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ADVANCES IN NEPHROLOGY

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NewYork-Presbyterian Nephrology ranks #4 in the nation.

Legitimizing Acute Kidney Injury: A More Precise Approach in the Making

In 2017, the Division of Nephrology at NewYork-Presbyterian/Columbia University Irving Medical Center was named one of the six recruitment sites for the nationwide Kidney Precision Medicine Project (KPMP) sponsored by the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK). With the purpose of understanding chronic kidney disease and acute kidney injury, the KPMP seeks to make precision medicine possible for kidney diseases. The five-year project, which will unfold in two main phases, has several objectives for the scientists involved:

- to understand the kidney at a detailed cellular and molecular level
- to create a Kidney Tissue Atlas identifying critical cells, regions, and disease pathways
- to identify new markers and treatment targets that make personalized, effective, and safe treatments possible for kidney diseases

> **"The Kidney Precision Medicine Project is trying to understand the cell types that are specific to kidney injury at the molecular level and that can be targeted in the future with new therapeutic agents."**
>
> **— Dr. Krzysztof Kiryluk**

Nephrologists **Krzysztof Kiryluk, MD, MS, Jonathan M. Barasch, MD, PhD**, and **Andrew S. Bomback, MD**, are leading the Columbia recruitment component of the KPMP cohort of patients with acute kidney injury (AKI). It is a perfect partnering of expertise. Dr. Kiryluk is a physician-scientist with a primary focus on human genetics and genetic susceptibility to different forms of kidney disease.

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Precision Medicine in Transplantation: The Narrative Continues

Dr. Manikkam Suthanthiran

It has been nearly 60 years since the first living donor kidney transplant was performed. In a presentation of outcomes of the earliest kidney transplants at a World Transplant Congress, data reported on 250+ kidney transplants showed the one-year survival rate was less than 10 percent if the patient received a kidney from a living donor. "And nobody survived if they received a kidney from a deceased donor," says **Manikkam Suthanthiran, MD,** Chief of the Division of Nephrology and Hypertension and Chief of Transplantation Medicine at NewYork-Presbyterian/Weill Cornell Medical Center. "Transplantation was a high risk, experimental therapy. Many people thought that doing transplantation was even unethical and wanted no such programs in their hospitals. Nevertheless, several pioneers persisted and today, kidney transplant, and most other transplants, have a survival rate in excess of 85 percent."

Over the past three decades, much of the progress in kidney transplantation derives from the groundbreaking research of Dr. Suthanthiran and his colleagues at Weill Cornell, where the success rate for kidney transplants is at 90 percent. Hospital stays

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Precision Medicine in Transplantation: The Narrative Continues *(continued from page 1)*

Advancing the Field of Kidney Transplantation – Selected Milestones at Weill Cornell

1984
Elucidates cytolytic mechanisms in humans, stimulating the development of targeted therapies for patients with organ grafts, type 1 diabetes, psoriasis, and rheumatoid arthritis
Journal of Clinical Investigation

1988
Discovers T cell co-stimulation and induction of transplantation tolerance
Cellular Immunology

1999
Demonstrates that cyclosporine induces cancer progression by a cell-autonomous mechanism
Nature

2001
Develops and validates urinary cell mRNA profiling of human kidney graft recipients
The New England Journal of Medicine

2005
Develops preamplification enhanced real-time quantitative PCR assays for the precise quantification of mRNAs in urinary cells from kidney transplant recipients
The New England Journal of Medicine

2012
Discovers and validates a molecular signature for the noninvasive diagnosis of human renal allograft fibrosis
Transplantation

2013
Demonstrates that noninvasively ascertained urinary cell mRNA profiles offer a noninvasive means of diagnosing acute rejection; anticipate future development of acute rejection; and serve as yardsticks of *in-vivo* immune status of the kidney graft recipients
The New England Journal of Medicine

2015
Discovers that a combination of urinary cell mRNAs and metabolites is diagnostic of acute cellular rejection in the kidney allograft with a high degree of accuracy
Journal of the American Society of Nephrology

have also experienced dramatic changes, down from two to three months to a current average length of stay of four to five days.

With that said, Dr. Suthanthiran notes that there are still challenges to be met. "First of all, any patient who has had a transplant will always be at risk for rejection," he says. "The transplant can function beautifully for 10 years and the patient can still have a rejection that cannot be reversed. This is a major issue that remains to this day, and this is where transplantation precision medicine and the bench-to-bedside and bedside-to-bench continuum come into play. A second issue is that uncommon infections are common in transplant patients due to a lifetime of needing immunosuppressive drugs. And the third issue is that we are actually paying a price for our success in the sense that now that transplants bring longevity, our patients are increasingly susceptible to malignancy, and not just a local malignancy, but a cancer that is likely to metastasize."

