The Use of Genomics to Drive Kidney Disease Drug Discovery and Development

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Abstract

As opposed to diseases such as cancer, autoimmune disease, and diabetes, identifying drugs to treat CKD has proven significantly more challenging. Over the past 2 decades, new potential therapeutic targets have been identified as genetically altered proteins involved in rare monogenetic kidney diseases. Other possible target genes have been implicated through common genetic polymorphisms associated with CKD in the general population. Significant challenges remain before translating these genetic insights into clinical therapies for CKD. This paper will discuss how genetic variants may be leveraged to develop drugs and will especially focus on those genes associated with CKD to exemplify the value and challenges in including genetic information in the drug development pipeline.

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Introduction

Accelerating the delivery of therapies to patients with kidney disease has proven a significant challenge. Research and development costs for drug development continue to increase; they are now estimated to range from US$3 to 12 billion per successful launch (1,2). These enormous costs are in large part due to our fundamental lack of understanding of the human biology underpinning disease and the incomplete translatability of preclinical animal studies to people. Human genetic information offers the promise to bridge this gap by providing evidence that a gene is directly involved in human disease and is therefore a valid drug target. Target validation typically follows the initial nomination of a protein or molecule as a potential drug target and involves experiments that aim to confirm a hypothesis that perturbation of the drug target will result in therapeutic benefit with minimal adverse effects (Figure 1). Although preclinical models are a critical component of target validation, the availability of supporting data for a mechanism in humans, especially in a relevant patient population of interest, is highly desirable and substantially enriches the odds of success (3). The evolution of genetics and genomics and its application to human disease cohorts collected over recent decades has provided new opportunities for drug discovery, implicating unexpected gene targets involved in human disease mechanisms at an earlier point in the drug development process (4). In many cases, human genetics offers information on direct perturbation of a target gene with directional insight on the functional effects with respect to both potential benefit and safety concerns. Genetic studies can provide insights on the consequences of perturbation of therapeutic mechanisms over time and provide a means to understand the pleiotropic effects of target mechanisms on phenotypic traits in advance of clinical development. This review will focus on the utility of genetics in drug discovery and development in more common complex forms of CKD, including diabetic kidney disease and IgA nephropathy. We will discuss approaches that have delivered clinically successful drugs and touch only briefly on newer aspirational approaches, including genome-wide CRISPR/Cas manipulation and induced pluripotent stem cell–derived organoids.

Genetics Contributions to Drug Discovery in Metabolic Disease

Human genetic and mRNA expression data have helped identify novel targets that have informed drug discovery and development for diverse diseases, particularly in cell autonomous disorders like cancer (5–7). Genetics has also significantly contributed to our understanding of metabolic diseases especially for drug development in disorders of cholesterol and triglyceride metabolism leading to atherosclerotic cardiovascular risk (4,8,9). Nevertheless, the discovery of drugs to prevent the progression of kidney disease has proven painfully slow with only two beneficial classes of drugs identified: angiotensin pathway inhibitors and the recent addition of SGLT2 inhibition for diabetic kidney disease.

In the field of cholesterol and lipid biology, insights from human genetics contributed to an improved understanding of causal links between LDL cholesterol and heart disease. The story of how coding variation in PCSK9 inspired antibody-based therapeutics and subsequent therapeutic modalities in clinical development has been well described (4,10). In the case of HDL cholesterol, observational epidemiology had established a relationship of HDL with protection from coronary diseases, but human genetic studies of a common coding variant in endothelial lipase brought the lack of a clear causal relationship between HDL and coronary disease to the fore (11). 3-Hydroxy-3-methyl-glutaryl-coenzyme A reductase, the target of

