Kidney organoids as models for hereditary kidney diseases: Toward precision medicine (Review)

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Abstract. Kidney organoids are important tools for modeling human development and disease, especially in chronic kidney disease (CKD), which is a global health challenge. Current treatment strategies focus on delaying disease progression by managing underlying causes, and in this regard, kidney organoids offer a platform for mechanism-based therapeutics. Advances in the understanding of human induced pluripotent stem cells (hiPSCs) and sophisticated 3D organ culture methods have enabled researchers to replicate human kidney development and disease mechanisms *in vitro*, thereby opening new avenues for drug testing. Although the methods for generating renal cell lineages are well established, new protocols for inducing lineages, such as the ureteric bud and collecting ducts, have emerged over the past 5 years. Patient-derived or genetically edited kidney organoids have been used to successfully model various genetic kidney diseases, notably polycystic kidney disease, and to generate kidney tissues that closely mimic the morphology of real organs. However, achieving more complex disease modeling and generating transplantable synthetic kidneys still has notable challenges. The present review discusses the application of hiPSC-derived 3D organoids in CKD research and addresses the limitations of current organ culture methods. The present review also examines the impact of CRISPR/Cas9 technology, and investigates potential future directions.

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Contents

1. Introduction

The kidneys are among the most structurally and functionally complex organs in the human body, with highly specialized nephron segments and vascular networks that coordinate filtration, reabsorption, secretion and endocrine functions Composed of millions of filtration units and a vascular network spanning several kilometers, they undertake a variety of physiological functions (1,2). Due to their intricate structure and complex functions, the kidneys are also prone to various abnormal conditions, including imbalances in the transport of sodium ions and other electrolytes mediated by the renal tubules, as well as congenital defects in tissue structure resulting from abnormal growth (3,4). When a single gene, or several genes, undergo mutations or deletions, this may trigger kidney disease, thereby disrupting the normal physiological balance of the body (3,5,6). Occasionally, patients with hereditary kidney diseases are diagnosed in infancy or childhood, often with a family history of inheritance, and the same gene mutation may occur in multiple relatives. However, a larger number of patients are diagnosed only after they have reached adulthood, by which time the kidneys often have suffered irreversible damage, and the condition becomes more complicated (5-7).

Chronic kidney disease (CKD) is a common kidney disease that endangers human health. Although diabetes, hypertension and glomerulonephritis are the primary factors

that induce CKD (8,9), genetic and congenital kidney diseases are also notable causative factors of this condition. According to the Global Burden of Disease 2023 study, CKD affected ~788 million adults aged ≥20 years worldwide in 2023, increasing from 378 million in 1990, and is ranked as the ninth leading cause of death globally, accounting for 1.48 million mortalities in 2023 (95% uncertainty interval, 1.30-1.65 million) (10). In addition, an analysis of the Global Burden of Disease 2021 data reported that CKD caused 1,527,639 deaths worldwide in 2021, corresponding to a mortality rate of 18.5 per 100,000 population, and that the CKD incidence rate was 233.6 per 100,000 population, with both incidence and mortality showing increasing trends from 1990 to 2021 (11). The World Health Organization has also recognized kidney disease as an increasing global priority among non-communicable diseases, noting that ~674 million individuals live with CKD, accounting for ~9% of the global population. Eventually, CKD develops into end-stage renal disease, and patients must undergo hemodialysis or kidney transplantation to survive. However, both of these treatment methods have drawbacks. For example, hemodialysis can only partially restore kidney function, but not the function of entire kidney, and causes discomfort to certain patients. The shortage of donor organs and a lifelong use of immunosuppressants following transplantation is a notable limitation of kidney transplants. Therefore, it is necessary to identify more effective treatment options to address the continually rising prevalence and annual incidence of CKD worldwide (8-11).

