placebo controlled trial of Niacin with minimum 3 years follow

up may answer the research question. The primary end point will be cardiovascular events and survival. The secondary end points are doubling of serum creatinine and need for dialysis.

**Title: Mitochondrial genetics**

Author: Dominic Raj

Votes: 1

Is it time to explore the role of mitochondrial genetics in the pathogenesis of CVD in CKD?

*Comments:*

*Dominic Raj—Traditional genetics is important has certainly yielded remarkable findings through GWAS yet it is time to look beyond traditional genetics to examine the missing heritability. For instance, progressive loss of genomic content of the mitochondrial DNA could lead to ineffective electron transport chain function resulting in energy depletion, increased generation of reactive oxygen species and apoptosis. These are key pathogenic processes in CVD. Given that patients with CKD have impaired mitochondrial function and increased mitochondrial DNA mutations, it is one area that needs exploration.*

**Title: What are the genetics for the congenital anomalies of the kidney?**

Author: Augusto Cesar S S Jr

Votes: 0

Congenital anomalies of the kidney and the urinary tract (CAKUT) represent a major source of morbidity and mortality in children. Understanding the pathways involved in these anomalies is essential for prevention and has broad implications in patients with kidney and urinary tract malformations.

**Title: Obesity and resistance to diuretics.**

Author: Sinasi Salman

Votes: 0

We encounter more obese people with fluid retention, resistant to diuretics. This is not explained clearly. There are "causes" to be discovered.

**Title: Direct renin inhibitors vs. ACEI/ARB for CKD**

Author: Bruce Carter

Votes: 0

Theoretical grounds suggest that direct renin inhibitors (Aliskiren) may be superior at slowing CKD progression compared to ACE-inhibitors or ARB, and is supported by some animal studies. Renoprotective effect in humans has been demonstrated, but whether this represents "superiority" remains an unanswered question. Larger trials, including head-to-head comparisons are needed to determine whether direct renin inhibition provides superior protection against CKD progression, or might replace or supplant ACE/ARB as the standard of care.

*Comments:*

*Alfred Cheung—AVOID and ALTITUDE are going for combinations thus more complete blockade of the RAS axis (without aldosterone antagonists). Is there still a role to study single agents?*

**Title: Approaching mineral disorders after parathyroidectomy**

Author: Augusto Cesar S S Jr

Votes: 0

Often parathyroidectomy results in unsuccessful treatment. The recurrence of hyperparathyroidism or (on the opposite side) the appearance of the hypoparathyroidism have critical long term consequences to the chronic renal patient. New approaches and investigations are needed.

**Title: Anemia management in sickle cell nephropathy**

Author: Edgar Lerma

Votes: 0

Sickle Cell Nephropathy patients frequently present as management challenges in terms of anemia. Certainly, the recent updated NKF/ KDOQI Guidelines on Anemia Management in CKD cannot be applied to this unique population. Is there any evidence-based guideline or recommendation that will solve this dilemma?

**Title: Optimal statin therapy to slow or halt CKD progression**

Author: Bruce Carter

Votes: 0

CKD sub-analysis from the large TNT and more recent JUPITER trials suggest that more intensive statin therapy can help slow and even reverses CKD progression.

It remains to be determined which statins and at what doses will be most effective, and how statin therapy should be adjusted over the course of CKD. Targeted head-to-head trials and varying-dose trials are needed to answer these questions.

<http://www.renalandurologynews.com/high-dose-statin-therapy-has-expanded-benefits/article/175689/>

<http://www.ncbi.nlm.nih.gov/pubmed/20097461>

Comments:

*Bruce Carter—And:*

*<http://www.renalandurologynews.com/high-dose-statin-therapy-has-expanded-benefits/article/175689/>*

*(TNT, post hoc CKD sub-cohort) found approx. 8% eGFR \*improvement\* over five years of the study for high-dose atorvastatin (80 mg).*

*Linda Fried—The SHARP results presented at the ASN did not show a benefit with regards to progression to ESRD*

*Bruce Carter—There is some evidence that not all statins are created equal with respect to CKD, so I am not totally surprised by SHARP. (SHARP has been rather controversial to say the least, beyond CKD.) And let us not forget Crestor with regard to renal risks. ESRD as an endpoint may not be feasible for earlier CKD statin trials. Some studies suggest atorvastatin may have an edge in reducing proteinuria, perhaps consistent with TNT, which claimed the most dramatic and dose-dependent results. (Slowing GFR decline was seen for the entire population, more pronounced in CKD sub-cohort where stabilization/net improvement were observed.) JUPITER also showed stabilization of GFR, but not nearly as dramatic or dose-dependent as TNT. At this point, I would not consider SHARP to be an outright refutation of TNT or JUPITER -but it certainly says that our understanding of statins with regard to CKD is far from complete. It would be a mistake at this point to consider all statins heterogeneous, and hence dismiss the greater body of evidence with respect to lipids lowering for CKD solely on account of SHARP.  
<http://www.nature.com/ki/journal/v71/n12/full/5002174a.html>*

**Title: Renin-Ang II system in HIVAN**

Author: Pravin Singhal

Votes: 0

Although Ang II blockade and diminished production of Ang II are associated with slow down the progression of HIVAN but the involved mechanism is far from clear. I am interested to the role of pro-renin and renin in particular.

**Title: Exact risk for cancer associated with each particular ARB**

Author: Yu Ling Chen

Votes: 0

New cancer data were available for 61 950 patients from five trials, including only three of the seven FDA-approved ARBs; most patients in this meta-analysis (85.7%) received

- (1) telmisartan (Micardis, Boehringer Ingelheim) as the study drug;
- (2) the other patients received losartan (Cozaar) or candesartan (Atacand).

The five trials with new cancer data were ONTARGET, PROFESS, LIFE, TRANSCEND, and CHARM-Overall. In addition, data were available for cancer deaths in LIFE, TRANSCEND, VALIANT, and Val-HeFT. It remains unknown whether other ARBs--irbesartan (Avapro, Bristol-Myers Squibb/Sanofi-Aventis), valsartan (Diovan, Novartis), olmesartan (Benicar, Daiichi Sankyo), and eprosartan (Teveten, Abbott)--are linked to a higher risk of new cancer incidence. So the exact risk for cancer associated with each particular ARB should be determined.

*Comments:*

*Kenar Jhaveri--- This might be related to VEGF effects and perhaps studying the role of VEGF and ARBS in more detail in cancer progression might be needed*

**Title: Is it valid to use slope in GFR?**

Author: Linda Fried

Votes: 0

Is the loss of GFR constant or step-wise? Is it valid in clinical trials to evaluate slope (which is usually evaluated linearly)? Clinically, one often sees individuals with nephropathy where the loss in GFR appears to accelerate or alternatively who stabilize. What causes a change in "slope"?

*Comments:*

*Bruce Molitoris—Please define how you are measuring GFR. Is eGFR too insensitive/non-specific to be a valid measure of progression or response to therapy?*

*Linda Fried—I was thinking of measured GFR, though there is not a consensus about iothalamate vs iohexol. Change in eGFR is essentially change in serum creatinine, as the change in age adds minimally.*



## Diabetic Nephropathy

### Postings and Comments

**Title: How do we promote translation in DN?**

Votes: 35

Mechanisms should be established to support research on drug and biologic development that will not be supported by industry. For example, expansion of programs such as the NIH-supported Type 1 Diabetes Rapid Access to Intervention Development (T1D-RAID) program, and establishment of clinical trial networks, would allow potential therapies to be developed and tested in early Phase I and II trials that could lead to NIH or industry supported Phase III trials to ultimately gain FDA approval.

*Comments:*

*Breyer Matthew—A significant impediment to translation of research from the clinic to the bench and back to the clinic is the lack of a public imperative for kidney disease research. This is striking when compared to diseases such as cancer, Alzheimer’s disease, arthritis or even heart disease. Part of this is due to a lack of awareness of kidney disease, by both patient and health care provider (HCP). From the patient’s perspective, kidney disease is a silent disease. It does not cause pain like arthritis or a heart attack or elicit the fear of death, like cancer. Even when a patient is seen by non-nephrology health care providers the disease may not be mentioned since there is not much different in terms of management. General practitioners and endocrinologists alike frequently focus on the components of the disease they can treat rather than that which they cannot, and as a result, there is little clamor for a cure. The addition of eGFR to laboratory reports represents an important change that has increased HCP awareness of kidney disease and referral to nephrologists (Hemmelgarn, Zhang et al. 2010; Kagoma, Weir et al. 2011). Nevertheless an eGFR of less than 60ml/min (stage 3 CKD) alone may not indicate progressive kidney disease. Increasingly the value of combining proteinuria with creatinine measurements in identifying patients at risk for progressive kidney disease and increased mortality has been recognized (Gansevoort and de Jong 2009; Hemmelgarn, Manns et al. 2010). Routine quantification of proteinuria would not only enhance the classification of patients with kidney disease but help refine patient and HCP awareness of the risks of diabetic nephropathy. Improved diagnosis of patients with kidney disease by non-nephrologist HCPs, would enhance the ability to recruit patients to clinical trials and increase the public mandate to find a cure. Creation of trial networks providing less expensive and resource intensive access to patients with rapidly progressing diabetic nephropathy would help decrease costs of clinical trials.*

*Maintaining the dialysis-ESRD population represents a huge socioeconomic burden that is directly borne by the US government. As such one can make a particular case for a national registry of patients with early chronic kidney disease in the U.S. linked to their electronic medical records. Such a registry would militate against the patients’ lack of awareness of kidney disease (Navaneethan, Jolly et al. 2011) and allow investigators to identify patterns of disease that might otherwise go missed. For instance, genetic family studies of patients with diabetic nephropathy are particularly challenging, given the late onset of disease and increasing mobility of families in the US. Identification of rare genetic variants amenable to deep sequencing and transmitted from parent to child associated with diabetic nephropathy, would be greatly facilitated by such a registry if it could link to genetic samples and family structure. A national kidney disease registry might significantly facilitate the recruitment of patients for clinical trials, and better characterize the heterogeneity of progression rates in diabetic nephropathy. Finally the data house in such a disease registry would provide enormous opportunity for training the next generation of*

clinician scientist nephrologists. From a basic research perspective a major hurdle remains a lack understanding regarding the molecular pathogenesis of human diabetic nephropathy. Genetic studies have been hampered by the relatively small numbers of patients included in the cohorts and inadequate phenotyping (i.e. the patients often only have a single eGFR available with no longitudinal information on the progression rate of the eGFR loss or whether proteinuria is present). Family studies with multigenerational information are almost wholly lacking. Inadequate access to patient material at early and late stages of disease has limited our ability to apply newer molecular tools (like mRNA expression arrays) to characterize the pathologic changes occurring the diabetic kidney. Because kidneys of patients with diabetic nephropathy are not routinely biopsied, other approaches to accessing such tissue should be considered. This includes identifying patients who have had a kidney removed for trauma, cancer, or normal kidney tissue sampled at the time of donor nephrectomy from which tissue may be obtained. Closer partnering with transplant surgeons and urologists who perform cancer nephrectomies might help address this deficiency. A national registry of kidney tissues would significantly facilitate molecular studies of kidneys from those with diabetic nephropathy versus patients with diabetes but without nephropathy. The lack of well-established animal models of diabetic nephrology that exhibit progressive kidney failure together with the histopathological changes characteristic of human diabetic nephropathy remains a significant gap hindering translational research in diabetic nephropathy. Mouse models have been particularly well studied in the past decade, but validation that at least one of these models behaves like human diabetic nephropathy as far as kidney disease progression response to therapy (glucose control, blood pressure lowering, etc.), remains lacking (Brosius, Alpers et al. 2009; Breyer 2011). A significant disconnect is the willingness of the renal community to accept quite different experimental endpoints for preclinical animal studies than those required by the FDA for registration of a drug for kidney disease. For a successful drug registration trial, regulatory agencies require that a therapy slow the rate of doubling of serum creatinine, impact the time to initiation of dialysis or reduce the death rate. In contrast, exploration of potential renal therapeutics in diabetic mice never focuses on reducing the rate of creatinine doubling. Instead, most laboratory studies focus on histopathologic changes and albuminuria with less attention to clinically relevant renal function outcomes. There also exist unique technical hurdles to phenotyping, renal histopathology, and renal function in mouse models of DN. In this regard it is notable that many patients with diabetic nephropathy experience a cardiovascular death before they exhibit a doubling of serum creatinine. Similarly early deaths in experimental animal models may hamper the ability to observe the later endpoints of creatinine doubling and capturing the late stage histopathologic features of DN. Measuring renal function using serum creatinine in small animal models like mice is particularly challenging due to lower blood creatinine concentrations, and inability to repeatedly sample adequate blood volumes. More sensitive, less laborious assays of kidney function in the same animal over time would substantially improve our ability to identify renal failure in rodents before it eventuates in a premature death.

#### References

- Breyer, M. D. (2011). "Translating experimental diabetic nephropathy studies from mice to men." *Contrib Nephrol* 170: 156-164.
- Brosius, F. C., 3rd, C. E. Alpers, et al. (2009). "Mouse models of diabetic nephropathy." *J Am Soc Nephrol* 20(12): 2503-2512.
- Gansevoort, R. T. and P. E. de Jong (2009). "The Case for Using Albuminuria in Staging Chronic Kidney Disease." *Journal of the American Society of Nephrology* 20(3): 465-468.
- Hemmelgarn, B. R., B. J. Manns, et al. (2010). "Relation Between Kidney Function, Proteinuria, and Adverse Outcomes." *JAMA: The Journal of the American Medical Association* 303(5): 423-429.
- Hemmelgarn, B. R., J. Zhang, et al. (2010). "Nephrology visits and health care resource use before and after reporting estimated glomerular filtration rate." *JAMA* 303(12): 1151-1158.

Kagoma, Y. K., M. A. Weir, et al. (2011). "Impact of estimated GFR reporting on patients, clinicians, and health-care systems: a systematic review." *Am J Kidney Dis* 57(4): 592-601.

Navaneethan, S. D., S. E. Jolly, et al. (2011). "Development and Validation of an Electronic Health Record–Based Chronic Kidney Disease Registry." *Clinical Journal of the American Society of Nephrology* 6(1): 40-49.

Robert Nelson—I interpret this question as being primarily about how to support development of promising therapeutic interventions that are not supported by industry and my remarks will focus on this issue specifically. Ruboxistaurin, for example, has shown promise in the treatment of diabetic nephropathy, but it has not received sufficient industry support to move to definitive trials for this disease. In another example, an antibody to CTGF was being tested for its efficacy in diabetic nephropathy in an active industry-supported clinical trial when resources for the project were abruptly withdrawn and moved to a different disease priority. Given the importance of diabetic kidney disease as a cause of morbidity and mortality and the urgent need to develop more efficacious medicines to treat this disease, NIDDK needs to find a cooperative way in which the federal government can work with industry to develop new interventions and ensure that promising new therapeutic agents are tested in a timely fashion. Identifying ways to meet this goal would address a critical barrier in diabetic nephropathy research. In addition to providing federal resources to test promising new agents that are not being tested by industry, initiatives might include federal support for sample repositories and encouraging industry to deposit unused specimens collected in their clinical trials in these repositories rather than simply discarding them when the trial is completed (as suggested by Dr. Breyer for another IdeaScale topic). By doing so, other important scientific questions could potentially be addressed for the benefit of all. This question illustrates the inter-relatedness of the various issues being considered by the diabetic nephropathy working group, since work on many of these proposals could be enhanced by robust collaboration with industry. Therefore, identifying mechanisms to promote collaborations with industry and between research institutions should be a core mission of the NIH.

John Sedor—Interesting question. Agree with Matt and Rob. My added comments are multipart. Perhaps promoting novel/unproven therapies could be the kidney communities' entre into NCATS funds. DN is a significant public health problem and has limited treatments that may have reached their limits in terms of patient benefit. Getting promising new treatments over the "valley of death" to the point PHARMA would become interested is one of the goals for NCATS [I think]. A second issue was highlighted by Rob: getting PHARMA to pursue drugs already in trial in definitive trials. Prior model is the market needed to be big. New cancer therapies have alters that paradigm. Identify the subset of patients likely to benefit [using "integrative science" technologies and genetics, for example]. Reduces costs of trials and usually has biomarkers that prove benefit in shorter time. Insurance companies have been willing to pay since the patients being treated are much more likely to have a response. You treat the melanoma patient with the mutation known to respond to the treatment. PHARMA makes \$, patient exposure to costly and perhaps toxic drugs is limited and who knows perhaps health cost go done because expensive drugs are NOT given to patients destined not to respond. If we can molecular phenotype DN in a similar manner, we may be able to move novel treatments into the clinic despite their cost.

**Title: Can miRNA signatures be exploited to diagnose and treat DN?**

Votes: 0

MicroRNAs are short ribonucleotides that bind to messenger RNA to modify protein translation or promote RNA degradation. Knowledge of the function and regulation of miRNA is rapidly expanding. They appear to be sensitive to the extracellular environment and could be important

regulators of a cell's response to diabetes. Can miRNA signatures detect early signs of DN? Can knowledge of miRNA signatures be translated to therapies based on novel antagomirs, synthetic analogues of miRNA, to interfere with their involvement in DN?

*Comments:*

*Katalin Susztak—The discovery of regulatory microRNA's has significantly changed our understanding of transcription and gene regulation. This is a newly emerging field and we are just beginning to understand how these regulatory RNA's are being made and how they regulate transcription and ultimately gene expression. While they appear to be fairly stable they appear to show only a modest change in their expression level. In addition each microRNA appears to regulate a large number of targets. It appears that pharmacological targeting of microRNA's will be feasible and specifically the kidney can be well targeted by these microRNA agomirs and antagomirs. To move the field forward first we would need to understand the regulation of these regulatory RNA's in control and diseased human tissue. This includes microRNA's and other regulatory RNA molecules. Another major question will be to understand the targets of the individual microRNA's. Nevertheless this is a newly emerging field with great opportunities and therapeutic possibilities.*

*Matthias Kretzler—I fully agree with comments above: miRNA have several aspects making them attractive, but also challenging targets in DN research. My understanding of the field is that groups of miRNA appear to work in concert in targeting multiple mRNAs in a tissue and disease specific functional context. In chronic diseases like diabetic endorgan damage it appears that modest changes in miRNA alter the function of a multitude of targets with modest changes in the levels of the targeted proteins. The effect on organismal function is seen by the synergy of these multiple changes initiated. As DN is a disease process affecting a multitude of regulatory cascades, miRNAs might be promising therapeutics as they might be able to modulate the disease process in a multi-stage manner with a single intervention. However, understanding the impact of miRNAs and their potential therapeutic modulation requires that we start to understand DN as a disease process affecting regulatory events in the kidney on multiple levels (see discussion point 7). miRNA diagnostic marker identification and therapeutic experimental intervention will have to take into account the mode of action of miRNA with the modest perturbations on multiple targets. As a consequence, some of the ongoing diagnostic studies assessing single miRNA in renal tissue homogenates will be limited in their ability to be validated in independent cohorts. Similarly, experimental studies overexpressing a single miRNA several folds in vitro might lead to quite different outcomes than the modest induction of a miRNA in a different regulatory context in vivo. In summary, miRNA are attractive diagnostic and therapeutic concepts, but need to be integrated into the larger regulatory context in vivo and in the model systems used to analyze their function (see also 5, 7)*

**Title: How does diabetes affect regeneration and repair?**

Votes: 0

Tissue injury in diabetes results from cell damage and death, impaired communication among cells, dysfunction of nerves and blood vessels, and detrimental responses to systemic signals, such as inflammation. The development of the clinical manifestations depends on tissue-specific responses to injury and impairments in repair and regenerative processes. The knowledge base of the pathologic process in different tissues varies considerably, but in all organ systems a better understanding of the mechanisms is needed. How does systemic inflammation from dysregulation of the innate and adaptive immune systems affect the kidney? What are the

mechanisms of injury in specialized cells, such as podocytes or tubular epithelial cells? What kidney disease is associated with diabetes from non-diabetes related forms of these diseases? Does diabetes accelerate the same pathologic processes or have unique components? What mechanisms are responsible for the increased mortality in people with diabetes and end-stage renal failure? Will aggressive treatment to normalize the blood sugar prevent this progression? Is there a point in the progression of diabetes complications when the pathologic process becomes relatively independent of the diabetes-related factors that initiate it? Is there a point when the progression becomes irreversible?

**Title: Can stem cells repair and reverse DN?**

Votes: 0

Normally, metabolic and ischemic insults stimulate repair and regeneration. In diabetes, however, these processes are impaired. Recent advances in cell reprogramming hold great promise for future cell replacement therapies. How are specific populations of stem/progenitor cells affected by diabetes? Are these abnormalities reversible through optimal diabetes treatment or therapies targeted to stem/progenitor cells? Will new cell reprogramming techniques, such as induced pluripotent stem (iPS) cells, lead to individualized cell therapy? A barrier to understanding the impairments includes the known heterogeneity within stem cell compartments, specifically mesenchymal stem cells. Protocols are needed for the culture of progenitor cells and their thorough analysis, including genetic, epigenetic, and transcription factor analysis of individual cells and stem cell populations. Can ex vivo therapies be developed that reverse stem cell dysfunctions? Though iPS cells created with current protocols are unlikely to be transferred to people for treatment, these protocols offer the opportunity to take cells from individuals and direct their differentiation into cell-based models of DN.

*Comments:*

*Katalin Susztak—The discovery that by changing the cellular epigenome we can in vitro reprogram differentiated cells into stem cells and then later we can redifferentiate them into differentiated cells is paradigm shifting. An exciting recent paper in JASN described that iPS cells can be generated from urinary cells. Unfortunately, we have a critical knowledge gap in understanding factor(s) that can redifferentiate iPS or ES cells into kidney specific cells (for example podocytes or tubular epithelial cells). Another related key question will be to understand the presence or absence of resident stem cell population in the kidney and the mechanism whereby stem cells or resident cells redifferentiate into tubular epithelial cells. In addition, by studying in vitro reprogrammed cells from patients carrying selected mutations or from DKD subjects can fill in a critical knowledge gap understanding disease mechanism. A recent paper for example describes that iPS cells can be made from a patients with Parkinson's disease due to a-synuclein mutation and the gene defect can be corrected in the iPS cells and then the iPS cells are later redifferentiated into neural cells. This is clearly an exciting new research direction with many new discoveries and tremendous possibilities, more research will be needed in this area to answer key questions. To fully realize the potential of in vitro reprogrammed cells, we need to understand the molecular and epigenetic determinants that convert one cell type into another.*

**Title: What new technologies will lead the field of DN forward?**

Votes: 25

Translation of the knowledge of the molecular consequences of diabetes to effective therapies requires better measures of disease progression, faithful models of the molecular and cellular pathology, and application of cutting-edge technologies. Validated biomarkers and surrogate end points will allow rapid screening of clinical interventions prior to larger clinical trials, and can assess risk factors and treatment adequacy for patients. Surrogate end points, if adequately validated as predictors, could enable shorter randomized clinical trials and require smaller sample sizes, factors that would accelerate acquisition of clinical information. The challenge is finding biomarkers that reliably characterize risk or the disease state among numerous biomarker candidates. Animal models exist or can be developed for specific aspects of DN, but cannot completely replicate the human clinical disease. Ready access to human samples and noninvasive imaging would allow testing hypotheses within the complexity of real people with diabetes. Without question, future advances in DN will come from emerging technologies and those not yet imagined. Will the artificial pancreas or other technologies that control the blood sugar prevent the systemic complications of diabetes? Currently, the field is poised to benefit from new imaging methods, systems biology approaches, and bioinformatics tools. Can early diabetes-induced changes in tissues and organs be detected by noninvasive imaging? Will computational models that incorporate several biomarkers and imaging results create a composite analysis that is a better measure of disease progression than the individual components? What are the indicators that predict an irreversible step in the progression of DN? How can the large amount of data generated by genomic, epigenomic, and high-throughput screening experiments be synthesized into new, testable hypotheses? DN arises at the molecular, cell, and tissue level, so novel high-throughput assays are needed to encompass these interactions. Is this an area where model organisms like *C. elegans*, *Drosophila* and zebrafish could be exploited?

*Comments:*

*Matthias Kretzler—This topic touches on all aspects of the entire discussion of the DN KDRN. I certainly share the expectation that high potential for clinical relevance in DN can be identified in the areas of imaging, systems biology and bioinformatic tools.*

*1. Systems biology (see also detailed comment in 7): Defining the regulatory landscape of DN along the genotype – phenotype continuum will allow to redefine DN in molecular and functional terms and can form the foundation for mechanistic biomarkers, non-invasive imaging parameters and key switches for therapeutic intervention. Integrating the multiple data levels from divers' data sources remains a major challenge to the field in general and engaging with these efforts early could attract significant expertise towards DN.*

*2. Molecular definition of model systems in relationship to human disease:*

*We need to define DN model systems in molecular terms in their relationship to human DN. This obviously requires that we define human DN in the first place (see above). Establishing a clearing-house of the large scale human data sets would facilitate genome wide comparison of existing and novel model systems with the human disease process. Prior to embarking on resource intense experimental studies, model systems could be tested if they recapitulate the human pathway under investigation. Vice versa, experimental outcomes obtained from the model systems could be mapped back into human disease pathways to assess their therapeutic potential for the human disease.*

*3. Non-invasive imaging of DN and intrarenal molecular activation:*

*With the limited access to renal tissue in DN, alternative modes to display intrarenal disease activity are warranted. Non-invasive biomarkers obtained from urine or blood might offer a window into the*

*functional status of the kidney, but direct imaging approaches are emerging with unprecedented spatial and molecular resolution. Defining the number of filtering glomeruli or live imaging of changes in transcriptional activity of key molecules in renal pathophysiology are promising approaches pursued in animal models. However, significant investments will be required to facilitate the interdisciplinary efforts required to establish technologies fits for human use. These approaches have the potential to address one of the main hurdles for compounds moving forward into the clinic, i.e. to serve as robust parameters of intrarenal effects in the time frame available for a phase 2 trial in DN and collaborative studies with industry might be an attractive way forward.*

*4. Defining DN mechanistically using strategies employed in 1 and 2 will allow pre-defining more homogenous groups of patients, an essential pre-requisite for biomarker definition and targeted molecular interventions (see 18).*

*John Sedor—Agree with Matthias and would emphasize that application of imaging technologies to patients may help us understand the disease better, develop surrogate markers and allow better trial design.*

**Title: How will personalized medicine alter patient care in DN?**

Votes: 0

One explanation for the discordant response of agents that treat complications in rodents versus humans is that deleterious pathways that are responsive to a certain drug may be widely expressed in inbred animal models, but expressed in only a small number of individuals. Should some agents be tested in primates or some other larger mammal? Pharmacogenomic, pharmacometabolomic, and pharmacoproteomic approaches could be used to identify markers for people who would be responsive to specific agents, such as the case for haptoglobin genotypes and responses to vitamin E therapy. In addition, genotyping of individuals participating in clinical trials through networks such as the DRCR.net can provide information on the relationship between a genetic profile and the likely response to a particular therapy. Individually-tailored therapy for DN is a goal with enormous public health and patient benefit. Do dietary maneuvers or treatments that prevent the development of DN also prevent the progression of DN? What is the impact of diabetes duration and pre-existing tissue damage on the ability to respond to therapies? What behavioral interventions improve nutrition, diabetes adherence and self-management, and prevent DN? Will combination therapies be more effective than single therapies? Can mechanisms for efficient testing combination therapies be developed? What approaches will lead to individualizing therapies? Should therapies be targeted to specific tissues or should systemic therapies be emphasized?

*Comments:*

*Linda Fried—This is an extremely broad question and is one that is can be seen as a future goal. One of the limiting factors is that we have few treatments for diabetic nephropathy. This is perhaps the greater issue than whether we can individualize treatments based on predictors of responsiveness. The current treatments are limited to ACEI/ARB and BP control to slow progression of established proteinuric DN and glucose control to prevent the development of diabetic nephropathy. More research could be done to understand who responds to ACEI or ARB (in addition to proteinuria) or perhaps who benefits from tight glucose control. Except for some studies showing an association of ACEI I/D deletion predicting response/lack of response to ACEI, we don't have an evidence base for pharmacogenomics.*

*Robert Nelson—As noted by Linda Fried, the potential for personalized medicine is presently limited by the restricted number of therapeutic options we have at our disposal to treat diabetic nephropathy. Moreover, the various ‘omic’ approaches used to identify markers for people who would be responsive to a particular therapy are quite new and still evolving. Nevertheless, work in this area could have significant potential for identifying new therapeutic molecular targets and therefore could help address these critical treatment barriers. Indeed, the near-term value of research in personalized medicine may be its role in identifying important molecular targets common to many individuals rather than those which distinguish them. Others on our work group have substantial expertise in this area and could comment on the value of personalized medicine in far greater detail. Given the substantial inter-relatedness of a number of the questions being evaluated by the diabetic nephropathy work group, it may be useful to consider whether some should be combined into a single research recommendation. Indeed, the answers to this question (Question 6) have direct relevance to the issues raised in Question 11 (What are the molecular pathways involved in DN?), Question 5 (What new technologies will lead the field of DN forward?), and Question 7 (Will systems biology discover new pathways and targets for DN?) to name just a few. Hence, consolidation of these research areas may help better define the path forward than dividing systems biology into its component parts.*

*John Sedor—Agree. A long term goal but are not even close yet as a community. We need to define the phenotypes, clinical and molecular, that would begin to allow us to stratify our patients for management. I really see "personalized medicine" as the outcome of successful resolution of many of the other questions be are discussing.*

**Title: Will systems biology discover new pathways and targets for DN**

Votes: 110

There has been an explosion of new genetic, biochemical, and cell biologic techniques. Appropriate systems biology tools are needed to facilitate integration of genotyping information, mRNA expression, microRNA expression, promoter analysis, proteome expression, and metabolome profiles in order to identify key biological processes and their interactions. In addition to better computational tools, a deeper understanding is needed of the control mechanisms of mRNA and protein expression levels in the diabetic state, such as ubiquitination, sumoylation, DNA methylation, histone modifications, and non-coding RNAs. Ultimately, this knowledge needs to be applied to clinical diabetes through better access and techniques for understanding pathobiology in individuals with DN. Large scale, longitudinal collection of CKD patients’ genetic, serum, tissue, and urine samples are required to allow use of these technologies to define the relationships between phenotype and multiple biomarkers. What is the best way to acquire tissue samples for these types of studies? Is their value in applying these approaches to human cadaveric tissue or from patients with End Stage Renal Disease?

*Comments:*

*Matthias Kretzler—Systems biology or I prefer the less ambitious term ‘integrative biology’, aims to define underlying regulatory principles in complex human diseases. Applied to DN it might lay the foundation to address many of the problems discussed in this forum.  
Translating integrative biology approaches to renal disease and DN:*



*We do see a rapid generation of large-scale data sets along the genotype phenotype continuum from small to medium sized cohorts of patient with renal disease and DN. Uni-dimensional dependencies between large scale data sets and clinical phenotypes are starting to be defined in ongoing studies and will need to be validated in independent cohorts. See Rob Nelsons comment to topic 1 and discussions on topic 18 and 20 concerning generations of these cohorts and data sets. Defining the regulatory landscape of DN along the genotype – phenotype continuum will allow to redefine DN in molecular and functional terms and can form the foundation for the identification of mechanistic biomarkers, non-invasive imaging parameters and key switches for therapeutic intervention. Truly novel insights into the key drivers of DN might be derived from the integrative biology concepts currently championed by E. Schadt and others aiming to integrate the large-scale data sets with each other and the clinical phenotype. First data integrations in diabetes are emerging (i.e. PMID:20463879). Our field might be of interest to the systems biology community in general, as large scale molecular data sets derived from renal tissue might be an attractive area to develop ‘integrative biology’ of diabetic end organ damage further. We are a long way from a true systems biology definition of DN, i.e. to define and predict the dynamic status of the human disease in a comprehensive quantitative level. The area most promising in this aspect might be metabolic regulations in DN, as the a prior quantitative knowledge is most advanced in this field and the genome wide data space significantly more limited compared to other–omics screening approaches. Finally, integration of the multiple data levels from diver’s data sources remains a major challenge to the field in general. Engaging in the development of platforms and data structures for communication and integration of large scale data sets between the public and private sector will be required to ensure optimal use of these rich data sources. Concerning the critical role of tissue samples and the unique opportunity for nephrology see 20.*

*John Sedor—Given the need for samples to be collected using strategies that best preserve target molecules of interest, cadaveric tissue, which has been fixed and processed for autopsy, may be difficult to use. Even genotyping from samples processed for "routine" pathology can be difficult due to cross-linking fixatives and potential contamination of equipment and reagents with cells from previously processed tissues and shed from laboratory personal. Other issues are falling autopsy rates, the move to put patients into palliative care facilities that are "distant" from the investigators and their staffs, and the time lag between death and obtaining consent [might be difficult to get consent for post-mortem studies prospectively] increasing the chance that any tissues harvested may be sub-optimal. Neptune is testing and optimizing protocols for collection of biological specimens for a variety of high through put analyses [perhaps even miniaturization of processing for epigenetics]. An alternative approach would be collecting biological specimens from a network of institutions that have top-tier EHR systems. Samples could be obtained and processed optimally and the longitudinal data could be extracted from the EHRs. Whether or not systems biology tools will permit discovery of new pathways that will improve diagnosis, management or prediction can only be tested empirically. No question new targets will be identified but the key will prove the target's validity and clinical utility. The questions need to be better targeted; it is not clear that measuring "everything in everybody" and then integrating the datasets using sophisticated computational methods has resulted in clinically actionable outcomes yet. However, the possibilities are intriguing and should be pursued, especially as the analytical methods evolve.*

**Title: What are the key genetic and epigenetic determinants of DN?**

Votes: 130

Metabolic control alone does not predict an individual’s risk for diabetic complications. Family studies suggest that genetic factors play an important role in the predisposition for a specific type of complication and its progression. In addition to more classic genetics, research in this area

has expanded to epigenetics and non-coding RNA. Epigenetic marks include modifications to the DNA or chromatin that do not change the underlying DNA sequence and may contribute to metabolic memory, the observation that the level of prior glucose control has persistent effects on the risk of complications. The elucidation of epigenetic mechanisms has the potential to identify novel therapeutic targets. Small regulatory RNAs, such as microRNAs (miRNAs), are accepted regulators of mammalian cell phenotype, and have been implicated in the regulation of biological functions associated with diabetes pathogenesis, such as metabolism, insulin secretion, and the immune response. Patterns of miRNA in various cells and tissues may provide useful disease biomarkers, while in vivo manipulation of specific subsets of small regulatory RNAs might be used for novel therapeutic strategies. What are the genes that predispose or protect people from developing diabetic nephropathy? How do candidate genes identified by genome-wide studies contribute to the pathogenesis of diabetic nephropathy? How do epigenetic mechanisms fit within the context of other known cellular mechanisms? Are epigenetic changes in chromatin responsible for metabolic memory? How do they interact with other persistent effects of glucose control, such as glycation and oxidation of long-lived macromolecules? How do persistently high fasting blood sugars or high 2 hour post-prandial blood glucose affect the miRNA of the cells? Will aggressive treatment of blood glucose reverse these destructive mechanisms? What is the role of small regulatory RNA, in particular microRNA, in the development of diabetes nephropathy? Genetic studies are particularly valuable when combined with careful phenotyping. Given the greater risk of kidney disease in African Americans and other minority groups, should GWA studies be performed in specific at-risk populations?

