**Topic:** Chicago KUH FORWARD Meeting hosted by Rush University  
**Time:** June 7, 2021 11:00 AM Central Time (US and Canada)

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### AGENDA

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<td>11:05–11:20</td>
<td>Therapeutics for Glomerular Disease</td>
<td>Eunsil Hahm, PhD</td>
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<td>11:20–11:35</td>
<td>Significant association of Apolipoprotein L1 (APOL1) and soluble urokinase plasminogen activator receptor (suPAR) in glomerular disease</td>
<td>Kwi Hye Koh, PhD</td>
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<td>11:35–11:50</td>
<td>Novel podocyte protective compounds identified using ultra-miniaturized high-content screening (HCS) assays</td>
<td>Manuel Noben, PhD</td>
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<td>11:50–12:00</td>
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Bio: I received a PhD in Immunology from the College of Medicine Seoul National University, South Korea. During my pre- and post-doctoral training, I was involved in a variety of research projects in the areas of cancer, diabetes, inflammation, and kidney disease. After joining Rush University, my career within the field of nephrology began in earnest and my research now focuses on the underlying mechanisms of idiopathic nephrotic syndrome, a collection of kidney diseases that are thought to be associated with immune abnormalities in humans. Approaching biological problems from an immunological perspective, our team is trying to elucidate the molecular basis of both pathologic and protective responses to renal injury and to develop new therapeutics that can treat the disease more effectively and safely.

Abstract: suPAR and ICOSL; Factors affecting renal function and therapeutic targets for glomerular disease

Inflammation and immune system activation have long been considered the major culprits of glomerular disease, yet the underlying mechanisms are still poorly understood. Currently, immunosuppressive drugs are the mainstay treatment, however, they are nonspecific, often ineffective and toxic. Thus, there is an urgent need to develop highly effective and safe treatments for glomerular disease. Focal segmental glomerular sclerosis (FSGS) is the most common primary glomerular disease leading to end stage renal disease (ESRD). Approximately 80% of FSGS cases are primary (idiopathic) and can recur rapidly after kidney transplantation. Circulating factors secreted from activated immune cells have been considered as being podocytopathic and responsible for recurrence of FSGS in renal allograft. Today’s talk will focus particular attention on the opposing effects of two immune-related proteins, suPAR and ICOSL, in regulating podocyte function in glomerular disease.
Speakers

Kwi Hye Koh, PhD
Instructor/Scientist
Internal Medicine
Rush University Medical Center

Bio: I am an Instructor of Internal Medicine, Division of Nephrology at the Rush University Medical Center. I joined at Rush in 2014 after postdoc-training at the Scripps research Institute in San Diego and at UIC in Chicago. I completed my PhD in Medical Science at the Yonsei University, College of Medicine, Seoul in South Korea. My interests have become focused on investigating how the key factors promote kidney disease. My principal focus is on the pathophysiologic mechanism of suPAR as an environmental factor and APOL1 risk alleles as genetic factors in glomerular disease.

Abstract: Significant association of Apolipoprotein L1 (APOL1) and soluble urokinase plasminogen activator receptor (suPAR) in glomerular disease

Genetic variants (G1 and G2) of the Apolipoprotein L1 gene (APOL1) are present in 13-20% of African Americans and have been associated with increased risk of developing certain forms of chronic kidney disease (CKD), especially including focal segmental glomerulosclerosis (FSGS). However, the underlying mechanism associated with the genetic variants developing certain forms of kidney disease remains unclear, in part due to a lack of APOL1-relavant experimental models. One of our previous studies suggested that the soluble urokinase plasminogen activator receptor (suPAR) can cause FSGS by activating integrin αvβ3. More recently, using surface plasmon resonance (SPR), we show that the risk alleles of APOL1 (G1 and G2) bind suPAR with much higher affinity than the non-risk allele (G0) when combined with activated αvβ3 integrin. Furthermore, when the G1 and G2 alleles are expressed in mice, they lead to proteinuria and podocyte autophagy. These results suggest an important role for APOL1 in mediating suPAR’s association with activated integrin αvβ3. This research will advance our understanding of diseases that stem from aberrant cell surface signaling and offers the potential to explore the use of endogenous integrin antagonists as novel therapies. Both APOL1 and suPAR are key targets for therapeutic intervention of glomerular diseases and therefore have particularly strong potential in translational medicine.
Manuel Noben, PhD
Postdoctoral research fellow
Internal Medicine
Rush University Medical Center

Bio: I am a researcher involved in high-throughput compound screening experiments to identify novel therapeutics for kidney diseases. I performed my PhD studies at the University of Leuven in Belgium, where I investigated the use of intestinal organoids in inflammatory bowel disease. The final aim was to look at the effect microbiota might have on intestinal stem cell and epithelial development. Directly after I was involved in a pre-clinical study for a novel therapeutic agent for celiac disease, at the University of Chicago, which has since been approved and is entering clinical trials.

Abstract: Novel podocyte protective compounds identified using ultra-miniaturized high-content screening (HCS) assays

Podocytes are specialized epithelial cells, which are part of the filtration barrier in the kidney. Podocyte dysfunction is part of kidney pathology hallmarked by proteinuria. Using a high-content imaging based assay, we have shown that podocytes can be used to identify novel therapeutic compounds. Differentiated mouse podocytes were seeded on collagen-I coated multi-well plates. After 10-14 days of differentiation, cells were exposed to puromycin aminonucleoside (PAN, podocyte injury inducing agent), with compounds from the screening library or newly identified targets, or DMSO as control, for 48 hours. Cells were fixed and labeled with cytoplasmic stain HCS CellMask Green, and actin fibers were detected by using labeled phalloidin. Cell images were taken with using Opera High-Content Screening (HCS) System. Columbus software was used to quantify morphology properties such as roundness, as well as the overall F-actin signal. We utilized commercial libraries containing >50k unique compounds to identify podocyte protective hits. Using PAN as a podocyte damaging agent, we noticed marked reduction in F-actin fiber numbers and intensity, and increased roundness in podocytes. Screening of a library of chemical compounds identified >25 hits which had favorable profiles. We are now further characterizing the pathways involved using in vitro assays and using animal models of proteinuria to validate our findings.