Research on organoids dates back to 1907, when Wilson (12) mechanically separated sponge cells and allowed them to form functional organisms *in vitro*. In the following decades, separation-recombination experiments were performed using embryonic tissues from amphibians and chickens, generating organ-like or tissue-like structures, including amphibian pronephric kidney structures and chick limb-bud-derived mesenchymal/cartilaginous structures, thereby demonstrating that embryonic cells are able to self-organize *in vitro* (13,14). In 1975, a study by Rheinwald and Green generated a stratified squamous epithelial community resembling human epidermis by culturing primary human keratinocytes together with 3T3 fibroblasts (15). By the 1980s, pluripotent stem cells (PSCs) were first isolated from mouse embryos, and subsequently mesenchymal stem cells (MSCs), human embryonic stem cells (ESCs) and induced PSCs (iPSCs) were revealed (16). Subsequently, the development and progress of stem cell technology has provided novel insights to the field of tissue engineering. In 2009, a study by Sato *et al* (17) revealed that adult intestinal stem cells form small intestinal tissue bodies with crypt-villus structures *in vitro*. This represented a milestone in the field of tissue engineering, and demonstrated that stem cells have the potential to differentiate into spatial structures similar to those of internal organs. Since then, organoid cultivation technology has flourished, and an increasing number of organoids have been developed, including brain, retina, lung, stomach, liver, bile duct, pancreas and kidney (18).

In the present review, the literature on human iPSC (hiPSC)-induced kidney organoids that are used to model experimental diseases associated with gene mutations or deletions are discussed. Furthermore, the application of this methodology in building experimental models and treatment protocols is summarized. Finally, the present review assesses the current understanding of the role of hiPSCs-induced organoids in disease modeling.

2. From kidney development to kidney organoid cultivation

Nephrons are formed during pregnancy. Although there are variations among individuals, on average, each kidney generates ~1 million units. The kidneys originate from the ureteric bud (UB), which is derived from the anterior mesoderm, and the metanephric mesenchyme (MM), which is derived from the posterior mesoderm (19,20). The nephric duct (or Wolffian duct) grows outward by extending processes, under the main influence of glial cell line-derived neurotrophic factor (GDNF) from the surrounding MM. This protrusion forms the UB, which then begins to develop into MM. UB branching morphogenesis is regulated by reciprocal epithelial-mesenchymal interactions, particularly a positive feedback loop between cap mesenchyme (CM)-derived GDNF and UB-derived Wnt family member 11 (21). The establishment of this signaling loop depends on the condensation of the MM around the UB tips, giving rise to the SIX homeobox 2-positive ($SIX2^+$) CM (22). This iterative signaling exchange ensures repeated dichotomous branching, patterning the collecting ducts (CDs) and ureters. The UB-derived signaling protein Wnt9b instructs adjacent CM cells to form a pretubular aggregate. The cells in this aggregate subsequently respond to local fibroblast growth factor (FGF) and Wnt4 signals, which act together to sustain the expression of LIM homeobox 1 [LHX1 (previously Lim1)], a transcription factor required for early nephron patterning and renal vesicle maturation (23,24). The onset of this genetic program initiates the mesenchymal-to-epithelial transition, a fundamental process that generates a polarized epithelium with a central lumen, which establishes the renal vesicle. The renal vesicle then undergoes a series of morphological changes, including bending, elongation and patterning, to first form the comma-shaped body, and subsequently the S-shaped body (25,26). This patterning process is regulated by multiple signaling pathways, including Wnt4, FGF and Notch signaling pathways (23,26,27). Within the S-shaped body, vascular endothelial growth factor-A (VEGF-A) isoforms are produced by podocyte precursors in the proximal region, which recruits endothelial cells that contribute to glomerular formation (28,29). These endothelial cells subsequently secrete platelet-derived growth factor subunit B, which attracts mesangial progenitors and supports the organization of glomerular capillary loops (29,30). As development continues, the S-shaped body further differentiates into a mature nephron (29,31-33). The renal stroma is derived predominantly from Forkhead box D1-positive ($FOXD1^+$) stromal progenitors located at the periphery of the MM, with additional contributions from invading T-box transcription factor 18-positive ($TBX18^+$) ureteric stromal progenitor. These $FOXD1^+$ and $TBX18^+$ progenitors differentiate into fibroblasts, smooth muscle cells, pericytes and mesangial cells. Furthermore, stromal cells provide regulatory signals, such as GDNF, which influence UB branching and CM differentiation (34-41). Notably, nephrogenesis concludes permanently at approximately gestational week 36.

