SPECIALTY REPORT | WINTER 2018

Division of
Nephrology

Mount Sinai

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African Ancestry and Blood Pressure: New Study Provides Insights

People of African ancestry have long had higher blood pressure rates than any other population—something many health professionals realize but few have researched. A Mount Sinai study published in the March 2017 edition of the *Journal of the American College of Cardiology* is providing some overdue insight on this phenomenon, revealing that genetic factors found only in this population significantly increase both the risk of high blood pressure and end-stage renal disease.

The study involved data from Mount Sinai's Bio*Me*™ BioBank Program, an electronic medical record–linked biological repository that contains DNA and plasma from 39,000 patients. Girish Nadkarni, MD, MPH, an Assistant Professor of Medicine (Nephrology) at the Icahn School of Medicine at Mount Sinai, discovered a link between the presence of Apolipoprotein L1 (APOL1)—a mechanism that evolved to protect people in Africa against the *trypanosoma brucei* parasite—and high blood pressure.

"We analyzed blood pressure readings based on whether patients had zero, one, or two copies of APOL1," Dr. Nadkarni says. "What we found was that the risk of hypertension and higher blood pressure increases with each copy of APOL1, which means if you have only one copy of the gene, you still have a higher risk of developing earlier hypertension and higher blood pressure at a younger age than someone who does not have any copy of the gene."

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John Cijiang He, MD, PhD

The Division of Nephrology continued in 2017 to advance in a broad variety of areas, both clinical and scientific.

Mount Sinai's unique hemodialysis unit in a shopping mall, which we discuss in this issue, grew to serve approximately 220 patients under the medical direction of Vijay Lapsia, MD. In addition, we have expanded our home hemodialysis program and reached an agreement with DaVita to provide medical directorship for several new units in Brooklyn and the Bronx.

On the research side, we maintained our National Institutes of Health (NIH) funding of $12 million last year and are part of several major NIH consortiums, including the NIH Kidney Precision Medicine Project, for which Mount Sinai serves as a central hub together with the University of Michigan and the University of Washington. Mount Sinai is also part of the NIH-funded APOL1 Long-Term Kidney Transplantation Outcomes Network (APOLLO) Clinical Centers.

Among the research breakthroughs covered in this year's report are work by Girish Nadkarni, MD, MPH, and Erwin Bottinger, MD, showing that genetic factors found only in people of African ancestry significantly increase the risk of both high blood pressure and end-stage renal disease; progress by my colleagues Bhaskar Das, PhD, Barbara Murphy, MD, and me in identifying antifibrosis targets, pathways, and treatments; and studies by Kirk Campbell, MD, identifying kidney podocytes as a key target whose injury may be implicated across a variety of renal disorders.

As the Icahn School of Medicine at Mount Sinai enters its 50th anniversary year, our training efforts, including the fellowship program run by Dr. Campbell and profiled in this report, continue to bear fruit. We recruited seven outstanding new fellows this year; added a new critical care nephrology program to existing programs in geriatric palliative care nephrology and transplant nephrology; and saw two junior faculty members receive their first R01 grant, indicating that we have successfully trained young investigators in the Division.

I am proud to note that The Mount Sinai Hospital raised its *U.S. News* ranking in Nephrology to No. 10 in the nation last year, but I am even prouder of what we have achieved for our patients, colleagues, and trainees. I hope you find this report enjoyable and informative. ■

Podocytes and Proteins

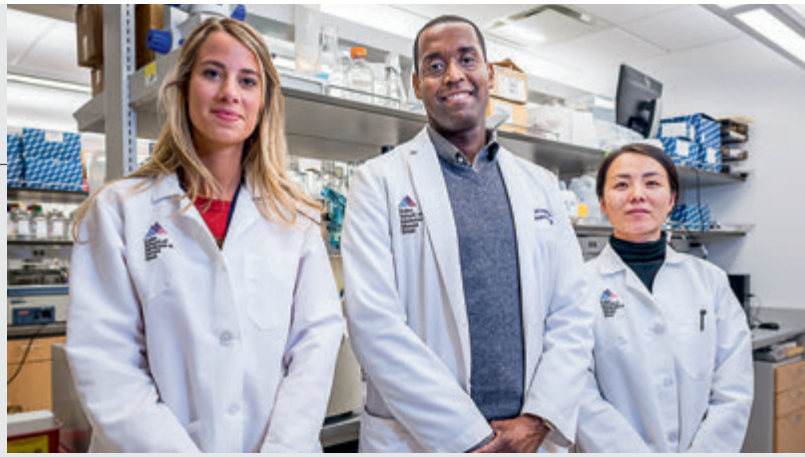
A series of Mount Sinai studies involving two proteins holds the promise of new therapeutic treatments for the 26 million Americans who have kidney disease.