*Comments:*

*Katalin Susztak—There are 2 specific questions here 1, the genetics of DKD and 2, epigenetic regulation in DKD. DKD appears to be a prime example of a gene environmental disease, while genetic predisposition plays an important role in the DKD development, the environmental changes, hyperglycemia, and hypertension plays a key role in disease development. To get closer to the genetics of DKD it will be critical to run a genome wide association study with a large sample size. Based on experience of other disease conditions a sample size of at least 10,000 cases and controls might be necessary to identify the key genetic component of the disease. Better phenotyping would definitely increase our chances of finding the key genetic component. Based on the clinical experience maybe it would be easier to find genes for type1 DKD than for a more heterogeneous type2 DKD, in addition analyzing patients with rapidly declining GFR and comparing them to patients with stable GFR could also help. In summary larger sample size with improved phenotyping will be essential for future DKD genetic studies and understanding the genetic component of the disease is a key barrier in the field and we need to answer this question to move the field forward. (This question therefore can be merged with the question on type1 and type2 DN genes) Contrary to the mutation-centric model, which assumes alterations in function or activity based upon either somatic or inherited mutations in DNA, an epigenetic model implies dysregulation of a gene or set of genes. Thus, phenotypes resulting from the expression of such genes would make biological sense under other physiological conditions. There are multiple lines of clinical evidence suggesting that “programming” and “memory” is important in disease development. First of all it seems in utero environment and programming is critical in addition the DCCT trial seems to suggest a hyperglycemic memory effect. Evidence is accumulating that these events are coded in cells by histone and DNA modifications. Therefore understanding DNA and histone modifications in the kidney at baseline during normal development and different disease conditions will be essential. Furthermore*

recent studies indicate that based on the different epigenetic marks we are able to identify regulatory regions in the genome and identify promoter, enhancer, insulator, and transcribed regions. GWAS performed for different polygenic disease conditions indicate that genetic polymorphism preferentially occur on regulatory regions; sometime in promoters but more often in enhancer regions and the altered gene regulation is responsible for the phenotype development. Furthermore defining the epigenetic (histone) landscape of human kidney will give us multiple incredible opportunities, which will be way beyond the understanding of DKD, this will be highly relevant for kidney development, for the generation of iPS cells and their in vitro reprogramming into kidney cells, for kidney injury, repair, biomarkers and genetics. Therefore research into understanding the epigenetic landscape of the healthy and diseased kidneys will be essential.

John Sedor—I believe unraveling the issues addressed in this question will be critical to future progress in treating and perhaps preventing diabetic nephropathy. As Kaitlin indicates, this issue has generated a “multiplex question” that focuses on defining the underlying genetic architecture and its associated regulatory landscape in DN pathogenesis. Our failure to crack these issues leaves the research community dependent on candidate hypotheses, which may or may not translate into a reduction in DN. Identifying variants is a critical step in determining causality and defining the genetic architecture [broadly defined] of human DN using unbiased mapping strategies is an ideal approach to achieve this goal. Many of the other questions being addressed in KRND Phase II identify corollary issues to the fundamental goal identified in this question. Barriers have included sample sizes, genetic (especially LD heterogeneity), phenotypic heterogeneity of collected cohorts, and need for multiple consortia to combine efforts to make progress and lack of appropriate samples to test hypotheses related to the “regulatory landscape.” In particular, we need to understand much more clearly if epigenetic analyses of PBMC DNA will be useful in understanding the epigenetic changes in the kidney. Given the amount of money already investing in gene mapping strategies and their failure to have a “hit,” allocating further funds to these approaches is high risk. Yet I believe building on the resources assembled already [FIND, GOKIND, CRIC, etc] and thoughtful application of new strategies will be informative. Identification of variants could be game-changing in our approaches to DN. Studies of Crohn’s disease illustrates the power of genomic approaches to elucidate the biology of complex diseases. Analysis of genes in regions, discovered by GWAS of Crohn’s patients, identified mechanisms that were unknown or underappreciated. Subsequently, animal models of Crohn’s disease have been developed, biological pathways have been defined, and chemical screens for new treatments have been initiated. Similar outcomes are possible for DN. Although risk is inherent in targeting funding to defining the genetic regulatory architecture regulating DN, clever and targeted use of emerging novel and complementary tools [which are being discussed in review of other questions], provides a unique opportunity to advance DN research.

**Title: Is mitochondrial (dys) function a major component of DN?**

Votes: 0

Genetic mutations in mitochondrial fission/fusion proteins and changes in ROS production have been linked to diabetic complications. Why does the apparently global pathogenic mechanism of increased mitochondrial activity have variable consequences in different cell types? Can we develop better tools to assess mitochondrial function, transport, number, and fission/fusion states? Can we improve mitochondrial function in cell types in which mitochondrial dysfunction contributes to DN?

Comments:

*Raymond Harris—One of the existing paradigms for the pathogenesis of diabetic complications is Brownlee's formulation that ROS production resulting from diabetic complications is a common underlying feature. However, although attractive, this hypothesis needs to be validated and the mechanisms mediating mitochondrial dysfunction have to be more completely elucidated to determine whether it is causal or just another result of the diabetic milieu. The question also appropriately asks why diabetic complications occur primarily in certain tissues and cell types, although mitochondrial dysfunction would be expected to be seen globally. Therefore, a better understanding of how diabetes affects cellular energetics and how these alterations lead to observed diabetic complications is crucial for understanding pathogenesis and development of targeted therapies. Such studies may well require development of new modalities for the study of mitochondrial function, which could have broad utility even beyond the study of diabetic complications.*

**Title: Are immunologic pathways causative factors in DN?**

Votes: 15

Recruitment of the innate and adaptive immune responses is increasingly linked to the development of both type 1 and type 2 diabetes. Inflammation, triggered by the actions of immune cells such as T and B lymphocytes, monocytes/macrophages, and dendritic cells, along with the interaction of these immune cells with vascular cells, contributes to the development of diabetes. These various cell types have also been implicated as causative factors for the complications of diabetes, including nephropathy. Identifying shared pathways that may reflect, in part, a mechanistic continuum from cause to complication is an important research goal.

Comments:

*Katalin Susztak—DKD gene expression studies highlighted the common regulation of multiple pathways linked to inflammation. The question is whether the activation of the immune system is the road or a post-sign in DKD development. Animal studies showed that DKD development can be significantly influenced by immune modulation, indicating the functional role of the immune activation in DKD. The question is whether this is a clinically translatable strategy. While we observe increased inflammation in diabetic kidneys, overall diabetes is associated with an immunocompromised state and patients with diabetes are already highly prone to different life-threatening infections. Mice that are kept in a specific pathogen free environment could be different from diabetic patients walking around the streets of the Bronx. Based on the encouraging and consistent results of the animal experiments it will be important to better dissect the "inflammatory reaction" associated with DKD development this will important for better understanding of the disease condition.*

*Robert Nelson—The effects of immune activation within the glomerulus have been best explored in the mesangial cell, which is both a target of inflammation as well as a source of inflammatory mediators. Further research could help us understand the cause and effects of inflammation on other glomerular cells, i.e. podocytes and endothelial cells, as well as the causes and effects of inflammation on the renal tubules. Obesity itself is a pro-inflammatory state and there may be value in exploring further its role in progressive DN?*

*John Sedor—We characterize a number of chronic diseases, DM and DN prominently, as pro-inflammatory states. Yet the term is ill-defined and connotes different meanings to individual scientists. Addressing this question would begin to confer some substance to the term. The role of innate immune mechanism in DN pathogenesis is intriguing. The microbiome of the urinary tract has not been well-characterized and the possibility that viruses may promote chronic kidney diseases only superficially explored.*

**Title: What are the molecular pathways involved in DN?**

Votes: 90

The abundance of molecular pathways affected by diabetes presents the challenge of understanding complex interactions among the pathways, but also the opportunity of providing multiple and potentially complementary targets for drug development. How do the identified molecular pathways associated with diabetic nephropathy interact within each cell and does this vary for different cell types? Are there undiscovered molecular pathways that contribute to diabetic nephropathy? What is the best way to identify and interrogate these pathways? What protective pathways are present and how do they interact with other pathways? Does nephropathy arise from an imbalance of maladaptive to adaptive responses in animals or patients who are genetically prone to diabetes? What are the relative contributions of hyperglycemia versus impaired insulin and other growth factor signaling in the development of diabetic nephropathy? Why do tubular and glomerular cells initially exposed to the same systemic factors have different pathologies? What is the clinical significance of the identified biochemical changes in the cell induced by diabetes?

*Comments:*

*Raymond Harris—This question underscores the complexity of the pathogenesis of diabetic complications and how little we still understand. There have been numerous studies in the past decade or so that have identified alterations in multiple molecular pathways. This question poses whether it will be possible to develop a "unified field theory" of the pathogenesis of diabetic complications. Aside from mitochondrial dysfunction as a possible common mediating event (see question #9), it is not clear that such potential molecular pathways have been identified that are common to all complications. Therefore, continued research into the underlying pathogenic mechanisms mediating diabetic complications should continue to be highly encouraged. Further understanding of the pathogenic role of pathways that have been identified, as well as other possible pathways either in general or in organ-specific complications, should be a high priority because of the possibility of identifying potential therapeutic targets that are amenable to long term therapy with agents with relatively minimal side effects. It is likely that effective treatment of diabetic complications will end up being a cocktail to target multiple molecular pathways, rather than our current reliance on RAS blockade.*

**Title: Is autophagy a major contributor to DN and its progression?**

Votes: 0

Autophagy was discovered in yeast as a stress response and may contribute to the excess of cell death and progression of complications. The human homologues of yeast autophagy genes and drugs known to affect autophagy are available to test the role of autophagy in diabetic nephropathy.

Comments:

*Breyer Matthew—Autophagy, which mediates auto-digestion of cellular organelles like mitochondria, is such a fundamental response to availability of nutrients that it is almost unquestionably involved in the complications of diabetes mellitus. Since it is highly regulated by tyrosine kinase coupled growth factor receptors like IGF1 receptors and their downstream coupling to mTOR, the emerging data that implicates dysregulated mTOR signaling in diabetic nephropathy (J Clin Invest. 2011 Jun 1;121(6):2181-96 and J Clin Invest. 2011 Jun 1;121(6):2197-209) provide potential pathways for testing this hypothesis. However targeting autophagy for the treatment of diabetic nephropathy will likely be very challenging, given its fundamental cellular role and the complexities of its regulation.*

*John Sedor—Recent publications [cited in Matt Breyer's comments] that demonstrate autophagy to be a player in glomerular injury and the link between autophagy and nutrient state are intriguing. However data directly supporting the importance of this mechanism in DN pathogenesis are limited and I would suggest more work, that almost certainly will emanate through R01 pipelines, should be completed before the Institute targets this area. Agree that experimental design will be tough.*

**Title: Will aggressive treatment of blood sugar prevent progression?**

Votes: 0

Hyperglycemia could cause albuminuria. Should we find out with certainty that either high FBS and/or high 2 hrs PP sugar be treated aggressively before a clinical diagnosis of DM is made?

Comments:

*Linda Fried—While there are unanswered questions about glucose control in diabetes and its effects on nephropathy, I don't believe that this addresses a current barrier in kidney disease/clinical care and it has been evaluated in recent trials. I would also be concerned about the feasibility of addressing this question in the time frame of most clinical trials. The comment associated with the question actually addresses a different question than above and asks whether aggressive treatment of glucose before a diagnosis of diabetes would be of benefit. This may be answered in part by the long-term follow-up of the DPP study. With regards to treatment of glucose and progression in individuals with diabetes. ACCORD, VADT and ADVANCE all found that tight control decreased the risk of incident microalbuminuria or progression to overt nephropathy. However, in none of the studies was there a benefit seen on loss of eGFR. It may be that the studies were not of long enough duration to see a benefit. NIDDK could consider a long-term F/U of patients in ACCORD. Alternatively, a study in those with overt nephropathy could be considered, but it's notable that HbA1c did not predict progression to ESRD in RENAAL (Appel et al).*

*Robert Nelson—I agree with Linda Fried that the issue of glucose control to prevent diabetic nephropathy does not represent a critical barrier in kidney research at this point. Ample data from large clinical trials over the past several decades have demonstrated the ability of glycemic control to prevent the microvascular complications of both type 1 and type 2 diabetes. Recent trials added to the evidence that intensive glycemic control reduces the development of elevated albuminuria, but at the risk of a substantial increase in the frequency of hypoglycemia. On the other hand, the evidence that aggressive glycemic control prevents other intermediate endpoints, such as declining GFR and doubling of serum creatinine is sparse and there is no evidence that it slows progression to the clinical endpoint of end-*

stage renal disease. Potentially important questions to address regarding the role of glycemic control are likely to be found in more advanced kidney disease. I am unaware of prospective randomized studies evaluating the level of glycemic control on outcomes in diabetic patients with CKD stages 3-5. Extended follow-up of patients with type 1 diabetes in EDIC showed a small benefit of prior intensive therapy on later CKD outcomes, but the numbers of patients was very small. Accordingly, I suggest that the critical barrier is actually in more advanced CKD and clinical trials to assess aggressive glycemic control that focus on clinical outcomes in more advanced CKD will help address this barrier.

John Sedor—I believe this issue is being addressed in the continued follow-up of the ACCORD cohort. The evidence is convincing to me that control of glycemia beyond current targets [HgbA1C] is likely to have only marginal additional benefit at great cost to the research budget. Time to look beyond this issue. We are losing the battle even with intensification of blood pressure, blood sugar and cardiovascular risk. Time to move on!

**Title: What is the role of the tubule in early DN?**

Votes: 0

The primary focus of the pathophysiology of diabetic renal disease has been on the glomerulus. Albuminuria has been shown to be a very sensitive biomarker of proximal tubule injury. Early changes in the proximal tubule may lead to secondary pathology which is typical for diabetic nephropathy. Thus the tubule may represent a therapeutic target for early diabetes.

*Comments:*

Moderator—I agree with the idea above that more research effort should be placed on the tubule in hyperglycemia/diabetic nephropathy and that the tubular damage may be the initiator. Since tubulointerstitial lesions are an important part of progression of renal diseases, especially DN, this critical area needs much more emphasis.

Breyer Matthew—What is the role of the tubule in early DN? The signature lesion in diabetic nephropathy is nodular glomerulosclerosis, however even prior to the onset of overt proteinuria; mesangial expansion is typically present in patients with only microalbuminuria or even normoalbuminuria (Mauer, Steffes et al. 1984; Steffes, Osterby et al. 1989). However it is notable, that tubulointerstitial changes are as closely correlated (if not more so) with diabetic kidney failure, than the glomerular changes alone (Bohle, Wehrmann et al. 1991). The significance of this association is unclear. Some have argued that tubulointerstitial changes are the result of, rather than the cause of renal failure in DN (Fioretto, Steffes et al. 1995; Dalla Vestra, Saller et al. 2000). Still increased tubulointerstitial expression of inflammatory biomarkers in progressive diabetic nephropathy has been widely reported (Kosugi, Yuzawa et al. 2007; Ninichuk, Khandoga et al. 2007; Berthier, Zhang et al. 2009; Sanchez-Nino, Sanz et al. 2009). Since the bulk of the kidney is predominantly comprised of tubules, altered expression of these proteins in the tubulointerstitium might provide sensitive bio-markers of the progression of diabetic kidney disease if not actively contribute to the pathogenesis of the process (Wada, Furuichi et al. 2000). Alterations in tubule production of trophic factors such as 1,25 (OH)<sub>2</sub> vitamin D or tubular renin might also affect the course of kidney failure. So it would be imprudent to ignore the role of altered tubule function in the pathogenesis of diabetic nephropathy. Nevertheless, at present one cannot directly ascribe any one of these functions to progression DN. Availability of robust mouse models of DN, may provide a means to test this hypothesis through the selective deletion or over-expression of candidate genes in specific nephron segments.

*References:*

- Berthier, C. C., H. Zhang, et al. (2009). "Enhanced expression of Janus kinase-signal transducer and activator of transcription pathway members in human diabetic nephropathy." *Diabetes* 58(2): 469-477.
- Bohle, A., M. Wehrmann, et al. (1991). "The pathogenesis of chronic renal failure in diabetic nephropathy. Investigation of 488 cases of diabetic glomerulosclerosis." *Pathol Res Pract* 187(2-3): 251-259.
- Dalla Vestra, M., A. Saller, et al. (2000). "Structural involvement in type 1 and type 2 diabetic nephropathy." *Diabetes Metab* 26 Suppl 4: 8-14.
- Fioretto, P., M. W. Steffes, et al. (1995). "Sequential renal biopsies in insulin-dependent diabetic patients: structural factors associated with clinical progression." *Kidney Int* 48(6): 1929-1935.
- Kosugi, T., Y. Yuzawa, et al. (2007). "Midkine is involved in tubulointerstitial inflammation associated with diabetic nephropathy." *Lab Invest*.
- Mauer, S. M., M. W. Steffes, et al. (1984). "Structural-functional relationships in diabetic nephropathy." *J Clin Invest* 74(4): 1143-1155.
- Ninichuk, V., A. G. Khandoga, et al. (2007). "The role of interstitial macrophages in nephropathy of type 2 diabetic db/db mice." *Am J Pathol* 170(4): 1267-1276.
- Sanchez-Nino, M. D., A. B. Sanz, et al. (2009). "The MIF receptor CD74 in diabetic podocyte injury." *J Am Soc Nephrol* 20(2): 353-362.
- Steffes, M. W., R. Osterby, et al. (1989). "Mesangial expansion as a central mechanism for loss of kidney function in diabetic patients." *Diabetes* 38(9): 1077-1081.
- Wada, T., K. Furuichi, et al. (2000). "Up-regulation of monocyte chemoattractant protein-1 in tubulointerstitial lesions of human diabetic nephropathy." *Kidney Int* 58(4): 1492-1499.

*Linda Fried—From a clinical perspective, there have been a number of studies over the years suggesting that markers of tubular dysfunction (e.g. presence of retinol binding protein) in the urine add to microalbuminuria. I agree that we don't know enough about the pathophysiology of tubular dysfunction and progression of kidney disease. Further research could also inform the development of biomarkers for studies for early studies of progression that can either supplant or supplement albuminuria.*

**Title: Can we restore GBM function in DN?**

Votes: 0

What are the regulators of glomerular basement membranes? Can we target glomerular endothelium and podocytes to restore normal barrier components and functions?

*Comments:*

*Moderator—Examining the specific molecular mechanisms of regulation of basement membrane components, including proteins like collagen etc., under diabetic conditions, can provide more insights into basement membrane dysfunction under diabetic conditions. Then we might have a handle on how to target the glomerular endothelium or podocytes. The glomerular capillary loop is an integrated unit. Studies on Angiopoietin-like proteins show that increased expression of podocyte secreted proteins directly influence GBM permeability and reach all the way up to the endothelial surface. Studying the mechanism by which GBM binding proteins secreted by podocytes or endothelial cells alter GBM permeability in the setting of diabetes would provide substantial insight into the pathogenesis of proteinuria and changes in the glomerular capillary loop noted in diabetic nephropathy.*



*KUH DN Moderator—Hyperglycemia causes extensive glycation of extracellular matrix (ECM) proteins that leads to their cross-linking, accumulation, and altered binding properties for growth factors and circulating stem cells. This sclerotic process contributes to the pathogenesis of complications and the slow reversal of pathology with euglycemia. Methods that prevent these modifications are needed to understand their role in impaired tissue turnover rate and accumulation of glycated proteins. Novel animal models are also needed that duplicate, in the absence of hyperglycemia, the diabetic changes in ECM.*

*Raymond Harris—Although GBM thickening and alterations in its sieving function is a fundamental abnormality in diabetic nephropathy, we still do not understand the underlying pathogenic mechanisms. This is a relatively understudied area. There needs to be continued study of the basic mechanisms mediating the synthesis and assembly of GBM components and exactly how the diabetic milieu alters them. There is really no clear understanding of why GBM thickening occurs; also, although glycation of GBM is thought to underlie alterations in function, exactly how this occurs, or whether it is truly important, has not yet been determined. Finally, the interactions between glomerular cells and the diabetic GBM may provide new insights into progression of diabetic nephropathy. Therefore, this is a fertile area for further research. A better understanding of the pathogenic mechanisms could lead to development of more targeted therapies.*

*Katalin Susztak—Diabetic nephropathy is a primary glomerular disease where all layers of the glomerular filtration barrier are affected; GBM, endothelial cells and podocytes. Understanding the pattern of injury to each component will be critical. For example novel imaging methodologies including multiphoton microscopy can help to understand cell-cell interaction and damage in the context of DKD. Specific transcriptome analysis could help to define cell-cell interaction pathways and identify critical cell types and pathways.*

**Title: Does aldosterone breakthrough occur in DN?**

Votes: 0

Failure of ACE inhibitors in advanced diabetic nephropathy is an increasing problem. Studies suggest that it is due to aldosterone breakthrough. The mechanism for this escape mechanism is unclear.

*Comments:*

*Moderator—Do we know that there is failure of ACEI in advanced diabetic kidney disease? The disease progresses, which could indicate aldosterone escape or perhaps non-RAAS mechanisms. Yes, this area is well deserving of a study. Italians' work in this area seems especially dramatic (e.g., <http://www.ncbi.nlm.nih.gov/pubmed/20097461>; <http://www.ncbi.nlm.nih.gov/pubmed/18354029>). Yes, it is definitely time to revisit the aldosterone question, including larger clinical trials to validate such work.*

*Linda Fried—Is there really failure of ACEI in advanced kidney disease or is it that ACEI alone is not sufficient? The small randomized studies in non-diabetic proteinuric disease suggest that ACEI are effective in stage 4 CKD. Individuals progress but at a slower rate. We may need to be more like the heart failure community where ACEI decrease risk, but a multimodal approach (e.g. ACEI, beta-blocker, mineralocorticoid receptor blocker) is more effective.*

*The posed question regarding aldosterone breakthrough and the Italian study cited raise a few scientific questions.*

*1. Why does aldosterone breakthrough occur and if it occurs does it portend a lack of response to RAAS blockade in proteinuric kidney disease?*

*2. Should we evaluate in a phase 3 studies whether aldosterone blockade prevents the progression to ESRD?*

*I think this is a valid question, but a number of questions remain in my mind before it's ready for a large study. Aldosterone blockade decreases proteinuria but at the potential risk of hyperkalemia. You also get proteinuria decline with any increase in diuretic (the Italian study cited used diuretics, not mineralocorticoid receptor blockade). Is the effect a diuretic effect or an aldosterone effect? This could be tested for example in a study evaluating adding amiloride or spironolactone and seeing if the effects differ on proteinuria. The risk of hyperkalemia increases as GFR declines. Can mineralocorticoid receptor blockade be used in all stages of GFR?*

*3. The Italian study evaluates whether proteinuria should be a target for treatment, rather than an aldosterone mechanism. The approach outlined in the Remission clinic paper is salt restriction, combination ACEI/ARB, add verapamil, add statin and then diuretic/antihypertensives to target BP < 120/80. It was applied to all individuals in clinic. Those who responded had a slower decline- so, does this mean that proteinuria should be a target or is it that the lack of response is a marker of risk? If effective, which components are important or are they synergistic? There was a study by Hou et al (JASN) that looked at individualizing ACEI or ARB compared to standard therapy and showed a benefit, however the standard therapy was only moderate doses of ACEI or ARB (e.g. losartan 50mg) and thus the benefit could be interpreted as a dose effect (need to target higher ACEI or ARB doses) and not a benefit of individualized dosing targeted to maximal proteinuria lowering.*

*Robert Nelson—This question also has relevance to Question 17 (What next after RAAS blockade?). Although agents that block RAAS play a key role in the management of diabetic nephropathy because of their ability to slow progression of disease, response to therapy is highly variable. Given the experimental evidence about the role that aldosterone plays in the development and progression of diabetic nephropathy and the emerging evidence from short-term studies of both type 1 and type 2 diabetes of a rise in plasma aldosterone during long-term treatment with RAAS blockade, studies to identify the mechanisms involved in aldosterone breakthrough could have a significant impact on clinical care. The need for research in this area is amplified by the fact that RAAS blockade is the mainstay of current therapy. In evaluating potential mechanisms for aldosterone breakthrough, we should not forget behavioral mechanisms such as lack of treatment compliance and variation in sodium intake as we examine the more exciting pharmacogenetic mechanisms that may interest more investigators.*

*John Sedor—Interestingly, the laser intensity focused on RAAS blockade may reflect the dearth of treatment options. We need to understand better the patients who benefit and if some CKD patients really do worse by targeting RAAS pathways with multiple agents (Ontarget). I would suggest focus on better understand of the molecular pathways causing DN, would allow us to develop more effective drug regimens. We don't treat hypertension with multiple agents targeting a single pathway.*

**Title: What next after RAAS blockade?**

Votes: 0

At the current time, we only have RAAS blockade and hypertension control to slow progression to ESRD. What mechanisms should be targeted to slow progression (loss of GFR) in diabetic nephropathy?

Comments:

*Moderator—Is there a reason to narrow this to diabetes? I think that overall we need to develop an enhanced understanding of why RAAS blockade seems so effective in delaying progression of all proteinuric renal disease, starting with a better understanding of how the filter works and malfunctions. The mechanism of glomerular damage in diabetes and glomerular disease may not be the same. So, for next steps in stopping progression, would you look for a disease specific agent or one that addresses final common pathways? A related question might be is whether proteinuria should be a target in and of itself? Fibrosis is a key pathologic feature of diabetic nephropathy. It would certainly be a good idea to target one common pathway leading to fibrosis. Hence more work is needed to identify such pathways and mechanisms. Examining signaling pathways and novel nuclear mechanisms, including epigenetic factors would be worthwhile. It is critical to identify good biomarkers to detect early stages of diabetic nephropathy in order to commence aggressive therapy to prevent progression to ESRD. Some of the areas that are worth paying more attention include the study of urinary podocyte markers, fibrotic growth factors, exosome components (including proteins and RNA) and microRNAs. Recent technological advances (proteomics, microRNA deep sequencing, exosome isolation) can assist in these ventures. I think we need an infrastructure that allows rapid assessment of novel agents to determine futility vs. larger trials. Oncologists have set up these networks. Patients are stratified by risk, new agents are added to standard of-care and small cohorts of patients are used to expeditiously determine if further trials are needed. For nephrology to do this, we need to be comfortable with prediction algorithms and surrogate markers. Waiting longer for these issues to be resolved seems imprudent. We should rapidly testing new agents chosen on the basis of known mechanisms and risk-benefit ratio of the candidate drug. Diabetic glomerular disease may be "different", but RAAS blockade strategies are universal. Narrowing this topic unnecessarily weakens it, scientifically and vote-wise. Therefore, the suggestion to broaden the scope still seems valid. ("What next after RAAS blockade" is JUST as much a looming question for other forms of CKD, and underscores the dire need for NEW strategies, (after milking RAAS for modest incremental gains for 2+ decades. It is time begin seriously developing alternatives, (and explore them far more rapidly.) However, it is not really "fair" to alter an idea people have already voted for, so probably stuck with how it is currently worded. I actually think it is ok to look at the mechanisms of RAAS blockade in different etiologies of CKD. The mechanisms of progression are clearly only partly shared and the mechanisms of protection by such pleiotrophic agents are also likely to be only partly shared. I do believe that concerted systems biological approaches will help identify the next set of pathways that can be best modulated, possibly by agents that are already extant. But I agree 100% that the bugaboo, even with the approach articulated above, is the lack of validated predictive biomarkers. It's pretty hard to get high throughput when your primary endpoint is doubling of serum creatinine. I think systems approaches may help us here as well, and I actually think that urinary metabolomics will get us there first. We'll see. RAAS and BP control may be "all we have" but some researchers are already reporting higher success through more intensive therapy. While we do need to ask "what next?", meanwhile should not neglect to determine whether RAAS can be used more effectively. As to whether proteinuria should be its own target, is exactly the premise these groups are pursuing, with seemingly remarkable results at slowing and even halting CKD progression for far more patients than would normally be expected on standard therapy. Reviews of various strategies include: <http://www.ncbi.nlm.nih.gov/pubmed/17700639>; More recent: <http://www.nature.com/nrneph/journal/v5/n7/full/nrneph.2009.76.html>). Several agents (e.g., tranilast/Rizaben) now have a very well established human safety profile, so at the very least these can now be brought forward to human trials for CKD applications. It is time to move beyond treating just the symptoms of CKD, and target the root causes of progression pathways. Trustworthy biomarkers will be*

key, as creatinine-doubling and similar endpoints present an excessive barrier to more rapid assessment of such a wide array of potential new therapies. Accomplishing the goals of this topic will require investigating many of these. The next step after RAAS blockade is to enhance the degradation of AngiotensinII. There is good experimental data in Hypertension and Diabetic models of Kidney disease that amplification of ACE2 leads to the degradation of Angiotensin II and it may be reno-protective. Also, direct renin inhibition (e.g., Aliskiren) might accomplish similar goals, but needs to be tested through direct head to head testing specifically for CKD protection vs. ACE/ARB. (Whether DRI's will represent ""superiority"" remains an open question, but there are plausible reasons to believe they may be so.)

You—There is a strong need to identify novel therapeutic targets and develop more effective approaches for the prevention and treatment of DN. New therapies that reduce ROS levels through decreased production or increased clearance could attack a critical early step in complications. Agents that could reverse glycation may help prevent the sclerotic process in the kidney and vascular tree and improve the ability of a tissue to respond to other therapies. Inflammation plays a key role in the development of diabetes and complications. Novel anti-inflammatory approaches that act on diabetes-related inflammation may prevent the progression of complications. A promising target for further investigation is RAGE, because blockade of this pathway in animal models shows protection from diabetes and inflammation. Therapies targeted at molecular mechanisms underlying metabolic memory could provide novel strategies to reduce the development of complications. For example, epigenetic changes might be targeted, possibly through inhibition of key histone methylases. In conjunction with inhibitors of AGEs, inflammation, and ROS, these therapies may prove effective in people who are prone to complications despite glycemic control. Testing in animal models for both efficacy and toxicity are required for all of these new therapies and new devices.

Robert Nelson—RAAS blockade has had a moderate but important effect on slowing the progression of overt diabetic nephropathy. We do seem to have reached a critical barrier, however, in identifying treatments to further slow the progression of diabetic nephropathy. Much effort has been expended to identify new therapies to address this problem by targeting various mechanisms. Medicines, such as pyridoxamine and the vitamin B1 derivative, S-benzoylthiamine monophosphate, that inhibit the formation of advanced glycosylation end-products (AGEs) may help decrease the downstream effects of AGE deposition, inflammation, and oxidative stress on the pathogenesis of diabetic nephropathy. Ruboxistaurin, an inhibitor of protein kinase C, decreases microalbuminuria and needs further clinical evaluation in diabetic nephropathy, as do the anti-inflammatory effects of pentoxifylline. Antifibrotic medicines and VEGF inhibitors also hold promise for diabetic nephropathy, as do therapies directed toward improvement of endothelial cell function and restoration of the glycocalyx. Identification of efficacious medicines that do not have major adverse effects and successfully slow progression of diabetic nephropathy by mechanisms that differ from or augment RAAS blockade could have substantial impact on patient management, and I believe support of such studies is within the mission of NIH. Expansion of cooperation between industry and NIH may be needed to move this work forward most expeditiously, as outlined in my comments under Question 1. Consideration might also be given to finding ways to optimize and maximize the efficacious use of RAAS blockade. In the U.S., 23% of CKD patients with diabetes do not receive RAAS blocking medicines, and the proportion decreases in later stages because of potential concerns about acute worsening of kidney function and hyperkalemia. Small studies have shown promise in aggressively combining RAAS blockade with other existing management strategies using intensive multifactorial intervention and it may also be useful to identify cost-effective ways to provide such intervention more broadly.

Tom Coffman -While this is an important practical clinical question, I believe new approaches to therapy are more likely to emerge from broad and basic mechanistic studies (see questions 3 and 11 for example). Moreover, I submit that we still don't understand the basic mechanistic pathways underlying the benefits of RAAS blockade.

**Title: Can biomarkers predict T2D DN?**

Votes: 95

The value of currently available urine biomarkers that identify those at risk for diabetic nephropathy is increasingly called into question. The development of new urine and plasma biomarkers to predict diabetic nephropathy may shed light on disease mechanisms. Also, rational clinical trial design will be made possible by such markers.

*Comments:*

*Moderator—"Urine proteomics has yet to identify a robust biomarker for diagnosis/prognosis. Do you think couple tissue proteomics of kidney compartments [glomerulus v. tubulointerstitium] for biomarker discovery with targeted assay development in urine makes sense? Here is an interesting article discussing biomarkers in general and biomarkers used in diabetic renal disease in detail:*

*<http://diabetes.diabetesjournals.org/content/57/6/1459.full>*

*What I got from reading this article is:*

*1. Albuminuria is virtually useless as an identifier*

*a. Low-grade albuminuria (microalbuminuria) is a poor predictor of diabetic nephropathy*

*b. High-grade albuminuria, which is a strong predictor of disease progression, only develops at advanced diabetic nephropathy, a stage when less can be done to prevent the development of end-stage kidney failure.*

*2. Smad1 plays an important role in the development of mesangial expansion (using well-established mouse and rat models of diabetic nephropathy)*

*3. Trying to determine whether urinary Smad1 levels measured at the time of diabetes development correlate with the development of mesangial expansion at later time points*

*Yes, this is an important area of research that will yield targeted therapies regarding who should be treated and who should not. While I disagree that albuminuria is virtually useless, there is a need for more specific biomarkers ideally those that have some pathogenic significance. For instance is the renin-angiotensin system overactive and when in the course of diabetic kidney disease. It was written above that ""urine proteomics has yet to identify a robust biomarker for diagnosis/prognosis. Do you think couple tissue proteomics of kidney compartments [glomerulus v. tubulointerstitium] for biomarker discovery with targeted assay development in urine makes sense?""*

*I think tissue proteomics coupled with targeted urine assays is absolutely a valid approach. In studies of SLE, Brad Rovin at OSU is using proteomic analysis of laser capture specimens to approach this problem. Now if only the people doing proteomics understood the complexities of biomarker research and how to integrate clinical findings and parameters and disease progression with proteomics.*

*I think the comment above is correct about a disconnect between the -omics folks and biomarker development. Nevertheless, the ability to analyze large matrices would benefit the evaluation of renal disease.*

*It seems too much biomarker effort goes into markers that correlate with currently known ones. This is the least beneficial strategy since an orthogonal marker is most likely to add to predictive value. The identification of unknown orthogonal markers is most likely to come from -omics work; however I would*

*hate to see it restricted to proteomics. I'd expand it to include metabolomics... since that's what's being regulated..."*

*Linda Fried—There were some discussions of biomarkers at the recent NIH CKD conference. There are a number of potential roles for biomarkers/proteomics. In addition to identifying who is at risk for progression of kidney disease, biomarkers could have a pharmacoepidemiology role in helping to understand who benefits from different therapies. What the conference highlighted as well is that the current endpoint of doubling of serum creatinine, ESRD, death is late. Biomarkers could be useful in early phase 2 studies to help choose what therapies warrant the more expensive and complex phase 3 testing based on "hard" outcomes.*

*Matthias Kretzler—Biomarkers still have to deliver in the field of DN and the reasons have been described above. In addition, the best biomarker studies in DN have used state of the art molecular profiling technologies obtained in prospectively established DN cohorts, i.e. taking a sample at time point 0 and correlating molecular parameters with outcomes observed during prospective follow-up. To be able to serve as an effective biomarker with this design, a parameter has to be associated with the outcome irrespective of the initial heterogeneity in the patient cohort concerning mechanistic disease type and state. In DN, as in most other chronic progressive diseases, we can expect to see a mixed bag of disease mechanism being activated in patients in a cohort specific manner. Subsequently many of the most promising specific candidate biomarkers fail in validation cohorts as a consequence of unrecognized differences in molecular mechanism operational between cohorts. Those biomarkers who work across cohorts are most likely representing non-specific markers of inflammation or fibrosis and will therefore be very sensitive to non-renal confounders. Integrating biomarker discovery with efforts to define the molecular heterogeneity of patients studied would allow the definition of functional distinct patient groups in a first step. Subsequently correlation of parameters reflecting the functional status in the molecular define disease with clinical outcomes will define molecular classification biomarkers. Validation in independent cohorts would require first stratification according to molecular disease type / stage, followed by assessment of the respective biomarkers for prediction. If the biomarkers efforts are combined with the current studies in systems biology (see discussion point 7) and patient cohorts for mechanistic study of DN (point 20) this might be an achievable and worthy goal.*

**Title: It is easier to find genes in DN for T1D than T2D?**

Votes: 0

It has been difficult to identify SNPs with even modest effects in studies of type 2 diabetic nephropathy. One possible explanation is that patients with kidney disease who have type 2 diabetes may not have a single disease. Indeed the old biopsy data suggest that there is a diversity of diseases in this population. Should gene finding efforts focus exclusively on type 1 diabetic nephropathy for the short term?