In 2015, two studies established the modern kidney organoid research field by demonstrating that human PSCs (hPSCs) can be directed to form kidney organoids containing nephron-like structures and multiple renal lineages (42,43). The core principle of this strategy is the stepwise recapitulation of *in vivo* nephrogenesis (33,42-44). Through the precise temporal activation and inhibition of key signaling pathways, primarily the Wnt, FGF and bone morphogenetic protein (BMP) signaling pathways, hPSCs are directed sequentially through primordial mesoderm, intermediate mesoderm, and finally, a self-organizing kidney progenitor population (expressing markers such as the zinc-finger transcription factor odd-skipped related 1 and SIX2) that forms 3D organoids containing glomeruli, proximal tubules, distal tubules and stromal elements (42-44). This classic protocol has been applied to different hPSC lines, including the H9 human embryonic stem cell line and the BJFF.6 human induced pluripotent stem cell line; nevertheless, kidney organoids generated from these lines showed substantial variation in nephron segment ratios, with a coefficient of variation of ~30%, as reported in a follow-up study by Wu *et al* (44).

Building upon the classic protocol, subsequent efforts have focused on streamlining the process to reduce cost and complexity. An example of this is provided by the protocol developed in the study by Freedman *et al* (45), which minimizes the number of recombinant growth factors required. Following initial mesoderm induction, the protocol relies predominantly on FGF9 to support the expansion of nephron progenitor cells and their subsequent self-organization. This approach offers notable advantages in cost-effectiveness and simplicity, and its robustness is demonstrated across multiple cell lines, making it suitable for large-scale drug screening initiatives, and also as a starting point for disease modeling. However, this protocol is not able to resolve the inherent heterogeneity of the resulting organoids.

To obtain a purer population of kidney progenitors, alternative strategies have been sought after, which are aimed at specifying the lineage earlier in the differentiation process. A study by Taguchi *et al* (20) demonstrates that, through modulating factors such as BMP4, hPSCs could first be directed toward a ventral mesoderm fate, a precursor population that gives rise to the kidney lineage. This method aims to enhance the purity of the resulting kidney progenitors by reducing contamination from non-renal mesodermal lineages (for example, skeletal muscle and bone). The trade-off is that this approach often requires more precise signaling modulation, which potentially increases the complexity of the protocol.

Unlike conventional kidney organoid protocols that primarily rely on spontaneous self-organization after kidney progenitor induction, nephron subtype induction strategies use additional signaling cues to enrich specific nephron segments.. Subtype patterning aims to bias differentiation toward specific nephron segments. For example, sustained Wnt or BMP signaling following nephron progenitor aggregation favors proximal tubule formation (46), whereas VEGF supplementation supports glomerular maturation. This provides more precise models for segment-specific studies.

However, assembly or co-culture strategies take a 'bottom-up' approach. This involves separately differentiating distinct kidney progenitor populations (for example, nephron progenitors and UB progenitor cells), and then combining them in a 3D environment to promote tissue-tissue interactions (47). A key example of this is provided in the study by van den Berg *et al* (48), which demonstrates that transplanting pre-formed organoids under the renal capsule of mice leads to enhanced vascularization and maturation as part of an *in vivo* assembly process. The subcapsular transplantation model is associated with improved vascularization and glomerular maturation, including the formation of fenestrated endothelium and podocyte foot processes. However, the procedure is also low-throughput, surgically invasive and not amenable to high-throughput drug screening. True *in vitro* assembly is still challenging, although it represents the frontier of generating organoids with higher-order architectural features, such as branched collecting systems. A recent study by Shi *et al* (49) at Cincinnati Children's Hospital Medical Center describes the development of a system of CDs by inducing the assembly of induced nephrogenic mesenchyme with UB progenitors. This leads to a CD network that is functionally integrated in kidney organoids through fusion with the distal tubule. This provides an important step toward functional renal tissue regeneration (Table I).

