Search for therapeutic reagents by modeling Alport syndrome in mice and humans
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Alport syndrome (AS) is a hereditary kidney disease that is caused by a mutation in Type IV collagen (COL4A) α3, α4 or α5 gene. A mutation in one of these genes disrupts the ability of COL4A3/4/5 proteins to form a heterotrimer, an important component of the glomerular basement membrane (GBM). Failure of heterotrimer formation in GBM leads to the malfunction of the podocyte and the glomerular filtration barrier. We have recently shown that p53 in podocytes is a key modulator of the severity of kidney symptoms in a mouse model of AS (X-linked *Col4a5* mutation; *G5X*). In addition, we are the first to induce human iPS cells to form glomeruli composed of podocytes with slit diaphragm and GBM containing COLA3/4/5. Thus, our proposal combines our efforts on mouse genetics and human iPS cell-based technology, as well as high throughput screening (HTS). Specifically, we will perform HTS using nanoBRET to identify chemical compounds that induce COL4A3/4/5 heterotrimer formation. We will also find responsible factors downstream of p53 in AS podocytes, as well as p53-activating reagents, to ameliorate the AS mouse phenotypes. Furthermore, we will model the human AS by utilizing iPS cells derived from AS patient, visualize the COL4A formation/degradation in real time, and examine the p53-related defects in human AS podocytes. Finally, chemical compounds identified by HTS and from the mouse studies will be validated in human iPS cell-derived glomeruli. These plans will not only accelerate our understanding of the pathogenesis of AS but also leads to the identification of lead compounds that could be effective in humans.