Kirk Campbell, MD, Associate Professor of Medicine (Nephrology) at the Icahn School of Medicine at Mount Sinai, has been studying kidney podocytes as a key target whose injury may be implicated across a variety of renal disorders. Using cell culture and mouse models, he has determined that the Yes-associated protein (YAP) expressed in podocytes is essential in protecting them from injury.

"When the expression of YAP is decreased, there is a leakage of protein in the urine, which leads to progressive disorders like focal segmental glomerulosclerosis (FSGS)," Dr. Campbell says. "This suggests that YAP is essential for maintaining normal homeostasis of the kidney filter."

Since YAP is activated in several solid malignancies, such as hepatocellular carcinoma, these findings raise questions about the potential impact of cancer therapies under development that inhibit YAP function. "Based on these findings," Dr. Campbell says, "it is possible that YAP inhibitors could result in proteinuria as a side effect of podocyte injury."

YAP also has the potential to block pro-injury properties of dendrin, a protein that Dr. Campbell has identified as having a deleterious impact on podocytes. Using an FSGS mouse model, he found that deleting the dendrin gene enhanced podocyte protection from injury and significantly extended renal survival.



Kirk Campbell, MD, center, with researchers Christina Cuttitta and Xiaoxia Yu, MD, PhD, is studying kidney podocytes as a key therapeutic target.

"The life span almost doubled," Dr. Campbell says. "We observed a delayed onset of proteinuria and renal failure, suggesting that dendrin could be a therapeutic target in glomerular disease."

More studies are required, but Dr. Campbell believes that both proteins have the potential to advance the quest for targeted therapeutics in proteinuric kidney disease.

"This is a field with a significant unmet clinical need," Dr. Campbell says. "We have no cell-specific therapy, so this work is vital in revealing pathways that could be harnessed for novel therapeutic drug development." ■

Miriam Chung, MD, seeks to bring Mount Sinai's research and clinical strengths together to help patients with a multidisciplinary approach.

A Coordinated Center for Glomerular Disease

When Miriam Chung, MD, was approached to help establish a center for glomerular diseases at Mount Sinai Health System, she readily accepted the invitation.

"I knew Mount Sinai had a well-established basic and translational glomerular disease research program based on the work that Kirk Campbell, MD, and John Cijiang He, MD, PhD, are doing," says Dr. Chung, an Associate Professor of Medicine (Nephrology) at the Icahn School of Medicine at Mount Sinai.

"I was also familiar with Mount Sinai's clinical trials in glomerular diseases, as well as the glomerular disease registry and tissue bank. I saw an opportunity to help bring all of these strengths together in a concentrated way that could lead to improved clinical outcomes for patients."

Launched in 2017, the Glomerular Disease Center establishes a more multidisciplinary and coordinated approach to glomerular disease research, clinical trials, and treatments. Dr. Chung says the goal is for it to serve as both a diagnosis and treatment referral base for complex cases and a resource for outside physicians in treating their patients.

"Primary glomerular diseases are relatively rare," Dr. Chung says. "As a result, some health care providers may not feel comfortable treating them, and patients may have difficulty finding the care they need. By consolidating and building on our current knowledge, services, and research efforts, we can play a key role in addressing these issues."

The Center has launched an initiative to create patient-friendly materials about glomerular diseases and has enhanced Mount Sinai's Nephrology Fellowship Program by providing more teaching tools and experience with glomerular diseases for fellows. "We already had a glomerular curriculum in place, but the goal is to have a more comprehensive and easily accessible version, so all fellows gain the necessary knowledge and confidence to treat patients," Dr. Chung says.