The utility of these differentiation strategies is through their integration with disease modeling. Either by utilizing patient-specific iPSCs or introducing known pathogenic mutations into wild-type hPSCs using CRISPR/Cas9 gene editing, studies have phenocopied a range of genetic kidney disorders, including polycystic kidney disease (PKD) and podocytopathies, in organoids (50,51). A particularly powerful application is the use of isogenic controls, specifically in cases in which iPSCs of a patient have had the disease-causing mutation corrected, which provide an unmatched control for validating disease phenotypes and conducting drug screens. This synergy enables kidney organoids to serve as a platform for personalized medicine and investigation into mechanistic disease and drug discovery.

In biomedical research, the kidney organoid system is well suited for studying the underlying mechanisms of renal diseases, drug discovery and toxicology (42,43,45,46,50,52). Especially in hereditary kidney diseases, with the advent of genome engineering technologies such as CRISPR/Cas9, it is possible to modify hiPSCs, either to introduce or correct disease-specific mutations, or to introduce reporter genes for drug screening. This provides a favorable approach to investigate genetic diseases (Fig. 1). At present, the interest in disease modeling using kidney organoids continues to grow as their potential is progressively investigated and a large number of human diseases are successfully modeled.

3. Disease modeling

Autosomal dominant polycystic kidney disease (ADPKD). ADPKD is genetically heterogeneous, dominated by two genes, *PKD1* (located on chromosome 16.p13.3) affects ~78% of families and *PKD2* (located on chromosome 4p21) affects ~15% of families. In 2016, a rare (affecting ~0.3% of families) third locus, the glucosidase II α subunit gene (on chromosome 11q12.3) was revealed (53). A study by Freedman *et al* (45) generated CRISPR-mutant kidney organoids from hPSCs and demonstrate that knocking out PKD1 or PKD2 induces

Table I. Differentiation strategies for kidney organoid generation.

Type of protocol	Core principle	Key signaling manipulation	Advantages	Limitations	(Refs.)
Classic multi-stage	Stepwise recapitulation of nephrogenesis via temporal modulation of Wnt, FGF9 and BMP	Mesoderm induction: High-concentration CHIR99021; kidney lineage induction: CHIR99021 withdrawal with FGF9 supplementation; aggregation/early nephron induction: Transient low-concentration CHIR99021 pulse, achieved by short-term CHIR99021 exposure followed by withdrawal; vesicle formation: Continued culture after CHIR99021 withdrawal.	Standardized; highly reproducible; generates complex organoids with glomeruli and proximal/distal tubules	Efficiency varies across cell lines; heterogeneous nephron segments; limited vascularization; Overall differentiation period of 20-30 days from hPSCs to analyzable kidney organoids.	(42-44)
Optimized/ simplified	Reduces the use of exogenous recombinant growth factors, such as BMP4 and activin A, and relies mainly on FGF9; relies on cellular self-organization	Mesoderm: CHIR; kidney lineage and aggregation: FGF9 only; vesicle formation: CHIR pulse	Lower cost and simpler operation than classic multi-stage protocols; robust efficiency across multiple cell lines	Limited control over nephron subtype specification	(45)
Ventral mesoderm	Enhances purity of kidney progenitors via early ventral mesoderm induction	Posterior/ventral mesoderm induction: 3 μM CHIR99021, 3 ng/ml BMP4 and 0.1 μM retinoic acid; nephron progenitor induction: 1 μM CHIR99021 and 5 ng/ml FGF9; later stages: Nephron progenitor aggregation and 3D culture for renal vesicle, tubule and glomerular-like differentiation.	Reduces contamination from non-renal lineages (such as muscle and bone)	Requires precise signaling control; increased protocol complexity	(20)
Nephron subtype induction	Biases differentiation toward specific segments (such as the proximal tubule or glomerulus)	PT enrichment: Sustained Wnt agonist or BMP7 after vesicle stage; glomerular enrichment: Addition of VEGF	High purity for target segment; precise model for segment-specific diseases, such as podocytopathies, Alport syndrome, Gitelman syndrome and proximal tubule disorders	Sacrifices overall organoid complexity; less mature phenotypes	(46)
Assembly and co-culture	'Bottom-up' combination of separately differentiated kidney progenitors	Differentiate nephron progenitors and UB cells separately; combine in 3D co-culture (such as in transplantation)	Enables study of tissue-tissue interactions; potential for branched collecting duct structures	Technically challenging; low throughput; not yet widely used	(47-49)