In his current research, Dr. Suthanthiran is targeting the immunosuppressive drugs that can impede transplant patients from enjoying long-term good health. "For some time, it has been thought that these immunosuppressive drugs can make the patient an immunological cripple susceptible to cancer progression," says Dr. Suthanthiran. In fact, he and his colleagues at Weill Cornell reported on their study in *Nature* nearly 20 years ago that showed one of the most important drugs used in transplantation, cyclosporine, has a direct effect on the cancer cell, making it more potent.

"We now know that there are other immunosuppressive drugs that fight fire with fire, using them to suppress the cancer cell," notes Dr. Suthanthiran. "But there was no clinical yardstick to determine whether or not your patient is too immunosuppressed or not enough."

This began to change for kidney transplant recipients in 2001, when Dr. Suthanthiran and his research team developed and validated urinary cell mRNA profiling of human kidney graft recipients. In 2013, the team demonstrated in the largest, NIH-sponsored Clinical Trials of Transplantation study to date that urinary cell mRNA profiles offer a noninvasive means of diagnosing acute rejection, providing a surrogate for transplant biopsy; can anticipate future development of acute rejection; and serve as a yardstick of *in-vivo* immune status of the kidney graft recipients (*The New England Journal of Medicine*). The breakthrough noninvasive test could detect whether transplanted kidneys are in the process of being rejected, as well as identify patients at risk for rejection weeks to months before they show symptoms. Their innovative discovery was recognized by the National Institute of Allergy and Infectious Diseases as one of its top 20 research advances for 2013, and in April 2014, the Clinical Research Forum selected the work as one of the Top 10 Outstanding Clinical Research Achievements in the United States.

In 2015, another study by the Weill Cornell researchers validated that a combination of urinary cell mRNAs and metabolites is diagnostic of acute cellular rejection in the kidney allograft with a high degree of accuracy.

More recently, Dr. Suthanthiran and his colleagues undertook a study to examine the causes and predictors of death-censored kidney allograft failure in light of corticosteroid-free maintenance immunosuppression regimens, now applied in many centers and which was adopted by the Weill Cornell kidney transplantation program in 2001. The retrospective study included 1,670 kidney recipients transplanted at Weill Cornell and identified 137 recipients with allograft failure, confirming their previous observation from a study of 634 kidney graft recipients that early corticosteroid withdrawal in recipients of renal allografts is safe and efficacious.

Causes of allograft failure, which were validated by physicians and confirmed by biopsy, were:

- Acute Rejection (21%)
- Glomerular Disease (19%)
- Transplant Glomerulopathy (13%)
- Interstitial Fibrosis Tubular Atrophy (10%)
- Polyomavirus-Associated Nephropathy (7%)
- Medical Conditions (21%)
- Unresolved (9%)

Importantly, the Weill Cornell investigators noted, "With growing emphasis on antibody-mediated rejection, we identified that acute cellular rejection continues to be an independent risk factor for graft failure. In addition to resolving leading causes of kidney allograft failure, the study suggests that novel approaches to target these post-transplant complications may help realize the full benefits of kidney transplantation."

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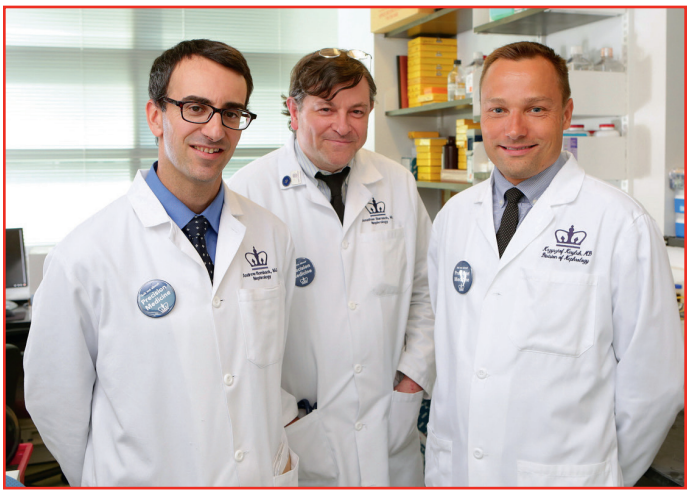
Legitimizing Acute Kidney Injury: A More Precise Approach in the Making *(continued from page 1)*



Dr. Andrew S. Bomback, Dr. Jonathan M. Barasch, and Dr. Krzysztof Kiryluk

Dr. Barasch is a cell biologist who has been studying the pathogenesis of AKI for many years. And Dr. Bomback is a clinician with specific expertise in performing kidney biopsies. The team also includes **Vivette D. D'Agati, MD**, Director of Renal Pathology at Columbia, who oversees one of the largest renal pathology laboratories in the country.