Prior to joining Mount Sinai, Dr. Chung was a nephrologist at Rogosin Institute and NewYork-Presbyterian Weill Cornell Medicine and an Assistant Professor at Weill Cornell Medical College, where she was active in the education of fellows, residents, and medical students. Her glomerular disease interests include IgA nephropathy, lupus nephritis, ANCA vasculitis, and nephrotic syndrome. These interests are reflected in the clinical trials currently underway at Mount Sinai, which address lupus nephritis, membranous nephropathy, IgA nephropathy, and focal segmental glomerulosclerosis.

"Therapeutic options typically involve a long course of immunosuppressive medications, many of which have side effects or result in subpar outcomes, so there is a real need for better treatments," Dr. Chung says. "The more multicenter trials we participate in, the more treatment options we are able to offer our patients, and that fulfills the ultimate goal of this Center: better patient care and outcomes." ■

A focus on clinical trials and broadening a fellowship program

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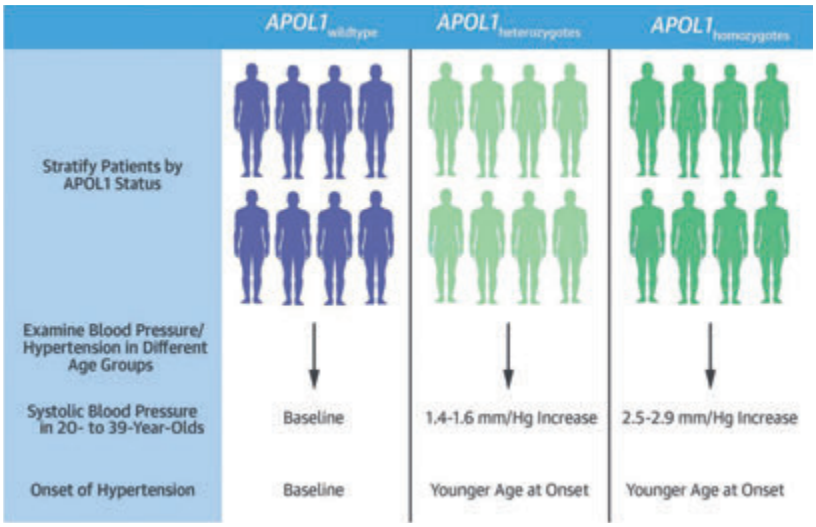

APOL1 Genotypes and Phenotypic Data from EMRs. Nadkarni, G. N. et al., J Am Coll Cardiol. *2017;69(12):1564-74.*

According to Dr. Nadkarni, the presence of one copy of APOL1 resulted in a blood pressure increase of 1.6 mm of mercury, which he says "might not sound significant, but it is almost like having the blood pressure of someone 10 years older than you are. If you have two copies of the gene, your blood pressure is 3 mm higher. Ultimately, this could explain to a large extent the difference in blood pressure between people of African ancestry and other populations."

For that reason, Dr. Nadkarni says, this finding may be one of the most significant developments in nephrology over the past 20 years; yet, it raises the question as to why no one had discovered this link before. Dr. Nadkarni says several factors were at play: genomic studies have traditionally focused on people of European ancestry; the APOL1 gene was not present on standard genotyping arrays; and studies related to hypertension typically have focused on patients ages 40 and older.

"We know that blood pressure and kidney disease are tightly linked," Dr. Nadkarni says. "Yet by older ages, patients may likely develop kidney disease, so this independent effect of blood pressure couldn't be seen, as the mean age in previous studies has been 50 to 57. In our analysis, we found that APOL1 is associated with higher blood pressure in young people of African ancestry even before the onset of kidney disease."

Dr. Nadkarni, who collaborated on the study with Erwin Bottinger, MD, Professor of Medicine (Nephrology), and researchers from Vanderbilt and Northwestern Universities, says the goal now is to determine why APOL1 causes hypertension, whether it is linked to other diseases, and whether the gene can be safely blocked using medical treatments. In the meantime, he says, the results of the study may establish a biomarker for a population that, when two copies of APOL1 are present, has twice the risk of developing kidney disease and five times the risk of developing end-stage renal disease.

"If we test for this genetic factor early enough and intervene to help people control blood pressure, we might be able to help them prevent kidney disease from happening later on in life," Dr. Nadkarni says. ■

Investigational Device Shows Potential for Treating Immune Dysregulation Disorders

A recent case at Mount Sinai Beth Israel suggests that an investigational device may have potential benefits as a life-saving therapy for nephrology, immunology, and hematology patients with immune dysregulation disorders.