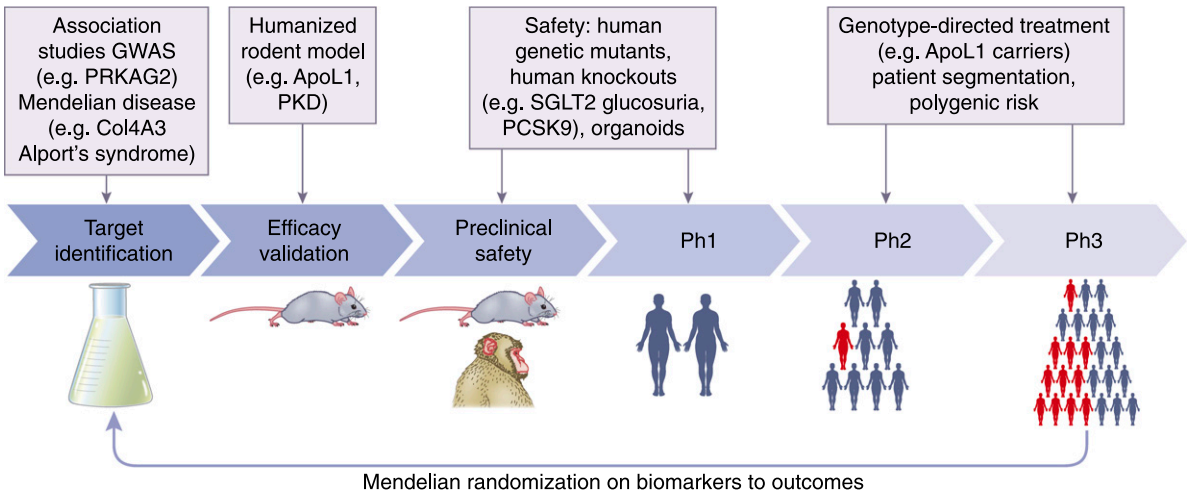

Figure 1. | **The use of genetic information in drug development.** The blue arrows depict the multiple stages of drug development from preclinical testing to validation in large clinical studies. Development of a drug to treat kidney disease begins with target identification and generation of a molecule that affects activity of the target. A gene involved in human kidney disease may itself present a drug target or at least validate pathways involved in human disease. Once pharmacologic tools have been generated to the target, their activity is often validated in animal models of the disease as a means to de-risk extremely costly clinical trials. Genetic diseases may also inform extrarenal consequences of the genetic disruption and thereby de-risk safety concerns. Once safety has been established, genetics might be used to segment disease populations into those subjects who may derive greater benefit from the drug. Finally, patients carrying polymorphisms for genes may themselves be studied to validate involvement of altered gene activity in progression of a disease through Mendelian randomization and further inform target identification or validation. GWAS, genome-wide association study; Ph1/2/3, phase 1/2/3; PKD, polycystic kidney disease.

statin medications, is supported by genome-wide association studies (GWAS) data that emerged after the development of the drugs, but the small effect sizes of these alleles were capable of replicating clinical observation of incident diabetic risk associated with lowering of LDL cholesterol (12). Thus, insight relating to efficacy and safety for putative kidney disease therapeutics may similarly lie within the association data for kidney disease and kidney function (13).

Certainly, the exploration of genomic sequence has been essential for elucidating the basis of monogenic diseases like cystic fibrosis and polycystic kidney disease; however, successful application of these genetic insights toward drug development for kidney disease has not proven straightforward. Several recent publications have dealt with monogenic kidney diseases, including polycystic kidney disease (14), FSGS (15,16), and Alport disease (17). The ability to sequence the coding exome (see Table 1) of patients with kidney diseases of unclear etiology may also help inform the cause of kidney disease and thereby the clinical approach to treatment (18).

Monogenic Disease Informs Drug Discovery

Cystic fibrosis represents a prototypic example of genetics advancing drug discovery in rare disease. It had long been recognized that patients with cystic fibrosis exhibit elevated sweat chloride concentration and cellular chloride permeability (19,20). The identification of the p.Phe508del in the cystic fibrosis transmembrane conductance regulator (CFTR) gene in 1989 advanced the understanding that CFTR plays a role in ion transport regulation (21). Key insights were derived from the study of CFTR coding variants, including correlation of chloride channel dysfunction with cellular manifestations and clinical features, provision of a tool enabling cystic fibrosis diagnosis, and connecting CFTR dysfunction with other observed phenotypes. Substantial progress has recently been achieved with small-molecule therapy for select disease-causing variants (22). It is sobering to consider that despite existing understanding of the functional ion transport defect, this translation took >30 years from cloning of the CFTR gene to delivery of a clinical therapy.