CHIR, CHIR99021 (Wnt pathway agonist); FGF9, fibroblast growth factor 9; BMP, bone morphogenetic protein; VEGF, vascular endothelial growth factor; RA, retinoic acid; PT, proximal tubule; UB, ureteric bud.

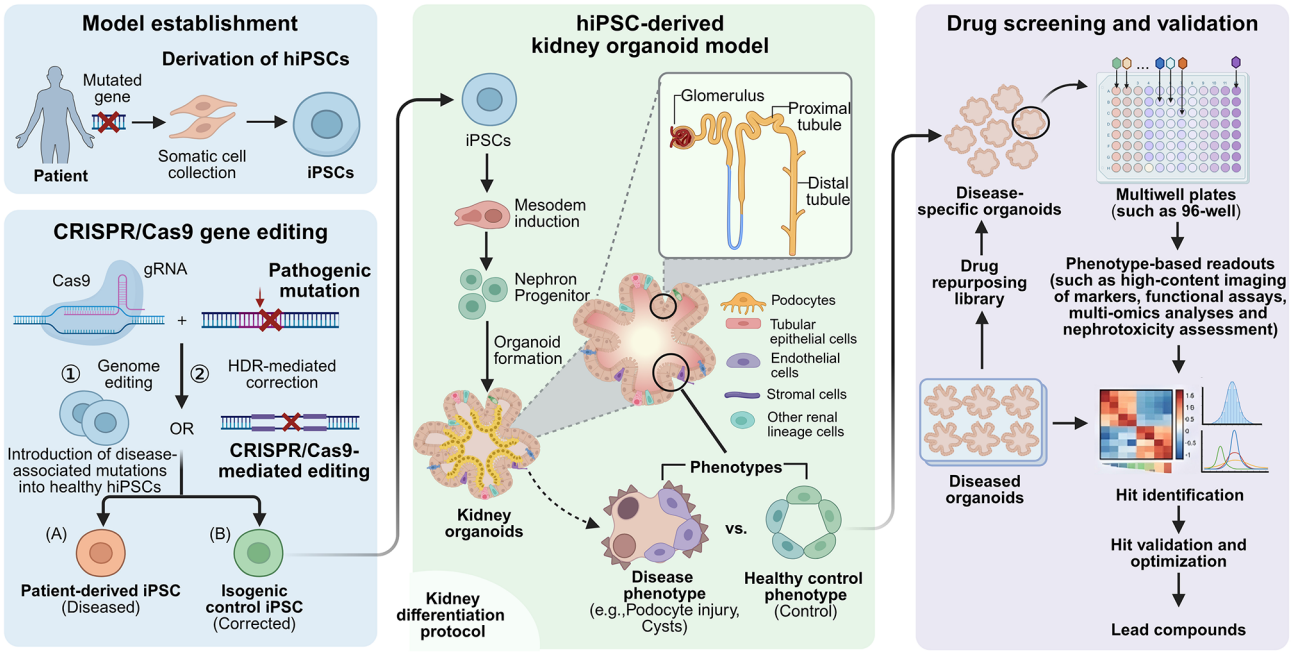

Figure 1. Establishment of hiPSC-derived genetic kidney disease organoid models and their application in drug screening and validation. The schematic illustrates the workflow for generating kidney organoid models of hereditary kidney diseases using patient-derived hiPSCs and CRISPR/Cas9-mediated genome editing. Somatic cells obtained from patients carrying disease-associated mutations are reprogrammed into hiPSCs. In parallel, CRISPR/Cas9 gene editing can be used either to introduce pathogenic mutations into healthy hiPSCs or to correct disease-associated mutations through HDR, thereby generating patient-derived disease hiPSC lines and isogenic control hiPSC lines. These hiPSCs are subsequently subjected to a kidney differentiation protocol involving mesoderm induction, nephron progenitor specification and organoid formation to generate hiPSC-derived kidney organoids containing nephron-like structures, including glomeruli, proximal tubules and distal tubules, as well as podocytes, tubular epithelial cells, endothelial cells, stromal cells and other renal lineage cells. Disease and control organoids can then be compared to identify pathological phenotypes, such as podocyte injury and cyst formation. Diseased organoids may further be applied in drug repurposing and multiwell plate-based drug screening, together with phenotype-based readouts, such as high-content imaging, functional assays, multi-omics analyses and toxicity assessment, thereby facilitating hit identification, hit validation, optimization and lead compound selection. hiPSC, human induced pluripotent stem cell; CRISPR, clustered regularly interspaced short palindromic repeats; Cas9, CRISPR-associated protein 9; gRNA, guide RNA; HDR, homology-directed repair.

cyst formation in kidney tubules. The subsequent study by Xu *et al* (54) reveals a distinct population of $CD24^+$ renal epithelial cells with unique metabolic and gene regulatory programs and generates adult human kidney organoids from these cells. By combining $CD24^+$ cell-derived tubule-like structures with multiplexed CRISPR-Cas9 gene editing, an ADPKD organoid model that enables rapid cyst induction was established, highlighting the potential of lineage-specific differentiation strategies for improved disease modeling (54).