"What is becoming clear, albeit still under investigation, is that the national standards for the diagnosis of acute kidney injury (AKI) are not specific enough to be applied to all of our patients, and as a result have obscured our understanding of AKI," says Dr. Barasch. "Many fields in medicine utilize multiple tools – cellular, functional, and imaging – for the diagnosis and for understanding disease. Nephrology is the only field in medicine to have a single analyte and a single assay test for acute organ injury, namely the serum creatinine test. By definition, a single mode of testing cannot represent the complexity of 21 different cell types in the kidney. The Kidney Precision Medicine Project, which seeks to rethink the process of acute kidney injury on a cell by cell and a gene by gene level, is exactly the cure for our problem."

"The Kidney Precision Medicine Project is going to take a completely new approach to two problems that have been around forever: chronic kidney disease and acute kidney injury," adds Dr. Bomback. "These are the two most common conditions that we see in nephrology. Over the last 10 to 20 years, we have done a very good job of identifying these entities. However, we haven't done a very good job of getting to the core question of why they happen to certain people and not to others. The bigger question is can we identify any specific targets that will enable us to treat patients who have these entities so that we can reverse the process? Currently, if someone is diagnosed with acute kidney injury that is not due to dehydration, medication, an obstruction, or autoimmune related, but rather is the more common form of a global insult to the kidney, we don't have a definitive treatment. All we can do is provide supportive care."

"The Columbia project site is concentrating on acute kidney injury," says Dr. Kiryluk. "This acute form of kidney damage often occurs in hospitalized patients and carries high morbidity and mortality. This means there is an elevated risk of dying if a patient is diagnosed with AKI during hospitalization."

A Closer Look at AKI

In the February 2011 issue of *Nature Medicine*, Dr. Barasch and his co-authors reported that the protein, Ngal, is intensely expressed in the urine of animal test models and also in humans with damage to the kidney. "The protein appears in the urine within three hours of the damage," explains Dr. Barasch. "The rapidity of gene expression of this protein is such that you can see it earlier than the standard markers of kidney damage and it is extremely sensitive to the injury. As a result of the appearance of Ngal in the urine, one can detect damage initiated in the kidney hours or even days before the usual clinical indications alert the physician to the fact that there's a problem."

Most kidney injuries are linked to an infection, severe heart failure, or extremely low blood pressure, notes Dr. Barasch, but they also may be associated with toxicity to medications, including chemotherapy, as well as allergic reactions that affect the kidney. "In the setting of any of these circumstances, Ngal rises very quickly and is secreted from the kidney into the urine alerting the physician. In contrast, simple dehydration, mild heart failure, and diuretic use fail to raise the level of Ngal, meaning that the physician can rule out the effect of these states on the kidney after measuring Ngal. We know this both from animal models and from extensive clinical studies in different Emergency Departments led by **Thomas Nickolas, MD, MS,** and **Sumit Mohan, MD, MPH**."

> **"As a result of the appearance of Ngal in the urine, one can detect damage initiated in the kidney hours or even days before the usual clinical indications alert the physician to the fact that there's a problem."**
>
> **— Dr. Jonathan M. Barasch**

While Ngal has been patented as a biomarker and is known worldwide, it is not yet clinically in use in the U.S. while it undergoes further study. "We have conducted several studies on this protein and found that not only does it have the genetics to be expressed very quickly, but it derives from specialized cells within the collecting duct – a part of the kidney that was not known to participate in kidney damage," explains Dr. Barasch. "This has opened up a new biology as to how kidney cells respond to injurious stimuli. From the data, we have found many new pathways and developed many fresh ideas about the kidney and kidney damage."

The Conundrum of Creatinine

The implications of these studies are far-reaching and have the potential to refine the diagnosis of acute kidney injury. "Our findings indicate that probably every cell in the kidney responds to damage in unique ways," says Dr. Barasch. "In comparison, serum creatinine cannot provide etiological information and it changes too slowly to be useful, especially in time-pressured locations, such as the emergency room or postoperatively. Most importantly, Ngal responds to some stimuli but not to other stimuli that also raise serum creatinine."