*Comments:*

*Moderator—The familial aggregation of diabetic nephropathy (DN) has been demonstrated whether in type 1 (T1D) or in type 2 diabetes (T2D)... the extent of DN familial aggregation ( $\lambda$ -S) is significantly less than that for T1D ( $\lambda$ -S  $\sim$ 15) but similar to that of T2D ( $\lambda$ -S  $\sim$ 3). Thus, if the genetic architecture for DN is similar to that of T2D, it will take thousands of cases/controls or families to detect common variants of small effect to robustly identify genes. It does not seem possible to collect*

those sample sizes in reasonable time. There does not seem to be definitive evidence that the source of diabetes (T1D or T2D) significantly alters the risk of DN, even though the genes contributing to T1D do not overlap (to this point) with those that contribute to T2D, and the underlying etiology of T1D and T2D may be inherently different. My point is that to account for the genetic basis of DN, one may have to approach it as "nephropathy from dysfunction in glucose homeostasis", collect large numbers of subjects, and target less frequent variants through sequencing approaches (in parallel with obvious follow-up dense mapping and sequencing in candidate regions). If we go down the path of splitting the phenotype into many subgroups, there will never be sufficient sample size for robust inference. Agree with idea. It is not clear to me that the people with T2D that get DN have the same disease (i.e. the same form of T2D) as people who don't get DN. Perhaps it's not that some people with T2D get DN and others don't, but those that do and don't have different forms of T2D. This has implications for study design. For example, pts. with T2D and no DN are not the right controls for people with T2D and DN. I agree with the comment above. For GWAS, we should follow the "roadmap" provided by other complex traits and maximize our power to detect common variants by combining data from the existing consortia and enrolling new subjects by recruiting from LDOs. Phenotypic entry criteria be based on demographic and lab values used by clinicians and that would result in interindividual consistency. GWAS datasets comprised of healthy individuals could be used for contrast. The problem of DN vs. DM genes could be sorted out subsequently if necessary. In addition, strategies need to be developed to evaluate the family datasets organized by NIDDK and other organizations.

I think that it's important to remember what the two major risk factors for diabetic nephropathy are: diabetes duration and long-term glycemia. Trying to find genes without taking these into account may drastically reduce the power: like trying to find causes of lung cancer without knowing who was a smoker, and how much they smoked. The problem with trying to identify genetic loci for diabetic nephropathy in type 2 diabetes is that in most studies it is difficult to obtain information regarding the two major risk factors. Most people with type 2 diabetes are diagnosed years after the disease begins: therefore there is great imprecision in diabetes duration prior to the development of diabetic nephropathy. This has knock-on effects on the measurement of long-term glycemia - if we do not know when the diabetes began, and then the glycemia during the undiagnosed period is unknown. In contrast, the onset of dysglycemia in type 1 diabetes is usually accurately known. Long-term glycemia is usually well documented, and because of routine screening for diabetic nephropathy in type 1 diabetes allows definition of when nephropathy began. Therefore the major risk factors can be easily measured with well-designed studies. It is likely that having measures of these two important risk factors improves the power to detect loci for diabetic nephropathy. Finally, we have to be careful about the assumption that nephropathy in a person with type 2 diabetes is due to diabetic nephropathy, as opposed to hypertension, or other causes of nephropathy. Several issues arise. First, there is little empirical evidence that finding type 1 DN genes is easier. While one may look at the lambdas, these tend to artificially inflate or deflate risk depending not on the numerator but on the denominator so are not a good guide. Searches for both type 1 and type 2 nephropathy genes have been compromised by lack of appropriate samples. The majority of dialysis patients with diabetes have T2D, Thus, any hypothetical advantage in lambda is offset by difficulty in finding appropriate samples. The reality is that there is rarely a free lunch in looking for complex disease genes. In almost every case where investigators have projected panacea results from narrowly targeted efforts have been disappointing. Any single targeted effort is almost certain to be a failure. While the idea's premise is that identifying genes will be easier in T1DN, we find the potential implications disturbing. As a group that works on T2DM in African Americans and diabetic nephropathy, if such a suggestion leads to decisions on access to resources the implications for African Americans could be very negative. There is little evidence that "European" genes contribute to inter-individual variation in risk in African Americans for T2DM or nephropathy. The same can be said for most other discoveries in the European population. This is an especially important observation, given that

*African Americans make up well over a third of the dialysis population in the US. Focusing on nephropathy in a disease which is rare in African Americans has every likelihood of disenfranchising this large group of patients from any benefits of research. From a social equity perspective alone a focus on type 1 diabetic nephropathy is unsupportable. The identification of APOL1/MYH9 in non-diabetic African Americans should awaken anyone to the dangers of assuming African American disease can be viewed from a Eurocentric perspective. If type 1 DN genes should be easier to find, it seems empirical efforts would have been more successful given the commitment of resources to date. The case that diabetic nephropathy genes have been unambiguously identified in type 1 diabetes is weak and does not come close to the level of evidence for T2DM genes for example. Replication samples are few in number. The reality is that all efforts to identify diabetic nephropathy genes to date have been compromised by lack of appropriate patient resources. No robustly powered effort has been completed with the exception of studies of quantitative measures of kidney function in healthy European-derived individuals. These have demonstrated little relevance to ESRD. With few exceptions investigators have avoided the time consuming and unrewarding task of recruiting adequate samples for well powered studies. It is ironic that the obvious case group, individuals with diabetes on dialysis, is usually underrepresented in most studies. The way to find genes is to invest in collecting samples for well powered studies in multiple ethnic groups and use the entire spectrum of modern molecular genetics: GWAS, exome sequencing, etc. Given the numbers and prevalence. Identifying African Americans with diabetes-associated ESRD is much more cost effective than recruitment of any other sample. Any serious effort would be expensive and time consuming. The impact of gene discovery for prediction, prevention, and treatment is immeasurable.*

*John Sedor—Most of the following was written with Tom Coffman.*

*The data supporting arguments for putative differences in kidney disease pathogenesis between patients with type 1 and type 2 diabetes mellitus (DM) were generated from analyses of kidney biopsies from diabetic patients with microalbuminuria and preserved renal function (Diabetologia 2008 Aug;51:1347-55; Ibid 1996 Dec;39: 1569-76; Nat Rev Nephrol. 2010 Sep;6(9):508-10). These studies had small sample sizes and reported pathological changes in renal biopsies from type 2 DM patients, which were not seen in kidney biopsies from type 1 diabetic patients. This morphological heterogeneity primarily reflected pathologies characteristic of aging and comorbidities, such as hypertension, heart and vascular disease, that frequently co-segregate with type 2 DM and can cause microalbuminuria and renal disease independently of hyperglycemia. Despite these differences, an analysis by Fioretto and Mauer, who have championed the concept that renal disease has different mechanisms in types 1 and 2 DM, indicated that risk for progressive nephropathy in patients with type 2 DM is proportional to the severity of GBM thickening and expansion of mesangial matrix (Diabetes 2000 Mar;49(3):476-84). Other groups also demonstrated similarity in renal histopathology in type 1 and 2 DM patients (Am J Kidney Dis. 1996 Feb;27(2):167-94; Ditscherlein G: Nierenveränderungen bei Diabetikern. Jena, Germany, Gustav Fisher Verlag, 1969; Diabetologia. 1996 Dec; 39(12):1638-45; Kidney Int. 1992 Apr;41(4):749-57) and conservation of structure-function relationships between type 1 and type 2 DN (J Am Soc Nephrol. 2000 Sep;11(9):1667-73). Importantly, the Research Committee of the Renal Pathology Society developed a single consensus classification for DN due to type 1 and type 2 diabetes because of the substantial overlap with respect to histological lesions and renal complications (J Am Soc Nephrol. 2010 Apr;21(4):556-63).*

*The similarities in the clinical phenotypes and treatment responses of patients with type 1 and type 2 DN further supports their shared pathogenesis. Common characteristics include: (1) the time courses of nephropathy onset and progression after diabetes onset are similar in both type 1 and type 2 DM patients; (2) only subsets of patients, with similar glycemic control and blood pressures, are at risk for developing nephropathy; (3) familial clustering strongly supports genetic susceptibility in nephropathy*



*pathogenesis; (4) both blood pressure and glycemic control reduces nephropathy incidence and slows progression; (5) blockade of the renin-angiotensin system attenuates progression; (6) features of kidney injury are virtually identical in animal models (including primates) of type 1 and type 2 DM; and (7) the defining pathological lesion, nodular glomerular sclerosis, is indistinguishable between DM types (discussed above). Furthermore, recent micro-array analyses indicate activation of similar gene expression pathways in type 1 and type 2 DM mice and humans (AMDCC funded pilot study [Kretzler] and Diabetes 2006 Nov; 55, 2993-3003).*

*Based on the preponderance of evidence indicating common pathogenesis of nephropathy, we'd advocate studying [using meta-analytical methods] cohorts of patients with both type 1 and type 2 DN to identify associated variants. Although pathological heterogeneity in the patients with type 2 DM may increase the noise in the analyses, the statistical power should substantially increase by including all DN patients. Other strategies can reduce phenotypic variability. For example, subjects enrolled in FIND were ascertained by severe clinical nephropathy phenotypes, which are similar in type 1 and type 2 DM patients. In contrast to FIND, both GENIE [type 1 DN consortium] and SUMMIT [European type 2 diabetic complications consortium] enrolled diabetic patients with much broader range of nephropathy phenotypes (microalbuminuria to ESRD). When metaanalyses are initiated, sub-groups of patients, who are enriched for similar degrees of nephropathy severity, can be identified using standard clinical phenotyping criteria.*

*Although potential differences in pathogenesis of renal disease between type 1 and type 2 DM have been debated for many years, there is very little experimental or clinical evidence for distinct pathogenetic mechanisms. Genetic studies provide a unique and incisive approach for distinguishing such mechanisms, if they exist. Samples from patients with rigorously phenotyped type 1 DN are limited. Increasing sample size would be expensive and exome sequencing of these samples may be premature. The first step should be an efficient and cost-conscious approach to identify variants for DN. Hypothesizing that at least some common mechanisms exist, we would advocate for strategies that leverage available datasets, and if needed, increase sample sizes by using simple clinical phenotyping strategies to collect more cases. Publically available GWAS datasets from healthy/community based populations would be reasonable controls for contrast, especially since a number of diabetes genes have been replicated. Genetic studies provide a unique and incisive approach for distinguishing such mechanisms, if they exist. If these approaches are successful, funds could then be invested in identifying diabetes type-specific mechanisms. If not, the Institute and its advisors should carefully consider the next steps so funds are wisely spent.*

**Title: What is the best way to collect patient samples?**

Votes: 25

Identifying robust association between genetic variation and severe human CKD phenotypes has been hindered by lack of collections of patient sample collection of sufficient size to use effectively in GWAS. The community could address this issue by developing reproducible but simple clinical phenotyping criteria and collecting samples from ESRD patients in dialysis units. Contrast can be made to publicly available datasets of healthy volunteers with GWAS data. I am assuming, for example, that patients with diabetic nephropathy can be compared to healthy non-diabetic patients since the genetic architecture of type 2 diabetes common variants has been characterized.

Comments:

*Moderator—This is a great idea. Could be effected through collaboration with dialysis providers. In fact they could be mandated to collaborate since they receive most support for renal replacement therapy from Medicare and Medicaid. Indeed a great opportunity to get genotype and phenotype data from a large cohort of patients with CKD, particularly with the enforcement issues commented. One caveat is the survival bias, i.e. patients on IHD are depleted for those patients who succumbed to CVD prior to reaching end stage kidney disease, making comparisons with the available large-scale CVD genetic studies mandatory.*

*This is great idea. A universal data collection form could help harmonize data elements.*

*You—Animal models exist or can be developed for specific aspects of DN, but cannot completely replicate the human clinical disease. The study of DN would benefit from the establishment of a bio-repository of well-characterized human samples. However, the desire to study the effect of diabetes on human tissue is tempered with the complexity of individual variation, inaccessibility of many tissues, and uncontrolled and unknowable variables in patient history and sample processing. Are there more accessible tissues, such as skin or subcutaneous fat, which could be used as surrogates for the major organs (kidney, heart, pancreas) that are affected by systemic diabetes? Some of these factors can be lessened by technological advances in testing and analyzing large numbers of samples. Patterns that could not be seen with small numbers of individuals and end points may emerge with broad platform testing. Coordination of a major effort to obtain clinical samples from carefully characterized individuals under standardized processing procedures has started in the National Cancer Institute, and a similar effort could be initiated for DN. Currently, a large amount of material (including DNA, urine, serum, and immortalized cells) is in storage from multiple clinical trials and large-scale genetic studies of people with diabetic complications. These samples and new collections could be analyzed by mechanistic, genomic, epigenomic, and proteomic studies, with similar samples evaluated by multiple platforms simultaneously to facilitate comparisons.*

*Breyer Matthew—At present serum creatinine and proteinuria are the two major biomarkers used to track progression of chronic kidney disease and identify those patients at risk for progressing. Of these creatinine is the only biomarker accepted by the FDA as a registration endpoint for drugs that slow kidney disease. The lack of robust and dynamic biomarkers of progressive kidney disease is a major gap in the field, contributing to the high cost and long duration of clinical trials for drugs to treat kidney disease. Clearly performing research to facilitate the development of drugs to treat chronic kidney disease is within the mandate of the NIH. Discovery of more dynamic biomarkers that predict progression of kidney disease would allow shorter and less expensive trials and greatly increase the ability to test therapies for kidney disease. The endeavor to discover the biomarkers will require sample banks of biological materials from large numbers of patients known to exhibit different rates of kidney disease progression.*

*The value in analysis of any clinical material (e.g. DNA, Urine, and Blood) is largely dependent on the clinical annotation associated with the samples. The information associated with genetic samples, body fluids, or tissue samples associated with kidney disease is often limited by inadequate phenotype information including change in serum creatinine over time, blood pressure, medications, level of proteinuria, intercurrent illnesses, associated retinopathy, and anatomic imaging records. As U.S. medical care moves towards more comprehensive implementation of electronic medical records, could each sample be systematically coupled to the samples, annotating them with all relevant clinical information in a way not hitherto possible? Observational studies of kidney disease (e.g. CRIC) provide one such source of clinical trials material, however clinical trials of drugs for patients with kidney disease represent among the best phenotyped cohorts of patients. These patients are chosen from a subset of patients with kidney disease chosen for rapid progression (typically high proteinuria), and therefore a unique population. Unfortunately, when trials are conducted by small biotech companies focused on a*

*single product, the samples are frequently collected under informed consent documents that limit sample use to that particular study, and if study not achieve the critical success factors, these small companies shut the program down, and simply discard the samples due to cost. Can there be some means of recovering these samples, and mandating a standardized consent document to facilitate further research on these samples by the renal community? There might need to be a centralized biobank to house and record sample accessibility. Other significant limitations in the broad usage of precious clinical DNA samples, plasma, urine and other fluids include repetitive freeze thaw cycles and improper processing prior to freezing. For instance, should a biomarker require isolation of urinary or plasma exosomes, special handling steps must be implemented prior to freezing. Prospective aliquoting of these samples prior to freezing would maximize their utility, by allowing multiple investigators to study each samples without having to subject them to repeated freeze-thaw cycles. Even frozen materials are susceptible to oxidation of proteins limiting their utility and optimally storage under an inert gas would prevent this.*

*Matthias Kretzler—In addition to the above raised points, the following topics might be relevant for discussion: Effective bio repositories require combination of high-resolution prospective phenotyping with standardized sample procurement, processing and storage. To do all of the above in large cohorts (several thousand patients) of renal disease patients is very resource intense. However, as outlined above, we already have multiple highly valuable collections in place in the NIDDK biorepository. Most of these studies are very rich concerning clinical characterization of patients, but rel. limited concerning usability of bio samples for large scale molecular screening. For molecular disease definition, a modest size cohort (100-200 DN patients) with a comprehensive biorepository (including biopsy specimens) and careful prospective follow-up data would have the potential to serve as the critical link between the capabilities of systems biology (see topic 7 of discussion) and the established large scale cohort studies available. The modest sized cohort of early DN with an initial protocol biopsy processed for molecular analysis would allow to link intra-renal genome wide profiling studies (mRNA, miRNA, epigenetics, potentially proteomics / metabolomics in the future) with the non-invasive samples or imaging data available from the same individuals. As the link between intrarenal pathophysiology and non-invasive analysis is established in the medium size core cohort, the population wide association can be validated in the established large cohorts using the non-invasive parameters on the banked large scale cohort samples. These parameters with established links to intrarenal pathophysiology can be followed over time in the observational cohorts or their response to treatments can be assessed in interventional trials. For early DN, protocol biopsies might be the only way to obtain tissue of sufficient quality for genome wide profiling technologies, for established DN carefully selected clinical biopsies should be available. Alternative approaches (tumor nephrectomies, brain dead donor tissue or early autopsy tissues) are significantly impacted by tissue procurement artifacts overlying and in many instances overwhelming the underlying DN pathophysiology for many of the genome wide profiling technologies. In many fields there is no alternative to these types of tissue procurements, but DN protocol biopsy studies, where available, have offered significant insight into DN pathophysiology in the past and can provide a truly unique window into diabetic end organ damage in general.*

**Title: A role for the study of non-mammalian model systems?**

Votes: 35

Non-mammalian model organisms have been underutilized to understand diabetic nephropathy pathogenesis. These simple model organism systems that permit ease of genetic manipulation, rapid throughput and precise measurement of phenotypes. Work published earlier this year (PNAS 107: 775, 2010) demonstrated that type 2 DM risk loci could be characterized in zebrafish. Interestingly, this study demonstrated this study shows that zebrafish embryo can

respond to human regulatory elements [even if not highly conserved in teleosts] in a time- and tissue-restricted manner.

*Comments:*

*Moderator—Even more interesting, there are indications that specific cell lineages recapitulation molecular machineries seen in podocytes are found in drosophila. However, defining cross-species orthologous mechanism is significantly more challenging than in the mammalian system. Fish remain the premier system for unbiased mutagenesis approaches in vertebrates. There are several examples of novel genes positionally cloned in fish that lead directly to human disease gene discovery. Of course fly genetics has lead the way for decades and constitutes the foundation for our understanding of the majority of development (pax/hox/gli/hh/wnt/...need I say more?) I agree that more could be done with large scale screens. I agree with the first comment that this requires establishing congruencies between model organisms and mammals. Mostly the relevance can be established at the level of cell biology and cell substructure. For instance, slit-diaphragms in podocytes. The organs in flies fish and mammals function quite differently. Differences in overall organ physiology often limit acceptance of a model; I think this is a strategic mistake. Developing better transgenics/reporters for live imaging of subcellular dynamics or cell physiology would enable new broad, high-throughput screens.*

*Katalin Susztak—Non-mammalian model organism has been instrumental to define multiple phylogenetically conserved pathways and understand core biochemical mechanisms. They could be very useful to understand the causal role of a single gene (non-synonimus mutation), however their use and contribution to understand complex trait and disease development is yet to be established. For gene regulatory function, differences between the non-mammalian vs. mammalian genome structure could be important. To this end the zebrafish kidney is very different from the human kidney. Kidney repair and regeneration in the zebrafish is different from humans. With the discovery of novel through-put methodologies and with their decreasing cost it is becoming increasingly easier to study the human species, which we ultimately aim to cure. In summary, while these model organisms could be useful to answer specific questions on specific coding mutations at present it is unclear how we would use them to understand human DKD, which does not appear to be monogenic, coding mutations have not identified and gene regulation and the diabetic environment appears to be critical for the disease development.*

**Title: Can we develop "humanized mice" for the study of DN?**

Votes: 60

While the mouse has many advantages, the human diabetic nephropathy phenotype has been difficult to faithfully replicate in the mouse using candidate gene approaches. Future work should focus on developing "humanized mice," in which loci associated with human diabetic complications are knock-in to the mouse. These animals could then be used to study mechanisms and therapeutics using systems biology approaches.

*Comments:*

*Moderator—I like this idea a lot, but think the idea may be premature to have a high chance of success. Aside from insufficient knowledge of which human loci to knocking, I would worry about which mice to use for this purpose. One lesson from the Animal Models of Diabetes Complications Consortium is that different mouse strains vary in their susceptibility to different complications. Some of the complexity*

*underlying this may be result of networks of signals that involve communications of multiple organs that may not be first realized on association screens between genomes and a single complication of interest. Yes, I agree with the idea that using human genetic information to make new mouse models could be a great idea - but I also agree with the first comment that choosing the correct mouse background would be a critical factor. In addition, we would need to consider an epigenetic component. I agree that this is an approach with significant potential. While the AMDCC experience has highlighted some of the difficulties in completely recapitulating all of the features of human diabetic nephropathy, a number of important characteristics are reproducibly seen. As such, I think the mouse can be a very useful system for testing the capacity of human genetic variants to affect kidney injury in diabetes. The first comment on the importance of strain differences is well taken, but assay systems testing human allelic variants side-by-side on identical, inbred backgrounds could actually be quite powerful. It seems to me that such systems in mouse, and perhaps other lower organisms, can provide a solution to the problem of defining the functional relevance of SNPs identified in human GWAS for diabetic nephropathy and other complications.*

*Breyer Matthew—I think the situation where humanization makes most sense are those diseases where there is no evidence for a mouse homolog of a gene, and that specific gene is found to be causative of diabetic kidney disease. APOL1 would be an example of such an opportunity for kidney disease, albeit perhaps not diabetic nephropathy. Alternatively if the human therapeutic target were susceptible to a pharmacologic, but the mouse homolog not, humanization would make sense.*

*Tom Coffman—I think development of humanized mouse models for studying DN is feasible and will be quite valuable. The major utility will be in functional testing of candidate human susceptibility alleles emerging from ongoing GWAS and other analyses. The technology for recapitulating these human variants in mice is mature and this will be one of the few options for direct functional testing of human variants in a mammalian system. Along with their value for causality testing, they also provide unique models for testing therapies and systems analysis. Emerging data from large animals suggests that the difficulty in completely recapitulating human DN is not unique to mouse and may relate to the time (ie, years) required for development of nodular nephrosclerosis and renal failure. As such, the mouse may be as good a model as any for testing the consequences of specific genetic variants on the development of kidney injury.*

## GENERAL DISCUSSION:

Please use this GENERAL DISCUSSION board to post “general” comments to the group about the relative priority of different Questions, the possibility of merging two or more similar Questions, identifying themes that cut across multiple Questions, etc. Please continue to add “specific” comments to the individual Questions.

*You said—I read through the reviews and many of you suggested “merging” two or more Questions. To get the ball rolling, several of these suggestions are listed as comments below. Please review and discuss. If folks generally agree that merging makes sense, then we will do so. However, you should absolutely feel free to disagree – although we ultimately want to identify the best 5-10 Questions (which makes it very tempting to simply merge the existing 22 Questions until we get to 10!), our goal is to identify the Questions that address a critical barrier in kidney research. This is where we need your expertise to make the hard decisions and tell us which ones are of the highest priority. This is particularly important considering that funds will likely be hard to come by in the next several years.*

*You said - REGENERATION/REPAIR. It was suggested to merge question #4 (Can stem cells repair and reverse DN?) into #3 (How does diabetes affect regeneration and repair?). Agree?*

*You—MOLECULAR PATHWAYS. It was suggested by several folks that multiple Questions – including #9 (Is mitochondrial (dys) function a major component of DN?), #10 (Are immunologic pathways causative factors in DN?), and #12 (Is autophagy a major contributor to DN and its progression?) – could be merged into #11 (What are the molecular pathways involved in DN?). Agree?*

*You—RAAS. It was suggested that #16 (Does aldosterone breakthrough occur in DN?) is relevant to #17 (What next after RAAS blockade?) and that perhaps both could be merged with #1 (How do we promote translation in DN?). Agree? It was also suggested that we don’t fully understand the basic mechanistic pathways underlying the benefits of RAAS blockade and that this component of #17 (What next after RAAS blockade?) could be merged into #11 (What are the molecular pathways involved in DN?). Agree?*

*You—INTEGRATIVE BIOLOGY. It was suggested that components of #2 (Can miRNA signatures be exploited to diagnose and treat DN?), #5 (What new technologies will lead the field of DN forward?), and #20 (What is the best way to collect patient samples?) were all relevant to “integrative biology” and could be merged into #20 (Will systems biology discover new pathways/targets for DN?). Agree?*

*You - BIOMARKERS: It was also suggested that components of #1 (How do we promote translation in DN?), #7 (Will systems biology discover new pathways/targets for DN?) and #20 (What is the best way to collect patient samples?) could be merged into #18 (Can biomarkers predict T2D DN?).*

*You—GENETICS/EPIGENETICS. It was also suggested that there may be value in splitting # 8 (What are the key genetic and epigenetic determinants of DN?) into one Question on Genetics and one on Epigenetics. Agree?*

*Linda Fried—I cannot comment on the relative strengths of the basic science areas, and will defer to others. With regards to biomarkers, the topic crosses a number of the questions. It makes sense to combine #18 and #20 for biomarkers. We need better clinical biomarkers to predict who will progress to ESRD. Analogous to AKI, this will be useful in trials to identify who responds to various treatments, as well as whether the treatment under study appears to be effective and should be*

*studied for hard endpoints. To accomplish this, what is needed are robust databases with samples and detailed phenotypes. The development/choice of these biomarkers will depend on a better understanding of the physiologic pathways. To be useful clinically, markers of these pathways will need to be measurable in the urine or blood. This aspect of biomarkers could perhaps be merged into number 11 (molecular pathways).*

*Linda Fried—While I am studying aggressive RAAS blockade in diabetic nephropathy, I would place RAAS blockade and aldosterone blockade lower on the priority list for future limited NIH funds. While all information is not known, a new area may have greater impact*

*John Sedor—I actually think these "merged questions" further simplify into three domains: 1. Collection of phenotype, clinical and demographic data and biological samples for discovery science (perhaps a DN or DM complications Neptune); 2. Using new technologies of "integrative biology" to develop hypotheses; 3. Hypothesis testing science to prove the molecular pathways regulate DN pathogenesis couple with tools (e.g. regenerative medicine) to treat.*

*Obviously #1 above is not science but could be coupled with #2 to become science.*

*Although most of the 22 questions raise important issues, all are predicated on someone's notion of important mechanisms in DN development and progression. Pursuing promising mechanisms would be a function of the R01 portfolio, which will remain the foundation of our investigative community. However, I have to say that using cells and animals have resulted in a lot of interesting biology; we have not made much progress in understanding of human kidney disease. However KUH specifically and NIDDK in general needs to find ways to promote the "big science" that will provide the resources and synergize with R01 science to make progress. We have been hampered by the relative paucity of cohorts and samples to apply emerging high throughput technologies that require large sample sizes to reach thresholds consistent with reproducibility. For example NHLBI has the cohorts ready to test utility of sequencing when the technology became usable. A challenge now is how to preserve the R01 and not stifle the big science to allow R01s to be innovative.*

*John Sedor—I disagree with separating genetics and epigenetics. Conceptually understanding variation and its superimposed regulatory modifications are intimately connected. Integration of these data is needed to define the DNA architecture that controls DNA pathogenesis.*

*Matthias Kretzler—Fully agree with John's stratification of the main problems into the three categories. For domain 1, building cohorts and infrastructure for molecular medicine is painfully slow, but is a crucial pre-requisite for an effective translational medicine pipeline.*

*If we have these cohorts in nephrology / diabetic nephropathy, we will also become interesting again for the key partners we need to bridge the gap between targets identified in academia and getting new drugs into patients. These partners can also facilitate maintaining the translational research infrastructure. The southwest oncology group (SWOG, <http://www.swog.org/>) is one of the success stories, for rarer diseases the RDCRN Vasculitis consortium*

*(<http://rarediseasesnetwork.epi.usf.edu/vcrc/>) has implemented this effectively. A significant programmatic effort from NIH is essential to establish the basic infrastructure for these cohorts.*

*The molecular information generated by linking genome wide data sets and phenotypic measures in domain 2 of John's strategy can serve as the bridge to the mechanistic research pursued in domain 3, anchoring mechanistic studies in model systems in human disease. Developing the data ware house and communication infrastructure in domain 2 to present the information in genome wide datasets in an accessible manner is a critical, but often underestimated step in this process.*

*Michael Flessner—I concur with John Sedor's suggestion of addressing clinical translation in diabetic nephropathy in three general areas. Integrated within the loop could be mechanistic studies in animal models and/or humans that lead to large scale trials of drugs/therapeutic maneuvers.*



## End Stage Renal Disease

### Postings and Comments

#### **Title: Technology for self-care dialysis**

Author: William Fissell

Votes: 38

Expansion of the existing ESRD system to accommodate intensive dialysis for many or most patients will require widespread self-care home hemodialysis. There is a need to make that process easier for patients to accept, and that probably means changing the devices we prescribe and they use.

Needs include devices to promote self-cannulation, prevent/detect accidental disconnect, improved water supply and ways to reduce the complexity of therapy.

Additional involvement by the research community might derisk programs to being new devices to market for home hemo, and in so doing, encourage all stakeholders - academia, inventors, practitioners, and most importantly, industry to work towards facilitating home intensive dialysis.

#### *Comments:*

*Kevin McBryde—I agree that this is an important area of research that has been untapped. Home hemodialysis for daily or nocturnal therapies should be developed from the ground-up, with careful attention to risk identification and mitigation, monitoring/surveillance, device/drug quality, and outcome measures. Improvements in design should be validated with improvements in outcome, as the technology and the provision of care will be costly. What we currently have available is grossly inadequate and reflects a simplistic approach to a very complicated disease and therapy.*

*Kristina Paquette—What about adapting home hemo so that a patient who lives alone can do it at home without a helper?*

*Stephen Ash—I agree fully that the greatest challenge in the care of ESRD patients is to create methods of dialysis that are radically simpler and safer and easier to implement in the home environment. CAPD is already one such option, but it still requires considerable skill, strength and training. A bedside machine using single needle access and sorbent regeneration of dialysate is one approach. Radically improved access is also possible using end-to-side connections. Silicon membranes as created by Dr. Fissell and coworkers would also be a great step forward. S.R.Ash*

*William Fissell—I (obviously) consider this an extremely important area. The barriers to widespread implementation of home hemo have been fairly well explored: fear of accidental disconnect, concern about manual competence to operate the instrument, and concerns about burden on caregivers. I think the barriers lend themselves to technological solutions that more closely mimic long slow therapies, yet have limited complexity and can be realized in the near future.*

*Bruce Carter—Subcutaneous guide devices may help enhance buttonhole cannulation or even help facilitate automatic needle insertion devices. A feasibility study for such system, "Venous Window Needle Guide" is planned in Australia:*

<http://apps.who.int/trialsearch/trial.aspx?trialid=ACTRN12610000416099>

*Such an approach could facilitate accurate self-cannulation perhaps even by the relatively unskilled, without entailing the level infection risk inherent in catheter approaches. Thus, while seemingly simple, such concept would constitute an key "enabling" technology for self-care dialysis with or without a caregiver partner, especially when combined with "single needle" dialysis.*

**Title: Access flow as contributor to morbidity and mortality**

Author: Dirk Hentschel

Votes: 30

Access flows in autologous and prosthetic/biograft accesses vary widely. Upper arm accesses, more frequent in patients with DMII and HTN, in general have higher flows. This higher flow can be detrimental for the access itself in the setting of outflow stenoses, as venous pressures would rise more leading to aneurysms and rapid skin deterioration. Systemic effects of higher flows result from increased shear stress on endothelial cells as well as blood cells, in addition to demands on cardiovascular output.

Studies are needed to a) observe differences in m&m associated with different magnitudes of flow and b) interrogate if "control" of access flow alters outcome. It is prudent to include whole genome/proteome data in these studies, as they may modulate outcome.

*Comments:*

*Rajnish Mehrotra---I concur with the importance of studying the effects of access flow rates on systemic hemodynamics, and cardiovascular function - not only short term but also long-term effects. While fistula is the most desirable access, there is sufficient concern that high flow rates may lead to high-output heart failure.*

**Title: Comparative effectiveness of dialysis modalities**

Author: Rajnish Mehrotra

Votes: 29

We are long past the time when in-center HD and PD were the dominant dialysis modalities. The FHN examined daily in-center dialysis but did not evaluate the increasingly popular NxStage system for daily home HD. There is great need to understand how different dialysis therapies - daily in-center or home HD, nocturnal in-center or home HD, compare with thrice-weekly HD and PD - modify known risk factors and effect patient morbidity and mortality. In the absence of support for a RCT, cohort studies will be critical to elucidate the effects of these dialysis modalities on patient outcomes to better inform us about their role in clinical practice.