Nikolas Harbord, MD, an Assistant Professor of Medicine (Nephrology) at the Icahn School of Medicine at Mount Sinai, saw a 39-year-old male who presented with fever, dyspnea, and lymphadenopathy. An extensive malignancy and infection workup followed, including biopsies of bone marrow, lymph nodes, and liver, resulting in a diagnosis of hemophagocytic lymphohistiocytosis (HLH), an often deadly disease that is diagnosed in one out of every 800,000 people annually but may be undiagnosed in many more.

Recognizing that the patient had a relatively poor prognosis, the nephrology and intensive care team obtained institutional review board approval for compassionate use of CytoSorb® to treat the patient. Manufactured by the CytoSorbents Corporation in New Jersey, CytoSorb is an extracorporeal cytokine adsorber approved for use in Europe in situations where cytokines are elevated, such as systematic inflammatory response syndrome, sepsis, liver failure, and post-cardiac surgery. It is not currently FDA approved.

"One of our emeritus faculty is an expert in hemoperfusion and sorbent technology and a consultant for CytoSorbents," Dr. Harbord says. "We knew based on that experience that it

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Bringing Dialysis to a Shopping Mall

Every week, Harlem residents visit the East River Plaza shopping mall, at 520 East 117th Street, to purchase groceries, browse household items, and undergo dialysis therapy at the Mount Sinai Kidney Center.

As odd as it may seem to locate a dialysis unit at a mall, Vijay Lapsia, MD, Associate Professor of Medicine (Nephrology) at the Icahn School of Medicine at Mount Sinai, says it has proven quite popular among patients.

"Most of the patients we see are in an older demographic, and regular dialysis can be time-consuming and somewhat dispiriting for them," says Dr. Lapsia, who is Medical Director for the Center. "The fact that we are not in a clinic or hospital environment, and the fact that they can combine treatments with shopping or other errands, really appeals to them."

The Mount Sinai Kidney Center, formerly located on East 94th Street, has been providing patients with hemodialysis treatments at the East River Plaza since 2015. Dr. Lapsia says the decision to relocate to the mall was not a deliberate one; it was more the result of happenstance.

"We needed to expand the Center from 24 dialysis units to 35, which we could not do at the previous site," Dr. Lapsia explains. "It was very hard to find a space that offered a reasonable rent and addressed logistical issues such as parking. This new location is less clinical and more practical for our patients, most of whom live in Harlem."

Warm, welcoming, and spacious, the new space has enabled Dr. Lapsia and his team not only to expand the Mount Sinai Kidney Center but also to upgrade services and equipment. The Center invested in 40 new 2008® Series Fresenius Hemodialysis Machines, including five backup machines. The units are electronic medical record–enabled and use bicarbonate bags, which are easy to manage, are environmentally friendly, and reduce the risk of contamination. The Center has also installed sophisticated dual reverse-osmosis-based water purification systems to better remove bacterial contaminants from water during patient treatment.

"Patients are exposed to approximately 360 liters of water during each treatment," Dr. Lapsia says. "When we upgraded the water purification system, it was very important that the new system delivered something very close to ultra-pure water for up to 40 or more dialysis patients at a time and have redundancy built in, in case of an outage. Significantly reducing the risk of treatment-related complications such as pyrogenic reactions or chronic inflammation was a top priority."

Since opening, the Center has experienced a steady increase in patients from 165 to approximately 220. "We are seeing an increased incidence as well as prevalence of kidney disease nationally, which is one factor in that growth," Dr. Lapsia says. "But part of it is the fact that this location significantly cuts the travel time for our patients. Given that treatments can average four hours, this location is more convenient for them."

Vijay Lapsia, MD, is Medical Director of a Mount Sinai dialysis center in the East River Plaza shopping mall, a location chosen for its convenience to patients like Roxanne Holder.

Dr. Lapsia is looking to build on that sense of convenience by eventually providing fully integrated care at the Center. He envisions on-site primary care, vascular surgery, an interventional nephrology suite, diabetes care, and a complete home-dialysis program, among other offerings. In some ways, what he envisions mirrors the shopping mall that houses the Center: a one-stop medical home for dialysis patients.

