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In search of targeted, mechanism-based therapies for kidney diseases

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Focal Segmental Glomerulosclerosis (FSGS) is the leading histopathology underlying progressive kidney diseases characterized by proteinuria and podocyte loss. Inherited forms of FSGS are caused by Rac1-activating mutations. In podocytes, Rac1 induces TRPC5 ion channel activity and cytoskeletal remodelling. However, it is unknown whether TRPC5 activity mediates the onset and progression of FSGS, and whether blocking this activity can provide therapeutic benefit. We identified a small molecule, AC1903 that specifically blocks TRPC5 channel activity in glomeruli of proteinuric rats. Here we demonstrate that chronic administration of AC1903 suppresses severe proteinuria and prevents podocyte loss in a transgenic rat model of FSGS. The efficacy of AC1903 was confirmed in a well-established preclinical rat model of hypertensive proteinuric kidney disease. These data indicate that TRPC5 activity is induced to drive disease, and TRPC5 inhibitors may be valuable for the treatment of progressive kidney diseases.