Building on this foundation, a study by Vishy *et al* (55) develops base-edited PKD kidney organoids that have four clinical non-sense mutations in *PKD1* and *PKD2*, which enables allele-specific modeling of cystogenesis and therapeutic testing. A key finding is that heterozygous mutated organoids do not spontaneously form cysts, suggesting a potential therapeutic window for intervention. Furthermore, from a translational perspective, the study by Vishy *et al* (55) identifies eukaryotic ribosome-selective glycosides as candidate therapeutics, demonstrating that these compounds are able to mediate non-sense mutation readthrough, which is potentially a targeted treatment strategy for patients with such mutations.

Autosomal recessive polycystic kidney disease (ARPKD). ARPKD is a kidney disease that differs from ADPKD. Although both disorders are classified as ciliopathies, sharing core pathological pathways such as ciliary dysfunction and abnormal epithelial cell proliferation, ARPKD has unique clinical and genetic characteristics (56). It has an autosomal recessive inheritance pattern, primarily caused by mutations in the polycystic kidney and hepatic disease 1 (*PKHD1*) gene (and less commonly in the DAZ-interacting zinc finger protein 1-like gene) (57,58), with the onset of the disorder typically occurring in neonates or childhood. The hallmark features of ARPKD, namely fusiform dilatation of the renal CDs accompanied by congenital hepatic fibrosis (59,60), differ to the widespread cyst formation that occurs throughout the kidneys and adult-onset presentation that are characteristic of ADPKD.

A study by Low *et al* (46) established an ARPKD model using patient-derived iPSCs harboring biallelic *PKHD1* frameshift mutations. The aforementioned study demonstrates that cAMP activation via the natural compound forskolin induces extensive cystogenesis specifically in the $PKHD1^{-/-}$ organoids, a response that is markedly attenuated in heterozygous and wild-type controls (46). Furthermore, a study by Hiratsuka *et al* (61) integrates ARPKD organoids with an organ-on-chip platform. This revealed a novel pathogenic mechanism, demonstrating that fluid flow-induced mechanical stress, mediated by the mechanosensors Ras-related C3 botulinum toxin substrate 1 (RAC1) and Fos proto-oncogene (c-Fos), promotes cyst formation (61).