*Comments:*

*Bruce Carter—Unrealistic demands for fully randomized designs have indeed hindered progress. Well-designed, carefully matched cohort studies can still be meaningful, especially when a result as profound as survival-doubling has been suggested. Yes, we need to move forward, but this will also require a return to common sense--to guide making informed decisions when a "traditional" RCT design is unrealistic.*

*Perhaps a new conference is the right approach, although similar efforts have been done fairly recently, such as Parker's 2009 Boston workshop: <http://cme.med.harvard.edu/cmeups/pdf/02924219.pdf> -- although this meeting had more of a "call to action" than a "framing questions" outcome."*

*John Stokes—I agree that comparative effectiveness studies are needed to develop a more detailed understanding of the role of hemodialysis frequency (and intensity) in improving outcomes. We will never be able to conduct randomized, controlled trials on these questions - the FHN trial demonstrated this point clearly.*

*The questions relate to:*

- 1. Frequency - 4, 5, or 6 times a week?*
- 2. Intensity - overnight or short daily?*

*The comparison to PD is interesting. To date, outcomes (mortality) for PD look about the same as conventional hemodialysis when patients are matched. Comparisons with transplant may also be viable. We must focus on mortality as the major outcome measurement. Secondary measures could include hospitalizations, solute removal, blood pressure, anemia, and the many factors reported in the FHN trial. A simple analysis compiling the results of several studies leads to the preliminary conclusion that nocturnal (and perhaps short daily) dialysis doubles life expectancy compared to conventional dialysis. If these analyses are close to being correct, we are on the brink of a major breakthrough in dialysis therapy. We have lots of details to consider. I think we need a forum or special conference to frame the questions and the information we need to move forward. Conventional RCT approaches won't work. I think we need a forum or special conference to frame the questions and the information we need to move forward. Conventional RCT approaches won't work.*

*Bruce Carter---I think we are essentially saying the same thing. Yes, PD vs. home HD vs. daily home HD are additional considerations needing head-to-head comparisons. To enable this, daily/frequent home HD needs to be directly supported. No data. No study. If the converts are mistaken, time will tell. Again, this topic needs to be made a top priority.*

*Bruce Carter---At least one recent cohort study on frequent nocturnal HD found survival comparable to transplant: <http://ndt.oxfordjournals.org/content/24/9/2915.full> Such low mortality over such long followup is truly remarkable. Daily or nocturnal home HD achieving similar results is entirely plausible, assuming comparable delivery. However, even if daily home HD were even just survival-neutral, there are quality-of-life reasons justifying such an approach. Patients report feeling, sleeping, and eating better and this has value in its own right. Better technology, remote monitoring, improved cannulation, dialysate regeneration, etc. stand ready to eliminate many of the "safety" concerns of an earlier era.*

*Therefore:*

- 1. In this context, the safety risks of home HD should be rigorously reexamined in controlled studies. Advocates of daily home HD argues that we already have sufficient trials and studies showing benefit. FHN was supposed to settle this. Now we need yet MORE studies? Their point is that NO amount of "science" can solve a \*political\* problem. As long as frequent home HD remains unfunded, a self-sustaining lack of data will persist, a barrier to the studies proposed by this post.*

*Therefore:*

- 2. Changes in CMS payment rules which would allow a substantial "pilot program" are needed to allow far more frequent in-center, and frequent home hemodialysis modalities to create the necessary missing cohorts for these studies.*

*Politics aside, this topic needs to be made a top priority. It seems the next logical step to be taken in light of FHN results.*

*Rajnish Mehrotra—I have to admit that as much as I believe that more frequent dialysis is better, I don't think I can share the certitude of the "converts". There are several unresolved issues:*

- 1. The way that most patients are currently being treated with daily dialysis is at home using the NxStage system. What I don't know if this "PD-like" HD is the same as conventional HD delivered daily.*
- 2. The comparison of the daily with the three-times a week HD notwithstanding, there is currently limited - if any - data comparing the effects of, for example, Nxstage daily HD with PD. And reimbursement changes are likely to increase use of PD.*
- 3. Finally, I believe that LVH regression is a good thing - the outcome of the FHN study suggests that daily dialysis will reduce CV risk. But will it? I remember the time when Kt/V was the be all and end all of all things dialysis. And then there were the "hemoglobin" days - every conceivable benefit was demonstrable with higher hemoglobin levels. To close the loop of LVH regression with hard outcomes is critical. And that is why I think we need multicenter cohort studies of clinical effectiveness.*

*Rajnish Mehrotra—On Dr. Star's suggestion, I am including the hypotheses that could be tested using such CER:*

- 1. In a propensity-score matched analysis, patients treated with non-traditional forms of in-center hemodialysis (nocturnal in-center, four or more times per week, self-care) is associated with better risk factor control, lower hospitalization and lower mortality*
- 2. In a propensity-score matched analysis, home hemodialysis using the Nx-stage system and peritoneal dialysis provide equivalent risk factor control, hospitalization rate, and mortality."*

**Title: Social worker using CBT to improve medical compliance in ESRD**

Author: Sharon Smitherman

Votes: 28

With the increasing need for managing health care cost in ESRD settings more needs to be done to increase patient medical compliance. The effectiveness of using SW trained in Cognitive Behavioral Strategies, should be evaluated. Given that most ESRD patients will not seek behavioral counseling on their own, clinical social workers, already available in outpatient clinics, could be trained in CBT or REBT programs developed by the Albert Ellis Institute or the Beck Institute for Cognitive Behavioral Therapy specifically medical compliance for the ESRD population.

*Comments:*

*Johan Rosman—This is by no means meant to discredit the profession of Social Workers, but I have concerns taking CBT out of the hands of the professionals who have this in their scope of practice, e.g. psychiatrists and clinical psychologists. We should not underestimate the consequences of, and potential side effects of CBT, leave alone the competency to diagnose and find the right indication for CBT.*

*Johan Rosman—My apologies, I never intended to offend a group of professionals, social workers in this case, that I respect very much for what they do. I was not aware of this scope of practice in the US and apparently also UK. My working experience is in continental Europe, Australia and New Zealand. Nephrologists in New Zealand do not routinely read the Royal College of Psychiatrists website in the UK.*

*Beth Witten—I believe you're from New Zealand so you must be aware that the Royal College of Psychiatrists states on its website that a patient's GP can refer him/her to a social worker for cognitive behavioral therapy.*

<http://www.rcpsych.ac.uk/mentalhealthinfoforall/treatments/cbt.aspx>

*Sharon Smitherman—Many of the clinical social workers currently working with the ESRD population are Licensed Clinical Professionals. To imply that CBT is not within the scope of practice of a Licensed Clinical Social Worker is to discredit a significant number of the practicing mental health professionals in the US.*

**Title: Collaborating with Medicare/HHS**

Author: Manish Ponda

Votes: 26

The government spends billions of dollars on ESRD care. Large portions of these costs are driven by therapy to conform to opinion-based guidelines. The history of ESA therapy is a glaring example of harmful practice and financial waste. It seems that patient care and biomedical science could benefit with large cost-savings if definitive clinical trials informed clinical practice. The cost may be too great for NIDDK, but given the ESRD-related expenditures of Medicare, HHS should view investing in such trials as a financial imperative.

**Title: Dialysis Patients with Marked Improvement in LVEF**

Author: Scott Pace MD

Votes: 24

I have noticed over the last few years some of our extremely ill dialysis patients with severe CHF/cardiomyopathy with an LVEF (10 - 20%) have shown marked improvement in LVEF (40 - 60%) without surgical intervention (CABG, stent placement, valve replacement. etc.) Some of the cardiologists have attributed this to Coreg, but are they overlooking other meds like ARBS or others? Has anyone else seen this in their patients? Any thoughts on why this could be occurring?

*Comments:*

*Magdy El Sharkawy—adequate dialysis in patient starting HD with low LVEF resulted in improvement of LVEF in many patients we have seen this frequently*

**Title: Comparative Effectiveness Research in ESRD**

Author: Daniel Weiner

Votes: 24

There are a paucity of quality and systematically ascertained data comparing commonly used treatment Votes strategies in dialysis. This ranges from topics discussed elsewhere on this board (middle molecule clearances) to dialyzer reprocessing to exit site care to best strategies for anemia management to lipid management, etc... The hemodialysis and peritoneal dialysis infrastructure in the US and elsewhere is ideal for natural experiments, quality improvement projects and controlled studies (on a unit or shift basis) comparing widely used strategies methodologies for patient care in a safe and efficient manner. Although often atypical in design,

this type of CER should be promoted as a means to gain knowledge that may otherwise remain elusive, with CMS and NIH facilitating regulatory issues that may otherwise limit the ability to conduct these types of studies.

*Comments:*

*Isak Prohovnik—Due to the interaction of disease and treatment characteristics with social and cognitive factors, the design and choice of dialysis modes is complicated and poorly understood. Unconventional designs are often necessary, and unappreciated, in this context. This area critically needs enhanced effort.*

**Title: The goals for the overlap btw ultrafiltration & BP in ESRD**

Author: Lynda Szczech

Votes: 21

To define markers of volume status and blood pressure control to minimize cardiovascular stress or burden in the ESRD patient. To validate novel markers of cardiovascular stress or burden as surrogate outcomes.

Ultrafiltration to a “dry weight” and blood pressure control are all clinically interrelated concepts that cannot be examined in isolation as the attempt to affect one has indirect effects on the other. Further, it is clear that the interaction between these two parameters is affected by patient specific parameters. While we have historically considered each of these parameters as valid surrogates of the reduction of cardiovascular stress, observational studies demonstrate that a single numerical goal for each of these benchmarks is not practicable in all patients. Therefore consideration must be given to finding a more “proximal” surrogate marker of stress that can be subsequently used as the goal allowing for differential manipulation of ultrafiltration and blood pressure within each patient.

*Comments:*

*Kevin McBryde—Unfortunately, the research has been poor in this area. We seem to believe that only intravascular and extravascular extracellular water is affected by ultrafiltration. However, I can't find literature demonstrating anything other than total body water is increased in ESRD. Thus, the impact of UF on blood pressure may be much greater than simply inducing intravascular volume contracture. I think that we need to go back to our "roots" as nephrologists and actually define the physiology of water balance in the intra- and extracellular compartments, and the impact of hyperosmolality and dialysis upon the distribution of fluid. Bioimpedance may have some benefit, but the technology needs to be validated against direct measurement. Perhaps noninvasive measurement of cardiac output using echocardiography or pulse-contour analysis.*

**Title: Vitamin D and mortality among ESRD patients**

Author: Bill McClellan

Votes: 21

Does vitamin D supplementation reduce the risk of mortality among ESRD patients? A RCT

*Comments:*

*Lawrence Fine—In other populations such as the VITAL trial, vitamin therapy is compared to a placebo, the question is whether one should wait for the completion of this phase 3 trial before undertaking the expense of a phase 3 trial in CKD patients. I also wonder what is the epidemiological evidence for a relationship between the progression of either CKD or vascular disease in the setting of CKD and D vitamin levels.*

*Linda Fried—Another issue would be a human studies one- would practitioners be willing to randomize ESRD patients to a placebo. Could you design a study with an active comparator (i.e. a comparative effectiveness approach). Alternatively, you could study this in non-dialysis CKS where PTH levels are not as high and active vitamin D is not used in as large a proportion.*

*Bruce Carter—Petchy et. al., has assembled a recent review of Vitamin D (with respect to CKD), including summarizing epidemiological evidence and relevant animal and in-vitro rationale (and not limited to ESRD):*

*<http://onlinelibrary.wiley.com/doi/10.1111/j.1440-1797.2011.01450.x/pdf>*

*Identifies many unknowns, but also presents some compelling reasons why this could be a productive avenue of research, since vitamin D interacts with so many other processes relevant to CKD, ESRD and mortality.*

**Title: Syndrome of rapid onset ESRD**

Author: MACAULAY ONUIGBO

Votes: 20

We recently described the previously unrecognized syndrome of rapid-onset end-stage renal disease (SORO-ESRD) in a high-risk 100-CKD patient cohort in the September 2010 issue of the journal, Renal Failure. This is the unanticipated and unpredictable accelerated progression from CKD to ESRD following acute medical and surgical events. The majority of the patients who exhibited this syndrome were aged >65 years old. The US population is an aging one. The prevalence of this new unrecognized syndrome in the general US ESRD population and the predilection of the aging US population calls for further study. The impact of the findings on AV Fistula First programs, on reno-protection strategies in general and the whole neglected area of preventative nephrology especially as it pertains to the aging baby boomers may be most significant and could call for paradigm shifts in current standards of practice and care of older (>65 year old) CKD patients.

**Title: Renal Palliative Care**

Author: Mark Unruh

Votes: 18

This year, 85,000 Americans with end-stage renal disease (ESRD) will die and legitimate questions will be raised as to whether unnecessarily aggressive and expensive treatments were or were not provided, whether patient quality of living/dying could have been improved, and why most hemodialysis deaths take place in institutional settings where a majority of individuals suffer distressing end-of-life symptoms. All of these issues are linked to a failure to plan for death using available palliative care and hospice services. The rate of hospice use among

patients dying with ESRD is half that of the national average and one-quarter the rate for patients with terminal cancer. The importance of addressing end-of-life issues in HD patients is underscored by rapid growth in spending since ESRD patients constitute only 1.5% of the Medicare population but consume 10% of its budget. Greater use of hospice by HD patients can improve the quality of care while simultaneously lowering costs.

*Comments:*

*Mark Unruh—One may also extend this topic to include conservative management of CKD such as the work by Brunori et al. published in AJKD demonstrating the efficacy of a low-protein diet in conservative management. I would think that this issue, and others in Renal Palliative Care, could be examined using both traditional and non-traditional clinical trials.*

*Dorian Schatell—It is vital to assess for treatable depression/adjustment disorder in patients who choose to stop dialysis. On one hand, we have patients who have intractable pain, multiple comorbidities, and very poor quality of life, for whom palliative care is appropriate. On the other hand, there may also be a group who choose to stop treatment because their lives are miserable on standard in-center hemodialysis 3x/week for 3-4 hours and they see no light at the end of the tunnel-- but who could have fuller and more rewarding lives if they were using another modality, including PD, longer and/or more frequent HD, or transplant. These two groups (if we can even verify such a thing) should be treated in the same way.*

*Rasheeda Hall—I agree. We need to further study the barriers to implementation of these recommended practices. One could start with case-control study of different healthcare providers.*

**Title: Time on Dialysis**

Author: Eduardo Lacson

Votes: 17

Over 2000 patients nationwide are now on in-center nocturnal hemodialysis with anecdotally improved outcomes reported. It provides a great opportunity for experimentation because it allows for productive use of potential additional capacity of an outpatient facility. In this setting, patients may be randomized to 4 hours vs. 8 hours of nocturnal treatment, 3x/week. NIH may need to consider compensating dialysis staff and patients as incentive to participate.

*Comments:*

*Yu Ling Chen—Frequent hemodialysis, as compared with conventional hemodialysis, was associated with favorable results with respect to the composite outcomes of death or change in left ventricular mass and death or change in a physical-health composite score but prompted more frequent interventions related to vascular access. (Funded by the National Institute of Diabetes and Digestive and Kidney Diseases and others; ClinicalTrials.gov number, NCT00264758 .).*

*Comment: There is no debate daily nocturnal dialysis is better than 2, 3, or 4 dialyses a week. It is believed no longer dialysis, but more frequent dialysis will improve outcomes.*

*Eduardo Lacson—Thank you for posting this abstract on the site. I just actually referred to this abstract in*



*a manuscript I am currently working on.*

*Eduardo Lacson—I agree based on evidence that greater dialysis frequency improves dialysis efficiency. It is in enhancement of intercompartmental transfer of these solutes into the vascular space where longer time may allow for better uremic toxin/waste removal, within the context of thrice weekly dialysis. The impact of longer dialysis treatment time will likely increase small molecule clearance to a lesser degree than larger molecule clearance.*

*Pravin Singhal—Ideally daily nocturnal dialysis will provide better outcome than three times. IN creasing to 8 hours will not serve much purpose as time passes clearance gradient goes down.*

*Dorian Schatell—A brand new study out of Turkey suggests this IS a productive area to study:*

*Nephrol Dial Transplant. 2010 Dec 9. [Epub ahead of print]*

*Comparison of 4- and 8-h dialysis sessions in thrice-weekly in-centre haemodialysis: A prospective, case-controlled study.*

*Ok E, Duman S, Asci G, Tumuklu M, Onen Sertoz O, Kayikcioglu M, Toz H, Adam SM, Yilmaz M, Tonbul HZ, Ozkahya M; On behalf of the 'Long Dialysis Study Group'.*

*Abstract*

*BACKGROUND: Longer dialysis sessions may improve outcome in haemodialysis (HD) patients. We compared the clinical and laboratory outcomes of 8- and 4-h thrice-weekly HD.*

*METHODS: 247 HD patients who agreed to participate in a thrice-weekly 8-h in-centre nocturnal HD (NHD) treatment and 247 age-, sex-, diabetes status- and HD duration-matched control cases to 4-h conventional HD (CHD) were enrolled in this prospective controlled study. Echocardiography and psychometric measurements were performed at baseline and at the 12th month. The primary outcome was 1-year overall mortality. Results. Overall mortality rates were 1.77 (NHD) and 6.23 (CHD) per 100 patient-years ( $P = 0.01$ ) during a mean  $11.3 \pm 4.7$  months of follow-up. NHD treatment was associated with a 72% risk reduction for overall mortality compared to the CHD treatment (hazard ratio = 0.28, 95% confidence interval 0.09-0.85,  $P = 0.02$ ). Hospitalization rate was lower in the NHD arm. Post-HD body weight and serum albumin levels increased in the NHD group. Use of antihypertensive medications and erythropoietin declined in the NHD group. In the NHD group, left atrium and left ventricular end-diastolic diameters decreased and left ventricular mass index regressed. Both use of phosphate binders and serum phosphate level decreased in the NHD group. Cognitive functions improved in the NHD group, and quality of life scores deteriorated in the CHD group.*

*CONCLUSIONS: Eight-hour thrice-weekly in-center NHD provides morbidity and possibly mortality benefits compared to conventional 4-h HD.*

*Eduardo Lacson—Points well taken - and you may be right. However, just like in any discussion, for every ardent believer that longer HD time leads to improved hard outcomes, there is a non-believer who will argue otherwise. Such disagreement is what constitutes equipoise - the appropriate situation when a well-designed clinical trial can advance the general state of knowledge. Please keep your comments coming.*

*Bruce Carter—Just ask any dialysis patients' advocacy group: This question has been studied \*numerous\* times since literally the 1970's. Large trials just recently published late 2010 (some cited above) - again same basic result for all types. Just my \$.02, but maybe we should stop re-confirming what we \*already\* know (more of, and more often, are better), and shift focus on which funding and regulatory mechanisms will actually \*result\* in optimal dialysis care delivery."*

**Title: Prevention of Catheter-Related Bloodstream Infections**

Author: Kevin McBryde

Votes: 15

Catheter-Related Bloodstream Infections (CRBSI) is a leading cause of morbidity and mortality in the Hemodialysis population in the US. According to the USRDS 2010 ADR, CRBSI has an incidence of nearly 130 per 1000 patient-years, and an incident hospital admission rate of approximately 100 per 1000 patient-years. The costs for hemodialysis, as a total and per person per year remain disproportionately greater than for peritoneal dialysis and transplantation. Despite KDOQI and Fistula First, the use of catheters remains stable at nearly 20% of prevalent hemodialysis patients.

Given the impact of CRBSI, industry is interested in developing catheter-lock solutions or antimicrobial-impregnated catheters. In contrast, CDC and KDOQI recommend improved vascular access care and strict adherence to aseptic technique during insertion and care of catheters. Now, clinical studies are demonstrating a nearly 40-80% reduction in CRBSI rates using CDC and KDOQI guidelines.

I think that we need to join this discussion for several reasons:

- 1) Why are simple aseptic techniques not being adopted in the community?
- 2) What endpoints do we recommend for clinical investigations, and how strictly do we believe the definitions need to be defined?
- 3) What role, if any, should a financial analysis play in the determination of the role of catheter-lock solution studies?

*Comments:*

*Stephen Ash—I agree that this is a huge problem, but there have been a number of good, randomized studies demonstrating a 70% decrease in CRBSI incidence using antibiotic or antiseptic catheter locks. However, the FDA has insisted that clinical trials use unrealistic definitions of CRBSI and has essentially blocked one catheter lock from approval in spite of excellent safety and decrease in CRBSI by stringent criteria. Other effective locks didn't make it to clinical trials in the US due to difficulty in defining the clinical trial protocol. We should look into the economic impact this has on companies trying to solve significant medical problems.*

**Title: Reducing PD Catheter Morbidity**

Author: Prabir Roy-Chaudhury

Votes: 13

Primary PD catheter morbidity compared to other types of access is extremely low. PD is also likely to result in a better quality of life with equivalent survival, at a significantly reduced cost. What is needed is more widely available expertise in PD catheter insertion and training programs to this end should be established. In addition we need to establish process of care guidelines that give equal or greater importance to peritoneal dialysis. Research into establishing these guidelines is urgently required. We also need to be able to develop PD catheters that never get infected or obstructed through the use of advanced bioactive coatings. This idea was identified as

a priority area of research by the ASN Interventional Nephrology Advisory Group and the American Society of Diagnostic and Interventional Nephrology.

**Title: Multi-center interventional trials in ESRD**

Author: Srini Beddhu

Votes: 13

We need large interventional trials in ESRD to address three important issues - cardiovascular disease (eg - beta blockers and sudden death), inflammation (eg - PPAR gamma ligands and inflammation) and malnutrition (eg - growth hormone in those with sarcopenia) in this population.

*Comments:*

*Paul Kimmel—I would add anticytokine therapies (the subject of an NIDDK conference) and consideration of the use of ACEs / ARBs as antihypertensive agents*

**Title: Inflammation from central lines or catheters**

Author: Michael Flessner

Votes: 13

Catheters are used in chronic and acute situations to gain access to the blood or a body compartment. Acute inflammation can be noted within hours of insertion of the foreign body. How does this inflammation affect tissues in the body, both locally and distant from the foreign body?

**Title: Racial Survival Disparities within Dialysis Populations**

Author: Kamyar Kalantar-Zadeh

Votes: 12

There are counterintuitive but consistent observations that African Americans maintenance dialysis patients have greater survival despite their less favorable socioeconomic status, high burden of cardiovascular risks including hypertension and diabetes, and excessively high chronic kidney disease prevalence. The fact that such individuals have a number of risk factors for lower survival and yet live longer when undergoing dialysis treatment is puzzling. Similar findings have been made among Israeli maintenance dialysis patients, in that those who are ethnically Arab have higher end-stage renal disease but exhibit greater survival than Jewish Israelis. The juxtaposition of these two situations may provide valuable insights into racial/ethnic based mechanisms of survival in chronic diseases. Survival advantages of African American dialysis patients may be explained by differences in nutritional status, inflammatory profile, dietary intake habits, body composition, bone and mineral disorders, mental health and coping status, dialysis treatment differences, and genetic differences among other factors. Prospective studies are needed to examine similar models in other countries and to investigate the potential causes of these paradoxes in these societies. Better understanding the roots of racial/ethnic survival differences may help improve outcomes in both chronic kidney disease patients and other individuals with chronic disease states.

**Title: Role of serum potassium in ESRD and CKD mortality**

Author: Csaba Kovesdy

Votes: 11

Observational studies suggest an association between hyper- and hypokalemia and mortality in ESRD and CKD. In chronic dialysis patients serum potassium is usually measured once a month, and dialysate K concentration is adjusted accordingly. This practice pattern ignores the real possibility that serum potassium could change significantly from day to day as a result of dietary changes and intercurrent illnesses, resulting in potentially harmful effects from dialysis (i.e. dialyzing hypokalemic patients with low K dialysate or hyperkalemic patients with higher K dialysate). The consequences of this are unknown. A re-evaluation of our current potassium-monitoring practices is needed. Testing of interventions to prevent hyper- and hypokalemia, and to avoid rapid fluctuations in serum K are needed.

*Comments:*

*Kevin McBryde—I think that this is a really interesting idea. There is literature demonstrating prolongation of the corrected QT interval and increased QT dispersion, particularly when dialyzing with a dialysate potassium concentration of < 2 mmol/L. This may certainly increase the risk for cardiac arrhythmias and sudden cardiac death in our ESRD patients. Perhaps the serum potassium concentration is less useful than the total body potassium concentration, given the impact of acid-base balance on serum concentrations.*

**Title: anticoagulation in ESRD patients**

Author: Sijie Zheng

Votes: 11

Many ESRD patients with atrial fibrillation are anticoagulated with Coumadin for stroke prevention. The benefit of anticoagulation in ESRD patients has not been proven, instead it may increase hemorrhagic stroke and stimulate vascular calcification. Propose a RCT to compare Coumadin vs. no Coumadin in ESRD patients with atrial fibrillation.

**Title: Sudden cardiac death in renal dialysis patients**

Author: Flora Sam

Votes: 11

Many pts on dialysis have CAD, heart failure or arrhythmias. Do automatic implantable defibrillators decrease the risk of sudden cardiac death in these patients?

*Comments:*

*Flora Sam—This has not been studied with most EP physicians reluctant to place AICD (or chronic resynchronization therapy) in patients on hemodialysis because of the presumed increased risk of endocarditis*

*Daniel Weiner—One other critical issue is loss of AV access due to wires leading to stenosis/occlusion of the subclavian vein. It may change some of the risk: benefit in dialysis patients.*

**Title: Vaccination Outcomes in ESRD**

Author: Eduardo Lacson

Votes: 11

Reports from the general population indicate improved hospitalization and/or mortality outcomes associated with influenza +/- pneumococcal vaccination. Annual flu vaccine is recommended but pneumococcal vaccine booster is only recommended at 5 years, without regard for waning titers. Because pulmonary infection is a major source of morbidity and mortality in ESRD, it may be worthwhile to do a cluster-randomized clinical trial comparing outcomes from patients who receive re-vaccination for pneumococcus based on protective titers vs. standard practice - with all patients in each arm receiving flu vaccine annually.

**Title: Safety of Erythropoietin stimulating agents (ESI)**

Author: Waqas Ahmed

Votes: 10

ESI agents have been associated with tumor progression. Since they are commonly used in patients with ESRD, but their safety in patients with either active malignancies or history of previous cancers is unknown. RCI trails are required to assess the safety.

**Title: Long-Term comparison of Standard vs. New Biocompatible solutions**

Author: Dimitrios Oreopoulos

Votes: 10

It is more than 5 years now that new Biocompatible ( neutral Ph-Low GDP ) solutions have been developed but there has not been any study to establish their long term benefit in preventing long term complications of peritoneal membrane . Suggest a large number of patients (number to be decided ) be randomized to standard vs. new solutions and be followed for 5 years . Initially and annually thereafter they should be tested with CT and peritoneal ultrasound for permit membrane thickness, D/P create and 4 hour UF, and effluent Ca125 and Il6. If the catheter is removed for whatever reason a standard peritoneal Biopsy is performed patient and technique survival will be compared between the two groups.

**Title: Mechanisms of APOL1-induced nephropathy/ESRD**

Author: Barry Freedman

Votes: 7

Although APOL1 coding variants exhibit strong association with non-diabetic forms of ESRD/CKD in African Americans, the mechanisms whereby renal impairment develops remain unknown. Hypertension treatment, including with ACE inhibitors, failed to halt progression of non-diabetic nephropathy in AASK participants. Efforts to dissect the mechanisms whereby APOL1 gene variants lead to nephropathy are urgently needed - in order to develop novel treatments to halt and prevent non-diabetic forms of nephropathy in African Americans. Existing therapies appear to be sub-optimal.

**Title: Effect of different PD solutions on patient outcomes**

Author: Rajnish Mehrotra

Votes: 5

Over the last two decades, two new PD solutions have been introduced in the United States - icodextrin and now low-GDP solutions. There is a relatively robust body of trial evidence for the benefits of icodextrin. However, the benefits - if any - of low GDP solutions are unknown. With renewed interest in PD in the United States, it is critically important to understand the effects of these new solutions on patient outcomes. Before investing resources in a RCT, undertaking well designed cohort studies (of which there are currently none) would help us better define the role for these PD solutions.

**Title: Diameter of arterial anastomosis governs successful maturation**

Author: Dirk Hentschel

Votes: 5

Large trials of autologous accesses (fistulas) in the US have been limited in their interpretative value by higher than before reported failure-to-mature rates. This contrasts sharply with the experience of dedicated centers of dialysis access excellence in England, Germany or France. A uniform finding in interviews with European experts, which in fact is mirrored by access focused surgeons in the US, is that choosing the diameter of the anastomosis matters. A randomized trial of upper arm brachial-cephalic autologous accesses randomized to 3-4mm diameter versus 6-8mm diameter anastomosis should be performed.

**Title: Forearm Wearable Artificial Kidney Breakthrough**

Author: Arnold Lande'

Votes: 5

World Conference on Portable-Wearable and Miniaturized Systems for Dialysis and Ultrafiltration" was hosted recently in Vicenza by Prof. Claudio Ronco. Many points of view were expressed over three days. Prominent, to my mind, were wearable and daily and nightly hemodialyses. Either 168 hours/week wearable or 48 hours/week nightly would supply vastly greater time on dialysis. Unobtrusive, under the sleeve forearm wearable, might offer even greater mobility and cost savings (nursing and real estate as well as only two disposables/week). Based on accessing A/V pressure and flow via InSitu Debranched Vein Fistula Graft (VFG). Alternating transcutaneous pressure over isolated vein results in arterial pressure upstream and venous pressure downstream. Eliminates most, if not all, electrical pumps and so encourages high degree of miniaturization. Modulation of extracorporeal blood flow to 20-40 ml/min permits full anticoagulation through the device, resulting in no more than prophylactic anticoagulation of the ambulatory patient. 2,4,8 hour sorbent cartridges or other technologies. Numerous other applications to artificial pancreas, liver, congestive heart failure, phereses. Interesting choice between (1) early resorts to un-intimidating wearable (2) Still restrictive daily or nightly or (3) Transplantation? Author is Arnold J. Lande

**Title: The next barrier - successful dialysis access needle insertion**

Author: Dirk Hentschel

Votes: 4

In dialysis access care centers with access coordinators, dedicated interventional nephrologists/radiologists, and available surgeons time to access creation and maturation by KDOQI guidelines (>6mm, >600ml/min, <6mm depth, though often after 6weeks) can increasingly be achieved. However, competence of needle insertion into new accesses is very variable among different dialysis units as well as among different staff at the same unit. Economic pressures are often mentioned as one obstacle; however, the magnitude of the problem is completely unknown.

Studies need to be performed that a) document the true frequency of access infiltrations (minor and major), b) test the success of staff training models, c) compare button hole with conventional needle insertion technique, d) compare novel button hole device aids in certain populations. The large dialysis providers in the US should participate in this effort (financially).

**Title: Hemodialysis Vascular Access**

Author: Jamie Ross

Votes: 4

Genetic and biologic markers of successful fistula development

**Title: Should LDOs become ACOs for ESRD care?**

Author: Manjula Kurella Tamura

Votes: 4

What are the implications for costs, quality and access to care if large dialysis organizations become Accountable Care Organizations for ESRD patients?

*Comments:*

*Daniel Weiner—Very interesting idea, particularly given the role of nephrologists in all facets of care for dialysis patients. Wonder about the already existing forces leading to increased consolidation of the industry with a limited number of LDOs and the effects on SDOs and MDOs.*

*Stephen Fadem—*

- 1. Would it lead to decreased emphasis on transplant?*
- 2. What are the other choices? Hospitals, health plans, IPAs, etc.*
- 3. LDOs are centrally managed from other countries and states. Will remoteness of authority compromised care at the local level?*
- 4. Will it set up a conflict between the physician advocating for the patient and the corporate manager advocating for the stockholder?*

**Title: Patient engagement in ESRD self-management tasks**

Author: Dorian Schatell

Votes: 3

To do well over the long-term with chronic kidney failure, patients need to take an active role in their care, which includes:

- Choosing a treatment modality
  - Obtaining a PD catheter and/or vascular access
  - Following a complex treatment regimen
  - For those who are suited, learning to self-cannulate and self-dialyze in-center or at home
- These tasks require both education AND motivation--merely providing patients with facts is necessary but not sufficient (as we have seen for many years) to change behavior and facilitate intrinsic motivation. Study of decision-making, motivation, and educational techniques that are effective in stimulating active patient engagement could help transform ESRD care.

**Title: Effect of low sodium and low phosphate diet on outcomes in ESRD**

Author: John Daugirdas

Votes: 3

Data by Ozkahya et al (NDT 1988) suggested that sodium restriction and volume control could markedly reduce left ventricular mass index (LVMI). Ayus et al. (JASN 2005) found that LVMI reduction with daily dialysis correlated with better control of serum phosphate (P). Guida et al found that serum P could be reduced in 3/week patients using a low P, whey-substituted diet. The ability to maintain a low sodium (e.g., ~1.0 g/day) or low P (~0.6 g/day) diet in ESRD patients, or the effect of such diets on either surrogate outcomes (e.g. LVMI) or hard outcomes (survival, hospitalizations) has not been examined in a randomized trial. Proposed is a study, with patients randomized to either low Na / normal Na, and low P / normal P diets using a 2 x 2 factorial design in 3/week hemodialysis patients; a pilot study to look at feasibility with a main surrogate outcome of LVMI (200 patients), and a hard outcomes study (2000 patients) to look at mortality and hospitalizations.

**Title: Uremia: What are we treating? Does size of molecules matter?**

Author: Mark Unruh

Votes: 3

Three types of uremic retention solutes have been described using a classification based on characteristics that influence their dialysis clearance: small water-soluble compounds, protein-bound compounds, and middle-molecules. Small water-soluble compounds are easily removed by diffusion and have an upper molecular weight of 500 D. Protein-bound solutes are hydrophobic compounds that bind to proteins, most commonly albumin. Middle molecules have a molecular weight higher than 500 D and the classic middle molecule has been beta2-microglobulin and  $\beta$ 2M was the middle molecule marker used in the HEMO Study. Substances with lower molecular masses may behave as MM's because of steric configurations, electric charge, hydrophobicity, or binding to plasma proteins. The recently completed FHN study did not directly address what solute is critical to improving outcomes since volume, phosphate, and small molecule clearance would be improved by daily dialysis. What are we treating with dialysis? What should be the targets of therapy or the marker of adequate dialysis? If we are going to have artificial kidneys, what should these kidneys remove? Does middle molecule clearance matter? It seems to me that a great deal of work is done by the EuTox group in describing more and more potential toxins, but there is little clarity on what we are treating with dialysis.



*Comments:*

*Tom Hostetter—More attention to molecules that are dialyzed differently from urea is important. In a sense we keep doing the same thing - removing urea and its analogues- and expecting different outcomes. I'd suggest 3 non urea attributes: large > 1000 kD, protein bound and intracellularly sequestered. Middle molecule is a now loose term that has lost its original meaning 350 - 2000. Such studies require several things: assays, description of dialysis/ filtration and outcomes. The last should focus on quantifiable outcomes but not necessarily mortality. Outcomes such as neurologic, strength, and nutrition.*

**Title: Tunneled catheters - flow induced injury?**

Author: Dirk Hentschel

Votes: 2

Shear stress can elicit profound cellular responses in a variety of tissues. In dialysis access the focus has mostly been on endothelial cells. However, white blood cells are likely to be equally affected.

Increased mortality observed with dialysis using tunneled hemodialysis catheters may in part be due to shear stress induced cytokine release from white blood cells: 350ml/min blood flow/min through a 15 French tunneled hemodialysis catheter (assuming 2.5mm diameter for each lumen) has similar motion of blood over a fixed surface as blood flow of ~3500ml/min through a 6mm graft and >8000ml/min through an 8mm fistula. Thus, a) detailed studies of inflammatory markers and white blood cell function before, during and after dialysis are needed. Based on these findings b) intervention trials of at least two kinds in patients with dialysis catheters could be formulated: 1) Does pre-dialysis blunting of inflammatory response with medication improve m&m in long-term tunneled catheter dialysis patients, and 2) Is in fact dialysis with lower catheter flow rates 200 vs. 400ml/min better, albeit with increase of dialysis time.

**Title: Quality of Life**

Author: Stephen Fadem

Votes: 2

The Rand KDQOL-SF currently used in dialysis units is onerous to use. It comprises 78 questions, is difficult to administer and to take. Furthermore, there seems to be differences in what populations gauge as quality of life changes and what patients actually report in clinical settings. Herein lays an opportunity to update and modify patient reporting and quality of life metrics.

*Comments:*

*Dorian Schatell—The Medicare clinical performance measure requires use of the KDQOL-36--not the KDQOL-SF. It's just 36 items, and the first 12 are the SF-12, the results of which predict hospitalization and death in people on dialysis. That's the QOL metric that is being routinely collected in the renal community.*

*Stephen Fadem—The KDQOL-36 is fabulous for dialysis patients, but does not cross talk to CKD pre*

*dialysis. Thus, it is hard to use when validating the usefulness of CKD education. For CKD we must use the older KDQOL-SF, and would need to use it in dialysis as well for valid comparisons. I really think that we need a test for CKD comparable to what is being used for dialysis patients.*

**Title: pre-probiotics in uremia**

Author: Deepak Sharma

Votes: 2

pre-probiotics hold a promising role in the management of uremia by potentially bringing down the uremic toxins by supposedly enhancing their catabolism. It will be a great idea to hold a large scale RCT for the same.

**Title: The implantable bioartificial kidney**

Author: Chi-yuan Hsu

Votes: 2

I think that an objective if achieved “would be worthy of a Nobel Prize in nephrology” (the challenge as specified in the solicitation by NIDDK/KUH) is the creation of a functional implantable bio-artificial kidney.

