Drug discovery in focal and segmental glomerulosclerosis

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Despite the high medical burden experienced by patients with focal segmental glomerulosclerosis, the etiology of the condition remains largely unknown. Focal segmental glomerulosclerosis is highly heterogeneous in clinical and morphologic manifestations. While this presents challenges for the development of new treatments, research investments over the last 2 decades have yielded a surfeit of potential avenues for therapeutic intervention. The development of many of those ideas and concepts into new therapies, however, has been very disappointing. Here, we describe some of the factors that have potentially contributed to the poor translational performance from this research investment, including the confidence we ascribe to a target, the conduct of experimental studies, and the availability of selective reagents to test hypotheses. We will discuss the significance of genetic and systems traits as well as other methods for reducing bias. We will analyze the limitations of a successful drug development. We will use specific examples hoping that these will guide a consensus for investment and drive greater translational quality. We hope that this substrate will serve to exemplify the tremendous opportunity for intervention as well as facilitate greater collaborative effort between industry, academia, and private foundations in promoting appropriate validation of these targets. Only then will we have achieved our goal for curative therapies for this devastating disease.

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Focal segmental glomerulosclerosis (FSGS) is a common cause of primary nephrotic syndrome, with a peak age of onset between 10 and 45 years and with about 2000 individuals reaching end-stage kidney disease each year.[1] As the prevalence and incidence cannot be precisely estimated due to lack of population-based studies, the implementation of longitudinal cohorts of patients affected by nephrotic syndrome as well as the development of national and international registries will be key to understand disease pathogenesis, estimate disease impact, stratify patients, develop alternative clinically meaningful outcome measures, and design feasible clinical trials. This is even more important if we consider that the clinical disease course of patients with biopsy-proven FSGS is highly heterogeneous, as well as the recurrence rates after transplant, the response to treatment, and the morphologic pattern, as reviewed elsewhere.[2] Successful drug development in the field of FSGS has also been hampered by the fact that the etiology of FSGS remains largely unknown (with 80% of cases being idiopathic) and little consensus as well as confidence on key interventional nodes has been reached, as we will discuss.

While FSGS, and more broadly chronic kidney disease, represents a silent killer, and affected vulnerable populations such as underrepresented minorities and children are often characterized by a worse clinical outcome, the investment in experimental studies has been somewhat limited in contrast to other disciplines. First, this clearly reflects the influence of the public opinion in the community, which overall is more sensitive to specific areas of research characterized by high morbidity and mortality, such as cancer and heart disease. Interestingly, however, the risk of dying from chronic kidney disease is equal or superior to that of dying from certain forms of cancer,[3] yet patients are surely more afraid to be informed they have cancer than chronic kidney disease. While a cultural shift and education are needed to generate awareness about this, there is perhaps also a need to make the discipline more glamorous and attractive to researchers. Second, dialysis and transplantation remain a lucrative therapeutic alternative to preventive or curative strategies in kidney diseases, thus decreasing the attractiveness of drug development. Finally, the lack of alternative outcome measures considered acceptable by the regulatory agencies,[4–6] as well as methods for better stratifying patients on their risk profile has discouraged industry from investing in drug development and requires further studies. Alternative biomarkers are being explored, for instance the measurement of

podocyturia and urinary podocyte mRNA, which may be especially relevant in FSGS where damage to the podocyte appears to be a key determinant in the disease pathogenesis. These alternatives may help stratify patients and predict disease progression or sensitivity to drug intervention,[7] and certainly more investment as well as qualification is warranted.

The path moving forward

The limitations discussed in the prior paragraph are among the factors that have led to the limited success in the development of new effective drugs for kidney diseases. In fact nephrology, among other subspecialties in internal medicine, has performed very poorly when it comes to conducting randomized clinical trials.[8] Table 1 summarizes ongoing clinical trials in FSGS or treatment-resistant nephrotic syndrome. There is a relative paucity of innovative and tailored approaches in development. This may be due to insufficient understanding of the disease pathophysiology, or the confidence in translation of experimental efficacy studies in animals to studies in humans or the cost of clinical development. With this in mind, the National Institutes of Health (NIH) established in 2012 a National Center for Advancing Translational Science (NCATS). Through 2 initiatives, Discovering New Therapeutic Uses for Existing Molecules (New Therapeutic Uses) (http://www.ncats.nih.gov/ntu) and Pfizer's Centers for Therapeutic Innovation for NIH Researchers (http://www.ncats.nih.gov/cti), NCATS

Table 1 | A snapshot of ongoing clinical trials in FSGS captured from ClincalTrials.gov

Identifier (NCT)	Indication	Study design	Asset	Mechanism	Sponsor	Stage	Comments
02382874	FSGS	Single-arm open-label pilot safety study ($n = 5$)	Allogenic AD-MSC transplant	Not known	Royan Institute	I	No substantial supporting preclinical data
02235857	FSGS	Open-label POM study ($n = 35$) Primary = change in UACR at 10 wk	Liposorber LA-15	Not known	Kaneka Pharma America LLC	Ib	No substantial supporting preclinical data
02000440	FSGS	Single-arm open-label POM study ($n = 24$) Primary = 50% reduction in UACR at 24 wk	Losmapimod	p38 kinase inhibition	GlaxoSmithKline	Ib	Pathway appears to be altered in FSGS. Some supporting preclinical data[96,119]
02585804	FSGS	Single-arm open-label POM study ($n = 12$) Primary = change in inulin GFR at 8 wk	Dapagliflozin	SGLT2 inhibition	AstraZeneca	Ib	Rationale is based on observed effects of SGLT2 inhibitors on renal hemodynamics in other diabetic populations (e.g., renal hemodynamic effect of sodium-glucose cotransporter 2 inhibition in patients with type 1 diabetes mellitus)[120]
01164098	FSGS (post-transplant)	Randomized open-label study ($n = 60$) Primary = prevention of proteinuria recurrence at 4 wk	Rituximab	CD20 B cell depletion SMPDL3b	Genentech/ University Miami	II	Supported by clinical and preclinical observations[38]
01573533	FSGS (treatment resistant)	Open-label study in treatment Primary = remission & change in UACR at 12 mo	Rituximab	CD20 B cell depletion SMPDL3b	Genentech Mayo	II	Supported by clinical observations
02394106	Nephrotic syndrome (treatment resistant)	Double-blind, 2-parallel-arm, placebo-controlled randomized study ($n = 50$) Primary = remission and change in UACR at 6 mo	Ofatumumab	CD20 B cell depletion	Istituto Giannina Gaslini	II	Supported by clinical observations
01613118	FSGS	Multidose randomized placebo-controlled efficacy study ($n = 100$) Primary = change in UACR at 8 wk	RE-021/ sparsentan	ETRA/ARB	Retrophin	II	ETRAs appear to improve UACR and fibrosis in preclinical models. As a class, though, ETRAs have been associated with liver and CV AEs
02257697	Nephrotic syndrome	Randomized controlled open-label study ($n = 238$) Primary = remission at 52 wk	Mizoribine	IMPDH Podocyte target not known	Asahi Kasei Pharma	III	Preclinical supporting data[40]

AD-MSC, adipose tissue–derived mesenchymal stem cell; ARB, angiotensin receptor blockade; CV AEs, cardiovascular adverse events; ETRA, endothelin receptor antagonists; FSGS, focal segmental glomerulosclerosis; GFR, glomerular filtration rate; IMPDH, inosine-5′-monophosphate dehydrogenase; NCT, National Clinical Trial; POM, proof of mechanism; UACR, urinary albumin-to-creatinine ratio.