Mount Sinai

Division of Nephrology

"Kidney on a Chip" Shows Cells in a New Light

A Mount Sinai Health System researcher is taking kidney disease research out of the petri dish and into the future to advance our understanding of disease pathology, improve the identification and definition of patient phenotypes, and accelerate the development of new therapies.

Evren Azeloglu, PhD, an Assistant Professor of Medicine (Nephrology) at the Icahn School of Medicine at Mount Sinai, is one of a handful of researchers nationwide who is exploring the potential of organ-on-a-chip technology to facilitate kidney disease research. Using induced pluripotent stem cells, Dr. Azeloglu is replicating specific aspects of kidney architecture and function on 3-D biomimetic polymer chips.

"These chips have tiny microfluidic chambers where we grow the cells," Dr. Azeloglu says. "We can recapitulate the cytoskeletal architecture of the glomerulus, we can feed it, we can introduce different aspects of kidney physiology, and we can monitor pathological processes, all in an environment that induces the cells to behave more as they would in the body."

According to Dr. Azeloglu (above, with, from left, PhD student Smiti Bhattacharya, medical student Benjamin Adegbite, and research associate Alecia Muwonge), the technology offers a complementary perspective to organoids grown in petri dishes. "Because an organoid more closely mimics the actual tissue of a human kidney, it is considerably complex and thus it could be more difficult to image, or conduct experiments on one particular segment," he explains.

"Organ-on-a-chip technology represents a super-simple cell culture system that enables

continued on page 3 ›

John Cijiang He, MD, PhD

Finding ways to speed up drug development in kidney disease, as well as the diagnosis of the disease itself, is the theme of this year's report from the Mount Sinai Health System's Division of Nephrology.

Our cover story details work by Evren Azeloglu, PhD, to explore whether organ-on-a-chip technology can provide an alternative to both organoids and animal models. Because the organ on a chip is much easier to image, drug impacts can be seen quickly at the molecular level, potentially greatly speeding up preclinical drug development.

KidneyIntelX™, developed by Steven Coca, DO, MS, and Girish Nadkarni, MD, MPH, uses artificial intelligence to more effectively identify chronic kidney disease (CKD) early. Using data from electronic health records and disease-specific blood biomarkers, KidneyIntelX generates a personalized risk score indicating the likelihood that a patient will develop CKD, or advanced and potentially end-stage renal disease, over the next five years. Once approved by the U.S. Food and Drug Administration, KidneyIntelX will be commercialized by Renalytix AI Plc, a Mount Sinai-associated company that recently had an initial public stock offering in London. This approach could also help us identify high-risk patient cohorts for clinical trials to test the efficacy of drugs for kidney disease.

ShangPharma Innovation is working with me and my colleague Bhaskar Das, PhD, to conduct pharmacokinetic studies of a promising new anti-fibrosis drug, BT 173. This collaboration could significantly shorten the time needed to bring this compound into clinical trials and, we hope, into clinical use. And as we work on new treatments, we also seek to provide the best in patient care, exemplified by the home dialysis program at The Mount Sinai Hospital, nationally ranked by *U.S. News & World Report*. The program gives patients the flexibility, control, and comfort that they need to live full and enjoyable lives.

The Most Comfortable Place for Dialysis: a Patient's Home

Every week, approximately 100 Mount Sinai Kidney Center patients undergo dialysis in the most comfortable and welcoming environments in the area: their own homes.

Jaime Uribarri, MD, leads Mount Sinai's Home Dialysis Program, the largest in New York City and a leader in patient care.

"Home dialysis gives patients more flexibility and control, which they really appreciate," says Jaime Uribarri, MD, a Professor of Medicine (Nephrology) at the Icahn School of Medicine at Mount Sinai and Director of the Renal Clinic and the Home Dialysis Program at The Mount Sinai Hospital. "Instead of making time to visit a dialysis center several times a week, they can do it when it is convenient for them."

That freedom is one reason why the Mount Sinai Home Dialysis Program has become the largest in New York City. Launched in the 1980s, the program, which consists of home peritoneal dialysis (PD) and home hemodialysis (HHD), has continually distinguished itself as a leader in patient care, from its early adoption of innovative dialysis technologies, to its multilingual, multidisciplinary team, to the dedicated support of the Mount Sinai Health System.

"We are able to collaborate with other disciplines within The Mount Sinai Hospital more easily because we are a large institution and share a medical charting system," says Lauren Perler, a social worker at the Mount Sinai Kidney Center. "This enables greater continuum of care for each patient and more accessible communication among disciplines."

The program aims to be accessible and inclusive; however, inclusion criteria and a multidisciplinary evaluation protocol ensure that only patients who will be safe, compliant, responsible, and accountable to their home dialysis prescription are enrolled. Before acceptance, patients and their caregivers meet with members from each discipline—a physician, registered nurse, social worker, and registered dietitian—for interviews and evaluations. Following a review of each applicant's needs and medical chart, a home visit evaluation, and feedback from their previous dialysis team, the patient is accepted with or without conditions. Training typically lasts one to two weeks for PD patients and up to five weeks for those who choose HHD. Once enrolled, patients perform dialysis using either a Baxter Amia Automated PD system or a NxStage System One cycler.