TRPC6 Mutations

Drug targets inspired by human monogenetic kidney diseases are less advanced than cystic fibrosis. Current CKD standard-of-care medications have emerged from the traditional physiologic understanding of therapeutic mechanisms, rodent and human physiology and pharmacology. Nevertheless, the identification of dominant activating mutations in TRPC6 in familial FSGS (23,24) and expression in podocytes has inspired studies exploring the role of this target in hypertensive and diabetic kidney diseases (25,26). Study of TRPC5 inhibitors, a channel with a function similar to TRPC6 and also expressed in podocytes, were inspired by these studies and showed protective effects of this small molecule inhibitor in a rat model of hypertensive kidney disease (27). TRPC5/6 has attracted the interest of several large pharmaceutic companies for further exploration and development to treat FSGS and nephrotic syndrome, as well as its possible applicability to diabetic kidney disease and hypertensive kidney disease.

SGLT2 Mutations

Identification of humans with familial isolated glucosuria provided an important foundation for studying its mechanistic basis defect, leading to identification of the glucose

Table 1. Definitions of some commonly used terms

Term	Definition
Complex diseases	Common multifactorial human disorders caused by a combination of genetic, environmental, and lifestyle factors, many of which are not yet identified.
Exome	The exome is composed of all of the exons within the genome, the sequences which, when transcribed, remain within the mature RNA after introns are removed by RNA splicing. This includes untranslated regions of mRNA and, importantly, the protein coding sequence.
GWAS	A now-fundamental approach to analyze genetic sequence variation throughout the genome that correlates alleles to different diseases and traits.
iPS	Cells derived from skin or blood that are reprogrammed back into an embryonic-like pluripotent state before subsequent development toward a desired human cell type.
Mendelian disease	Diseases (typically rare) caused by mutations in a single gene that sometimes run in families. Pedigree analyses of large families can determine disease-associated genes on autosomes or on a sex chromosome, and whether the related disease phenotype is dominant (involve damage to only one gene copy) or recessive (involving both gene copies).
Penetrance	The proportion of individuals carrying a particular variant of a gene that also express an associated trait. In medical genetics, the penetrance of a disease-causing mutation is the proportion of individuals with the mutation who exhibit clinical symptoms.
Pleiotropic	Pleiotropy occurs when one gene influences two or more seemingly unrelated phenotypic traits.
Polymorphism	A genetic variant within a population, upon which natural selection can operate.
PCSK9	An enzyme encoded on chromosome 1 that is causally linked to LDL cholesterol and has emerged as a prototypic genetic target
RNAi	Biologic process in which RNA molecules interfere and inhibit gene expression or translation by neutralizing targeted mRNA molecules
UMOD	Also known as Tamm–Horsfall protein, UMOD is a large glycoprotein normally found only in the ascending limb of the loop of Henle extending into the very early portion of the distal tubule. It is a major protein of normal urine and is the primary component of waxy nephron casts.

GWAS, genome-wide association study; iPS, induced pluripotent stem cells; PCSK9, proprotein convertase subtilisin/klexin type 9; RNAi, RNA interference; UMOD, uromodulin.