The current most workable model mimics nephronal function by combining stacks of synthetic hemofilter membranes with renal tubule cell bioreactors within a compact biocompatible cartridge. Blood will be filtered under circulatory system pressure to remove uremic toxins, salts, small solutes, and water. The resulting ultrafiltrate will be processed by the bioreactors to selectively transport most of the salts, and water back into the blood, thereby maintaining volume homeostasis and electrolyte balance. The cells will also perform some of the metabolic and endocrinal functions such as excretion of ammonia and enhanced glutathione metabolism and Vitamin D production.

*Comments:*

*Michael Goligorsky—I've spent quite a lot of time attempting to make this two-cartridge bioartificial system work in 1986-8, long before the first publications from Ann Arbor. The problem is the uncertainty whether the integrity of monolayers has been achieved, which is never the case.*

*John Daugirdas—Perhaps initially a staged approach might be wise, with stage 1 being demonstration of ability to maintain blood flow through an completely implanted (nonfunctioning) device for a protracted period (e.g. at least 3 months).*

**Title: Moving from a KDOQI-mature access to successful needle insertion**

Author: Jack Work

Votes: 1

With specialized services more available a larger number of “marginal” accesses come to use in dialysis units, although access flows may be >1000ml/min, depth <6mm, etc. There are varying skill sets among HD unit nurses and technologists in dialysis units and there is no non-patient

training in needle insertion available. Access examination skills that would enhance needle insertion success are rarely taught. The true morbidity of poor needle insertion technique is unknown. Initiatives to develop training modules and guidelines for cannulation using computer simulations or state of the art models are needed.

**Title: Use of nutraceuticals in ESRD**

Author: Ray Chow

Votes: 1

There is promising evidence of the benefits of nutraceuticals in ESRD. What collaborative mechanisms are there to continue building the scientific evidence? Will nutraceuticals use ever have the credibility to be used in ESRD on a routine basis?

**Title: Risk factors for delayed translation of EBM care for CKD**

Author: Bill McClellan

Votes: 1

Are there modifiable risk factors associated with facility-to-facility variations in care of ESRD patients?

*Comments:*

*Mark Unruh—Bill, i agree with you.... looking at the source of variability in practice in both CKD and ESRD (and access to kidney transplantation) is important. I guess i thought of this from a different direction. could we use these units of care in testing whether the guidelines are beneficial?*

**Title: clinical trials for the WAK**

Author: Victor Gura

Votes: 0

Our WAK has completed bench, animal and 2 feasibility human trials. As we prepare for further clinical human trials all suggestions and ideas for the design of those trials are welcome

*Comments:*

*Bruce Carter—Perhaps a "bedside" unit based on otherwise identical technology could be used as an additional comparison for such trials. This would help distinguish which outcomes or complications arise solely from the "wearing" of a portable device (distinct from dialyzing this way). An additional benefit of this approach is that such technologies could have potential to improve HD technology more generally, reducing consumables and costs, at home or in-center. Still, the reduced water requirements of the UCLA prototypes are quite remarkable, perhaps \*finally\* making a wearable HD device attainable after so many failed attempts have led to a "not in my lifetime" discouragement.*

**Title: Process of Care Guidelines for Ultrasound in Dialysis Vasculature**

Author: Prabir Roy-Chaudhury

Votes: 0

Ultrasound examination (US) is helpful in the pre-surgery phase to evaluate venous and arterial vasculature for diameter, flow and calcifications. Post-creation of the access, US can determine flows as well as collateral veins, determine depth and stenoses and potentially help in the identification of a mature AVF. Finally US could help in early cannulation thus reducing the duration of catheter dependency. This idea was identified as a priority area of research by the ASN Interventional Nephrology Advisory Group and the American Society of Diagnostic and Interventional Nephrology.

**Title: Process of Care Guidelines for Dialysis Vascular Access**

Author: Prabir Roy-Chaudhury

Votes: 0

This addresses the issue of choosing the “right” access for the “right” patient at the “right” time; i.e. a patient with advanced cancer might benefit from a tunneled catheter rather than an autologous access, while a young patient with primary GN without peripheral vascular disease should almost always have an attempt at a forearm autologous access. These process of care guidelines also need to identify and then break down the barriers that currently result in only 18% of incident hemodialysis patients beginning dialysis with a functional AVF. Specific topics that could be studied include: (a) referral patterns (b) mandated interventions at specific GFR cutoffs (c) role of monitoring (physical exam) and surveillance (d) appropriate training of personnel especially cannulators (e) randomized trial of secondary fistula after forearm PTFE graft versus immediate upper arm fistula (brachial-cephalic or transposed) with long term follow up (f) access creation in patients in need of cardiac rhythm devices or cardiac rhythm devices in patient with existing accesses. This idea was identified as a priority area of research by the ASN Interventional Nephrology Advisory Group and the American Society of Diagnostic and Interventional Nephrology.

**Title: Establishing Process of Care Guidelines for the Creation and Mai**

Author: Prabir Roy-Chaudhury

Votes: 0

This addresses the issue of choosing the “right” access for the “right” patient at the “right” time; i.e. a patient with advanced cancer might benefit from a tunneled catheter rather than an autologous access, while a young patient with primary GN without peripheral vascular disease should almost always have an attempt at a forearm autologous access. This process of care guidelines also need to identify and then break down the barriers that currently result in only 18% of incident hemodialysis patients beginning dialysis with a functional AVF. Specific topics that could be studied include: (a) referral patterns (b) mandated interventions at specific GFR cutoffs (c) role of monitoring (physical exam) and surveillance (d) appropriate training of personnel especially cannulators (e) randomized trial of secondary fistula after forearm PTFE graft versus immediate upper arm fistula (brachial-cephalic or transposed) with long term follow up (f) access creation in patients in need of cardiac rhythm devices or cardiac rhythm devices in patient with existing accesses. This idea was identified as a priority area of research by the ASN Interventional Nephrology Advisory Group and the American Society of Diagnostic and Interventional Nephrology.

**Title: When all else fails...**

Author: Dirk Hentschel

Votes: 0

With growth of the dialysis population in general as well as improvement of medical care leading to longer survival of dialysis patients a larger number of patients may exhaust all usually used access options. For these individuals the following topics are of relevance: (a) lower extremity autogenous accesses, (b) bioengineered accesses, (c) (at least) observational collection of outcomes of rare types of prosthetic/biograft accesses (e.g. venous anastomosis in right atrium, tunneled from circulation above to below heart or vice versa, etc.) (d) studies of access creation in the setting of ipsi-lateral central vein occlusion. This idea was identified as a priority area of research by the ASN Interventional Nephrology Advisory Group and the American Society of Interventional Nephrology.

**Title: Long-term study of dialysis access outcomes**

Author: Dirk Hentschel

Votes: 0

Establishment of registries using a public-private partnership model are needed for long-term outcome comparison of different types of accesses (upper arm versus forearm), in particular with regard to development of aneurysms. Outcomes of interventions such as angioplasty, stent/stent graft insertion, surgical patch angioplasty or interposition grafts with regard to i) site of treatment and ii) access survival need to be studied, as some treatments are associated with simple transfer of recurrent stenosis to up-stream location, potentially jeopardizing alternate access options. This idea was identified as a priority area of research by the ASN Interventional Nephrology Advisory Group and the American Society of Interventional Nephrology.

**Title: Improving endovascular and surgical procedures**

Author: Jack Work

Votes: 0

Endovascular and surgical procedures are repeatedly performed on patients with dialysis access stenosis. Yet we have no idea about: (a) are we doing too many angioplasties (b) are we not doing enough angioplasties (c) how many angioplasties is too many (d) whether it is possible to deliver anti-stenotic therapies at the time of angioplasty (e) what the true complication rate is post angioplasty (particularly for thrombectomies where there is a risk of potential embolization towards hand (arterial) and lung (venous) (f) how this potential embolization contributes to pulmonary hypertension, hypoxia, and hand ischemia.(g) randomized controlled comparison of surgical and endovascular treatments for common access complications such as juxta-anastomotic stenoses and basilic swing point stenoses.

**Title: Genetic Polymorphisms in Dialysis Access Stenosis**

Author: Jack Work

Votes: 0

Genetic polymorphisms that affect the occurrence of dialysis access stenoses offer the potential for triaging patients to more suitable access options, as well as initiating targeted pharmacological treatment.

**Title: Tunneled Dialysis Catheter coatings to prevent infection and thr**

Author: Anil Agarwal

Votes: 0

Tunneled dialysis catheters allow for immediate vascular access but are by far the worst form of dialysis vascular access due to a triad of complications (infection, thrombosis and central venous stenosis). Imagine, however, a world in which a catheter could be internalized and also coated with an anti-infective, anti-thrombotic, anti-stenotic substance!! This could result in a complete paradigm shift in that catheters could now potentially become the preferred mode of dialysis vascular access!! Urgent investigation into these possibilities is needed. This idea was identified as a priority area of research by the ASN Interventional Nephrology Advisory Group and the American Society of Interventional Nephrology.

**Title: PTFE**

Author: Anil Agarwal

Votes: 0

Although PTFE grafts allow for patients to be dialysed within 4-6 weeks post placement they have a dismal primary patency rate (23% at 1 year); primarily as a result of an aggressive venous segment stenosis due to venous neointimal hyperplasia. Potential areas of investigation could include (a) pathogenesis of venous neointimal hyperplasia – why does it develop and how can we intervene? (b) treatment of existing venous anastomotic stenosis – can we improve angioplasty and stent outcomes? c) how can we prevent in graft stenosis (d) novel local and systemic therapies (e) can we use the graft as a conduit for drug or cell delivery? This idea was identified as a priority area of research by the ASN Interventional Nephrology Advisory Group and the American Society of Interventional Nephrology.

**Title: AVF Maturation**

Author: Anil Agarwal

Votes: 0

1. Arteriovenous Fistula (AVF) Maturation

Although AVFs are the preferred form of dialysis vascular access, over 60% of surgically created AVFs are not suitable for dialysis between 4-5 months post-surgery; often resulting in prolonged catheter dependency. Observational and randomized studies which could focus on one or all of the following are desperately needed: (a) pre-surgery arterial and venous vascular evaluation (b) surgical technique including experience of operator (c) physical and pharmacological therapy at different temporal periods following creation, (d) endovascular and surgical intervention for the non-maturing access (e) evaluation of novel local therapeutic interventions to enhance AVF maturation (cells, drugs, chemicals, genes and devices) (f) optimization of upstream hemodynamics (g) advances in cannulation technologies (h) process of care interventions focused on logistics and communication. This idea was identified as a priority

area of research by the ASN Interventional Nephrology Advisory Group and the American Society of Interventional Nephrology.

**Title: Effectiveness of Percutaneous Transluminal Angioplasty**

Author: Jack Work

Votes: 0

PTA is the treatment of choice for a hemodynamically significant access stenosis, however, the primary patency post PTA is only 55% at 6 months for elective angioplasty and 30% at 6 months for angioplasty after thrombectomy. Studies have shown that angiographic response is not predictive of outcome.

Studies are needed to: better define hemodynamic significance; identify intra-procedural measurements that will predict outcomes (pressure, flow), identify methods to improve outcomes (local anti-inflammatory drug delivery vs systemic), utilize intra-procedural imaging (IVUS or OCT) correlation with outcome.

**Title: The study of the pathogenesis of arteriovenous fistula failure**

Author: Karl Nath

Votes: 0

The AVF is the preferred hemodialysis vascular access. However, approximately 50% AVFs fail to mature, and with time, functional AVFs cease to do so. Such access dysfunction is a critical contributor to morbidity of patients on hemodialysis. By understanding the pathogenesis of AVF failure, new therapeutic strategies may be devised that may either promote maturation or prevent failure

**Title: Perioperative optimisation of CKD patients**

Author: Andrew Ferguson

Votes: 0

CKD is associated with major cardiovascular alterations, nutritional impairment, and functional decline. A very significant number of ESRD/CKD patients undergo major surgery, and are at increased risk of postoperative complications. Perioperative haemodynamic optimization protocols have been beneficial in some patient settings but often exclude these patients. We need to understand whether a protocol of functional assessment, haemodynamic optimization, and attention to microvascular perfusion can improve outcomes in this population.

**Title: Cost Effective HD reimbursement**

Author: Steve Shen

Votes: 0

Many ESRD patients signed off HD before full length Rx prescribed by their doctors, many patients are willing and could benefitted from more frequent, but shorter HD sessions. By changing HD reimbursement based on actual hours of RX, not number of HD, CMS can save

money from those poor compliant patients while providing better HD to other willing patients without higher cost.

**Title: Atrial Fibrillation in Elderly HD patients**

Author: Zvi Barnea

Votes: 0

A big trial whether we should treat them or not should be started

**Title: Hemodiafiltration with no replacement fluids or special machines**

Author: Noshi Ishak

Votes: 0

Since we started using the hollow fiber dialyzer more than 3 decades ago the only change we had was in the membrane quality. A change in the dialyzer design will allow the separation of the plasma ultrafiltrate from other blood components in one compartment then dialyze each component separately in the second compartment. This will result in marked increase in the convective forces that cannot be achieved by regular dialysis but only by some form of hemodiafiltration. No special replacement fluid is required and no change in the dialysis machine or procedure is required. All what is needed is pure water.

**Title: Technology for self-care dialysis**

Author: William Fissell

Votes: 0

I think it would be very exciting if NIDDK invested in technology development to facilitate self-care dialysis, perhaps through participation in BRP.

NIDDK could significantly derisk the effort to bring new technology to market for home hemo. This would encourage all sectors - academia, inventors, entrepreneurs, practitioners, and, most importantly, industry, to find ways of implementing home care.



## Glomerulosclerosis/Inflammation

Postings and Comments

### **Title: Integrated systems biology to define renal disease**

Author: Matthias Kretzler

Votes: 127

To take advantage of the rapidly emerging approaches in genomic medicine to define disease on the molecular level, cohorts of patients with large-scale molecular and clinical data sets on the same individual are the rate-limiting step. Establishing these cohorts requires a long-term effort, but renal disease offers a unique advantage compared to other chronic diseases as we have access to the primary disease mechanism in humans via renal biopsy and urine derived biofluids. Technologies are emerging to obtain comprehensive genome wide information spanning genotype, tissue compartment specific epigenetic, transcriptional, proteomic and metabolomic datasets from blood, urine and renal tissue. Matching this information with in vivo imaging, digital histopathology and prospective clinical disease course including drug and environmental exposures can aid to define underlying molecular events of phenotypic measures. Systems biology approaches can be employed across the entire genotype – phenotype continuum to redefine renal diseases on the molecular level and identify the key regulatory hubs most amenable to therapeutic manipulations. These data sets will be a reference base to test novel hypotheses and model systems for human disease relevance.

#### *Comments:*

*Patrick Brophy—Development of centers of excellence is paramount for the collection, study and translational aspects of these diseases (like aHUS and DDD). There is so much to be done- collaborative approaches are the only way we will make headway with these types of diseases.*

*Martin Pollak—Agree, but would emphasize the importance of intelligent analysis of these large datasets over their collection!*

*Karol Bomsztyk—These are all important ideas. But I would like to add that there is a great need to advance biotechnologies and computational tools (software, bioinformatics, mathematical modeling and visualization) to interrogate pathways associated with renal disease. Greater efforts are needed to foster collaborations between computer scientists, mathematicians, physicists, engineers and renal investigators. In that regards, grant opportunities between different NIH institutes would be one way to stimulate innovative multidisciplinary teams to address enormous challenges of progressive renal disease.*

*H. William Schnaper—Matthias and Pat, please see my related suggestion, just uploaded, about a specific area for application, regarding phenotyping cells and tissue (in the Other section). I think this approach could be very helpful for relating hypothesis-based studies and results from newer, "unsupervised approaches to understanding disease pathogenesis and treatment, and not just for glomerular disease.*

*Charles Alpers—I really want to support this concept, and believe the ideas expressed by Patrick and Matthias are very important to achieving success. I believe the ASN, and other kidney organizations, can be and should be enlisted to partner with the NIH to foster development of an infrastructure for studies of all types of Glomerular Disease (GD). This infrastructure will need to be multi-institutional in order to*

*enroll sufficient patients that clinical studies and even interventional trials taking advantage of this patient base can have robust numbers of cases.*

*Patrick Nachman—I think the collaborative multicenter/national networks should not be limited to the "rare forms" of GN, but be inclusive of all GN, as progress in understanding and managing even the "major" forms of GN has been hampered by the relative small number of patients at any one site.*

*Matthias Kretzler—Strongly support the concept, we have to transition as a community to consider each patient seen a study patient, otherwise this will remain the rate limiting step for T1 in renal disease. Costs might not be as prohibitive as envisioned, as core infrastructure elements should most likely be genuine for all research networks and could be shared between projects.*

*Matthias Kretzler—Certainly, analysis tools are effectively employed in model systems and are currently scaled up to mammals in the 'big disease categories'. They should be transferable to renal disease if we establish cohorts and train our next generation in these approaches.*

*Pierre Ronco—I fully agree with the approach described. Recent findings in glomerular disease suggest that GWAS studies can also provide very important information in small cohorts of well phenotyped patients. Pangenomic studies are nice adjuncts to integrative biology performed on tissues,*

*Michael Braun—The development of treatment protocols, and studies in pathogenesis of rare forms of GN are hampered by a lack of sufficient power. These diseases can get lost because of "lack of impact" in terms of overall public health. Programmatic structures to foster collaborative multicenter or national networks is needed.*

**Title: Identify components of podocyte - endothelial feedback loop**

Author: Sumant Chugh

Vote: 85

Development of nephrotic syndrome involves derangement of feedback loops between podocytes and endothelial cells. Podocyte secreted components (migrate against the flow) of this loop are likely to be large in size, and either abundant and neutral, or not so abundant, but charged. Endothelial secreted components (migrate with the flow) are likely to be neutral cleaved peptides or small molecules.

*Comments:*

*Daniel Battle—This is a good area of research and the cross talk between podocytes and endothelial sites remains to be understood.*

*Kevin McCarthy—This is an area that really needs to be explored in more detail. The studies by Dale Abrahamson's laboratory back in the 1980's suggests that one mechanism of GBM renewal comes about by "splicing" new GBM made by podocytes into existing GBM. The actual mechanism by which "splicing" is accomplished is still uncertain. However, one can envision if "splicing" a packet of basement membrane material into the existing GBM occurs, then any growth factors/cytokines/etc. that were co-packaged with that material might be placed into position close to the endothelial side of the GBM.*

*Pravin Singhal—Dysregulation of podocyte and endothelial feedback loop seems to be a critical event for the development of collapsing form of glomerulopathy in general and HIV-associated nephropathy in particular. These entities provide morphological support for the devastating effects on the maintenance of capillary phenotype when associated with dysregulated podocyte growth. However, at present we have only morphological support, it will important to have understanding of the involved mechanism and subsequent development of therapeutic strategies.*

*Pierre Ronco—One important aspect of this cross-talk may reside in the different glycocalyx coating endothelial and epithelial cells. Very little is known in this field. A multidisciplinary approach with biochemists, physicists, spec massists, physiologists and immunologists should be encouraged to solve this important issue.*

*Sumant Chugh—I agree with Pierre. The glycocalyx of the glomerular endothelial cell likely contributes several cleaved peptides that migrate with the flow and affect baseline podocyte and GBM function.*

### **Title: What Triggers the Development of Autoantibodies Responsible For?**

Author: D S

Votes: 64

Anti-GBM, ANCA/LAMP-2, anti-PLA2R and IgG antibodies to aberrantly glycosylated IgA1 are now well established autoantibodies in Goodpasture disease, ANCA-associated vasculitis, membranous nephropathy and IgAN, respectively. However, the primary events that trigger loss of tolerance to their respective autoantigens remain a mystery. Each of these is a potentially tractable project with cooperation between immunochemists, basic immunologists with the appropriate skills and nephroscintists.

#### *Comments:*

*Scott Wenderfer—Very important and successes in one area will feed progress in others. Renal parenchymal involvement is likely important at early and late stages of these diseases, and there remains a lot to be learned about the role of endothelial cells, epithelial cells, and mesangial cells in immunity/autoimmunity.*

*Ronald Falk—Defining immunopathogenesis in addition to pathogenesis in humans is one of the great unmet areas in medicine. Answering the question of what triggers an autoimmune response in the first place and what actually causes disease in the first place is a critical issue. These studies must be done in humans with human material for us to gain real insights. Animal models are important tools to refine and test what is learned in human biology. But human translational studies are imperative.*

*Warren Bolton—Certainly a critical area to investigate and understand to design better diagnostic tools, discovers biomarkers, and fashion disease specific interventions.*

*Bogdan Borza—I couldn't agree more. I would add that refined mouse models of anti-GBM, ANCA GN, MN and IgAN would be immensely helpful to address the proximal determinants of autoimmunity in these antibody-mediated glomerulonephritides. A powerful tool would be transgenic mice expressing the respective human autoantigens and/or disease-associated HLA alleles.*

*Pierre Ronco—The issue of the triggering event in autoimmunity is key to understanding the pathogenesis and designing innovative immunointervention. Antigen mimicry, antigen spreading, dysregulation of tolerance mediated by Treg and Breg, and the role of environmental factors should be extensively investigated. I agree with David that this would require a multidisciplinary approach including biochemists, basic immunologists, cell biologists, crystallographers.....The information obtained in a particular disease could be extremely helpful for the understanding of other diseases of autoimmunity.*

**Title: Epigenetic factors in acquired glomerular disease**

Author: Frederick Kaskel

Votes: 49

Identify role of environmental exposures, i.e., viruses, toxins, and effect on dysregulation of the epigenome in the development of glomerular diseases without genetic mutations. Characterize an individual's genetic propensity for adverse epigenomic changes.

*Comments:*

*Rama Natarajan—It is clearly worth examining the role of epigenetic factors in CKDs especially in patients who develop CKDs like diabetic nephropathy even when they have reasonable glycemic control. This can tell us why genetic mutations do not always correspond to disease phenotype. Epigenetics can provide a key molecular link between genes and the environment*

*Karol Bomsztyk—Epigenetics of disease is an emerging field with potential to provide powerful tools to diagnose (biomarkers) prevent and treat disease. Most progress in this area has been made in cancer where biomarkers are proving to be clinically useful and already epigenetic therapy is used to treat lymphomas. Although the use of epigenetic therapy to treat disease has just merely began and it has already provided the proof-of-concept for its application. Thus, combined application of genetics and epigenetics will undoubtedly be important in personalized medicine.*

**Title: What is the molecular clock that orchestrates podocyte development**

Author: D S

Votes: 33

Podocyte plasticity is a feature of proteinuric glomerular diseases—sometimes reversible other times not. This may represent a reversal of the podocyte developmental process elegantly described by Reeves, Caulfield and Farquhar in 1978. The sequence of changes in morphology and protein expression that the developing podocyte manifests as it evolves from a simple cuboidal cell with a subapical tight junction to a highly differentiated arborizing cell with slit diaphragm are now well established; however the molecular clock, genes and transcription factors that orchestrate this process have not been studied. This, in my opinion, is the next frontier in podocyte cell biology.

*Comments:*

*Greg Dressler—I think the intricate patterning of foot processes must depend on both chemoattraction and chemorepulsion mechanisms, very much like axon guidance, which also depends on matrix interactions. What are the molecules and how might they be disturbed in effacement. Also, how dynamic are the foot processes in an adult podocytes?*

*Jeffrey Miner—Well put. I will add that the factors regulating the developmental transitions in glomerular basement membrane laminin and collagen IV isoform synthesis must be identified, and perhaps they overlap with those that regulate synthesis slit diaphragm components.*

*Pierre Ronco—This is a very interesting topic. I agree with Jeffrey that the changing composition of the GBM during embryogenesis may play a key role in podocyte differentiation and slit diaphragm biogenesis.*

*Pravin Singhal—It may also be important to look into podocyte maturation and associated GBM matrix components in disease model which take place genetically or phenotypically during embryogenesis and compare them with normal development of podocyte and GBM during the same time frame.*

**Title: Glomerular diseases**

Author: Howard Trachtman

Votes: 30

It is important for people interested in clinical trials for glomerular disease to support collaborative efforts that will facilitate the performance of multicenter studies. This can begin with creation of a national registry of all cases of glomerular disease including pediatric and adult patients who have biopsy confirmation of their diagnosis. This would help establish a bench mark for the number of cases and allow efforts to begin regarding phenotyping and genotyping glomerular disease.

*Comments:*

*Daniel Cattran—This is precisely what the glomerular disease advisory group of ASN would like to do in the order suggested. The template for this process has created and successfully implemented in at least three centers in North America and Europe. Support that would integrating these as well as other interested centers with the other major ideas (# 76 ) would immediately create a synergy between the clinical, epidemiological and "omics" domains. This is doable now with adequate support.*

*David Charney—I agree wholeheartedly with this. In fact, I tried to establish this 20 years ago when I was still in academic medicine. NIH told me they had no mechanism to fund such a registry, and there was little interest at academic centers that I contacted. However, the literature remains poor, and gives no real guidance to the treatment of patients. Our model should be the collaborative oncology groups, where there are ongoing studies in any number of disease processes, and when a patient presents the protocol can be offered. The concept I proposed was to initially work through the renal pathologists (being more centralized than the nephrologists) to establish the registry. A uniform data sheet would replace the myriad types of clinical information sheets given to the individual pathologists, to facilitate clinical data gathering. Representative slides and photomicrographs would be submitted for retrospective analysis when needed. The second, clinical research phase would have a central committee evaluating the study design, with the ability to tailor the study and consent forms to any local IRB*

*necessary, allowing the local investigators to get on board with a minimum of work load. This would hopefully allow clinical nephrologists interested in participating to do so without a large drain of time, and would therefore increase the number of patients entered into the studies. Study generation would preserve the publication need for the academic nephrologist by having the nephrologist submitting the study be the principal investigator, but ONLY at the price of then having that academic center supporting all other ongoing studies generated by the group.*

*THEN, perhaps, we would finally know how to treat a glomerular disease, something that remains as elusive now as it did in the days of my renal fellowship so many years ago.*

*My goodness, if cardiologists can recruit thousands of their patients for clinical trials, why can't nephrologists?*

*Jeremy Duffield—I totally agree that this is a great idea. Nephrology has suffered from inability to study larger numbers of patients in a meaningful way so a centrally co-ordinated database would be a major step forward.*

### **Title: Biomarkers of Renal Pathology**

Author: Brad Rovin

Votes: 15

A focus in proteomics has been to classify types of glomerular disease through urine biomarkers. The idea is that we could use the urine to distinguish between proteinuric GNs, for example. I would like to push this further, and use urine proteomics to define specific pathologic lesions of importance to treatment. For example, glomerular and interstitial inflammation would require a different clinical action than interstitial fibrosis. Once a disease is diagnosed (with a biopsy), these types of biomarkers could be used to follow how treatment was affecting specific pathologic lesions. For diseases that flare, these could be used to decide on additional therapies without repeat biopsies.

#### *Comments:*

*Daniel Cattran—Need to attach to ongoing biomarker since tissue single use (usually) What about a clue from tissue and identify resultant in urine or blood.*

*Charles Alpers—I think the validation of urinary biomarkers- clearly of great potential clinical utility- will require protocol biopsies to establish they indeed are surrogate measures of pathology and not just renal function. This will be difficult to achieve in practice.*

*Daniel Batlle—Yes, it is very important to develop biomarkers that predict renal pathology and particularly to distinguish glomerular from tubular interstitial injury.*

*Matthias Kretzler—Having both tissue and urine biomarkers at the same time point should help to define where urine is reflective of intra-renal pathology and where not. Including several diseases should allow compensating for disease stage specific events versus disease specific events. The renal protocol biopsy issue will need a careful discussion; the information gained using state of the art tools can be considerable.*

**Title: Glomerular biomarkers based on podocyte products**

Author: Roger Wiggins

Votes: 10

Podocyte injury and depletion drive glomerulosclerosis and progression in glomerular diseases. The podocyte is on the urinary space side of the GBM so that urine is the logical place to look for markers of podocyte injury and the urine pellet is well known to contain valuable information. Several investigators have demonstrated that podocytes and their products can be detected in urine and are altered in a major way in association with progression in model systems and in man. Development and validation of biomarkers is a complex process that NIDDK has experience with for AKI. It is time to bring together groups working on glomerular disease urine biomarkers and define how they should be evaluated and validated in the clinic. We can thereby accelerate introduction of potentially game-changing technology to our clinics that can reduce the costs/morbidity of ESRD.

**Title: Regulatory B cells in Glomerular Diseases**

Author: Kenar Jhaveri

Votes: 9

Regulatory B cells exist and they have been noted in mice studies to retard lupus and other autoimmune diseases. Human Regulatory B cells have not been studied in Glomerular Diseases or any disease. Perhaps the role of these B regs might be helpful in future targeted therapies in these conditions

*Comments:*

*Pierre Ronco—The role of B cells is increasingly recognized in fully tolerant grafted patients who have interrupted IS therapy. Similarly, search for Breg cells should be performed in glomerular diseases including ANCA vasculitis and anti-GBM disease because they could be targets of therapy.*

**Title: Development of Targeted Delivery of Immunotoxins For the Treat**

Author: Lauren Brasile

Votes: 5

Systemic administration of immunosuppressive agents, such as MMF and steroid, for the treatment of autoimmune diseases of the kidney represents the state-of-art treatment. The ability to target delivery of immunotoxic agents to the kidney could be beneficial for several reasons: Targeted delivery of specific immunotoxins would theoretically spare or reduce the adverse effects associated with systemic administration of immunosuppressive agents. Similarly, targeted renal delivery could also enhance the concentration of the drugs in renal tissue raising the therapeutic potential. Such immunotoxin technology could include recombinant fusion toxins, cytotoxic proteins, chimeric proteins, etc.

*Comments:*

*D S. —This is a good idea, however I think it would have its greatest application in targeting antigen-specific T and B cells in autoimmune diseases of the kidney. The identification of target antigens in anti-*

*GBM disease, membranous nephropathy, IgAN and AAV opens the field for such an undertaking.*

*Lauren Brasile—Yes, I agree. The idea was to target the relevant antigen(s) involved in autoimmunity by using a highly specific antibody conjugated with an immunotoxin. The technical hurdle would be to identify the relevant antigens.*

**Title: Quantitative PCR in hemodialysis patients**

Author: Jorge Brukman

Votes: 0

While routinely screening for quantitative PCR in chronic hemodialysis patients, we often come across many patients with unexplained high titers of PCR, not exactly knowing how to proceed and how to follow.

It'd be enlightening to pursue a prospective study that could correlate PCR with other parameters, biochemical markers, clinical findings, etc. to try to explain its occurrence and further conduct.

**Title: Bilirubin and Renal Disease**

Author: Kenar Jhaveri

Votes: 0

Gilbert's Syndrome is fairly common in the population. UGT1A1 polymorphisms serve in many instances to be protective in many diseases. Recently a large study showed respiratory disease protection. Prior studies have shown cardiac protection for having a mildly elevated indirect bilirubin. Is there any data on this on CKD and renal disease? There is one paper on mice that showed that bilirubin was protective in kidney disease. We need to investigate this pathway and perhaps explore in all renal fields if indirect bilirubin has anti-oxidant properties and protective in nature for the kidney?

*Comments:*

*Kenar Jhaveri—<http://www.ncbi.nlm.nih.gov/pubmed/21411679>*

*This study showed that bilirubin might be protective for HD patients. Perhaps a larger study should be done and even in non HD patients and having this polymorphism. This might have therapy implications.*

**Title: SGLT1 and FSGS?**

Author: Kenar Jhaveri

Votes: 0

Four members of two glucose transport families SGLT1, SGLT2, GLUT1 and GLUT2 are expressed in the kidney. Mutations in SGLT-1 are associated with glucose-galactose malabsorption, SGLT-2 with familial renal glucosuria and GLUT-2 with Fanconi Bickel Syndrome. In Familial renal glucosuria, majority of patients don't have any problems except for glucose in their urine. SGLT2 has been linked with glucose loss in urine and possible development of a drug for DMII. The other transporter is SGLT1 and it also absorbs galactose. No studies have been done of that linkage to recurrence FSGS or even FSGS. Since galactose potentially binding this "permeability" factor in FSGS, perhaps these patients have an underlying



mutation in SGLT1 and cannot absorb galactose leading to the "freedom" for the permeability factor.

*Comments:*

*Jeffrey Kopp—We have DNA from recurrent FSGS (39) and non-recurrent FSGS (>49) patients and could address this hypothesis. Perhaps this dialog is a good way to raise questions that prompt collaborations.*

**Title: IgA and possible genetic benefit**

Author: Kenar Jhaveri

Votes: 0

Similar to the APOL1 story and FSGS in African descent individuals is there a genetic benefit perhaps in the Eastern part of the world (where IgA is most predominant). Perhaps a benefit against a common parasite that is more endemic to Asia? Any suggestions on work on this

## Hypertension

Postings and Comments

### **Title: Sex/gender differences in hypertension/renal injury**

Author: Jane Reckelhoff

Votes: 5

Important to know what roles that sex steroids and/or gender play in impacting hypertension and renal disease. Important to develop gender specific therapeutics. Important for disease control/prevention in both males and females.

*Comments:*

*Paul Kimmel—I think this is a very important issue at both the clinical and the basic science level -- another issue is that cell work should be done in combined cets from both male and female sources to assess strain / gender and hormonal variation issues.*

*Daniel Battle—Yes, there are many unexplained gender differences in the susceptibility to kidney injury that deserve a study, particularly within the renin-angiotensin system.*

*Alfred Cheung—There has been a fair amount of work performed in the vasculoprotective effects of estrogen. In addition to gender differences, age and uremia as factors modulating vascular responses probably deserve more studies.*

### **Title: Pediatric Hypertension and risk for cardiovascular disease**

Author: Frederick Kaskel

Votes: 4

The development of hypertension in the pediatric age group serves as a model for the investigation of the natural history, risk factors, and prevention of cardiovascular disease. There is a need for GWAS studies in populations at risk, i.e., African Americans, Latino Americans, and obese children and those with sustained high blood pressure. Utilize existing databases, CKiD and compare to normal populations during growth and development.

### **Title: Hypertension--Scourge of CKD/CVD?**

Author: Myra Carpenter

Votes: 2

Hypertension appears to be the scourge of CKD and CVD. Is it any wonder that CVD events are elevated in the CKD (including post-transplant) population when it's a battle to control blood pressure? How much of the problem is medication compliance, drug interaction, or sub-optimal BP-lowering regimen? Does aggressive BP-control result in long-term benefit? Can anyone develop a BP-lowering med (or patch) that only needs to be used weekly or monthly?

*Comments:*

*Howard Trachtman—Infrequent dosing for hypertension would surely enhance adherence to treatment recommendations in adolescents and other difficult patients with kidney disease, this would be a tremendous help.*

*Alfred Cheung—We already have once-weekly BP meds. If the demand is there, longer-acting drug delivery systems can be readily developed.*

**Title: Elucidate the Basis of Salt-Sensitivity**

Author: Paul Welling

Votes: 2

Like other complex disorders, multiple genes with variant alleles and different environmental stresses are thought to contribute to essential hypertension. In the last few years, common and rare susceptibility alleles have begun to be identified, casting light on altered renal function and a specific environmental trigger--dietary salt--in the genesis of hypertension. The next challenge is to understand, in mechanistic terms, how the gene variants affect the ability the kidney to appropriately respond to sodium. Research in this area will provide new insights into the roles of the kidney in hypertension at a molecular level and reveal the molecular mechanisms for sensitivity to dietary sodium. It will also illuminate new substrates for therapeutic intervention and provide a strong scientific basis for the beneficial effects of the high potassium/low sodium DASH diet.