"That's an appropriate descriptor," Dr. Lapsia says. "We envisioned from the start that this would be a comprehensive, patient-centered shop for all our patients' needs, and that's what we intend it to be." ■

Identifying New Anti-Fibrosis Targets and Pathways

As the cost of dialysis treatment reaches $40 billion nationwide, Mount Sinai researchers continue to make significant advances in identifying anti-fibrosis targets and pathways and in developing new therapies that could prevent patient progression to end-stage kidney disease.

One such therapy, B173, inhibits homeodomain-interacting protein kinase 2 (HIPK2), a key regulator of multiple pro-fibrosis pathways, including TGF-β1/Smad3 and Wnt/-β-catenin. In a preclinical trial published in the February 20, 2017, edition of the *Journal of the American Association of Nephrology*, B173 was found to decrease Smad3 phosphorylation and reduce renal fibrosis in three mouse models of kidney disease: unilateral ureteral obstruction, folic acid–induced nephropathy, and HIV-1 transgenic.

Bhaskar Das, PhD, left, and John Cijiang He, MD, PhD, have identified a potential kidney fibrosis blocker in a preclinical trial.

"Kidney fibrosis is a common pathway leading to end-stage kidney failure and dialysis," says John Cijiang He, MD, PhD, the Irene and Dr. Arthur M. Fishberg Professor of Medicine (Nephrology) and Chief of the Division of Nephrology at the Icahn School of Medicine at Mount Sinai. "If you can effectively block it, you can prevent patients from needing dialysis. Until now, there has been no drug developed that is capable of doing that, but the results of our preclinical trial suggest that B173 has the potential to be an effective anti-fibrosis treatment."

Developed by Bhaskar Das, PhD, Associate Professor of Medicine (Nephrology) at the Icahn School of Medicine, B173 is unique in that it blocks pro-fibrotic pathways without disrupting the pathways of cell-cycle control and tumor suppression. "We like to have a broad inhibition of the fibrosis pathway," Dr. He says. "However, these drugs are often associated with side effects, such as an increased risk of tumor growth. Our drug acts allosterically, interfering with the ability of HIPK2 to associate with Smad3 by changing its structure. I would not call it completely novel, because other researchers have used this approach, but we are lucky to have this exciting new drug, which effectively inhibits pro-fibrosis pathways without blocking kinase activity. Therefore, we expect that side effects will be significantly diminished."

Dr. He's research dovetails to an extent with a related study led by Barbara Murphy, MD, Dean for Clinical Integration and Population Health and Murray M. Rosenberg Professor of Medicine and Chair of the Department of Medicine at the Icahn School of Medicine. Published in the December 7, 2016, edition of the *Journal of the American Association of Nephrology,* the study identified hematopoietic cell kinase (Hck), an Src family tyrosine kinase, as a key target in preventing chronic kidney injury, defined by interstitial fibrosis and tubular atrophy, in renal transplant patients.

Through analysis of human kidney biopsy specimens with chronic allograft injury (CAI), among other data, Dr. Murphy and her colleagues determined that Hck was a key driver of the genes associated with CAI. They further discovered that it acts as a key regulator, interacting with 23 out of 85 differentially expressed genes in human renal transplants.

Based on these findings, Dr. Murphy researched the Kinase Inhibitor Resource for Hck inhibitors. She identified dasatinib, a U.S. Food and Drug Administration–approved drug for chronic myelogenous leukemia, as a potential candidate. *In vitro* tests revealed that dasatinib inhibits both COL1A1, a well-known target of TGF-β, in renal tubular epithelial cells and fibroblast cell proliferation. Meanwhile, *in vivo* tests involving a mouse model with unilateral ureteric obstruction revealed that the drug also reduces pro-fibrotic markers, phosphorylation of Smad3, and renal fibrosis. These findings suggest that Hck is a novel target for the prevention of fibrosis.

More research is required on both fronts, but Dr. He is optimistic that these efforts will lead to effective renal fibrosis treatments. "If we can intervene at an early stage, we can prevent patients from progressing to end-stage kidney disease and hopefully reduce the number of people receiving dialysis," he says. ■

Fellowship Program Focuses on Academics

When the Nephrology Fellowship Program at the Icahn School of Medicine at Mount Sinai began accepting candidates for the first time in 1959, it established a high standard for excellence in nephrology education that continues to this day. More than 70 percent of the program's graduates have entered academic careers over the past five years; its alumni include three current New York City nephrology division chiefs and the editor of the *Journal of the American Society of Nephrology*.