transporter SGLT2 (SLC5A2) (28). In 1947, Marble *et al.* (29) defined diagnostic criteria for the condition that was originally thought to be autosomal recessive. Kidney titration studies later characterized kidney glucosurias into type A and type B (30) and type O for individuals with a complete absence of glucose transport (31). The vast majority of the 44 mutations identified to date in the SLC5A2 gene that are associated with kidney glucosuria appear to be private, with a range of missense, nonsense, insertion/deletion, and splicing defects implicated. A splice mutant allele IVS7+5G has been observed in several unrelated families with familial kidney glucosuria from different ethnic backgrounds (32,33). Type A and B may be heterozygous, whereas patients with type O were determined to have homozygous or compound heterozygous disruption of the SGLT2 protein (32,34). It is important that patients with kidney glucosuria are not typically affected by severe clinical sequalae (33) because this helps inform the potential clinical safety of drugs targeting SGLT2—a major hurdle for drug development. In this case, however, genetics did not predict the profound therapeutic benefit of canagliflozin in diabetic kidney disease (35). Leveraging the understanding of kidney glucose transport was significantly enabled by the availability of the natural product phlorizin, which was also known to inhibit kidney glucose absorption and served as a tool compound to enable development of SGLT2-selective pharmacologics (36). The low frequency of these identified private genetic variants did not enable advanced prediction of the cardio- and kidney-protective effects of inhibiting SGLT2 that was subsequently elucidated by clinical trials of the various marketed SGLT2-inhibiting agents (35,37–39).

Substantial challenges exist in translating genomic discoveries to approved medicines. Human genetics relies on the accumulation of informative alleles in target genes and their propagation through generations. When present, causal alleles represent a natural perturbation of a potential therapeutic target, but this perturbation may result from effects in noncoding regions with unclear interpretation. Although human genetics can help us gain additional insight on cause and effect, the mechanistic implications of a disease-associated genetic locus can be quite unclear when biologic characterization of the candidate causal gene is lacking.

Common Genetic Variants and CKD

Initially, GWAS offered great hope that they would provide a trove of new drug targets to treat disease (40,41). However, despite >200 gene polymorphisms associated with CKD being identified by GWAS of >1 million people (13), most implicated genes either do not appear readily "druggable" or their link to the pathogenesis of CKD remains unclear. These challenges are exemplified by the strongest CKD/diabetic kidney disease–associated polymorphisms near uromodulin (UMOD; also known as Tamm–Horsfall protein) (13,42,43). Although the Tamm–Horsfall protein was identified as the major protein normally excreted in human urine nearly 70 years ago (44), its physiologic function and role in the pathogenesis of CKD progression remains unclear. UMOD is an 85-kD, 616-amino acid, GPI-linked, membrane-associated glycoprotein (45) that is exclusively expressed in the kidney where its expression is restricted to the thick ascending limb and distal convoluted tubule. These nucleotide polymorphisms

do not affect UMOD amino acid sequence but are intergenic between UMOD and PDILT genes (43,46). The G risk allele at rs12917707 associates with increased urinary UMOD levels (47); however, whether altered UMOD excretion is a protective response, is itself pathogenic, or neither remains unclear. UMOD has been suggested to serve an anti-inflammatory role (48), however it may also serve as a chaperone for thick ascending limb membrane proteins contributing to increased sodium absorption and hypertension (49). Despite the 7 decades of work on Tamm–Horsfall protein, neither the cellular target nor the downstream effectors of UMOD action have been definitively identified. Biologic targeting using UMOD itself as a therapeutic would be complicated by its large size and requirement of proper folding and maintenance of 24 cysteine-cysteine disulfide bonds (50). Similar experiences complicate targeting genetic variants associated with type 2 diabetes mellitus and Alzheimer disease GWAS in which TCF7L2 (51,52) and ApoE4 (53) polymorphisms, respectively, strongly associate, yet the biologic mechanisms underlying their genetic association with disease remains frustratingly obscure.