*Comments:*

*Alfred Cheung—On a practical level, is it a good thing or bad thing to have tests for salt sensitivity readily available for individuals in a convenient and inexpensive manner? On one hand, it is attempting to say that, if an individual is not salt-sensitive, she or he should be free to enjoy salty food as much as she or he likes. On the other hand, one can also make a point that if the society at-large cuts down on salt intake, it is of public health benefit.*

**Title: CKD, hypertension, and autonomic neuropathy**

Author: Paul Drawz

Votes: 1

CKD, elevated nighttime BP, and autonomic neuropathy are all associated with increased morbidity and mortality (both cardiovascular and renal). The bivariate relationships between each of these "risk factors" have been well documented. The interaction between the three variables is not as well studied. A better understanding of this interaction could lead to novel therapies that significantly reduce cardiovascular and renal morbidity and mortality.

*Comments:*

*Alfred Cheung—While I like this topic, I wonder if we should include the study of the daytime BP in these relationships.*

**Title: Elective allograft nephrectomy & events after failed transplant**

Author: Alan Go

Votes: 1

Patients who return to dialysis after a failed renal transplant have a markedly increased risk for death and other adverse outcomes. The retained allograft serves as a nidus for excess inflammation that could contribute to cardiovascular and other clinical events. Other than repeat transplant, few effective options exist for reducing the risk of premature mortality. Observational data suggest a possible benefit of allograft nephrectomy, but those studies are limited by selection bias and potential residual confounding. A randomized controlled trial of elective allograft nephrectomy on the risks of death, other clinically relevant events & resource utilization in patients returning to dialysis after allograft failure would provide the evidence needed to determine whether this would be a therapeutic option for these high-risk patients. Other therapeutic approaches could be layered on to such a trial using a factorial design as well.

*Comments:*

*John Wang—We do not routinely remove the failed renal allograft unless it happened within the first year or there were some indications, such as pain or gross hematuria. Reasons are residual kidney function, erythropoietin production and risk of nephrectomy. If the observed benefit of allograft nephrectomy is confirmed, it may become standard of care. We will be interested in a well-designed RCT of elective allograft nephrectomy.*

*Jagdeep Obhrai—Very interesting idea. Similar to idea #291. Alfred Cheung - It may be useful to identify individuals who MAY benefit from transplant nephrectomy (e.g., very high CRP without other identifiable causes) and target that subpopulation in a randomized trial.*

**Title: Labile hypertension**

Author: Alfred Cheung

Votes: 1

Substantial fluctuations in blood pressure within an individual are not uncommon. Yet the definition, implications on clinical outcomes, pathogenesis and management are unclear. This would be an important and challenging area for translational and clinical research and later basic research.

*Comments:*

*Harold Feldman—One extreme form of BP liability occurs in the setting of hemodialysis. Here, we need additional research to help us understand what parameters of BP have the most clinical relevance and, therefore, become the target of our therapeutics.*

**Title: Pro-hypertensive role of GPR91**

Author: Frederick Miao

Votes: 0

GPR91 (a.k.a. succinate receptor) locates mostly in the kidney and may play an important role in hypertension. Administration of succinate increases systemic blood pressure and releases renin. The hypertensive effect of succinate is lost when both kidneys are surgically removed or when it

is injected to GPR91-deficient mice. Since succinate is a glucose metabolite, it could, potentially, contribute to the development of diabetic hypertension via a GPR91-mediated, kidney-dependent mechanism.

**Title: HtN and sleep disorder**

Author: Lissane A sres

Votes: 0

Relationship between hypertension and sleep disorder, could it be a cause or just comorbidity? How common is it Therapeutic benefit?

*Comments:*

*Paul Kimmel—Another issue is the extraordinarily high prevalence of sleep disorders in ESRD patients, and the less well-investigated but probably high prevalence of sleep disorders in CKD populations -- and their effect on hormonal systems and cardiovascular and psychosocial outcomes.*

**Title: Is BP therapy effective in preventing CVD events in stage 4 CKD**

Author: Lawrence Fine

Votes: 0

SPRINT will include 4500 patients with a eGFR between 59 AND 25 and therefore will hopefully answer the question of whether aggressive treatment of HTN in patients in this range of eGFR adds benefit beyond treating to a goal of 140/90, is it important to examine the HTN goal question in patients lower eGFRs.

*Comments:*

*Alfred Cheung—Sounds like a great study and lots of data will be generated. With this large CKD subpopulation, the opportunities to understand the effects of BP on various organs are vast and unique. More ancillary studies should be performed to exploit these opportunities.*

## Translation/National Kidney Disease Education Program (NKDEP)

### Postings and Comments

#### **Title: Evidence based management of CKD in primary care**

Author: Ebony Boulware

Votes: 26

Primary care providers provide care for a majority of patients at risk for CKD progression yet are shown to misdiagnose, poorly manage and under-treat patients. The potential for enhancing CKD care through multidisciplinary collaboration as well as translation and dissemination of evidence based practices in primary care is great, but effective interventions have not been developed. Research emphasis on identifying mechanisms to improve CKD care in primary care settings is sorely needed.

#### *Comments:*

*susan crowley—Demonstration pilots of collaborative models of ckd care are needed to identify novel healthservice delivery paradigms with the potential for scalability and thus broader implementation. To gauge the quality of the collaborative models, CKD metrics that reflect meaningful measures of quality of care are needed. Universal clinical informatics systems that can be embedded within EMRs and perform auto-surveillance and -reporting of CKD quality metrics are also needed.*

#### **Title: CKD and social networks**

Author: Jeffrey Fink

Votes: 23

Diseases like obesity and alcoholism have been shown to be clustered in social groups. The distribution of CKD in social groups (families, churches, neighborhoods, friend networks, etc) should be explored with the intent of introducing interventions into such networks to improve outcomes.

#### *Comments:*

*Jeffrey Fink—Using that methodology it might also be helpful to identify where potentially "hazardous" messages are coming from and what their influence is. E.g., advertisements for NSAID use, biphosphonates, salt-containing foods.*

*Andrew Narva—Good idea. To inform the National Kidney Disease Education Program's (NKDEP) strategy for reaching providers and the public online with information about chronic kidney disease (CKD), we are conducting conversation mapping research to determine who to reach and where to reach them. This involves taking a comprehensive look at the social media landscape (e.g., blogs, social networks, forums, and review sites) in which health professionals and the public are discussing CKD and NKDEP, and analyzing these "conversations" to determine who the influencers are, what they are saying, and where they are saying it.*

#### **Title: Multifactorial intervention to stop progressive CKD**

Author: Uptal Patel

Votes: 16

Patients with progressive CKD (diabetic and non-diabetic) benefit from aggressive treatment that improves control of its antecedents, such as poor control of blood pressure, blood glucose, lipid profiles, etc. Some multifactorial interventions have been effective (most notably, the Steno2 Study) but none have been widely translated to populations or conducted in a diverse US population. Telehealth approaches may help overcome barriers to implementing efficacy studies in the US while allowing a scalable solution for translation to large populations (T2) if results are favorable.

*Comments:*

*Deepak Sharma—multifactorial intervention for progression of ckd will definitely be the order of the day & shall reap benefits in the direction of retarding ckd progression.*

**Title: How to raise awareness and prevention of CKD**

Author: Augusto Cesar S S Jr

Votes: 16

Designing an effective CKD prevention program is important especially in developing and underdeveloped countries where sedentary behavior, obesity, diabetes and hypertension is rapidly growing. Studying how multidisciplinary teams can approach and implement CKD prevention strategies tailored to the needs of each region is an important step to stop this trend and reduce the costs with ESRD.

*Comments:*

*Vallabh (Raj) Shah—The prevention of CKD in rural America is as important as in developing countries. One of the goals is to create a CKD care team consisting of all players including local area health representatives who may not have bkg in CKD care but they can be trained in working with patients in one on one bases. The other useful thing is to have CKD health registry to help track the progression.*

*Augusto Cesar S S Jr—Ok Vallabh... I agree, we have difficulties with prevention, adherence and awareness even in developed countries. One of the strategies we are developing is to use sport activities to fight sedentarism and at the same time to gather people around CKD prevention and organ donation. We have a group called nefrorunners ([www.nefrorunners.org](http://www.nefrorunners.org)) with good results.*

**Title: Can we use Pay for Performance to improve assistance in CKD?**

Author: Augusto Cesar S S Jr

Votes: 11

The traditional "Fee for service" approach has fragmented health care assistance especially among chronic diseases. Establishing goals for health care providers could shift the outcomes in CKD. Can we achieve better health care services utilization and clinical results in patients with CKD using the P4P strategy?

*Comments:*

*Augusto Cesar S S Jr—Ok Bruce Carter... Thank you for your comment.*

*Chronic diseases (including CKD) management has become a global concern. Despite all the efforts toward prevention it seems there is a gap between early CKD and ESRD care. Strategies fail mainly due to lack of continuity in care. Innovations are necessary. Currently we have few studies in this area. This could be an alternative to foster prevention, healthy lifestyle and primary care interventions.*

*Bruce Carter—A recent report by RAND Corporation highlights some of the successes and challenges facing preventive and CKD care vs. ESRD care/dialysis. (6 case studies of integrated CKD clinics.)*

*[http://www.rand.org/content/dam/rand/pubs/technical\\_reports/2010/RAND\\_TR826.pdf](http://www.rand.org/content/dam/rand/pubs/technical_reports/2010/RAND_TR826.pdf)*

*A frequently cited "barrier" in each case study*

*is "lack of adequate compensation" for primary CKD care vs. ESRD care. (Or to put it more bluntly: failure is financially rewarded, better CKD management is not.)*

*Bruce Carter—The RAND study frequently touches on the continuity-of-care issue, with particular attention to challenges in obtaining early CKD referral, and better coordination between primary care physicians vs. nephrologists, vs. other relevant specialties (e.g. cardiology, nutrition, etc. Questions also concerned how to create a "team approach" vs. concerns about "stealing patients") all set against the tragedy of ""doorstep ESRD"" (which could have been delayed or prevented through better CKD management.) Perhaps "pay for performance" can help answer questions about how do we "reward" continuity. But how to even define ""performance"" (to be paid for) seems quite challenging, especially in early CKD or prevention settings. Despite the numerous challenges listed, the RAND study is on the balance optimistic, hence the ""quiet revolution" in title".*

## **Title: Health services in CKD: The need for Type 2 Translation**

Author: Mark Unruh

Votes: 9

Although many in this dialogue are nephrologists, primary care physicians care for the majority of pre-dialysis CKD patients; however, PCPs often do not recognize the presence of CKD based on serum creatinine levels. Prior studies suggest that both PCPs and nephrologists deliver suboptimal CKD care. There are many strategies to improve the care of patients with CKD using novel systems base approaches. One strategy to improve disease awareness and treatment has been estimated glomerular filtration rate (eGFR) reporting and routine screening of patients at risk for proteinuria. There are large health care systems where either providers or even regions could be randomized to either screening, or testing national guidelines in the care of patients with CKD. I would think that it is important for the NIDDK to take on this type of translational research.

*Comments:*

*Daniel Weiner—This is a critical issue, focusing on the best use of an expensive but effective technology (dialysis). A recent publication by Davison et al in CJASN was extremely revealing in as much as they showed that, if patients were fully 'informed', many would not have elected to initiate dialysis and, in hindsight, regretted their decisions. This research is a bit non-traditional as we are unlikely to see RCTs but rather a focus on quality improvement efforts, educational initiatives and tools to measure quality and satisfaction in this population. A final major focus here would be on enhancing fellow education in*



*decision making and in alternative modalities (e.g., PD), as a complete discussion of options with patients with kidney failure includes all modalities - PD, HD, transplant, and no kidney replacement therapy.*

*Andrew Narva—NIDDK is sponsoring a new initiative in Type 2 Translation in CKD. A meeting was held in October and there is an active FOA:*

*Written summary of the meeting is available at:*

*<http://www3.niddk.nih.gov/fund/other/ckdt2workshop/index.html>*

*FOA is at:*

*<http://grants.nih.gov/grants/guide/rfa-files/RFA-DK-10-011.html>*

*Mark Unruh—One may also extend this topic to include conservative management of CKD such as the work by Brunori et al. published in AJKD demonstrating the efficacy of a low-protein diet in conservative management. I would think that this issue, and others in Renal Palliative Care, could be examined using both traditional and non-traditional clinical trials.*

*Dorian Schatell—It is vital to assess for treatable depression/adjustment disorder in patients who choose to stop dialysis. On one hand, we have patients who have intractable pain, multiple comorbidities, and very poor quality of life, for whom palliative care is appropriate. On the other hand, there may also be a group who choose to stop treatment because their lives are miserable on standard in-center hemodialysis 3x/week for 3-4 hours and they see no light at the end of the tunnel-- but who could have fuller and more rewarding lives if they were using another modality, including PD, longer and/or more frequent HD, or transplant. These two groups (if we can even verify such a thing) should be treated in the same way.*

*Rasheeda Hall—I agree. We need to further study the barriers to implementation of these recommended practices. One could start with case-control study of different healthcare providers.*

**Title: NKDEP and Prevention of Risks for CKD in Pediatrics**

Author: Frederick Kaskel

Votes: 2

The epidemic of obesity in the pediatric population must be addressed using the resources available in translational research if we are to stem the onset of cardiovascular disease in this population. Educational initiatives set forth in the NKDEP are excellent starting points to extend into schools, communities, and other facilities aimed at identifying those at risk and facilitating appropriate guidance. Short- and long-term outcome studies are needed to assess for novel approaches to this emerging public health crisis.

## Polycystic Kidney Disease

### Postings and Comments

#### **Title: Cilia and Cyst Formation: Guilt by Association**

Author: Terry Watnick

Votes: 54

A convergence of data suggests that cilia are important in the pathogenesis of PKD. Despite intense investigation, the precise nature of this relationship remains unclear. It has been suggested that the the PKD1/PKD2 receptor channel complex acts as a flow sensor on renal epithelial cells. When this complex is inactivated (for any reason), cyst formation occurs. However, disruption of TRPV4 in MDCK cells results in absence of flow mediated signaling yet TRPV4 Knockout mice do not develop cysts. We need to understand the precise relationship of cilia to cystogenesis.

#### *Comments:*

*S Nauli—I definitely agree with Terry's comment. The idea of cilia and cystogenesis sounds great, but there is a big black hole that we need to work on to understand the relationship between cilia to cystogenesis.*

*Leonidas Tsiokas—I think there is little doubt on the role of cilia in PKD. However, there is no evidence connecting specifically the ciliary pool of PKD1/2 to any cellular function, at least in mammalian cells. One reason for this is perhaps difficulties in studying PKD1/2 function at the cilium and/or basal body/centrosome. Therefore, I see here the need to develop the tools and technology to study Ca<sup>2+</sup> signaling specifically in these organelles, as conventional methods such as patch clamp, fura/fluo-based fluorescence etc. cannot be applicable or difficult to work.*

*Horacio Cantiello—I agree with the other comments, and am glad there is a consensus about a need for addressing what the primary cilium does for a living. Despite the fact that the different players have been placed, there is no clear link between say ciliary PC2 function and ciliary structure. The techniques are now becoming available to address issues of ciliary function that go beyond showing whether the cilium changes in shape. It is important to note that calcium entry in the primary cilium may be essential for its size and structure. This could be a potentially relevant following step.*

*Xiangyi Lu—I agree with the posted comments that further in-depth understanding of the roles of cilia in PKD lies in connecting the ciliary pool of PKD1/PKD2 to cellular functions. The black box here concerns with what happens next after Pkd2-mediated calcium influx on the cilium. Due to high concentrations of calcium binding proteins in most cell types, it is generally thought that calcium rise in the cilium proper would not directly lead to calcium rise in the cell body. In other words, there must be intermediary steps between Pkd2-mediated calcium influx within the cilium and effector proteins/pathways located in the cell body. Giving that the role of cilium in PKD is now well established, the next important task is to identify these intermediary steps.*

*Angela Wandinger-Ness—I agree with the need for new technologies to analyze the specific functions of the proteins in the cilia. Whole cell assays are inadequate. We need better ways for looking at specific*

*subpopulations and assemblies of proteins that are defined by their locations and unique functions in those locations.*

**Title: What are the roles of polycystin-1 and fibrocystin?**

Author: Peter Harris

Votes: 28

Although we have known that these molecules are the most important causes of ADPKD and ARPKD, respectively, for many years, and despite the fact that many ideas about their functions have been published, I am not convinced that we have it all figured out yet. Thinking a little more how we can reconcile the published data and considering carefully how we can find out more about their real functions would be worthwhile.

*Comments:*

*S Nauli—I would also add polycystin-2 in Peter's list. And, I agree that the molecular functions of these so called cysto-proteins need to be further explored....*

*Iain Drummond—There are two main things that I think would improve our approaches to PKD gene function:*

*1. Validation of in vitro results in vivo.*

*2. Separation of disease initiating events from disease progression phenomena.*

*The first point may be difficult to achieve and may benefit from the development of new phenotyping tools as has been mentioned elsewhere in this forum. It would also benefit from open sharing of animal resources which has been instituted by some institutions.*

*The second point raises the idea that we need experimental criteria for assessing primary and secondary effects of PKD gene mutation. (i.e. should we always expect that effects of mutation should be present in pre-cystic tubules?) Initiation and progression are equally important in treatment.*

*One of the main challenges seems to me that PKD genes act in mechanosensory feedback; so without a stimulus of some sort, a PKD loss of function condition can be silent. We would do well to broaden our focus from cilia to mechanosensing in general (stretch); the PKD vascular phenotype (smooth muscle/endothelial cells) might be the most tractable in this regard.*

**Title: Sequencing to Identify Modifier Genes in PKD**

Author: Rebekah Rasooly

Votes: 28

Although expensive, sequencing numerous individuals from many pedigrees with multiple affected family members is our best chance to identify modifier genes. This is the best chance to identify new pathways and molecules that influence the course of disease progression.

*Comments:*

*Peter Harris—I am certainly in favor of using the new exon enrichment methods and next generation sequencing to better understand all forms of PKD. As this stage these methodologies are probably best suited to identify disease causing mutations in monogenic diseases. Diseases with evidence of oligogenic inheritance are also now becoming tractable by use of these methods. Finding important factors in true*

*complex diseases or finding modifiers for monogenic diseases, such as ADPKD, is more of a challenge. Results from GWAS analysis and screening candidates can help to focus our search, but as Iain mentions, it will still be a challenge to separate important, strong modifiers from neutral variants. We can use bioinformatic methods to sort through the variants but it is probably not possible to subject more than a small number to functional tests. (If we have such things!). Probably the most important thing that can be done right now is to collect together samples and clinical information on large, well-characterized ADPKD populations, including families, with different severities of disease and variable extra-renal manifestations. These well-characterized populations can help to understand the detailed genetic data and we should first focus on characterizing these groups.*

*Robert Bacallao—I think with next gen sequencing we could get some interesting information on modifiers in PKD but from a bang for the buck perspective I think understanding cystogenesis and cyst expansion will get us to a therapy faster. I would advocate for a targeted work-flow initiative that coordinates standard cyst assays (reagents are available) in cell culture (for understanding mechanisms and application in high throughput screens, moving to animal studies that meet FDA requirements for IND applications and continued work to make cyst size/volume/growth an FDA approved marker for PKD progression.*

*Iain Drummond—High-throughput sequencing is definitely changing the world. The question is how to use it in a conclusive way. The challenge will remain how to distinguish a benign polymorphism from a nasty missense mutation in a candidate modifier. Genetic linkage helps but this approach will no doubt identify hundreds of candidate modifiers; we would have to envision a secondary functional screen to validate them or rely only on sequence variants predicted to generate strong alleles (stop codons / deletions). I favor the approach but it has to be integrated with a functional screen to generate real value. Then the question becomes what do we consider a valid functional screen? Model organisms (including mice)? Or will sequencing human patients be good enough to identify strong modifiers?*

*Michael Caplan—While I enthusiastically support dedicating funds to PKD in general, I am not enthusiastic about the idea of dedicating funds to a specific sub-problem such as “the role of proliferation” or “modifier genes”. I think that this is the kind of decision that is ideally made by a study section that can consider such proposals in the context of other directions being pursued in the field—I think that this mechanism can react better to changes in a rapidly moving field such as PKD rather than a dedicated funding mechanism.*

*Sandro Rossetti—Although expensive, next-generation sequencing technologies are certainly and rapidly changing our approach to human genetics. Several papers have been published already on successful gene identification after whole exome sequencing, and it seems likely that the same approach may be used for the search of genetic modifiers in complex phenotypes such as PKD in fact. Following also Dr. Hildebrandt's idea/proposal posted elsewhere, I think that next-gen technology may offer the possibility to attempt the identification of rare, "Mendelian" alleles that may underlie the disease variability seen in ADPKD pedigrees as well as other inherited "complex" conditions. And identify new pathways and possible targets. Filtering and comparison of datasets within multiplex families is key, and these families will be an invaluable resource. I agree with the previous comments that the classification of missense variants is certainly going to be challenging, and will inevitably use bioinformatic tools, functional assays (if available), as well as the increasing datasets derived from several whole exome sequencing projects (the 1000 genome project for instance and other databases). Hence, well-characterized multiplex families are probably the best resource, together with the need to have large, well characterized populations.*

*Greg Dressler—That assumes the variation in the progression of the disease has a genetic basis. There may be many other causes, such as environmental or epigenetic mechanisms. One likely reason for variation is that some individuals have had more injury and regeneration. With each nephrotoxic incident, the number of cysts could increase. Thus two persons carrying the same PKD mutation could have very different rates of disease progression.*

*David Beier—Point taken, although we do know from mouse studies that genetic background has a profound influence on disease progression, at least for recessive models. No reason to imagine comparable modifier effects do not influence human disease.*

*Iain Drummond—What do you all think about this work:*

*<http://www.ncbi.nlm.nih.gov/pubmed/19808797>*

*do we have enough data to know if similar mutations manifest differently in different families? and whether severity is heritable?*

*Iain Drummond—Are there PKD mutation carriers that never get the disease? i.e. 70 year old siblings of ADPKD patients that are heterozygous for PKD1 or isolated families with heterozygotes that are healthy? These would be the families to sequence.*

**Title: Early Biomarkers for PKD (before TKV increases)**

Author: Ronald Perrone

Votes: 20

GFR decline is associated with advanced structural change in ADPKD. Total kidney volume (TKV) is an earlier biomarker, but may not be early enough. What are other directions to pursue for very early biomarkers of ADPKD progression and response to therapy?

**Title: Activation of the PKD1/PKD2 complex**

Author: Terry Watnick

Votes: 16

PKD1/PKD2 may function as a receptor channel complex. In over expression systems, which are frequently used in the published literature, the complex appears to be constitutively active. What activates the complex in vivo? What are the ligands for this complex?

*Comments:*

*Leonidas Tsiokas—There is no doubt in my mind that this one of the most significant questions in the PKD1/PKD2 field. However, identification and functional demonstration of a ligand for this complex would require a good knowledge of all of the critical components forming the receptor-channel complex. Searches for auxiliary proteins (either by genetic screens or biochemistry) could greatly facilitate solving the PKD1/PKD1 channel activation problem. Innovative expression cloning and/or biochemical approaches to identify extracellular ligand(s) and/or intracellular proteins should be supported despite the fact that may sound "non-hypothesis driven".*

**Title: PKD and renal repair**

Author: Melissa Little

Votes: 14

A lot of research has been focused on the potential of a renal stem cell. Even the identification of such a population is not a solution, even more so in some instances. Will regenerative options be the same for ciliopathies versus other dysplasias or renal disorders?

*Comments:*

*Angela Wandinger-Ness—A lot of stem cell research has focused on repair of acute injury and cancer stem cells. It would be very instructive to have a clearer understanding of stem cell biology in the context of chronic disease, i.e. what are the key mechanisms in chronic kidney injury with respect to repair, what are the roles of stem cells in such diseases, how long can a kidney stem cell pool contribute to repair before becoming exhausted and how do the genetic background and mutant gene products affect stem cell differentiation. I think these questions are highly relevant to understanding ciliopathies and potential for regenerative medicine in these, as well as other progressive kidney diseases.*

**Title: Fetal environment as a determinant of PKD severity**

Author: Vicente Torres

Votes: 11

There is evidence that the maternal and fetal environment affect the later course of ADPKD. Research on this critical period of disease development in humans is needed.

*Comments:*

*Jared Grantham—I agree and have suggested a protocol to address the issue.*

**Title: Time course of cyst formation**

Author: Terry Watnick

Votes: 11

In conditional mouse models of cystic disease, renal inactivation of PKD genes after P12-14 results in delayed development of cystic disease. What is going on in the kidney during that period of time? Does the same happen in human PKD, is gene inactivation occurring continuously?

*Comments:*

*David Beier—Given this consistent observation in very different disease models, I agree there is information to be mined in this transition that is fundamental to the disease initiation process.*

**Title: Early detection of renal cysts in ADPKD**

Author: Jared Grantham

Votes: 10

## A Proposal

Autosomal dominant polycystic kidney disease (ADPKD) develops in utero and the cysts progressively enlarge but usually go undetected until the 4th or 5th decades of life. Recent evidence indicates that injury to parenchyma accompanied by irreversible fibrotic changes may begin to develop in the cystic kidneys during the first decade of life yet patients are currently being denied many years of supportive treatment until they develop clear clinical signs that draw attention to the disease. This late discovery of the disease thwarts opportunities to stop or slow the processes contributing to late stage renal insufficiency before irreversible damage has been done.

Ultrasound examination of the fetus to search for congenital abnormalities is justified and commonplace since abnormalities discovered early can oftentimes be treated effectively post-partum. Magnetic resonance renal imaging is sensitive enough to detect cysts ~2 mm in diameter and can identify cysts in fetal and newborn children at risk for ADPKD. With recent changes in law protecting those with genetic disorders from discrimination the time is right to perform a systematic study to screen children of a parent with ADPKD as early as the late fetal stage.

The first step in such a study would be to convene a panel of adult and pediatric nephrologists, radiologists, ethicists and laity to thoroughly discuss the approach and set guidelines. If there is broad agreement that the study should be done, a multi-institutional study would follow to survey fetal and newborn kidneys in a cohort of children at risk for ADPKD to: 1) develop criteria for selecting candidates for the cohort, 2) develop safe, precise imaging methods relying primarily on MR to detect renal cysts 2 mm or less in diameter, 3) determine the total number of renal cysts pre- and post-partum, 4) determine total kidney and total cyst volume, 5) perform annual determinations of cyst number and kidney volumes, 6) develop quantitative measures of disease progression to be used in controlled clinical trials to reduce cyst formation and growth in the early stages of the disease.

### *Comments:*

*Kristina Paquette—What is the point of this if there is no treatment or cure???*

*It is highly likely that the Health Care Affordability Act will be overturned in the courts, which means that the health insurance companies will again be able to reject patients based on pre-existing conditions. If there is no treatment or cure for ADPKD, why should young people put themselves in danger of being denied health insurance until they qualify for Medicare when they go on dialysis? Until a treatment/cure is found for ADPKD, the results of the proposed study would benefit the researchers, not the patients.*

*Jared Grantham—Obviously this is aggressive and optimistic. Note that the first step is to invest time (probably years) in discussion until a strategy is decided that passes the ethical test. By then the health care issues will be resolved, the FDA will have come to its senses in respect to biomarkers including kidney volume, we will have more sensitive diagnostic and imaging tools and we will have more specific therapies to offer than good hydration, attention to BP in childhood and avoidance of harmful drugs, chemicals and diets. Evidence strongly indicates that the earlier we start even simple treatments the better chance we have of slowing progression. If we can slow kidney growth by 1/2 in childhood we will add many years of useful function in the late stages of the disease. Kidney growth, like compound interest, is an exponential process. So interfering with cyst growth early on will dampen massive renal enlargement later. So it costs little to start now. There will be treatments and "cures" down the road.*

## **Title: Proliferation in cyst growth**

Author: Terry Watnick

Votes: 9

It seems intuitive that there must be proliferation of cyst lining epithelia for renal cysts to expand. However, the degree to which this occurs has been debated in the recent literature. Proliferation may be more of a factor while the kidney is developing. This question has important clinical implications since many anti-proliferative therapies are being proposed to treat PKD. What experiments can be designed to rigorously address this issue?

### *Comments:*

*Jared Grantham—Most of the field, including the discussants up to this point on Idea #119, have overlooked a seminal finding by Wang et al (JASN 19:102, 2008) that addresses the roles of proliferation, cilia and second hits" in cyst formation and progression. Brattleboro rats were mated with PCK rats yielding animals null for pkhd1 and AVP. Double null pups were born with minimal renal cysts in contrast to wild-type pkhd1 mutants; moreover, they did not develop cysts over a 20 week period unless DDAVP was administered beginning on week 12 whereupon cysts enveloped and expanded to the same extent as in the pkhd1 mutants with normal amounts of AVP. Cysts in ARPKD (pkhd1) like ADPKD (pkd1 pkd2) are driven to proliferate by cAMP, which is increased by AVP in collecting duct cysts. The Wang experiment proves that in PCK mutated genes alone do not cause cysts to form or progress. A "third hit", in this case a hormone, AVP, is needed to drive the proliferation of the collecting duct cells that are programmed to respond by the mutations in both alleles. This experiment shows that cilia do not of themselves cause cysts to form. The experiment also illustrates that relatively low rates of tubule epithelial cell proliferation, beginning in normal sized tubule segments, will enlarge the lumen of a tubule in comparison to a normal sized neighbor to a degree seen easily in microscopic sections, but if examined over a longer time frame would take months or years to reach a diameter that could be detected by MR or CT.*

*Iain Drummond—I agree that proliferation must be happening in PKD but the degree to which proliferation is compensatory (to cyst expansion) vs. a driving force for cystogenesis is still debated. One could argue that it doesn't matter; if proliferation is permissive for cyst growth then "killing off" a cyst may slow disease progression. Overall I think the field would benefit from more effort to separate cyst initiation vs. cyst progression mechanisms with both being of importance as targets for therapy. As far as experiments to test the role of proliferation one could take advantage of the PKD conditional knockout mice. Perform postnatal KO (tamoxifen @ day 14+) in a genetic background that predisposes to proliferation and test the frequency/onset of cyst formation. I think this experiment has been done. I believe what this data would show is whether or not propensity to proliferate increases cyst initiation. I don't think that simple correlations of cell proliferation rates and cystogenesis (in timed conditional KO's) are in any way conclusive despite the claims some would like to make. I believe there is already data in the field that indicates proliferation is not sufficient for cystogenesis. Again i think the value of answering this question would be to distinguish initiation from progression; this raises another debate: is it all that important to know initiating causes of disease if we can block progression? Of course we would want to block both but it comes down to a practical matter of what works best for patients.*

*Michael Caplan—While I enthusiastically support dedicating funds to PKD in general, I am not enthusiastic about the idea of dedicating funds to a specific sub-problem such as "the role of*



*proliferation” or “modifier genes”. I think that this is the kind of decision that is ideally made by a study section that can consider such proposals in the context of other directions being pursued in the field—I think that this mechanism can react better to changes in a rapidly moving field such as PKD rather than a dedicated funding mechanism.*

*Ronald Perrone—Targeting initiation or early progression in human subjects is problematic based on likely need for genetic diagnosis, and lack of FDA-approved clinical endpoints that would be relevant to early stage disease. Therapies introduced early in the disease would likely have the most benefit but would be the most difficult to initiate and to study. Progression-related phenomena would likely be clinically translatable in a more rapid time frame.*

*S Nauli—There is no doubt that there is a problem with cell division or cell cycle regulation in PKD. But, I am not sure if PKD cells divide significantly faster than normal cells do. From our point of view, we should explore more carefully the term "proliferation".*

**Title: PKD and Cardiovascular diseases**

Author: S Nauli

Votes: 7

Does anyone have any opinion on the importance of studying cardiovascular aspects in PKD? This area has not been much explored....

*Comments:*

*Horacio Cantiello—This is a very interesting idea, which will require investigation. There is little known, but there is evidence for a PC2-like channel in cardiac tissue. When the actual biophysical nature of the PC2 channel is taken into consideration, quite possibly it may play an important role in cardiac function, either alone or in combination with TRPC-type channels. Particularly because it’s large conductance, its perm-selectivity to calcium, and the fact that it does not inactivate.*

*Ronald Perrone—The HALT PKD Study is performing cardiac MRI in 548 study A subjects (GFR>60) over a 5 year period.*

**Title: Proliferation of Pkd1 cleavage products**

Author: Terry Watnick

Votes: 7

There have been a number of cleavage products described for PKD1. Autoproteolytic cleavage at the GPS site yields two fragments and a knock in mouse model harboring a mutated GPS site develops cystic kidney disease. There have been at least 3 additional C-terminal cleavage fragments reported in the literature. Many of the studies were performed using recombinant over expression systems. The occurrence/relevance of these Pkd1-derived products in vivo is unknown. Rigorous studies are needed to better define the biologic significance of these observations.

**Title: Functional characterization of new cystic disease genes**

Author: Vicente Torres

Votes: 3

There is a widening gap between the pace of identification of new cystic disease genes and the functional characterization of the encoded proteins. More effort and resources should be dedicated to support research aimed at identifying the function of these proteins.

*Comments:*

*Jared Grantham—I agree, but with this proviso that derives from Torres' work. "Informed" searching can be productive, where a central process in a cascade of reactions becomes a target. One such central process is the phenotypic transformation of renal tubule epithelial cell response to cyclic AMP when polycystins and polyductin/fibrocystin are mutated. The phenotype switches in vitro and in vivo to a proliferative response and becomes perhaps the most important process driving cyst growth throughout the patient's life. I am unaware of any groups who are trying to identify the molecular bases of this phenotypic transformation that appears to a calcium-dependent.*

*Iain Drummond—I agree. It is likely that with new high-throughput sequencing methods, mutations underlying all human mendelian disorders could be identified in about 5 years. This is a general issue affecting all fields of genetics. What do we do next? How do we understand gene function? The pace of genomics/sequencing is driving pressure to move to high-throughput phenotyping although I'm not sure what this really means. It is almost old-fashioned to carefully study a single gene these days. [I heard one graduate student in a journal club recently refer to a mouse knockout study as "low-throughput" approach!] I expect that mechanistic/functional studies in general will need to be accelerated with new tools. i.e. a panel of mouse transgenic reporter lines for basic cellular functions (biosensors / signal transduction pathways) or broad panels of phospho-specific antibodies for example. Basically a microarray type approach to phenotyping. Some of this already exists with pathway analysis arrays etc. Specifically with regard to cystic disease genes we need good models where primary defects associated with mutant genes can be separated from secondary progression effects. We also need to validate the models in vivo.*

**Title: What causes the "second hit"?**

Author: Oliver Wessely

Votes: 2

While the two hit hypothesis is generally accepted as one of initiation factors in the development of ADPKD, little is actually known about how the second hit happens. I think it would be worthwhile to better understand this process. While it will not "cure" patients with PKD, it may provide an angle to prevent the occurrence of the disease in people that carry one mutated allele. It may be easier to prevent the second hit than treating the multi organ syndrome of PKD when it has completely manifested itself.

**Title: The mouse as the PKD model organism.**

Author: Oliver Wessely

Votes: 1

The community has invested a lot of resources in developing mouse models for PKD. Yet, none of these models "really" recapitulate the human disease. One obvious solution is to try to tweak

the mouse system even further. However, this "inability" may tell us something about PKD itself. Maybe the mouse is not the ideal system to study PKD and it is time to look at some other higher vertebrates.