In a review of the electronic health records of 3.8 million emergency and intensive care patients at NewYork-Presbyterian using an algorithm designed by **Nicholas P. Tatonetti, PhD,** Director of Clinical Informatics, Herbert Irving Comprehensive Cancer Center

at Columbia, the researchers detected more than 61,000 diagnoses of acute kidney injury as defined by rising creatinine level. Within three days, however, 73 percent of patients with an AKI diagnosis had creatinine levels that returned to normal, suggesting that many of these patients may not have had kidney damage after all.

"The data also showed that patients who have only transient rises in creatinine don't make the Ngal protein," says Dr. Barasch. "This all points to the inadequacy of creatinine in identifying acute kidney injury; that as a marker, it is too broad and encompasses entities that are not really an injury to the kidney; and it is too insensitive and too delayed compared to the proteins that the kidney is making. Previous studies have shown that a small but persistent change in creatinine level is a greater predictor of morbidity and mortality than a large, but transient, increase. But because the course of creatinine cannot be known when first seeing a patient, it is possible to deliver a misleading diagnosis. An initial misdiagnosis can lead to delayed or inadequate treatments."

Enter the Kidney Precision Medicine Project

"To further research in kidney precision medicine, the NIDDK assembled a network of clinical sites to recruit patients to obtain kidney biopsy tissue for next generation interrogation techniques to try to figure out the precise molecular mechanisms of injury," explains Dr. Kiryluk. "The recruitment sites – three for acute kidney injury and three for chronic kidney disease – essentially form a national clinical referral network for the KPMP."

"All of the data for individual patients and their samples, both kidney tissue samples and other biospecimens, will be sent to the KPMP Central Hub, which is responsible for data coordination," continues Dr. Kiryluk. "The Central Hub interacts with all of the clinical sites, harmonizes the data, and then forwards the tissues to five additional sites nationwide, which will perform tissue interrogation. Each of the tissue interrogation sites will apply a different kind of multi-omic method to interrogate kidney tissue, and all of these methods will be combined and compiled in the form of a multidimensional kidney atlas. Additionally, a patient panel is built into the KPMP consortium. The patients participate in our work groups and committees and they provide feedback to us about many different aspects of this study. This is a very complicated consortium structure and a remarkable investment by the NIDDK."

"The previous studies that we have done are the tip of the iceberg," says Dr. Barasch. "Now, through the KPMP, we will be able to use human biopsy tissue to really interrogate the gene response in all different kinds of cells in the kidney to get to the bottom of the response. Rather than a singular response of rising creatinine or a specific pathologic assay, we will find that every cell is responding in a stimulus-dependent manner, bringing