It is also notable that substantial differences in GWAS-identified risk alleles exist for kidney disease in type 1 diabetes mellitus versus type 2 diabetes mellitus. In a GWAS meta-analysis of 19,406 individuals with type 1 diabetes mellitus (54), both UMOD and PRKAG2 disease association polymorphisms replicated from larger CKD GWAS studies, but other single nucleotide polymorphisms did not achieve significance. Notably, the type 1 diabetes mellitus studies identified a significant protective coding polymorphism in collagen 4A3, a major component of the glomerular basement membrane. The strict inclusion of patients with type 1 diabetes mellitus represents an important distinction between these studies and GWAS studies associated with diabetic kidney disease in patients with type 2 diabetes mellitus, because kidney disease etiology in type 2 diabetes mellitus exhibits substantial heterogeneity with approximately 50% of subjects with type 2 diabetes mellitus exhibiting nondiabetic kidney disease (55). Subjects with type 1 diabetes mellitus kidney disease are younger (typically <50 years old) and likely represent a more homogeneous population of kidney disease etiology. These studies may be more representative of patients with pure diabetic kidney disease on biopsy than studies of patients with type 2 diabetes mellitus.

Other genes encoding membrane transporters primarily expressed in the proximal tubule have been identified in GWAS of both chronic nondiabetic and diabetic kidney disease and may prove tractable as pharmacologic targets (13,56). This possibility is underscored by the recent success of SGLT2 (SLC5A2) inhibition in the prevention of diabetic kidney disease progression (37,57). The mRNA expression of many of these CKD-associated transporters, including SLC22A2 (OCT2, rs316019), SLC47A1 (MATE1, rs111653425), and SLC34A1 (NaPi2a, rs3812036) (58,59), is either enriched in or completely restricted to kidney. Similarly, monogenic disease in these genes can inform the safety of novel drugs targeting these transporters; however, in contrast to glucose transport where phlorizin provided a valuable tool compound for designing SGLT2 inhibitors, similar pharmacologic tools are lacking for many of these transporters.

It is perhaps surprising that polymorphisms in SGLT2 or other current validated therapeutic targets including angiotensin-converting enzyme (ACE), angiotensin receptor blocker, renin, and the mineralocorticoid receptor do not emerge as major signals in GWAS. In the years before genome-wide genotyping was enabled by the Hapmap Project and the Human Genome Project, candidate gene studies were typically performed on genes such as those of the renin-angiotensin-aldosterone system where biologic function was well understood. Although many of these candidate gene studies failed to replicate (60), the ACE insertion/deletion variant (rs1799752), which results in higher levels of circulating ACE enzyme activity, did associate with microalbuminuria and diabetic nephropathy in type 1 diabetes mellitus in the Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications study (61). As the sample sizes of GWAS studies have grown, genome-wide significant signals of association have been observed at the ACE gene locus with diastolic BP (62) and ACE activity (63). The modest effect size of these mutations is typical of GWAS; however, despite the established variability in BP as a trait, signals for other known hypertension drug targets, including CACNA2D2 (calcium channel blockers), MME (omapatrilat), ADRA2B (β-blockers), SLC14A2 (nifedipine), and PDE5A (sildenafil), have been identified using this approach (62). Taken together, the preceding observations are consistent with the utility of GWAS in identifying authentic druggable targets for CKDs.

Nevertheless, drug discovery strategies that strictly rely on genetics may miss relevant targets. The recent SONAR trial of the endothelin receptor antagonist atrasentan in diabetic kidney disease showed a striking benefit in reducing kidney failure altogether (64). Although genetic variants at the endothelin locus associate strongly with coronary artery disease, BP, and other phenotypic traits, kidney disease was not among these traits (65). This experience underscores the necessity for understanding the potential pathophysiologic relevance of each gene identified through genetic approaches, without which the utility of an implicated gene as a drug target is lacking. Conversely, lack of a genetic link should not be considered a rationale for failing to pursue a CKD target.