Fabry's disease (FD). The original animal model of FD, developed in a study by Ohshima *et al* (62), used a targeting construct to knock out the α-galactosidase A (α-Gal A) gene in C57BL/6 male mice, which were then mated with normal C57BL/6 females to obtain heterozygous mice lacking the α-Gal A gene, generating α-Gal $A^{+/-}$ mice. The construction of the animal model was completed by mating α-Gal $A^{+/-}$ female mice with C57BL/6 male mice to obtain α-Gal $A^{-/0}$ mutant male mice (62).

Several years later, a study by Porto *et al* (63) carried out pharmacological investigations using fibroblasts from patients with FD. After the study by Freedman *et al* (45) that first applied CRISPR/Cas9 gene editing technology to kidney organoid disease models, several studies have applied CRISPR/Cas9 or related genome-editing approaches to kidney organoid models by disrupting, introducing or correcting disease-associated genes (45,54,55,64-68). A 2021 study by Kim *et al* (69) confirmed that, in kidney organoids derived from hiPSCs carrying mutations in *GLA*, the gene encoding α-Gal A, the deposition of the glycosphingolipid globotriaosylceramide (Gb3) led to structural deformation of podocytes and renal tubular cells, thereby exacerbating oxidative stress and apoptosis. The aforementioned study further evaluates two therapeutic strategies, namely enzyme replacement therapy (using recombinant human *α-Gal A*), which is shown to alleviate oxidative stress and repair cell structure by eliminating Gb3, and antioxidant therapy (glutathione replacement), which is shown to directly reduce oxidative stress, thereby alleviating structural damage to organoids (69).

A study by Cui *et al* (65) differentiated FD model kidney organoids using patient-derived and gene-edited hiPSCs. Kidney organoids were cultivated from hiPSCs of two male patients with different types of *GLA* mutations who had FD. Compared with the wild-type organoids, the patient-derived organoids had decreased α-Gal A activity and increased Gb3 lipid deposition. These abnormalities were more pronounced in organoids carrying the classic Fabry disease-associated *GLA* mutation, which was associated with markedly reduced α-Gal A activity and a more severe Gb3 accumulation phenotype. Using electron microscopy, multilamellar lysosomal inclusion bodies, also known as zebra bodies, were observed in the mutant organoids, thereby reproducing a characteristic pathological feature of Fabry nephropathy.

To further investigate treatment strategies, CRISPR/Cas9 was used to knock out the α-1,4-galactosyltransferase (*A4GALT*) gene, which encodes Gb3 synthase. The results demonstrate that, in the *GLA* mutant kidney organoids, *A4GALT* knockout reduces Gb3 deposition, and lysosome inclusion bodies are not observed (64).

Collectively, these findings not only confirm the potential of glutathione and *A4GALT* as possible new therapeutic targets for FD, but they also provide a reliable *in vitro* model platform for drug development (64).

Karyomegalic interstitial nephritis (KIN). KIN is an extremely rare hereditary form of chronic interstitial nephritis. Although a reliable population-based incidence rate has not been established, its estimated prevalence is <1 per 1,000,000 individuals, it accounts for <1% of kidney biopsies, and <100 native-kidney cases have been reported in the literature (70,71). In order to identify the causative gene for nephronophthisis (NPHP)-like ciliopathy, a study by Zhou *et al* (72) evaluates two affected siblings of Maori descent in New Zealand. Renal histopathology analysis reveals enlarged nuclei (nucleolar enlargement) in the renal cells, and a diagnosis of KIN is suggested. Subsequent pure-synteny localization and exome sequencing reveals a pure-synteny non-sense mutation in *FAN1*, the gene that encodes Fanconi anemia-associated nuclease 1. Additionally, through sequencing *FAN1* exons from the DNA samples of 10 families with KIN, it is revealed that a recessive mutation in *FAN1* is the important etiologic factor in KIN. Another study by Lim *et al* (73) generated kidney organoids using *FAN1*-mutant and wild-type hiPSCs. After inducing DNA damage via mitomycin C treatment, the FAN1-mutant organoids demonstrated increased expression of the DNA damage-associated marker H2A.X compared with their wild-type counterparts; Ki67 was also assessed to evaluate cell proliferation and viability within the organoids. Taken together, these findings demonstrate that *FAN1*-deficient kidney organoids successfully recapitulate the KIN phenotype, suggesting a potential model platform for investigating the mechanisms through which defective DNA repair contributes to the development of CKD.