*Comments:*

*Jared Grantham—Mouse models are good to understand specific molecular processes. Where they fall down is that in the aggregate the grand sum of all the molecular alterations is not expressed in the living animal as we might expect. Let's face it. The human is the ultimate experimental animal of importance in experimental design. In my view, drugs and diets that show efficacy in spontaneous rodent or transgenic models and have complimentary effects on human cyst epithelial cell cultures would be reasonable candidates to advance to pilot studies in patients with PKD until the penultimate laboratory animal model comes along.*

*Charles Edelstein—Results of the interventional studies in humans will tell us if the mouse model where the agents e.g. tolvaptan were tested, is goodis good*

**Title: Estrogens and Polycystic Liver Disease**

Author: Vicente Torres

Votes: 0

Women have more severe polycystic liver disease than men and estrogens likely contribute to its progression. The severity of polycystic liver disease is highly variable. Genetically determined differences in estrogen metabolism and downstream signaling may account for this variability and should be investigated.

## Training

### Postings and Comments

#### **Title: Recruiting the Next Generation of Nephrologists**

Author: Chris Ketchum

Votes: 101

How can nephrology identify, attract and retain outstanding junior investigators?

#### Comments:

*Donald Kohan—The ASN has put a very high priority on increasing interest in nephrology as a career choice. The NIDDK should work closely with ASN to promote ways to attract talented trainees into nephrology research, including further development of fiscal incentives, educational opportunities, and re-examination of whether the focus should primarily be on USMGs or also include visa holders.*

*Manu Varma—Thank you for all the comments. It's great to see so much interest in this topic. To answer Dr. Molitoris's question, I would basically be looking to gain the benefits listed above. Discounted or free subscriptions to JASN or CJASN would be nice, as my school's library has neither. The travel grants to Renal Week 2010 were limited to fourth year medical students or MSTP students, so extending eligibility for this program would help. Of course, if there was an opportunity to join a committee or task force to share the medical student perspective, that would be a great experience as well. However, I have been able to gain many experiences in nephrology outside the ASN, such as a coauthored publication in next month's AJKD, membership on the board of the Nephcure Foundation, and contact with several nephrologists who have provided great advice and mentorship. For medical students in general, I can think of two areas where outreach would have a great benefit. First, awareness of nephrology. The goal shouldn't be to lure future orthopedic surgeons or psychiatrists into nephrology. But if a medical student enters with the aptitudes and interests that would make a great nephrology investigator, yet hears more about neurology or oncology or infectious disease, that person may commit to another field long before NIDDK F or K series grants become relevant. Second, accessibility of nephrology. I find it hard to believe that renal physiology is inherently more difficult than neuroanatomy or electrocardiography. But there seem to be more resources for students to master those topics, from books to websites to enthusiastic teachers. Medical students don't tend to shy away from challenges, but the dedication that a field has to teaching can make the difference between the challenge being stimulating or painful. Of course, it can have the same impact on developing researchers for the next generation.*

*Janice Cobb—"Professional students", particularly those who erroneously believe that they must be content to merely follow medicine as "fans", pursuing their avocation from the metaphorical wings, through avid readings in medical texts and journals, must be encouraged to follow their respective dreams of nephrological research! Many such persons, whose original career paths reflect not their own desires, but those of their respective families, mourn that age will, of necessity, preclude admittance into graduate studies and medical school.*

*Frederick Kaskel—This must be a mission that all embrace; special programs aimed at high school or even earlier, promising students need to be increased. Medical undergraduates need to be exposed early to the excitement of nephrology and an investigative career and the concept of a "nephrology navigator"*

to walk them through the opportunities for entry into nephrology. The programs that the ASN has for sponsoring students and residents is excellent and should be enhanced possibly at a regional level in addition to the ASN meeting. Students engaged in research can then have an opportunity to present their findings in an informal constructive format.

*Heddwen Brooks—Training grant mechanisms for PhD students and post-doctoral fellows would be one way for NIDDK to invest in the next generation of basic scientists. Graduate programs already have the mechanisms in place to mentor both students and post-docs and the return on the investment is clearer.*

*Manu Varma—I am a first year medical student with an interest in nephrology and have found far fewer resources to explore nephrology as a career compared to other specialties. To my knowledge, the NIDDK offers the usual NIH student opportunities, though there are far more oncology-related positions and less competition in institutes such as NIDA, NIAAA, NIA, etc. A quick search of the RePORT database showed around eight extramural research training opportunities for medical students, most (all?) limited to students at the school sponsoring the grant. The ASN has one research grant program for medical students, requiring a minimum ten-week full-time commitment (which is longer than my summer break) and an application in December of the prior year (which has passed). There are NO provisions for: medical student membership in the ASN journal subscriptions free or subsidized, attendance at the annual meeting, travel awards, abstract/research awards, career advice, mentorship, etc.*

*From the NKF, ISN, and ASPN, I have found no programs for medical students at all. However, the following professional societies have provisions for medical students in any year to become members (for free or a nominal membership rate), with some or all of the opportunities listed above:*

*--American Academy of Pediatrics*

*--American College of Surgeons*

*--American Society of Anesthesiologists*

*--American Academy of Neurology*

*--American Heart Association*

*--Society for Vascular Surgery*

*--Society of Critical Care Medicine*

*--American Society of Transplantation (caveat: their trainee membership is limited to seven years, and I could be in training for twice that long!)*

*I strongly support this idea, particularly Dr. Kaskel's and Dr. Jhaveri's comments. It seems like it needs much more work."*

*Bruce Molitoris—To Manu, You have identified several weaknesses in the approach to attracting MS and Residents into Nephrology. The ASN has assembled a Task Force on this issue and the findings of their research have been submitted for publication. A workforce Committee is being assembled to prioritize and implement the strategies proposed. There were increased travel awards for MS to ASN Renal Week in 2010 and a further increase is expected in 2011. New and more grants are being planned at both the ASN and NIDDK to encourage college students thru residents to do research in Nephrology. I will take up your point regarding MS membership in the ASN with the ASN Council later this month. Is there anything in particular you are looking for in this regard?*

*Kenar Jhaveri—The roots of recruiting have to start at the medical school level. We as nephrologists have to sell our field to the medical students and make it more attractive for them to consider it as a career choice. More mentoring at the medical school level is what is needed.*

*Kenar Jhaveri—Manu's thoughts are excellent. This is what I was referring to. When I have asked medical students around the question about nephrology, it's a similar answer I get like Manu's. What we need to do is as a community-- is enthusiastic and gets ASN perhaps to have programs set up in medical schools to share some exciting times in Nephrology. I think the view of medical students of nephrology might be skewed. Just rotating on the consult service gives them only one side of nephrology. Having them do an outpatient rotation/dialysis component/transplant/ etc. can perhaps spark more interests? It's similar to Heme/onc service inpatients (the patients are always sicker in the hospital). Restructuring the rotations, showing them that how diverse nephrology is (lot of them don't know), perhaps is one of the ways this can be achieved. Other strategies might be as suggested earlier at the National level at conferences. Using social media and the internet should be used to our advantage and promote our field as many medical students are on line these days.*

*Bruce Carter—"Does this ASN "Task Force" also include medical students? Manu's astute observations are spot on, and he is the sort of person ASN should have been listening to all along.*

*Bruce Carter—Extending Janice's comments, - How about simply because no other disease is simultaneously so widespread, yet so close to major new understandings which will finally enable more effective treatment. An opportunity to benefit millions within your own lifetime. This should motivate both new researchers and potential funders. But giving the impression that there is no light at the end of the tunnel will motivate neither, and both resources and talent will continue to gravitate elsewhere. From animal results, CKD is arguably closer to a cure (or near-cure) than either HIV or most cancer, yet look where all the money and effort has been going.*

*Mary Leonard—On behalf of American Society of Pediatric Nephrology (ASPN) Council and the Workforce Committee, we appreciate Manu's comments regarding the paucity of opportunities for medical students. The ASPN has a longstanding workforce committee. This year the committee is focusing on efforts to increase the exposure of medical students and residents to pediatric nephrology. Specifically, we have created a medical student "tool kit" for our membership that includes a variety of specific actions (e.g. offer a pediatric nephrology elective for 4th year students; invite students to attend kidney camp; invite students to attend our national meeting, etc.). We have travel awards for medical students to attend our national meeting in the spring. We do have a section on our website about pediatric nephrology as a career and how to apply for a fellowship in pediatric nephrology:*

*<http://www.aspneph.com/t&c/ConsideringACareer.asp>*

*This section is geared to pediatric residents, but the information should be helpful to medical students as well. In our tool kit, we encourage pediatric nephrologists to be readily available to medical students seeking guidance about a career in pediatric nephrology. We believe that local pediatric nephrologists will generally be your best resource for career advice, but we agree with your suggestion to have more web-based information and the ability to receive direct guidance/mentorship through our website. Unfortunately, as you point out, there is not any pediatric nephrology specific research funding for medical students. However, there are pediatric research fellowships that could be utilized by a student working with a pediatric nephrologist: [http://www.aps-spr.org/Student\\_Research/Info.htm](http://www.aps-spr.org/Student_Research/Info.htm) Moreover, most of the nephrology opportunities are available to students who wish to engage in pediatric nephrology research. We agree that there should be more.*

*Bruce Carter—The high ranking of this topic illustrates its tremendous importance as a "policy" or "marketing the profession" issue--but has it also strayed from the stated KRND purpose of: "identifying important research questions in kidney biology and disease?"*

*Kevin McBryde—I admit I am a bit new at this, but I joined NIDDK as the Program Director in the Office of Minority Health Research Coordination. My office has several funding mechanisms to attract underrepresented individuals to NIDDK research and clinical areas, including nephrology. We offer Supplemental Funding awards to parent NIDDK grants to provide career development and training plans for underrepresented candidates (high school to early investigators; supplemental T32 funding to support existing NIDDK T32s to add an additional spot for an underrepresented candidate; summer research opportunities in the labs of NIDDK investigators for high school and undergraduate students; and R03 grants ("Small Grants for Clinical Scientists to Promote Diversity in Health-Related Research). NIDDK also supports the Medical Student Research Training (<http://www.niddk.nih.gov/research-funding/process/apply/about-funding-mechanisms/t32/t32-msrt/Pages/T32-medical-student-research-training-supplement.aspx>) to provide 12 months of research exposure for medical students (typically between years 2 and 3) with stipend. NIDDK also participates in the F30 (MD/PhD) and the F31 (PhD, through my Office) pre-doctoral National Research Service Awards, and these do not have payback obligations. Finally, both NIDDK and my Office support separate R25 Education Program Grants for institutions to develop education programs to recruit and retain individuals for clinical, translational or basic-science research careers in the NIDDK domains.*

*Tracy Rankin—Bruce--the issue of training is a cross-cutting one and one that will affect all of KUH's research areas. So, yes, I agree this topic is not a "research" question per se, it is quite important to address in terms of assuring a workforce for address the scientific research questions posed here in the Dialogue.*

**Title: Do we need a new model for Training Physician Scientists?**

Author: Terry Watnick

Votes: 36

There are fewer and fewer nephrology trainees opting for a career in laboratory based kidney research. In our own training program the vast majority of renal fellows who want an academic career pursue training in clinical science. There are many reasons for this including (but not limited to) an extended training period in a field in which they may have little prior experience, the perceived uncertainty of maintaining adequate funding over the long haul and the difficulty inherent in "wearing many hats". Another observation is that lab based science is like a cottage industry with each investigator ultimately working independently. There is less of a role for group interactions that might provide a more supportive environment for physicians who are under a lot of pressure to obtain salary support. If the community believes that practicing M. D.s can make valuable contributions to basic research, what do we need to do to recruit, train and retain these individuals? Should all M. D.s who choose a lab based career obtain a Ph.D.? Should M. D.s who want to do basic research participate in larger cooperative groups? How are M. D.s doing in comparison to M. D. /Ph.Ds.' and, Ph. D.s in terms of R01 grant funding?

*Comments:*

*Karen Moulton—The same is true in cardiovascular training programs. If the initial exposure to science is late (i.e. subspecialty stage), the "road" is perceived to be too long, uncertain and financially risky to follow. The trainees don't see how rewarding a science career can be or understand that scientific skills enhance their ability to conduct translational research. For fellowship programs that want to train*

*future academic faculty, the option to start research first may be helpful for those individuals that are interested in translational or more basic biomedical problems.*

*Vinai Modem—I agree early exposure to research training is essential. But, at the same time I feel the value of clinical experience in asking the right research questions is ignored in the current setup. If a mid-career clinician wants to come back into an academic and research setting, there are no mechanisms to either support or encourage such moves. It is an uphill task for someone to return to an academic environment.*

*Frederick Kaskel—The earlier exposure to the excitement of a career in investigation the better. What is lacking is a "navigator" as a role model for the young professional to see as someone who has successfully followed a career pathway leading to productivity and satisfaction. Also, new formats for translational research training are needed that emphasize the "team" approach across disciplines to research.*

*Terry Watnick—Would be great to take a look at this data. Since I was a fellow more than 15 years ago, our program has trained approximately 2 physicians who stayed in basic science. The other M. D. trainees who tried the lab either went to private practice or transitioned to the clinical/clinical research track. I do think that we seriously need to consider alternative models. Any ideas out there?*

*Tracy Rankin—I can try and find some data on dual degree holders vs. MDs vs. Ph.Ds. wrt R01 funding--NIH has certainly looked at this, as as the IOM. I think early exposure to research is essential to recruit clinical folks in to basic science--the question is how early and when to incorporate this exposure into the clinical training. From the opposite side--does the current structure of training the clinicians need to increase its flexibility to allow for "alternative" models?*

*Tushar Vachharajani—There is definitely a need for a physician-scientist in the new field of Interventional Nephrology. The clinical part of performing procedures is enticing for the fellows in training but the available opportunities are limited in an academic setting. The scope of translational research related to dialysis vascular access is tremendous but the academic interventional nephrologists in their mid-career are unable to devote time to train an academic interventionist due to lack of supportive resources. A new model that can support both clinical and research training would promote academic faculty in this new field of nephrology.*

*Mary Leonard—Manish's suggestion about increasing indirect costs associated with K awards is interesting. It would not have occurred to me until recently, when I heard a senior investigator at another institution make the observation that institutions lose money on K recipients because of the unfunded overhead. I wonder to what degrees this tempers some institutions' enthusiasm for investing in K recipients.*

*Manish Ponda—I agree that the overwhelming majority of fellows are not interested in pursuing a research career. This is true even when they are interviewing for a fellowship position. Even for those who initially contemplated a research career, many pursue clinically-oriented jobs. That said, I'm not sure that more exposure is the most efficient way of attracting more qualified physician-scientists. There are already a large number of trainees with research experience, but they choose not to pursue a career in research because it is not as attractive as clinical practice. Inflation-adjusted medical student debt is increasing. Research funding is increasingly more competitive. Job security for a physician-scientist is decreasing. These are major factors in choosing a career track that cannot be ignored. Why*



*is it that dermatology and ophthalmology are consistently amongst the most competitive residency programs? Is it because there is an obvious love for these fields amongst medical students or is it because of the compensation and lifestyle they offer?*

*Further, funding is essentially zero-sum. Where would the money come from for medical student funding? For example, a single K-award may be the rough equivalent of 4 pre-doctoral positions. Is there data that suggests that >25% of NRSA awardees pursue a career in research?*

*Increasing indirect costs is a potential mechanism for encouraging institutions to invest in early-phase physician-scientists. Are there data on how many K-awardees receive start-up packages or equivalent investments from institutions? It seems that the return on the NIH's investment would be greater if it led to a greater investment from medical centers.*

*As far as cost-neutrality, how many K-awardees go on to receive an R01 or equivalent? Would it be higher yielding to have fewer K awards with higher indirect costs and salaries? Are there data on the trade-off in yield between # of awards and amount per award?*

*Iain Drummond—Mary: I don't think the overhead issue dissuades us at all from applying for K awards. As regards physician research training in general I have to amend my comment above about how education in research methods for fellows could encourage more of them to engage in research. I made a point of asking all the prospective fellows this year whether they would opt for a more basic research track (vs. clinical) if training were offered. All said no. It became clear to me that the fellows interested in basic research had all had prior basic research experience and were committed to bench research (despite the pay issue) by the time they got to the fellowship stage of their careers.*

*Bottom line: the best investment to encourage more fellows to commit to basic research would be to support laboratory experience during their medical school years. By the time fellows get to be fellows they are terminally differentiated. The fellowship is a time in their life when they want to be maximally productive (based on what skills they already have) and they are not interested in taking a risk on a new direction in life/career.*

*We need to support funding opportunities for medical students to engage in laboratory research and encourage more medical schools to offer research programs. Many medical schools already do encourage/require students to do research so the structure is in place. Maybe an NRSA type award focused on medical students for a 6 month to 1 yr. research experience would be a good idea. Does such a mechanism already exist? Maybe more advertising/recruitment is what's needed.*

*Kevin McBryde—I think that some of the problem is in the "attraction" of a career and earning potential in subspecialty medicine. Academics will always be at a disadvantage to clinical practice. One way, I believe, to attract the "right" people for Physician-Scientist is to adopt research requirements by the American Board of Internal Medicine similar to the American Board of Pediatrics (I am a pediatric nephrologist). ABP states that "all fellows will be expected to engage in projects in which they develop hypotheses or in projects of substantive scholarly exploration and analysis that require critical thinking. Areas in which scholarly activity may be pursued include, but are not limited to: basic, clinical, or translational biomedicine; health services; quality improvement; bioethics; education; and public policy." ABP requires a minimum of 3-years of fellowship compared to 2-years by ABIM for nephrology. I also think that academic institutions have been "feeding at the trough" of the NIH for too long with their F&A rates. Scripps is reported to be around 85%, Salk Institute > 90%. F&A is supposed to cover building maintenance & utilities, library support, centralized administrative costs for the grant management and other administrative costs. Perhaps cutting/re-negotiating the R-awards F&A rates with HHS will allow for more than the 8% for K- & T-awards and 0% for F-awards.*

*Iain Drummond—When I interview fellowship applicants for our program I find that they all want to pursue research but for about 95% of them this means retrospective case studies and "outcomes" analysis. The rare fellow is prepared to do "wet" bench work (almost all of these are M.D./PhD's). This is not because M.D.'s are not interested; they don't know if they are interested or not because they lack experience. For a PI the question becomes do you take on an M.D. in your lab who for practical purposes is at the level of a first year graduate student? The gap for M.D.'s can be bridged with education. There are successful, short, intensive courses in clinical research offered and I think the same can be done for molecular approaches to disease. We are encouraging interested M.D. fellows to take a short intensive course at the outset of their fellowship (like a woods hole or cold spring harbor course) to train them in molecular approaches and techniques. Perhaps what is needed more than a course is reducing the perception of risk of doing something new. As long as clinical case study type work is offered, this is the easy choice for fellows. Perhaps a middle ground is genomics. The benefit here is that methods are evolving to be easier and higher throughput and the techniques are relevant to all diseases. A focused training in genetics / genomics coupled with institutional support for acquiring DNA samples might make for an easier transition of M.D.'s into research. This might go hand in hand with better training in recognizing genetic syndromes in patients and improve disease phenotyping.*

**Title: Should T32 stipends be increased?**

Author: Donald Kohan

Votes: 20

T32 stipends for fellows remain far too low. It is unreasonable to expect fellows to take a pay cut as they move from residency or clinical fellowship to the lab. In some places where the salary scale is set and salaries can't be decreased, the differential between the T32 stipend for a fellow and the salary set by the house officers union is quite substantial (we're not talking about an unreasonably high salary). There are some programs that do reduce the salaries of research fellows on NIH stipends but this is hardly in the interests of bringing trainees into the research fold.

*Comments:*

*Frederick Kaskel—The salaries are below the residency post-doctoral levels and we supplement them to parity. Increasing the stipends might be another way to encourage post-doctoral training in the specialty.*

*J. Kevin Tucker—I agree completely. The T32 stipends are too low to encourage trainees to enter research at the same time in their careers that they are beginning to take on the responsibilities of families. If we are serious about encouraging trainees to do research, this issue has to be addressed.*

**Title: Should visa holders be T32 eligible?**

Author: Donald Kohan

Votes: 12

Eliminate the exclusion of all but US citizens and green card holders from T32 eligibility. Many of our most committed and successful trainees are here on a visa.

*Comments:*

*Tracy Rankin—The eligibility for those individuals supported by the NRSAs (Ts, Fs) comes up frequently and, while is a fine idea, is totally outside of NIH's control. The authorizing legislation for the program explicitly limits it to citizens and green-card holders. An act of Congress could change it if there was enough support in that legislative body. Garnering that support has to be done by the research community through the channels available to them to lobby Congress.*

*Kenar Jhaveri—What is also very important is the amount of money involved when they use lawyers to get these visas established and able to stay and work in the US. ASN might want to create stipends to help some of the funding of top class researchers who are here on the visa as it's our loss if we lose them.*

**Title: Should we lengthen the time of NIH training support?**

Author: Donald Kohan

Votes: 9

Studies by the Institute of Medicine suggest that 2 years of research training is inadequate preparation for a research career. Fellows need more preparation in acquiring facility with the increasingly complex research armamentarium, particularly given escalating financial pressures once they become faculty. Should we increase NIH training support to three years?

*Comments:*

*Frederick Kaskel—There is clearly a need for additional support for select trainees who are pursuing an investigative career. It is possible that for those who receive extra support the outcome may be improved in terms of ability to obtain independent funding.*

**Title: Create training pathway attractive to Gen X and Millennium Gen**

Author: Robert Star

Votes: 6

Generational differences dictate career choice. Are we being sensitive enough to this issue?

**Title: Mentoring Components in R01s?**

Author: Tracy Rankin

Votes: 2

Should R01 grants that include students or post-doctoral fellows be asked to submit a mentoring plan for those individuals supported by the R? If so, how would this be evaluated during peer review and during annual progress reports?

*Comments:*

*Linda Fried—One of the scoring areas in the new system is investigators. I think this might dissuade investigators from including junior investigators. A concern might be that this score would not be as high if less experienced investigators are included.*

*Mark Unruh—I guess i would like to see the inclusion of fellows and junior faculty as more normative on*

*clinical research R01s. From the proposals I have submitted and evaluated, this doesn't seem to be the case.*

*Wolfgang Winkelmayr—I think that this is a very reasonable idea. Question is how this should be incorporated in the R01 mechanism (or others). I'd argue that such a training plan should be excluded from consideration for the scoring of the scientific application. However, one could make continuity of funds for fellows contingent on separate annual training progress reports. It would be good if one were to go down that route, that some additional funds for the training for that individual (e.g. tuition, travel to conference, etc.) should also be permissible. This mechanism could perhaps become an optional component of grant submissions and serve to expanding training resources (while preserving accountability and improving training) rather than substituting for existing training grant mechanisms...*

*Tracy Rankin—The investigator score is heavily weighted on the principal investigator. Junior investigators and fellows are almost always included in R proposals--primarily as co-investigators or "worker bees" but I have yet to read a summary statement comment about the qualifications of these individuals as a factor in a criterion score--unless the co-investigator is absolutely key to the successful implementation of the R award. Just reading the tea leaves, the implementation of the all personnel reports for R grants and new student reporting for R grants, NIH will now begin to be able to quantify the number of post-docs and students supported through R awards and compare their subsequent "success" in terms of publications/grant applications/academic appointments, etc... to those supported through formal training grants and CDAs. If there is a large discrepancy, we will be asked to "improve" this system. Might as well start thinking about it now...*

*Ronald Falk—Tracy I think that this is an interesting and perhaps very good motivator. Junior faculty and post docs and students are critical co investigators and "worker bees" in many of our studies. We should be required to do more than just list them but also describe why they are so critical and how we are going to help them in their careers. Yet on this issue, mentors are not born to be mentors. Many mentors need to be trained to be mentors. How would you propose to train mentors to mentor?*

**Title: Should National Research Training Centers be developed?**

Author: Donald Kohan

Votes: 2

Expand the role of or create new O'Brien or other core centers to promote research training and exposure of medical students, residents and fellows. Examples include spending 1-2 weeks to learn transgenic, electrophysiologic, proteomics, genetic association and other techniques at specialized centers. The focus and level of teaching could be geared differently depending upon the level of trainee experience.

*Comments:*

*Frederick Kaskel—I think the concept of a regional center that takes advantage of the expertise within the area is exciting. It could function like a regional ctsa with multiple cores of expertise. The training curricula are unlimited.*

*Donald Kohan—It could be part of a CTSA or could stand alone. An example is the Mount Desert Island course on renal physiology where trainees spend a week immersed in studies on renal transport.*

*Tracy Rankin—Would the above be similar to the current CTSA model, where there are training components linked to the primary center grant? And Nephrology specific?*

**Title: Should the NIH loan repayment program be broadened?**

Author: Donald Kohan

Votes: 2

If trainees could be relatively sure that going on a T32 or getting an F32 and/or K award would ensure support by the NIH loan repayment program, we might see a lot more US grads willing to go into research.

*Comments:*

*Mary Leonard—the NIH Loan Repayment Program has been an important piece of the puzzle for many of my trainees. Is there a way to streamline the process so that they don't need to submit both a career development grant and a LRP at the same time? The science and mentoring components of the applications are largely the same.*

*Frederick Kaskel—The outcome data should be examined to see how effective this program has been in facilitating young investigators to remain in academics. This program is critical in order to overcome the financial burden of the entering trainees. We need Congressional support for more funding of this program.*

*Ronald Falk—In my opinion the NIH loan repayment program has been one of the most successful programs to date to keep young and talented graduates in Academia. The lures of cash from private practice groups are really diminished if the young faculty wants an academic career and can get rid of their loans while doing research. A brilliant program. The question in my mind is how to expand it.*

**Title: Where is Homer Smith when we need him?**

Author: Jared Grantham

Votes: 0

The patron saint of nephrology created from his intellect an aura that attracted the brightest and the best to become renal physiologists, the precursors of modern nephrologists. His published work in renal physiology was seminal, but as important, his writings on evolution and the kidneys, his examination of the human condition and religion, and his influence on the training of American leaders in academic medicine laid a unique and powerful framework for the emerging discipline of nephrology. Unfortunately, we have strayed from that deep romance with the kidneys to more mercantile pursuits such as keeping a lab going by following trends rather than our own passions or by building nephrology practice numbers to fuel our distractions from nephrology. I think that one of our greatest needs in nephrology training is for the current leaders to restore and espouse their love affair with the kidneys in their local institutions and where ever they interact with other human beings - to become evangelical apostles of Smith's great teaching - "Superficially, it might be said that the function of the kidneys is to make urine; but in a more considered view one can say that the kidneys make the stuff of philosophy itself." May the ASN, the NKF, and the NIDDK work together to restore the kidney to its rightful place in the imaginations of young scientists searching for their life's work.

Comments:

*Gary Striker—This insightful comment deserves to be read by all in the field. I would also add that emphasizing the contribution of the kidney to all of the other organ systems could be a major incentive to young persons interested in research. The "making of urine" is but one of the multiple functions of the kidney. Similarly, dialysis is but one of the treatment options employed by Nephrologists. Finally, education of the other medical specialties to the fact that Nephrologists should be consulted early in the course of CKD would go a long way in the exciting trainees of other disciplines v/v the challenges and opportunities in Nephrology.*

*Bruce Carter—An eloquent summary of tensions and dilemmas in nephrology. Perhaps also facet to be combined into topic #27.*

*Agnes Fogo—Young talented would-be scientists must also find it possible to think about pursuing a research career- that means funding should be possible, debt from training and postdoctoral years in the lab should not prevent them from considering such a career, and mentors should have time and resources to nurture the talents of the next generation. Above all, to echo Jared Grantham's and Gary Striker's eloquent statements, we should show the students, residents, fellows by example how much fun such pursuits are, and how important this is for our patients!!*

**Title: Institutional versus individual training mechanisms?**

Author: Tracy Rankin

Votes: 0

Are larger, institutional, grants (T32s, K12s) the best vehicles for training young researchers? Some evaluation data suggest individual grants (Ks, Fs) are more effective with respect to keeping fellows in the academic pipeline than an appointment to an institutional grant. With limited resources, should more be spent on these latter mechanisms?

Comments:

*Frederick Kaskel—Institutional grants offer the opportunity to develop a cohort of trainees in a focused discipline rather than just one trainee out of many who may be encourage to pursue investigative careers. The addition of institutions with CTSA's has opened considerably the possibilities for expanding the training programs at that institution with new programs, courses, career paths and support for training grant recipients to be exposed to during the post-doctoral experience. My experience is that the trainees within a training grant grow with each other and the overall experience among the fellows is enhanced.*

*S Nauli—The only concern that I have with the institutional training grant is to leave smaller institutions behind. It's hard for small institutions to compete for a T32 grant, but it does not mean that small institutions won't be able to provide a high quality training. So, I would support for more individual grants.*

## Transplantation

### Postings and Comments

#### **Title: Management of the failing allograft**

Author: Allan Kirk

Votes: 48

A prominent high mortality cause of renal failure is now allograft failure. Patients approach dialysis burdened by years of immunosuppression, advanced CV disease, but become sensitized and untransplantable if immunosuppression is withdrawn. Strategies for management of this population of patients are lacking.

#### *Comments:*

*Jagdeep Obhrai—Very interesting problem. Similar to Idea #214.*

#### **Title: Biomarkers for monitoring graft function**

Author: Valeria Mas

Votes: 44

Important progress has been made in improving short term outcomes in kidney transplantation. However, long-term outcomes have not improved during the last decades. One key reason for explaining the lack of evident improvement of graft survival is the lack of objective biomarkers accurately reflecting allograft status and reliably predicting outcome for a single patient. There is a critical need for biomarkers for early diagnosis of graft injury, treatment response, as well as surrogate endpoint and outcome prediction in organ transplantation, leading to a tailored and individualized treatment. Genomic and proteomic platforms have provided a multitude of promising new biomarkers during the last years. Nevertheless, there is still no routine application of any of these markers in clinical transplantation. Identification of biomarkers (ideally non-invasive) for monitoring the graft using prospective studies with appropriate patient follow-up and associated clinical data are needed.

#### *Comments:*

*Roslyn Mannon—This research is actively supported by NIAID using a couple of mechanisms including U01's/CTOT and genomics RFAs.*

#### **Title: Using Biomarkers to Improve Organ Allocation and Reduce Discard**

Author: Chirag Parikh

Votes: 44

There is significant irreversible kidney injury during process of kidney removal and transport from deceased donors. More than 50% of kidneys are discarded by some OPO's. Novel biomarkers of kidney injury can guide allocation and reduce discard rate.

#### *Comments:*

*Kelvin Brockbank—The opportunity for more organs lies in extending the utilization of marginal donors and longer warm or cold ischemia times. The greatest opportunity is in potential donors who are not on life support so biomarkers would have to be obtained from pumped kidneys. Studies on secreted proteins have been performed previously and only one had a significant but weak correlation with in vivo function. High levels of  $\alpha$ Glutathione S-Transferase (over 200U/L) characterize delayed function or non-functioning grafts (Daemen,1997; Kosieradzki 2002). What is needed is a comprehensive search for biomarkers that correlate with function and non-function.*

*Sumit Mohan—19% of all kidneys procured from deceased donors in 2009. Based on UNOS data.*

*Sumit Mohan—The national discard rate for 2009 was 19% from deceased donors. Biomarkers that can help identify organs that should be used rather than poorly predictive donor characteristics could go a long way in lowering the current discard rate.*

*Kelvin Brockbank—Interesting comment, does the 19% mean 19% of kidneys that were procured or 19% of all potential organ donations? Regarding Biomarkers I would draw your attention to a recent paper "The Value of Machine Perfusion Perfusate Biomarkers for Predicting Kidney Transplant Outcome", Transplantation 2010; 90: 966–973. The authors conclude that "increased GST, NAG, or H-FABP concentrations during hypothermic machine perfusion are an indication to adjust post-transplant recipient management. However, this study shows for the first time that perfusate biomarker measurements should not lead to kidney discard." It is likely that the authors have not found the right biomarker yet. Sadly, in cases like this where the obvious markers have not performed as well as anticipated it is necessary to broaden the search. NIH reviewers usually shoot down broad searches for markers that are not directed to specific groups of biomarkers using terms like fishing expedition to dismiss the proposal to a low priority score.*

*Chirag Parikh—There is some good preliminary data however this area of research is also relatively new and will need support. This is one setting where there is no contamination by pre-renal azotemia (as the kidney is outside the body). Also, knowledge can be transformed into practice relatively quickly.*

*Paul Kimmel—Are there preliminary data regarding markers -- or is this a suggestion for an entirely new area of research?*

*Roslyn Mannon—Chirag---When you say no prerenal azotemia, many of the potential organs disposed of have issues with high preterminal creatinines and other issues of prolonged cold time. Do you hypothesize that these biomarkers will be obtained in situ (in the deceased donor while still living) or from pumped kidneys? I also think that a 50% discard rate is not current and very high. Organ utilization is much more effective these days.*

*Zhaoli Sun—Each year nationally there are around twenty thousand potential cadaveric organ donors. Yet only ten thousand of these ultimately convert to successful organ donation. Criteria for donor acceptability include both objective and subjective criteria and many donors are rejected based on relative exclusions like advanced age or BMI. These donor characteristics are known to be imperfect surrogates for subsequent graft function and their widespread utilization results in the discard of some usable organs and the utilization of some grafts which subsequently perform poorly leading to retransplantation or recipient demise. Novel screening methods are badly needed for donor organs that*



*may far more accurately predict which grafts are acceptable for transplantation and which should be discarded. It deserves an RFA.*

**Title: Addressing Ethnic/Race Disparities in Access to Transplantation**

Author: Ebony Boulware

Votes: 36

Despite significant work documenting stark race disparities in access to transplantation, there is little research identifying strategies (at patient, provider, and system levels) that are effective in narrowing disparities. Studies of interventions to improve attitudes, behaviors, and practice patterns that have been linked to disparities are needed.

**Title: Increasing the Supply of Transplantable Cadaveric Kidneys**

Author: Lauren Brasile

Votes: 28

A major limitation to expanding donor criteria for procurement of cadaveric renal allografts is our continued reliance on the use of hypothermic preservation. Cold preservation limits the warm ischemic times to recover kidneys to less than 60-minutes post-cardiac arrest. In the era of molecular biology and proteomics, hypothermic preservation - a 60-year old technology can be thought of as the "ice age". Technologies such as effective prospective evaluations of viability and function, treatments to repair damage to the cytoskeleton, prevention of reperfusion injury, etc. could impact the ability to procure increased numbers of warm ischemically damaged kidneys. Rather than fabricating a 3-trillion cell construct containing stem cells that must differentiate into the heterogeneous cells required for renal function, as a first step why not attempt to replace the several million acutely damaged renal cells in an ischemically damaged allograft with human progenitor cells.