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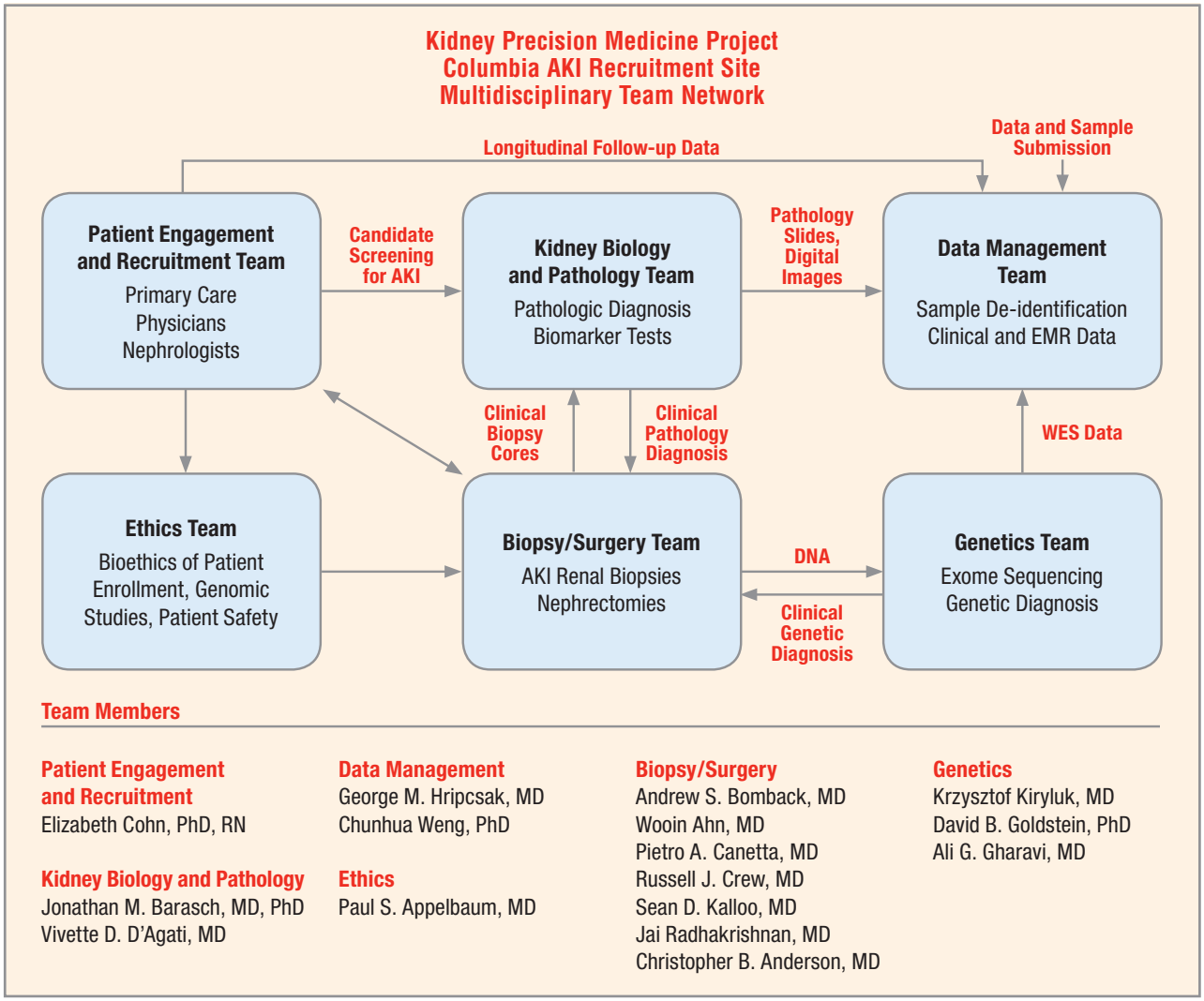

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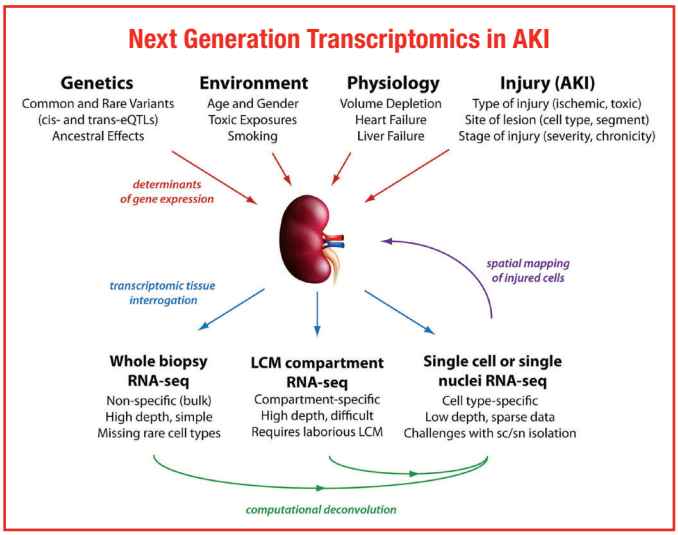
Legitimizing Acute Kidney Injury: A More Precise Approach in the Making *(continued from page 4)*

accuracy or precision to our diagnoses. KPMP will allow cutting-edge genetic and molecular determination of the process of acute kidney injury. This will not only open up the possibility of better diagnostics for each type of injury, whether it's chemotherapy, a kidney stone, or a response to sepsis, but it will also allow us to identify the pathways that are potentially druggable."



The interplay of genetic, environmental, and physiologic factors determines the baseline variability in normal kidney transcriptome that may confound tissue interrogation efforts. (Source: Seminars in Nephrology. *January 2018.)*

"The kidney biopsy is an underutilized tool for making the diagnosis of kidney disease," notes Dr. Kiryluk. "If we want to think about better ways of discovering therapeutic targets and identifying medications and interventions that can prevent kidney disease, we need to go after the kidney tissue. The idea behind KPMP is that we will be able to demonstrate the utility of kidney biopsy for molecular diagnosis, prognostication, and precise subtyping of kidney injury based on molecular mechanisms. The tissue-derived transcriptional information, combined with the analysis of whole genome sequence data for the same patients, will also provide a powerful tool for dissection of potential genetic mechanisms of kidney injury. This could change clinical practice in terms of indications for biopsy, the physician's willingness to perform a biopsy and, with increasing patient awareness, patients actually asking the physicians to have a biopsy done."