In light of that legacy, the program's director, Kirk Campbell, MD—a graduate of the program himself—says he gives considerable weight to academic accomplishments and career goals when selecting program applicants.

"We certainly welcome clinically gifted applicants who want to pursue careers in private practice," says Dr. Campbell, an Associate Professor of Medicine (Nephrology) at the Icahn School of Medicine. "But our goal has always been to train future leaders in industry, research, and medical education as well as clinical medicine. The achievements of our alumni speak for themselves."

Those achievements are the result of a program that distinguishes itself from other fellowships in several ways. For one, it shifts focus in the second year from inpatient nephrology training to individual clinical interests, enabling fellows to pursue elective rotations in specialties such as interventional nephrology, onco-nephrology, and palliative care nephrology. Fellows also benefit from intensive longitudinal outpatient hemodialysis and peritoneal dialysis experiences during their second year, something few other programs are able to provide.

"Because our hospital owns a dialysis center, our fellows are able to follow their own panels of patients over a 6- to 12-month period," Dr. Campbell says.

Fellows can pursue basic clinical or translational research under the supervision of faculty mentors, where they have access to two Ruth L. Kirschstein National Research Service Award Institutional Research Training Grants (T32) to pursue academic careers.

"We have a unique variety of clinical tracks for our fellows," Dr. Campbell says. "Some have been certified by the American Society of Diagnostics and Interventional Nephrology. Others pursue dual subspecialty training in fields such as palliative or critical care medicine."

The program is further distinguished by its dedication to ensuring the well-being of all fellows throughout training.

Karendip Kaur Braich, MD, left, a fellow in Mount Sinai's Nephrology Fellowship Program, reviews a chart with Kirk Campbell, MD.

Miriam Chung, MD, who became Associate Program Director for the Fellowship in 2017, says it is one of only a handful of fellowship programs nationwide that have implemented a night float system.

"Essentially, our fellows take turns covering at night without being on call during the day," says Dr. Chung, an Associate Professor of Medicine (Nephrology) at the Icahn School of Medicine. "The goal is to prevent fatigue that will compromise patient care, and this is the only program in the tristate area that I'm aware of that has adopted this system."

The program continues to evolve to ensure that the next generation of alumni is fully prepared to become leaders in the field of nephrology. Dr. Chung is launching a new glomerular disease center that will give attendees experience in these relatively rare diseases, and Dr. Campbell is looking for opportunities for fellows to be involved in the development of new nephrology therapies.

"Traditionally, nephrology had the smallest number of clinical trials of any medical specialty," he says. "That is starting to change. I believe we are on the cusp of a significant expansion in treatment options for our patients, and we will capitalize on that phenomenon." ■

A goal of training future leaders in industry, research, and medical education

› *continued from page 4* **INVESTIGATIONAL DEVICE SHOWS POTENTIAL**

could help, so we received institutional permission to use the device, and the company sent it to us."

The patient was started on a daily six-hour regimen of combined hemodialysis/hemoperfusion, which was performed by a dialysis nurse. After the patient's blood was cleaned through dialysis, it was passed through the CytoSorb device, where biocompatible porous polymer beads removed the cytokines. Dr. Harbord says the patient's clinical improvement was immediate and significant, with hemodynamic stabilization during the first treatment, followed by enhanced liver function and mental status.

"We were able to demonstrate marked improvement in the patient's clinical illness by removing the cytokines, which were responsible for his hypotension and shock," Dr. Harbord says. "The dose of pressors, the day-to-day bloodwork—all of it improved, and we saw a 56 percent reduction in cytokines over the course of therapy."

Dr. Harbord says that CytoSorb is nonspecific, removing many elevated cytokines (both pro- and anti-inflammatory), but he adds that the risks are not significant and that the risk of not intervening may be greater. Given the results achieved in this investigational use, he says, cytokine hemadsorption has potential as a treatment for HLH, a disease with a mortality rate in excess of 50 percent.

"I think we demonstrated real proof-of-concept benefit for patients through investigational use," Dr. Harbord says. "I would not hesitate to use it again, and I would hope it gives other nephrologists the confidence to adopt it based on our experience at Mount Sinai." ■