A major resource available to pharmaceutic companies is access to patients and samples from relatively large phase-3 kidney trials linked to hard outcomes (ESKD, death, and creatinine doubling). Although these sample sizes are insufficient for GWAS, they do allow for more limited exploration including the use of Mendelian randomization to test the causative association between biomarkers and outcomes. Focused study of genetic polymorphisms linked to drug mechanism of action has been used to identify VEGFR2 genotypes that are associated with outcome efficacy of tyrosine kinase inhibitors in renal cell cancer (87). Similar approaches might be taken in exploring efficacy of novel therapies linked to kidney outcomes in subpopulations with polymorphisms in the targeted molecule. Recent availability of resources linking genetic polymorphisms to variation in the human plasma proteins and their association with eGFR provide a tantalizing opportunity to identify novel drug targets. One can further explore causality of plasma protein level variation to kidney disease through Mendelian randomization studies (Figure 1) (88).

Mendelian Randomization for Biomarker Validation

Genetics may also be used to test therapeutic hypotheses. The possibility that interventions to reduce uric acid levels (*e.g.*, with allopurinol) might slow diabetic nephropathy has attracted substantial attention and is under current investigation in clinical trials (66). Mendelian randomization assumes that inherited genetic variants affecting levels of a biomarker (*e.g.*, serum uric acid) can be used as variables randomized at conception that can affect an outcome (*e.g.*, CKD). Common genetic variants can therefore be used as an instrument to assess causal relationships of biomarkers while minimizing the likelihood of reverse causation (67). Recently, the role of uric acid in diabetic kidney disease progression has been explored using polymorphisms in uric acid transporters. Polymorphisms in SLC2A9 (Glut9), SLC22A11 (OAT4), SLC22A12 (URAT1 or OAT4L), and ABCG2 account for up to approximately 5% of the variability in uric acid levels (68) and as the genetic risk score increases, so does the population mean uric acid (69). These genetic studies concluded that greater uric acid levels either did not predict risk for CKD (70) or in fact may be associated with higher rather than reduced eGFR (69). The results appear to presage findings from the recently completed negative PERL study—a randomized controlled trial of allopurinol versus placebo to prevent GFR loss in patients with type 1 diabetes mellitus—which found that, despite significantly reducing uric acid, allopurinol failed to improve either GFR loss or albuminuria in type 1 diabetes mellitus (66,71).

Apo L1 and CKD

The presence of an apo L1 (APOL1) variant in people of African descent carries one of the strongest associations with CKD for common genetic variation with a complex disease (odds ratios of 17 for FSGS and >30 for HIV-associated nephropathy) (72). APOL1 is the plasma-endogenous lytic factor for trypanosomes, which induces lysis by increasing lysosomal ion leak (73). Trypanolytic APOL1 protein is primarily synthesized by the liver (74) and is constitutively secreted into the circulation as part of a minor class of HDL particles. The disease-associated polymorphisms confer activity against otherwise APOL1-resistant trypanosomal strains that predominate in western Africa.

On the surface, drug targeting of APOL1-associated kidney disease would appear highly attractive. APOL1 polymorphisms themselves are not a disease. Despite their presence from birth, emergence of kidney disease occurs only in a subset of people with APOL1 risk polymorphisms (*i.e.*, incomplete penetrance of the trait), often later in adulthood, consistent with an environmental trigger often associated with a viral illness for kidney disease to emerge (75). Furthermore, the APOL1 gene is only present in humans and a few primates but not chimpanzees or most other species including rodents. Lack of rodent or lower primate orthologs of APOL1 significantly hampers preclinical investigation of APOL1 function. Humanized mouse models have been developed but have not been fully validated with respect to accurately modeling human kidney disease pathogenesis (76–78). Finally, the cellular pathogenesis of APOL1 kidney injury remains incompletely defined with altered partitioning to cytoplasmic lipid droplets, cellular potassium ion depletion, activation of stress-associated kinases, and impaired mitochondrial function all implicated in the cytotoxic effects of APOL1 risk variants (79–81). Which of these specific steps is optimal for therapeutic intervention remains unclear. Novel gene therapy approaches or RNA interference may provide novel and feasible approaches to mitigate disease in these patients (76).

