Miller School Physician-Scientist Identifies Compounds with Therapeutic Potential for Chronic Kidney Disease

A set of compounds that remove excess cholesterol from kidney filtration cells may hold the key to halting the progression of chronic kidney disease, according to a renowned University of Miami Miller School of Medicine researcher.

“Impaired cellular cholesterol efflux contributes to the progression of renal and cardiovascular diseases,” said Alessia Fornoni, M.D., Ph.D. professor of medicine and molecular and cellular pharmacology, and chief of the Katz Family Division of Nephrology and Hypertension.

“Through a drug-discovery process that lasted a decade, we identified a class of 5-arylnicotinamide compounds that increase cholesterol removal by targeting a cellular molecule called Oxysterol Binding Protein Like 7 (OSBPL7),” said Dr. Fornoni, who is also director of the Peggy and Harold Katz Family Drug Discovery Center and co-director of the Medical Scientist Training Program. She discovered the existence of fatty kidney disease and has been studying how to treat it since 2009 in collaboration with academic and industry partners.

Dr. Fornoni was the lead author of a new study, “Compounds
Targeting OSBPL7 Increase ABCA1-dependent Cholesterol Efflux Preserving Kidney Function in Two Models of Kidney Disease,” published August 2 in the journal Nature Communications. She collaborated with a team at Hoffman La Roche led by Marco Prunotto, Ph.D., a professor at the School of Pharmaceutical Sciences, Institute of Pharmaceutical Sciences of Western Switzerland, University of Geneva.

UM faculty collaborators included Armando Mendez, Ph.D., and Sandra Merscher, Ph.D.

Miller School co-authors and graduates included Javier Varona Santos, Ph.D., G. Michelle Ducasa, Ph.D., Alla Mitrofanova, Ph.D., Alexis Sloan, Ph.D., Christopher Pedigo, Ph.D., Mengyuan Ge, Ph.D., and Jeffrey Pressly, Ph.D.

Addressing Lipid Accumulation

Chronic kidney disease (CKD) is a major health burden in the U.S., affecting more than 30 million people. Dr. Fornoni’s work has shown that accumulation of lipids, such as cholesterol, occurs in diabetic kidney disease, as well as in non-metabolic rare kidney disorders like focal segmental glomerulosclerosis (FSGS) and Alport Syndrome.

Drawing on their prior findings that accumulation of lipids is mostly due to impaired cholesterol efflux, this industry-academic collaboration allowed for the screening of hundreds of thousands of small molecules, leading to the identification of few lead compounds.

“Further tests showed that several of these compounds were effective in preventing podocyte loss, proteinuria and renal failure in pre-clinical models of kidney diseases, with compound G showing the most promise,” Dr. Fornoni said. She
added that this agent has successfully completed phase I clinical trials and was demonstrated to be safe when administered orally in a cohort of healthy volunteers.

“In the next five years we expect to know if compound G can halt the progression of kidney disease and delay the need for dialysis and transplant,” she said. “Besides removing cholesterol from kidney cells, compound G may also help extract lipids from the heart and from blood vessels, thus offering a new therapeutic strategy for cardiovascular diseases often associated with kidney diseases.”