"What this project will be accomplishing is changing the paradigm of how we approach patients with acute kidney injury," adds Dr. Bomback. "Now, when a patient presents with one of these mysterious forms of acute kidney injury, instead of basing our management entirely on clinical suspicion and empiric diagnoses, we are going to suggest a kidney biopsy. We're going to have that kidney biopsy read by our world-class pathologist here, but we're also going to have some of that tissue sent to scientists around the country who will interrogate that tissue. Then they are going to try and figure out, by using the newer technologies, if there are signals within the tissue that can be identified and that might be amenable to therapy."

Each of the three KPMP recruitment sites for AKI has a goal of accruing 200 patients with acute kidney injury in the first five years. "This is a fairly ambitious target since we will need to convince patients that this is something that they should think about and that it's worth the risk," says Dr. Kiryluk. "But these are sick patients; they're hospitalized and things are not going well for them. So, this is going to be quite challenging. It is one of the reasons the project has an important ethics component. We are asking patients to contribute an extra piece of their kidney tissue during kidney biopsy. And that is not without risk."

> **"What this project will be accomplishing is changing the paradigm of how we approach patients with acute kidney injury."** — Dr. Andrew S. Bomback

That is why **Paul S. Appelbaum, MD**, Director of the Division of Law, Ethics, and Psychiatry at Columbia, and an expert in the ethical and legal aspects of precision medicine, is a key member of the Columbia KPMP team. And that is also why Dr. Kiryluk emphasizes the importance of patient engagement. "We will get feedback directly from patients in terms of what risks they are comfortable with, what they want to get out of the project, and how we can conduct this study in the most ethical way."

"We've really never been able to approach both acute kidney injury and chronic kidney disease from a curative standpoint," says Dr. Bomback. "We are hoping that someday we can actually use what we're learning from this study to be able to say to patients, 'This is the specific reason why this happened to you and we have a therapy that can cure this.'"

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Precision Medicine in Transplantation: The Narrative Continues *(continued from page 2)*

The Tolerant Patient

Research of the clinical application of urinary cell profiling for the individualized management of kidney allograft recipients continues in earnest by Dr. Suthanthiran and his colleagues. Currently, creatinine levels in the blood are used to monitor kidney allograft function, but studies have shown that changes in creatinine are not a sensitive marker for acute rejection in patients who are otherwise clinically stable. The current gold standard approach to diagnose acute rejection is an invasive needle biopsy. While this has become safer over the years, a biopsy still carries risk of bleeding, infection, arteriovenous fistula formation, and, although rare, allograft loss.

According to Dr. Suthanthiran, given the risks of the biopsy procedure and the need for continuous monitoring of kidney allograft status, the development of noninvasive biomarkers that are sensitive and specific for acute rejection would help avoid a for-cause biopsy to evaluate allograft dysfunction and also help manage immunosuppression over the life of the allograft.

To this end, the Weill Cornell team undertook a study to determine the feasibility of developing informative biomarkers of tolerance. Performing urinary cell mRNA profiling of 225 biopsy-matched urine specimens from 170 kidney allograft recipients, the researchers discovered a urine biomarker of allograft rejection and tolerance and also demonstrated the dominance of negative regulation (CTLA-4) over cytotoxic effectors (perforin and granzyme B).

"Identification of this marker enables us to technically say the patient is tolerant and begin to wean them from immunosuppressive drugs," says Dr. Suthanthiran. "The ability to adjust and even minimize immunosuppression based upon noninvasive molecular and mechanism-based monitoring should help to personalize transplant medicine, enabling us to titrate the drugs so that the patient is adequately immunosuppressed. Some patients may need more and some patients may need less. It's about the right drug for the right patient at the right time and at the right dosage."

"We now have a very good index of whether or not the patient is undergoing rejection or non-rejection, whether the patient will undergo rejection in the near future, and whether or not the patient is over-immunosuppressed or under-immunosuppressed," adds Dr. Suthanthiran. "This will provide us with guidelines for personalizing immunosuppressive therapy to help reduce life-threatening infections and malignancy due to over-immunosuppression, and allow us to take transplantation precision medicine to the next level – this capability is very unique to the research setting here at NewYork-Presbyterian and Weill Cornell."

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