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Mount Sinai leads unprecedented attempt to discover rules for assembling human tissue

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Researchers from Mount Sinai School of Medicine and two other academic institutions have received federal funding to systematically assemble functional human kidney tissue from tissue modeled on a computer. If successful, the research—which ties together several emerging technologies including virtual tissue modeling and nanofabrication—could lead to a more predictable way for researchers to engineer tissue outside the body and, consequently, to screen for new drugs.

To fund the project, called Dynamics Underlying Tissue Integrity, the National Institutes of Health (NIH) awarded a five-year, $6-million grant from its Transformative Research Projects (T-R01) program. T-R01 is a new program designed to support exceptionally innovative research initiatives whose anticipated outcomes have a major impact on broad, important problems in biomedical and/or behavioral research. T-R01 awardees—42 total this year—receive part of their funding from the American Recovery and Reinvestment Act.

The leader for this multi-principal investigator project, Ravi Iyengar, PhD, Director of the Experimental Therapeutics Institute (ETI) at Mount Sinai School of Medicine, said creation of a device for assembling tissue will require his team to solve a problem that has existed since pathologists first began examining human cells under microscopes.

"Pathologists typically characterize disease in patients by studying the shape of cells and tissues, and their diagnosis has always been largely

empirical," said Dr. Iyengar, who is also Dorothy H. and Lewis Rosenstiel Professor and Chair, Pharmacology and Systems Therapeutics, and Professor of Oncological Sciences and Psychiatry, Mount Sinai School of Medicine. "No one knows why cell shapes change or the rules by which tissues are organized. We want to start getting a handle on this by studying the kidney, and doing that will require the collaboration of several different disciplines."

The scientists plan to focus on the podocyte, a specialized kidney cell that sits on the organ's basement membrane and controls the filtration of small molecules from proteins. A breach in this filtration barrier is a main cause of kidney disease that often occurs among patients with diabetes, HIV, and hypertension. African-Americans with hypertension are four times more likely than whites with hypertension to develop kidney disease, a condition that currently has no cure and can eventually necessitate dialysis.

According to Dr. Iyengar, discovering the tenets underlying tissue assembly, as he and colleagues plan to do here, and having a more predictable method for assembling tissues within a nanofabricated device, would have broad clinical impact. "Lack of engineered tissue devices in vitro, or outside the cell body, is a big impediment in testing new drugs," he said. "If this experiment works and we have a methodology to assemble these tissues within nanofabricated devices, this could become a very useful screening approach for discovery of new drugs for kidney disease."

"The efforts of Dr. Iyengar's team to better understand kidney function at the cellular level will aid therapeutics research," said Dennis S. Charney, MD, the Anne and Joel Ehrenkranz Dean of Mount Sinai School of Medicine and Executive Vice President for Academic Affairs at The Mount Sinai Medical Center. "Mount Sinai, whose infrastructure is designed to foster translational research, is tailor made for

collaborative research projects such as this."

Much of the research will take place at the ETI, Mount Sinai's hub for developing new drugs and devices through integrating many facets of therapeutics research, and the NIGMS funded Systems Biology Center New York (SBCNY), which Dr. Iyengar also directs and which is also based at Mount Sinai. SBCNY researchers study at a systems level the molecular interactions within cells and their connection to the physiological function of tissues and organs.

"Dr. Iyengar has seized upon an extraordinary opportunity—the ability to harness systems biology to facilitate the development of new drugs and diagnostic tools," said Kenneth L. Davis, MD, President and CEO of The Mount Sinai Medical Center. "His work has the potential to create a new scientific paradigm."

The other principal investigators from Mount Sinai include John Cijiang He, MD, PhD, Associate Professor of Medicine and Nephrology and Assistant Professor of Pharmacology and Systems Therapeutics, and Susana Neves, PhD, Postdoctoral Fellow in the Department of Pharmacology and Systems Therapeutics.

Two other principal investigators sharing in the grant and lending their expertise are James C. Hone, PhD, of Columbia University, who will design and fabricate the micro- or nanometer-scale devices, and Leslie M. Loew, PhD, who pioneered the development of a computational modeling platform at the University of Connecticut Health Center called the Virtual Cell. Dr. Loew will develop computational models of how cells interact within kidney tissues.

These computational models, or virtual tissue, will form the basis for designing the device for recreating kidney function. The hope is to learn the rules of tissue organization as the team refines the device through

testing the computer models and imaging the flow of cell signals within the reassembled tissue from both mouse and human cells.

Commenting on the grant, Francis S. Collins, MD, PhD, Director of the NIH, said the T-R01 program "is intended to support research that has the potential to transform the way we think about and conduct science, so the recipients represent an elite few with truly bold ideas. Competition for the awards was fierce, and standards very high."

Source: The Mount Sinai Hospital