*Comments:*

*Paul Kimmel—Are there practical treatments to repair damage to the cytoskeleton?*

*Kelvin Brockbank—I completely agree with Lauren, although my focus would preferably be placed earlier in the treatment of kidneys to minimize or avoid ischemic and/or hypoxic injury. There is an extensive literature on drugs that interact with reperfusion injury and it is very likely that introduction of such treatments as close to donation as possible might dramatically increase donation of acceptable (viable, functional) kidneys for transplantation. Ex vivo repair by replacing damaged cells is also an exciting rational approach certainly more feasible than creating kidneys de novo as proposed elsewhere.*

*Kelvin Brockbank—Interesting, they placed the kidney on ice in a cooler. They should at least have employed hypothermic machine perfusion. Research on therapies targeting mechanisms of injury to retard the development of ischemic damage in shipment could also be very beneficial for this source of kidneys.*

*Lee Ann MacMillan-Crow—Did you guys read the recent article about a son donating a kidney (living) to his mother. But they were not a match, so instead his kidney went to another recipient, while another living kidney went to his mother. The sad part was that this kidney was placed in cold storage and*

transported across the county to his mother. I totally understand that this meant his mother got a kidney quicker than waiting for a deceased donor, but worry that long-term outcome will not be equal to a traditional living donor. Here is the link to the article:

<http://www.tampabay.com/news/health/donating-a-kidney-to-mom-part-of-a-cross-country-chain-of-events/1153933>

*Kelvin Brockbank—I think we are all in agreement. Methods for prevention of further damage to an organ during hypothermic storage (both static and machine perfused) are needed for kidneys currently being transplanted and for shipment of repaired organs that are not presently transplanted. Repair of damaged organs will require normothermic physiological conditions.*

*During development of hypothermic machine perfusion strategies my colleagues and I have always viewed the hypothermic transport device as an organ ambulance with a second device with the ability to work at multiple temperatures being used as an organ intensive care unit. The intensive care unit would be used for evaluation and therapy, regeneration, of questionable and damaged organs.*

*Perhaps now that benefits have been published for hypothermic machine perfusion in independent, controlled prospective clinical studies (including expanded criteria donors) it is time to look at inhibition of biochemical mechanisms of organ deterioration during hypothermic static and machine perfused storage, such as oxidative damage as proposed by Lee Ann. These studies may lead to improved kidney transplant outcomes for current practice. The suggestions made by Lauren could lead to further expansion of the "expanded criteria donor" group leading to many more organs being available for transplant.*

*Lauren Brasile—Lee Ann, I view hypothermic preservation technology, an essentially 50-years old technology, as the "ice age". We maintain a variety of normal mammalian cells in tissue culture for long periods with many population doublings so why not a whole organ? There are two major considerations: providing all the nutrients, co-factors, oxygen, etc. for continued oxidative metabolism and the maintenance of the normal barrier functions of the vascular wall. Where I whole heartedly agree with you is that after ischemically damaged organs are resuscitated in terms of a sufficient level of restored oxidative metabolism and repaired with new synthesis, the regenerated organs will have to be cooled down for shipment. Preventing subsequent damage will be pivotal. I believe the only feasible mechanism to solving the organ shortage will be the development of new technology that can be used to access the uncontrolled DCD, a huge untapped potential pool of organs. The uncontrolled DCD with the inherent ischemic damage cannot be recovered with traditional hypothermic preservation because if you procure a severely ischemically injury organ, inhibit metabolism with profound hypothermia, then you will still have a severely injured organ if it were to be reimplanted.*

*Lee Ann MacMillan-Crow—Great topic and comments! I agree with both Lauren and Kelvin. Clearly cold preservation induces renal damage- even at very early time points; however, the biochemical mechanisms responsible for renal damage remain elusive. It would be great if organs did not need to be placed in cold, but is this a real alternative? We are interested in oxidative injury and mitochondrial dysfunction that occurs during cold preservation. I would encourage NIH study sections to be a bit more open in regard to oxidant scavenger therapy during transplantation injury. There were some disappointing studies a long time ago with scavengers that were not nearly as specific or effective compared to newer compounds. I think it is very likely that more research in this area could lead to improved donor utilization for cadaveric kidney transplants by coming up with compounds that could be simply added to cold preservation solutions.*

*Kelvin Brockbank—I would like to point out another proposal #208 "Using Biomarkers to Improve Organ*

*Allocation and Reduce Discard" might also increase the supply of transplantable organs particularly if the biomarker assessment is applied to expanded criteria and non-heart beating donor groups that are not presently considered for clinical transplantation.*

*Lauren Brasile—Tight junctional integrity is dependent in large part on cell surface polarity that is lost following an ischemic insult. Restoration of the cytoskeleton following a pre-lethal ischemic injury (reversible injury requiring cell repair versus lethal injury requiring cell replacement) is dependent upon resuscitation of oxidative metabolism of sufficient magnitude to support new synthesis. In other words restore metabolism and the kidney will regenerate the cytoskeleton. Kelvin thanks for your comments and input.*

**Title: Outcomes in former living kidney donors**

Author: Didier Mandelbrot

Votes: 21

Young, healthy, Caucasians who donate kidneys have been shown to have excellent long term medical outcomes. However, there is no long term data on outcomes after donation by those who are African-American, hypertensive and/or overweight. There is a pressing medical need to better define risks of kidney donation for these and other groups at higher risk, to protect the safety of future living donors. The general nephrology community is increasingly being asked to evaluate donors, and make decisions on which risks are acceptable. In addition, general nephrologists are increasingly seeing former donors with estimated GFRs that place them in "CKD stage 3 or 4." Some of these patients may just require reassurance, while others may require further evaluation and management. Further awareness of living donor issues would be helpful for nephrologists, and further research on former living donors is needed to help guide living donor evaluations.

**Title: Autologous Replacement Kidneys**

Author: S. Steven Potter

Votes: 17

Nakauchi recently described a method for making replacement organs using interspecies chimeras. When combined with the Yamanaka method for making stem cells this opens the door for the production of autologous organs. Many challenges remain. Not just the specific organ, but the vasculature and hematopoietic system might also need to be strictly patient derived. Could genetically engineered pigs work, or would we need to go to a more closely related species? *Cell*. 2010 Sep 3; 142(5):787-99. Generation of rat pancreas in mouse by interspecific blastocyst injection of pluripotent stem cells.

Kobayashi T, Yamaguchi T, Hamanaka S, Kato-Itoh M, Yamazaki Y, Ibata M, Sato H, Lee YS, Usui J, Knisely AS, Hirabayashi M, Nakauchi H.

*Comments:*

*Kelvin Brockbank—This idea is similar to idea #101 in which autologous cells could be used to repair damaged allogeneic kidneys. The use of xenogenic kidneys from knockout pigs as templates would be an excellent but more complex next step without the issue of kidney supply.*

**Title: Mechanism of BK Virus Infection in Transplanted Kidneys**

Author: Kristina Paquette

Votes: 13

Based on recent FDA warnings about the link between immunosuppressant drugs and BK virus infection in transplanted kidneys, it seems prudent to conduct research into the mechanistic causes of BK-induced nephropathy in transplant patients so that appropriate and standardized prevention and treatment measures, and potentially a cure, can be developed.

Does BK infection originate from the allograft, the environment, or both? What tests can be developed to better detect BK in a donor kidney? Are there any lifestyle changes that the transplant recipient can make to reduce the chances of BK infection? What is the likelihood that a patient who has lost an allograft to BK will contract the virus in a second transplant?

There is evidence that the initially prescribed dose of mycophenolate mofetil is too high in some patients and that it acts as a gateway to BK. Blood tests for MMF levels are contraindicated because they are so expensive. Why are tacrolimus levels followed very closely after transplant while MMF levels are not? The FDA has issued warnings about the link between both these drugs and BK.

Many transplant centers do not routinely analyze the blood/urine of transplant patients for BK, so it is often not detected until significant damage has been done. Are routine analyses needed? How can biopsies of the allograft be prescribed and analyzed to better detect BK early? Currently, there is conflicting information regarding treatment -- do high doses of steroid help or hinder? Which immunosuppressants should be reduced (and by exactly how much) or stopped altogether? Can an antiviral medication be developed to cure BK infection?

**Title: Pathogenesis of Donor Specific Antibodies**

Author: Kenneth Kokko

Votes: 10

Why do we accommodate to some forms of donor specific anti-HLA antibodies but not to others? Increased research should focus on the pathogenic requirements on the ability of antibodies to fix complement, on the importance of binding affinity/avidity and on the identification/definition of pathogenic thresholds of antibody and strategies to normalize testing across different centers/platforms.

*Comments:*

*Lauren Brasile—Over the past decades there has been a concerted effort to use increasingly more sensitive crossmatch techniques. Prior to flow crossmatching, complement fixation assays were the standard technique to determine pre-sensitization. The idea was that any form of donor-specific antibody was potentially detrimental. A control crossmatch was considered important to identify true anti-donor antibody and eliminate false positive results. I think you are correct in suggesting that it may be important to distinguish the truly relevant pathogenic antibodies. This is particularly important when we consider that HLA identical living-related combinations do occasionally undergo humoral rejection and all would reject without adequate immunosuppression.*

**Title: Virome of the Kidney**

Author: David Perkins

Votes: 6

Investigate the virome (viral metagenome) in the kidney (urine) in disease (e.g., transplantation) and health

*Comments:*

*Jeffrey Kopp—I agree that we have much to learn about latent and integrated viral genomes in kidney, which may contribute to diverse kidney diseases, including glomerular diseases - and we have systematic approaches to identify these genomes.*

**Title: Vaccine development for Polyomavirus BK**

Author: Parmjeet Randhawa

Votes: 5

I propose T-cell & antibody based vaccine development against BK virus. It is envisaged that suitably designed active and passive BKV vaccines will also show efficacy against related polyomavirus species JC and SV40. With at least 100,000 transplant procedures performed annually worldwide, such a vaccine will result in health care savings of millions of dollars annually.

To highlight the polyomavirus associated disease burden in man, I note that 4.6 to 9.2% of U.S. kidney transplants are complicated by BKV-nephropathy or BK viremia. In addition, BKV causes hemorrhagic cystitis of variable severity in 5-60% of bone marrow transplantation recipients, and 5% of cancer patients treated with chemotherapy. JCV causes progressive multifocal encephalopathy, a functionally devastating and potentially fatal disease, in 0.5 to 5% of acquired immune deficiency syndrome (AIDS) patients. To put this in perspective, the World Health Organization (WHO) estimated 33.2 million HIV infected subjects in the year 2007. JCV has also been associated with human neoplasms, particularly brain tumors and cancer colon. SV40 DNA has been amplified from 40-100% of highly aggressive glial tumors, mesothelioma, and osteogenic sarcomas (estimated incidences of 6.7, 1.1, and 3.0 cases per 100,000 persons respectively, which imply approximately 100,000 affected patients in a world with 7 billion people).

In addition to the aforementioned direct clinical benefits, the proposed vaccine development program will enhance our understanding of interfering T-cells and antibodies that develop during the course of currently evolving gene therapy protocols using polyomavirus protein capsids as a vector.

Development of effective BKV T-cell and antibody based vaccines would eliminate health care costs currently incurred by regular virus screening programs in kidney transplant recipients. Developing a product that also affords protection against JCV and SV40 would be an added bonus. If successful, we have the potential of producing a product that will simultaneously reduce human suffering associated with both infectious disease and malignancy. For cancer patients the vaccine would not be a standalone intervention, but a potential adjuvant to standard

oncology therapies. Indeed, it could be argued that polyomavirus associated tumors are ideal candidates for antigen specific vaccination, since these malignancies express viral encoded tumor specific antigens not expressed by normal tissues.

Conceptually, both prophylactic and therapeutic vaccines can be designed. The best target for a prophylactic vaccine would be a polymer of VP1- protein arranged into ‘virus like particles’. These virus-like particles elicit strong neutralizing antibodies, a fact that was exploited in the development of human papillomavirus vaccines. For a therapeutic vaccine we need to induce T-cell mediated immunity against cells already infected by BK virus. A number of viral epitopes on the large T antigen have been recently described and could be used as the starting point for development of a T-cell vaccine.

*Comments:*

*Jeff Sheridan RN—Interesting concept. I received a kidney in May 2008, and on a regular screening, was found to have BK in July 2009. I still have BK detectable in my urine, and currently take Leflunomide. I'd much rather take the vaccine, than deal with both the potential damage to my kidney, as well as the potential problems with meds (Leflunomide affecting LFT's, and Cidofovir with its nephrotoxicity).*

*Andrew Wang—vaccine development is good approach. it is very helpful to develop a vaccine with high immunogenicity for effective treatment.*

### **Title: BK Virus in HIV patients**

Author: Kenar Jhaveri

Votes: 4

We don't see BKV Nephropathy as much in HIV patients on HAART therapy. Or to our knowledge it has been widely studied. This might be important in transplant world as perhaps BKV is suppressed by one of the HAART medications and a potential drug target for BK Nephropathy. We must look at other places besides Kidney Transplant for BKV Nephropathy for understanding the disease better perhaps.

*Comments:*

*Jeff Sheridan RN—Another group on chronic immunosuppression which may be worth studying are those with rheumatologic diseases, particularly those whose disease may lead to nephropathy (e.g. Lupus)*

*Roslyn Mannon—the presentation of CMV disease for example is also different in SOT versus HIV. And what is the research question?*

### **Title: Social Media for Improving Transplant Compliance**

Author: Patrick Brophy

Votes: 3

Teenagers are at high risk for losing their renal (and other solid organ) grafts due to medication non-compliance. With the use of social media a common way of communication in this age

group, it would make sense to develop a multi-faceted platform to develop interventions that improve compliance in this age group.

*Comments:*

*Robert Hurst—The problem with adolescents is they hate to appear different, plus their ability to extrapolate current behavior that feels good into future adverse sequelae is not fully developed. Thus, using social media to form groups that support health-appropriate data among peer's would seem to represent a very inexpensive but possibly very effective option for this age group.*

*Patrick Brophy—I think the research question to ask would be "Does the implementation and utilization of transplant (or any chronic disease) based social media platforms improve compliance (and health outcomes) in the adolescent population" Depending on the build one could also have med reminders and lifestyle choices. The problem would be developing a control group. I suspect that historical controls would be required. There are databases available with these data.*

*Roslyn Mannon—great idea but what is the research question here?*

*N/A—I think the idea is promising. Something like this has been done in adolescent liver transplant recipients and worked there (Pediatrics. 2009 Nov;124(5):e844-50). I believe the key will be mechanisms of reminding people, which could be done by text messages directly to the patient's cell phone or Email. It is of course also important, that any information sent to the patient is not visible to others (HIPPA and Facebook may not be a good match).*

### **Title: A strategy For Reducing the Kidney Allograft Discard Rate**

Author: Lauren Brasile

Votes: 1

The national discard rate has ranged from 12% to 18% over the years. Approximately 50% of the criteria for discard have been based upon kidney biopsies; although there are reports that when the kidneys have been transplanted glomerulosclerosis does not correlate well with 1-year graft survival, while pretransplant functional evaluations such as CrCl do. The development of novel biomarkers to reduce the rate suggested by Dr. Parikh is important. Another approach would be to develop prospective ex vivo evaluation of kidneys procured for transplantation but later discarded according to standard institutional criteria. This would necessitate transferring the hypothermically stored discarded kidneys to a near-normothermic perfusion. Quantifiable parameters such as restored metabolism, vascular dynamics, potential for regeneration and function could be used to develop a calculated index that would provide an objective basis for lowering the discard rate.

*Comments:*

*Lauren Brasile—Roz, I agree with you wholeheartedly. My suggestion was to remove the discarded kidney from the hypothermic preservation and transfer it to a near-normothermic perfusion for post-preservation evaluation. The identification of biomarkers relevant to the reason for the discard would in all likelihood be more easily detected if oxidative metabolism is resuscitated and of sufficient magnitude for*

*resumption of synthetic functions.*

*KUH Moderator—reassigned to TXN from AKI*

*Roslyn Mannon—too similar to other ex vivo approaches listed in ideas below, would combine to make a more effective research investigation*

**Title: Drug Discovery for Polyomavirus BK Infection**

Author: Parmjeet Randhawa

Votes: 1

The polyomaviruses are DNA viruses, with a 5 kb genome and virion diameter of approximately 45 nm. The most important human species is BK virus (BKV). This virus is latent in most healthy adults. In kidney transplant recipients, viral excretion in the urine is described in 20-60% of subjects, and BKV nephropathy, a disease characterized by damage to the graft parenchyma, develops in up to 10%. BKV is also commonly excreted in the urine of bone marrow transplant recipients. In this patient population, mild forms of hemorrhagic cystitis in up to 60%, while 5-10% develop severe disease characterized by pain and hematuria. BKV associated hemorrhagic cystitis also occurs in 5% of cancer patients treated with high dose cytotoxic agents, of which the best known is cyclophosphamide.

No effective drugs are currently available for the treatment of BKV infection. Cidofovir and Leflunomide are currently used empirically but efficacy has not been shown in well-designed studies. Both drugs have significant toxicity. Importantly, their in-vitro efficacy in BK virus cultures is very modest. Not surprisingly, clinical benefit is only seen when these drugs are administered for weeks to months. Thus, there is currently an unmet need for potent and safe compounds for use in the transplant clinics. The ideal drug would also have prophylactic utility, and could potentially eliminate the need to undertake expansive PCR or cytology based assays that are currently being used to screen for polyomavirus infections at major transplant centers. Rationally designed 'panpolyoma' drugs would likely also show efficacy against (i)SV40 virus that has been occasionally associated with renal disease, and (ii) JC virus, which may cause both nephropathy and a devastating neurologic disease called Progressive Multifocal Encephalopathy in AIDS patients.

Viral targets that could be targeted for drug development include the viral capsid binding protein that interacts with the cellular receptor, and Large T antigen which plays a key role in viral replication. Both targets are amenable to high throughput biochemical screens and protein crystal based computational methods to discover small molecule inhibitors of viral protein function.

**Title: Aggressive Government Stance to Increase Organ Availability?**

Author: Scott Pace MD

Votes: 1

First of all I'm only trying to stimulate thoughtful, well-meaning and useful dialogue and not start a controversial argument, but is it time for the government to get more aggressive in making more organs available for transplantation? I think one thing that is missing is a general lack of public awareness or central discussion about the need for all organs. I know where I live in rural



America it seems like renal transplantation is very slow to occur and kidney-pancreas, heart and liver is generally nonexistent. Would a government sponsored increase in public awareness make much of a difference or do Americans just generally want to keep their organs even after they have expired for religious or other reasons? Should patients who have used taxpayer funding for their health care be "forced" to give up their organs if the deceased patient would be buried with viable and badly needed organs? Again this is something that I have long thought about but never heard discussed and I can honestly say that I haven't formed a solid opinion on this. But again please limit any feedback to thoughtful and well-meaning dialogue and keep our emotions in check.

**Title: Immune Monitoring Biomarkers with Multiple Immunosuppressants**

Author: Vikas Dharnidharka

Votes: 0

Multiple immunosuppressant drugs are now used in a variety of diseases affecting both the native and the transplant kidney, as well for systemic immunological disorders. The total amount of immunosuppression then achieved in each patient at a given point in time is unknown. This sets the patient up for complications of over-immunosuppression (infections) or under-immunosuppression (inadequate treatment). Studies of biomarkers that can be used to judge net state of immunosuppression would be of immediate clinical impact.

*Comments:*

*Roslyn Mannon—CTOT supported by NIAID is looking actively at these questions*

**Title: Clinical Trials in Kidney Transplantation**

Author: Ajay Israni

Votes: 0

We spend a lot of resources on pre-operative cardiac evaluation of kidney transplant recipients. However, there are no trials of pre-operative cardiac evaluation in kidney transplantation. This is one of several examples of significant variation in how providers manage patients pre and post-kidney transplantation. The variation reflects uncertainty about the clinical standard and represents spending on potential ineffective care and contributes to soaring healthcare costs. Future clinical trials can provide guidance on appropriate management pre and post-kidney transplantation.

*Comments:*

*Roslyn Mannon—Do you see this as first a natural history study ala Framingham or go interventional immediately? The issues include as you point out variability in Center practices and also the population transplanted at each center.*

## Other

### Postings and Comments

#### **Title: In defense of serendipity: We cannot manage discovery by voting**

Author: Raphael Kopan

Votes: 20

Voting reflects the current makeup of our community and defines the common denominator of our imagination. Because we (scientists, administrators, politicians) cannot predict future need nor can we predict which idea will get us to any desired therapy, a certain amount of investment in avant garde hypotheses is essential to our continued success. The NIH has tried its best to put money to good and efficacious use but in doing so, efforts that do not fall within mission relevance and topic areas mandated by the congress, the administration or the "community vote" became a casualty of over-investment in near horizon projects. We must improve the balance between "community selected topics" and investigator initiated ideas. This will ensure the innovation pipeline continues as long as ROIs adhere to strict "best science" criteria (innovative, hypothesis driven, and evidence-based investigation into the mechanisms of development and disease; all broadly defined, whether or not included in a topic area listed to the left of this post). We should leave open a window for the unexpected as we all know that serendipity is the mother of invention.

#### *Comments:*

*Greg Dressler—I would agree that the current system of grant review discourages real innovation and risk taking. One alternative might be to set aside some percentage of NIH money to fund investigators, not ideas. I could imagine an NIH Investigator status, somewhat like HHMI, where proven successful mid-career PIs are funded directly for a significant period of time to essentially pursue whatever they wish without having to satisfy a voting committee. This may be perceived as elitist by some and not fair to new PIs, but I would say that one of the best metrics for success is a track record of success. Also, new PIs have many other additional sources of funding that are unavailable to established PIs.*

*Angela Wandinger-Ness—I strongly disagree with selecting innovators, only from an established investigator pool, as would be the case if one uses track record as a key criterion. Sometimes it is precisely those who are less fettered by old ideas and dogmas that may have the most creative ideas. So why not simply have a mechanism for high risk, high gain applications that in fact is anonymous. Only the idea is reviewed and evaluated independent of any identifiers.*

*Raphael Kopan—I believe the NIH Merit Award reflects the sentiment expressed by Greg. In my view, expanding the Merit Award system is a good idea, but one that should be considered independently from the point I made above.*

#### **Title: Systems biology for genomics, proteomics and metabolomics**

Author: Patrick Brophy

Votes: 4

This plays a bit off Dr. Kretzler's integrated systems biology suggestion and comments therein. With the multitude of data that is starting to emerge with large scale GWAS/CNV analysis it is

clear that analysis is a key factor. Given the centers of genetic excellence around the country- does it not make sense to develop a strategy forward to properly analyze these data? Perhaps developing centers of excellence in combination with the CTSA centers would move us toward the goal of personalized medicine? With renal metabolomics emerging in the biomarker and diagnostic fields we will be faced once again with volumes of data and poor abilities to properly analyze it. Investing in such expertise would have long term benefit and would be preferable than investing in more sequencing machines.

**Title: Urinary miRNAs**

Author: John Johnson

Votes: 3

microRNAs have been used as both biomarkers and to provide cues to pathophysiology of disease processes. miRNAs are abundant in the urine and screening in renal diseases could be a useful correlation to miRNAs in renal tissue and animal models.

**Title: Gene therapy for kidney disease**

Author: Patrick Brophy

Votes: 3

Developing gene therapy techniques for renal diseases would be a worthy goal. The vector technology has not lent itself to renal tropism, however this may be changing. Rescuing in-utero structural abnormalities or genetic causes of renal diseases would not only reduce healthcare costs, it may also allow our community to develop further analytical tools to understand the pathways of renal development.

**Title: Affordability of Renal Replacement Therapy: Health economics**

Author: Johan Rosman

Votes: 2

There is an undeniable tension between the demand for RRT and the costs to deliver this. With increasing pressure on health budgets to be expected in the years or decades to come, we are confronted with potential rationing of these services. A thorough study into the cost/benefit ratio of RRT is warranted now before the topic becomes politicized and irrational decisions being taken. The real costs of PD, HD, transplantation as well as palliative care need to be carefully analyzed and balanced with Quality of Life parameters. Such a study would have important ramifications for how we treat our patients, especially the elderly, based on clinical evidence and not solely based on the emerging drive to save costs.

**Title: Creating Enabling Technology Super Core?**

Author: Raphael Kopan

Votes: 2

Perhaps the best way to open the community to systems biology and emerging OMICS methods and standards would be to support the creation of a central biostatistics/bioinformatics intramural group at NIDDK whose main task will be to collaborate with extramural investigators. The

precise composition of such a "super core" should be flexible and evolve with need/technology. Under supervision of a few permanent senior scientists, members could be on sabbatical from other academic programs or postdoctoral fellows on route to independent positions. In this manner, instead of supporting a few groups to build community resource that may be released at the tail end of a technological wave, NIDDK will accelerate the dissemination of new technology into many laboratories.

*Comments:*

*You—This appears to be more resource-related than workforce pipeline related and may be better assigned to the other category.*

*Andrew McMahon—A common theme at many Institutions is inadequate support for statistical and bioinformatics analysis. As a result, data accrued at significant cost is not exploited either as well, or as fully, as one might wish. NIDDK's support in this way could significantly enhance its researcher's activities while more broadly building a valuable knowledge and data resource to educate and inform researchers and clinicians.*

*Dennis Brown—This is in principal a good idea, but in practice it is essential to have dedicated personnel to perform this type of work - especially the post-acquisition analysis. Otherwise this becomes no one's priority, and the analysis can fall very short of expectations. So any such center would need the capacity to support and train personnel from each individual lab - in my opinion. The analysis is very labor intensive and specialized.*

*Robert Hurst—As head of our unfunded systems biology group at my institution, I echo the above comments. The value of these approaches lies in their ability to move beyond what we know, but to achieve this requires a heavy and dedicated commitment of time. I think that the proposed idea is excellent and could move forward our ability to examine complex biological systems as systems that can be effectively modeled, but only if properly supported. Only a handful of academic institutions have the level of commitment to make it happen, mainly because such work is not concurrent with the "cottage industry" model of academic research.*

**Title: Affordability of Renal Replacement Therapy: Health economics**

Author: Johan Rosman

Votes: 2

There is an undeniable tension between the demand for RRT and the costs to deliver this. With increasing pressure on health budgets to be expected in the years or decades to come, we are confronted with potential rationing of these services. A thorough study into the cost/benefit ratio of RRT is warranted now before the topic becomes politicized and irrational decisions being taken. The real costs of PD, HD, transplantation as well as palliative care need to be carefully analyzed and balanced with Quality of Life parameters. Such a study would have important ramifications for how we treat our patients, especially the elderly, based on clinical evidence and not solely based on the emerging drive to save costs.

**Title: Is Deflux the solution for Vesicoureteral Reflux (VUR)?**

Author: Myra Carpenter

Votes: 1

VUR is the most common congenital urologic condition associated with urinary tract infections (UTI) in children. Deflux (dextranomer/hyaluronic acid copolymer) was developed in Sweden and was FDA approved for domestic use in 2001. The availability of endoscopic therapy (ET) has transformed the treatment of VUR but debate continues. "Fix it and forget it," is said to be a major advantage. Many advocate that all children upon diagnosis undergo ET, as this would eliminate the need for long term prophylaxis, repetitive uncomfortable studies and open surgery. Compliance with medicine taking would not be an issue. But the role of Deflux in the treatment of children is not fully defined, therefore, and remains controversial. Some use this as first line therapy immediately after diagnosis, while others might suggest its usage only after a failure of prophylaxis or persistence of VUR. Reports are now emerging questioning the durability of Deflux and, therefore, its clinical use. Initial reports from Sweden showed that 10% of children cured of reflux would be found to reflux again 1 to 5 years after treatment. More recently, up to 15% of children successfully treated have returned with recurrent pyelonephritis and documented new renal scarring. In the Deflux arm of the Swedish Reflux Study 20% of those in whom VUR was cured had pyelonephritis and VUR reappear during the 2 year observation period. Families and clinicians may not be able to "forget it" after all. Even though further treatment of VUR may be averted in some by the early use of Deflux, cost remains a factor. One cc of Deflux costs \$1,800 dollars. Up to 2 cc's per ureter may be needed with the newer HIT technique. The surgical, anesthetic, hospital and lab fees and post-operative radiographs are in addition. 14,500 cc's of Deflux were provided to hospitals in 2009, at a cost of over \$26,000,000. If we conservatively assume that 4,000 children underwent treatment at an additional cost of approximately \$10,000 each, a total of \$66,000,000 were spent in 2009 on this procedure. Therefore, significant questions regarding Deflux's role and durability remain. A prospective, multi-institutional trial is needed.

**Title: Biochemical "Mapping" of kidney cell and tissue phenotype**

Author: H. William Schnaper

Votes: 1

This is a proposal to utilize recent and anticipated gains in genomics, proteomics and metabolomics to precisely define the biochemistry of cells or tissues that have received stimuli that are associated with chronic kidney disease. A major controversy in the pathogenesis of CKD is the role of epithelial-to-mesenchymal transition (EMT). The argument centers upon the origin of cells producing ECM, and particularly intensely upon whether renal tubular epithelial cell EMT contributes to the population of fibroblasts. I believe that our inability to address this problem is partly definitional, and would propose that we re-frame the argument. The problem has been stated anatomically. While the anatomy is important, we do not yet have sufficient perspective to address it. We should first consider it as a problem of pathophysiology. Many investigators describe cells as undergoing EMT, yet they refer to almost as many different phenomena. We lack precise definitions of the events under study. Each cell might be characterized as existing on a continuum between what has been regarded as purely "epithelial" or purely "mesenchymal." Perhaps more accurately, each cell has a molecular "signature" that determines how it responds to a given stimulus. As this signature varies over different conditions, its response to the same stimulus also will differ. Thus, whether or not the tubular

epithelial cell dedifferentiates to become a fibroblast is only a part of the question; it also may dedifferentiate to present antigens, produce potentially fibrogenic cytokines, etc. We urgently need to develop a “map” of molecule expression and cell function that could be used to precisely characterize the nature of changes that occur during fibrogenesis. Such a map would not in itself solve the problem, but it would provide a new paradigm that could enhance our ability in:

- Basic science – Define what molecular signatures are associated with various cell activities (including the productive fibroblast), and permit lineage tracing studies to define the origin of cells with different fibrogenic functions (not only ECM production).
- Translational science – Define how specific molecular signatures are associated with different stages of disease pathogenesis and progression.
- Clinical science – Understand how molecular signatures obtained from biopsies correlate with response to specific treatment.
- Clinical medicine – Guide the clinician in applying a therapy appropriate to disease stage.

**Title: Patient Samples!**

Author: Richard Ransom

Votes: 1

As a Ph.D. who has (naively) embarked on a multi-center clinical study to examine nephrotic syndrome and glucocorticoid therapy, I have been repeatedly amazed at the potential available and the high barriers to making use of this potential. Many questions have come to my mind as I've gathered samples and begun analyses: Why do I have to re-invent the wheel at every institution (no unified IRB system)? Why aren't patient samples collected every time a patient visits a research hospital? Why does every patient receive a different course of therapy? My (naive) idea is to push hard for standardization of care, sample collection as part of standard of care, and for strong support for clinical sample collection and biorepositories. Incentives for clinicians, patients, and families to enroll subjects and provide samples? Support for research hospitals to buy centrifuges, freezers, and hire staff to process samples? Major efforts to push standards of care associated with clinical trials?

*Comments:*

*Krystyna Rys-Sikora—Any comments from our multi-center clinical trial experts?*

**Title: The fourth option**

Author: Stephen Ash

Votes: 0

We all know that there are three options in vascular access for dialysis: fistulas, grafts, and tunneled and cuffed central venous catheters. In over 20 years, there has not been a new concept for removing blood for dialysis in spite of the numerous problems and great cost of the current choices. What we need is a "fourth option" based somehow on mimicking the way Nature connects blood vessels. This would be a great advance, and certainly a challenge for our most creative physicians and scientists.

*Comments:*

*Arnold Lande—The “fourth option”, for your consideration, might be a combination of fistula and graft---The In Situ Debranched Vein Fistula Graft (VFG). Arteriovenous fistulae often fail to mature. A familiar intervention is to channel all of the arterial blood rapidly through a single vein, by accessory vein obliteration. The identical VFG, created electively some weeks after fistula surgery, when the best egress vein has declared itself, performs like a synthetic graft. But it consists of in situ endogenous tissue that retains all of its adventitial fibrous support as well as vasavasorum to foster prompt healing following small punctures. We believe that A/V differential pressure is a desirable energy source, especially for wearables. Percutaneous compressions alternating over two sites near the middle of the VFG on the forearm manifest and make accessible for twice-a-week cannulations, arterial pressures upstream and venous pressures downstream. Access to arterial and venous pressures and flows is expected to lead to safety, simplicity and reduced costs of utilizing a wearable hemodialyzer, by eliminating the need for most electrical pumps. Safety and efficacy will also be enhanced by slowing the whole process, consistent with 168 hours/week continuous treatments. Compressions (volar or dorsal) are usually against the firm, flat, interosseous membrane of the forearm or against the radius or ulna. Alternating compression sites and permitting a gush of blood flow, helps avoid clotting and pressure necrosis. The forearm, (where the blood is) worn device, volumetrically modulates the extracorporeal blood flow down to a predetermined low rate of ~30 ml/min, which is considerably less than the reticuloendothelial system's capacity to clear low dose heparin. While the extracorporeal circuit, including the dialyzer, benefits from full “therapeutic” anticoagulation, the systemic circulation experiences only safe, prophylactic anticoagulation. The “fourth option” might constitute a system, which combines virtues of fistula and graft, and more.*

**Title: Measuring kidney function**

Author: Gary Striker

Votes: 0

The recent flurry of papers and presentations on the use of markers, other than creatinine, for measuring renal function needs more emphasis in the general nephrology and medical community. Since some are now available in clinical laboratories, the nephrology community should come together and make some recommendations.

*Comments:*

*Gary Striker—The recent paper in Diabetologia on the underestimation of GFR using the MDRD equations in obese T2D patients emphasizes the need for attention being paid to this issue. The NIH would be a good vehicle to promote such an effort.*

**Title: KDOQI Research Recommendations**

Author: Dolph Chianchiano

Votes: 0

For a broad approach to critical research questions and objectives, the National Kidney Foundation suggests that participants in the Kidney Research National Dialogue consider the research recommendations that have been published as part of the KDOQI clinical practice guideline development program. In all, over 200 thought leaders were involved in shaping these recommendations, and they are based upon gaps in knowledge identified through structured literature reviews. The research recommendations cover topics ranging from the definition of chronic kidney disease (CKD) to vascular access for kidney replacement therapy. For example,

there are research questions that relate to diabetes and CKD, as well as hypertension and CKD, and studies suggested concerning hemodialysis adequacy, as well as adequacy of peritoneal dialysis. A document summarizing all the KDOQI research recommendations is available as follows: <http://www.kidney.org/professionals/research/pdf/KDOQIResearchRecom.pdf>

**Title: Improved Animal (Rat) Models**

Author: Richard Ransom

Votes: 0

A cogent point was raised by Dennis Brown in his post "Big and small science" that the availability of advanced -omics has led to a loss of emphasis on physiology. It is clear from my direct experience with mouse models of nephrosis and corticosteroid therapy that a major impediment to physiologic studies is the lack of adequate animal models. This lack is exacerbated by several factors, especially the cost and effort required to develop new models and the knowledge that the resulting publication is unlikely to be in a high-impact journal. I believe it is time to re-emphasize in vivo studies, and to reward in particular those who explore alternatives to transgenic mice, as their limitations in certain physiologic processes are becoming increasingly evident.

**Title: Predictive value of BMD loss in idiopathic hypercalciuria**

Author: Augusto Cesar S S Jr

Votes: 0

Idiopathic hypercalciuria (IH) is the most common metabolic abnormality in patients with nephrolithiasis. Several studies suggest that cells involved in bone formation and resorption take part in the mechanisms of increased urinary calcium excretion. Recent studies have shown strong clinical and epidemiological evidence supporting an association of bone loss and IH. However there is still no definitive conclusion about the possible results of this bone loss: are there increased fracture atherosclerotic risks?

**Title: Biomarkers for Active surveillance of RCC**

Author: Robert Veltri

Votes: 0

There are considerable small RCC discovered through routine CAT, MRI etc. There are new programs that are collecting such cases but few efforts to create biorepositories for such cases. The latter would permit new biomarker discovery as well as application of existing molecular biomarkers for early detection (i.e. microRNAs, copy number markers, nuclear morphometry, epigenetic and genetic biomarkers, metabolomics etc.). Such an approach has already been started in prostate cancer and it would be useful to support such critical, cost-effective and safe surveillance programs.

**Title: Rapid Fluid Retention Syndrome (RFRS)**

Author: Sinasi Salman

Votes: 0



In our nephrology practice we see many patients with rapid fluid retention syndrome. We need to find the cause(s) of this "new syndrome".

*Comments:*

*Deepak Sharma—IN my opinion one of the important contributor is pro-inflammatory state to this syndrome & capillary leak. If drug/drugs can be developed to counter this. Other contributory factor could be rapid fluid administration, so a customized goal directed protocol is the need of the hour*