"We have continually adopted new cycler machines for the benefit of our patients," says Shuchita Sharma, MD, an Assistant Professor of Medicine (Nephrology) at the Icahn School of Medicine. "The PD cycler is particularly attractive in that it features both voice guidance and animation to help patients set up and use the machine, and it is software-enabled so we can monitor each patient's home treatments remotely between monthly clinic visits to ensure that they are doing well."

The Mount Sinai Home Dialysis Program is participating in several studies to improve delivery of PD therapy, it has launched an initiative to train renal fellows in home dialysis, and it has expanded to accommodate patients in rehab facilities and nursing homes.

"There are very few PD programs that work in conjunction with nursing home facilities to provide peritoneal dialysis to long-term care or sub-acute rehab patients," Dr. Sharma says. "Our goal remains to provide as many options as possible for our patients."

New Collaboration Speeds Fibrosis Research

ShangPharma Innovation, a San Francisco-based health care venture capital firm focused on early-stage breakthroughs, is providing funding to conduct pharmacokinetic studies of a new compound, BT173, that inhibits homeodomain-interacting protein kinase 2 (HIPK2)—a key regulator of multiple pro-fibrosis pathways, including TGF-ß1/Smad3 and Wnt/ß-catenin. Developed at Mount Sinai, BT173 has proven effective in reducing Smad3 phosphorylation and renal fibrosis in mouse models with unilateral ureteral obstruction and HIV-1 transgenic-based kidney disease.

The fibrosis collaboration, launched in April 2018, is the first in a multiyear agreement between Mount Sinai and ShangPharma Innovation to accelerate early-stage therapeutics. ShangPharma Innovation will provide research and development funding to the clinical institutes at the Icahn School of Medicine at Mount Sinai and offer research support services from Shanghai ChemPartner Co. Ltd. In return, ShangPharma will receive financial remuneration when new therapies are licensed for clinical application.

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, believes the collaboration will significantly reduce the time and effort involved in advancing new therapies from preclinical to clinical-trial status.

"Our goal is to accelerate a process that typically takes five years or longer to complete," Dr. He says. "It is not usually a straightforward path, in part because researchers need to continually secure funding for their work. With ShangPharma, we have one dedicated partner providing the expertise and funding to make this possible on a faster timeline."

The compound was initially developed by Bhaskar Das, PhD,

A multiyear collaboration with ShangPharma Innovation is funding research by the lab of John Cijiang He, MD, PhD, into new therapies for fibrosis

Associate Professor of Medicine (Nephrology) at the Icahn School of Medicine. Dr. He says it is unique for a nephrology department to have a specialist in chemistry like Dr. Das on staff to lead research efforts in drug discovery, and it has enabled Mount Sinai to be an innovator in developing new approaches to prevent end-stage kidney disease, which currently affects more than 661,000 patients nationwide.

"By having that expertise in-house and entering into agreements with partners such as ShangPharma, we can make advances and then translate our discoveries more readily from the scientific realm to clinical care," Dr. He says, noting that Mount Sinai is increasingly emphasizing this approach to therapeutic R&D.

Dr. He says ShangPharma is working with Dr. Das to further optimize the structure of the BT173 compound, resulting in analogues that will be validated at Mount Sinai using animal models. Based on initial data, Dr. He is confident that the team can produce one that meets requirements for water solubility, potency, and toxicity that will enable them to license it for clinical trials. "I expect that we will achieve key milestones within 18-24 months, which means the compound could be in clinical trials in approximately three years," Dr. He says.

› "KIDNEY ON A CHIP" *continued from page 1*

high-power microscopy, which means we can introduce disease conditions to the cells, administer a therapy, and see the impact of that drug at the molecular level. Essentially, this technology replicates certain aspects of the kidney physiology without sacrificing experimental capabilities for visualization and high throughput."

Dr. Azeloglu anticipates that the technology will significantly reduce drug development timelines and costs, and increase the likelihood of success for new therapies. "There is little interest among pharmaceutical companies in spending up to 15 years and millions of dollars to develop new drugs for kidney disease when, at best, only 5 to 10 percent will succeed," he says. "This technology has disruptive potential to make preclinical work more relevant, which means we can bypass the traditional drug development pipeline and potentially increase the success rate substantially. That should encourage more investment in therapeutic candidates and lead to more treatment options for kidney patients."

Research led by Dr. Azeloglu has proposed mechanisms and pathways that could be manipulated to prevent kidney disease. In a paper published December 15, 2017, in *Nature Communications*, he and his colleagues identified specific integrin signaling pathways that determine cell shape, an indicator of kidney health or disease. In another study, published March 6, 2017, he used microbial transglutaminase-crosslinked gelatin to demonstrate that substrate stiffness can induce dramatic changes in podocyte phenotype. "These findings are invaluable because now, we can conduct tests with individual patients to see how people from different genetic backgrounds respond to fibrosis," Dr. Azeloglu says. "That opens the door for doing precision medicine, one of our long-term goals."