IgA Nephropathy

GWAS studies should also prove informative for drug development in IgA nephropathy. IgA nephropathy is the most common form of GN and a major cause of ESKD, particularly in Asia (82). In contrast to CKD and diabetic kidney disease, the diagnosis of IgA nephropathy is typically made only after kidney biopsy, and it is these subjects who are included in the GWAS cohorts for IgA nephropathy. GWAS identifies several polymorphisms in the HLA locus, the complement pathway (CFHR1 and CFHR3), the B-cell trophic factor APRIL, and defensin polymorphisms, consistent with an autoimmune pathogenesis of this disease (83,84). These findings further substantiate a strategy for directing therapy at modulation of complement. Therapeutics are being developed for this indication (85).

It is notable that distinct, nonoverlapping genetic polymorphisms are associated with IgA nephropathy versus diabetic kidney disease (56,83). Although IgA nephropathy GWAS identified polymorphisms of complement factor H, the major histocompatibility locus, and defensin-A, these genes were not identified in diabetic kidney disease GWAS. Conversely, polymorphisms near UMOD and PRKAG2 emerged for kidney function in diabetic kidney disease but not for IgA nephropathy. These differences could underscore the distinct pathophysiology of the two diseases. Alternatively, these differences might be due to differences in the diagnostic criteria for inclusion in GWAS for IgA nephropathy versus diabetic kidney disease (kidney biopsy findings for IgA nephropathy versus increased serum creatinine or albuminuria for diabetic kidney disease) (13,86). Because most patients with IgA nephropathy remit, and only a minority of patients with IgA nephropathy progress to ESKD, a more appropriate comparison to the diabetic kidney disease GWAS would be to limit inclusion to only the subset of patients with IgA nephropathy whose kidney function deteriorates; however, the sample size for this would likely be inadequate to power GWAS. Conversely, a GWAS on biopsy-proven diabetic kidney disease irrespective of kidney function might provide a more relevant comparison to the IgA nephropathy GWAS, but access to the necessary number of people with biopsied diabetic kidney disease seems unlikely. Nevertheless, the likelihood that distinct pathophysiology drives CKD progression in these two diseases must be considered when developing therapies.

Reasons for Optimism: New Modalities, but New Challenges

Ascribing function to genes identified by GWAS remains a significant challenge, but tools to do so are continuing to evolve. The vast majority of disease-association signals are noncoding and likely affect gene regulation in specific disease-relevant tissues and cells; thus, understanding

cellular context (89), the epigenome, and three-dimensional chromatin architecture will be critical to advance target identification from genetics, as exemplified by distant effects of noncoding polymorphisms on endothelin-1 expression or the FTO locus (65,90). The continued evolution of genomic technologies such as CRISPR gene editing (91), proteomics, single-cell and next-generation sequencing (92), induced pluripotent stem cells, and organoids (93) are continuously expanding the tools available for drug discovery. Some emerging technologies such as CRISPR and stem cell–derived cell types hold potential as therapeutic modalities in addition to their use as research tools (94). However, drug discovery and development are extremely challenging and advancing a novel modality to an approved therapy can take well beyond a decade (95) and is influenced by prevailing regulatory environment and patient circumstance, even for established modalities such as small molecules, peptides, and monoclonal antibodies. Challenges for novel modalities not previously tested in humans include off-target toxicity concerns, establishing a regulatory approval path, supply chain and manufacturing reliability, and anticipating and navigating the commercial landscape at launch and beyond. We have recently witnessed phase 3 success and regulatory approval of RNA interference (96) and *ex vivo* gene therapy (97), as well as the emergence of promising technologies in base editing, gene activation (98), and targeted degradation (99). Many currently undruggable targets in kidney disease may soon become druggable by harnessing a toolbox to replace defective genes, turn on cellular functions, or perturb systems with robust target validation from human genetics. Progress is on the horizon for several novel therapeutic modalities and, although delivery challenges are ever present, there is reason for optimism about the potential to harness recent innovation to deliver transformative medicines to patients with kidney disease.

Disclosures

M.D. Breyer and D.F. Reilly are full-time employees of Janssen Pharmaceutical Company.

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