That goal will be greatly facilitated by Mount Sinai's Bio*Me*™ BioBank, which contains genetic and clinical information from one of the largest, most diverse patient populations in the nation. "Using organ-on-a-chip technology, I can explore a clinical phenotype and find patients who match it, or I can home in on a particular genotype and look for a clinical correlation to a specific disease process," Dr. Azeloglu says. "It is a significant advantage to have access to such a vast repository of data because it enables a more patient-centric approach to understanding kidney disease, and that could lead to better outcomes."

Using Artificial Intelligence to Spot and Treat Disease

High-risk kidney disease patients could soon have access to a groundbreaking Mount Sinai Health System–developed tool that uses artificial intelligence to interrogate large pools of de-identified electronic health records (EHR) and disease-specific blood biomarkers to enable more effective identification, intervention, and treatment of the disease.

Girish Nadkarni, MD, MPH, left, and Steven Coca, DO, MS, are using artificial intelligence to more effectively identify and treat kidney disease.

This breakthrough is especially important given that the majority of patients with kidney disease do not present clinically until they have lost greater than 70 percent of their kidney function. Medicare currently spends $114 billion annually treating people with chronic kidney disease and end-stage renal disease.

Developed by Steven Coca, DO, MS, an Associate Professor of Medicine (Nephrology) at the Icahn School of Medicine at Mount Sinai, and Girish Nadkarni, MD, MPH, Assistant Professor of Medicine (Nephrology) there, KidneyIntelX™ is a predictive software ecosystem that plugs seamlessly into a patient's EHR and updates dynamically with changes to key health metrics and drug treatment utilization.

Using unique algorithms, KidneyIntelX processes longitudinal EHR, genetic, and blood biomarker data after each patient interaction to produce a personalized risk score indicating the likelihood chronic kidney disease will develop over the next five years or the risk of advanced kidney disease and potentially end-stage renal disease. Physicians can access the score through the patient's EHR and can take an in-depth look at factors driving a patient's risk through the company's web portal. Patients are also expected to be given access to their personalized risk assessment through the EHR and a mobile device app. KidneyIntelX will be commercialized by Renalytix AI Plc ("Renalytix"), which completed a public listing on the London Stock Exchange AIM market in November 2018. Both Drs. Nadkarni and Coca are shareholders in Renalytix.

"The main goal of assigning a score is to enable care providers to intervene and drive effective change in the patients' lives and disease management," Dr. Nadkarni says. "We can drill down to look at the different dimensions that contributed to that score and then start patients on new medications, help them better manage their blood pressure, or refer them to a dietitian to bring that score down and reduce the risk of disease progression."

KidneyIntelX uses the blood-based biomarkers tumor necrosis factor receptor 1 and 2 (TNFR1 and TNFR2) and kidney injury molecule 1 (KIM-1), and the apolipoprotein L1 (APOL1) genotype for patients of African ancestry, in combination with data from the EHR to generate the risk score. Dr. Coca says this work built upon previous data they had generated in the ACCORD and VA NEPHRON-D studies as well as research he and Dr. Nadkarni conducted using blood samples from Mount Sinai's Bio*Me*™ Biobank.

"We found very strong and reproducible signals for future kidney function decline when we analyzed these biomarkers in 1,000 Mount Sinai patients with type 2 diabetes and in 500 patients of African ancestry who had the APOL1 risk genotype," Dr. Coca says. The findings were published in the June 2018 edition of *Kidney International*.

Renalytix intends to begin a multicenter validation study involving approximately 4,000 patients this year for submission and review by the Food and Drug Administration. "No other center has developed anything replicating this type of multidimensional program with innovative AI tools, tracking portals, and suggested action items," Dr. Coca says. "Once we prove its efficacy, we can change the paradigm for clinical approaches to this disease."

Mount Sinai Health System

Icahn School of Medicine at Mount Sinai

Mount Sinai Beth Israel

Mount Sinai Brooklyn

The Mount Sinai Hospital

Mount Sinai Queens

Mount Sinai St. Luke's

Mount Sinai West

New York Eye and Ear Infirmary of Mount Sinai

South Nassau Communities Hospital

Mount Sinai Kidney Center at East River Plaza
520 East 117th Street
Fourth Floor
New York, NY 10128
212-987-7208

Kidney Disease Associates
5 East 98th Street
(between Madison Avenue and Fifth Avenue)
New York, NY 10029
212-241-4060

Mount Sinai Kidney Center Home Dialysis Programs
1450 Madison Avenue
(at 99th Street)
New York, NY 10029
Peritoneal Dialysis
212-241-5537
Hemodialysis
212-241-4967

Mount Sinai Kidney Center B1 Renal Unit
1450 Madison Avenue
(at 99th Street)
New York, NY 10029
212-241-8081

Dialysis for Traveling and International Patients
212-241-9780

Faculty Practice Associates
212-241-4060

Mount Sinai Renal Clinic Center for Advanced Medicine Internal Medicine Associates
17 East 102nd Street
(between Madison Avenue and Fifth Avenue)
New York, NY 10029
212-659-8551

Mount Sinai