Gitleman syndrome (GS). GS (online mendelian inheritance in man: 263800), also known as familial hypokalemia-hypomagnesemia, is a salt-losing tubulopathy that is characterized by hypomagnesiuria, hypocalciuria and secondary aldosteronism, leading to hypokalemia and metabolic alkalosis with autosomal recessive inheritance (74). GS is associated with mutations in the solute carrier family 12 member 3 (*SLC12A3*) gene, which encodes the thiazide-sensitive sodium chloride cotransporter (NCCT) in the distal convoluted tubule (75). A study by Lim *et al* (66) prepared general hiPSCs and gene-modified hiPSCs by sequencing the *SLC12A3* gene using CRISPR/Cas9 technology with peripheral blood mononuclear cells from patients with GS. Furthermore, in a subsequent study (68), the *SLC12A3* gene mutation was corrected using CRISPR-Cas9 technology, yielding genetically repaired hiPSCs. When both the mutant and corrected hiPSCs are differentiated into kidney organoids, the *SLC12A3*-mutant tissues exhibit reduced mRNA and protein levels of NCCT compared with wild-type controls. However, these levels are restored in the genetically corrected organoids. Although the aforementioned study models GS in kidney organoids for the first time and demonstrates reduced NCCT expression levels in E-cadherin-positive epithelial cells, as well as its rescue by genetic correction, it did not directly demonstrate the defective electrolyte transport associated with disease pathogenesis. Overcoming this limitation may require more advanced kidney organoid platforms that incorporate vascularization, tubular fluid flow and functional assays capable of assessing solute transport.

Alport syndrome (AS). AS is a one of the most common hereditary glomerular diseases. Its main clinical features include progressive glomerular injury and extrarenal manifestations, particularly sensorineural hearing loss and ocular abnormalities and it may eventually progress to end-stage renal disease (76). The causative genes for AS are *COL4A3-5*, which encode the α3, α4 and α5 chains of type IV collagen,

respectively. Mutations in these genes lead to abnormal type IV collagen structure in the glomerular basement membrane (BM) (77-79). Given the severity of the condition and the current lack of curative options, developing a preclinical platform that accurately recapitulates the disease phenotype is challenging.

Using kidney organoids derived from hiPSCs, studies have successfully constructed disease models that simulate AS (80,81). A study by Hirayama *et al* (80) reports on hiPSCs derived from two male patients with AS and differentiates them into kidney organoids. The organoids derived from these patients successfully reproduces the key disease phenotypes, including abnormal expression of the type IV collagen α5 chain, α5(IV). The aforementioned study confirms that the severity of the phenotype is associated with the type of genetic mutation, and that the normal expression of α5 (IV) can be restored through genetic correction. Furthermore, the chemical chaperone 4-phenylbutyric acid improves BM defects in mild-phenotype organoids, although it is ineffective in severe-phenotype organoids. These findings suggest the necessity of personalized treatment based on genetic typing (80).

A study by Morais *et al* (81) reports the BM pathology in AS. It is revealed that, although kidney organoids derived from iPS cells from patients with AS form normal-appearing glomeruli and tubules under a light microscope, their molecular composition is already abnormal, manifesting as an increased deposition of laminin β2, specifically in the extraglomerular BM. Furthermore, the aforementioned study reveals that BM composition is regulated from development to adulthood, a process that is disrupted by pathogenic *COL4A5* variants. Consequently, the model successfully recapitulates the laminin dysregulation in patients with AS, suggesting that kidney organoids may serve as a potential platform for studying aberrant BM assembly in human developmental diseases (81).

Nephrotic syndrome. The normal function of glomerular podocytes relies on the slit diaphragm, a protein complex composed of molecules including nephrin (NPHS1) and podocin (NPHS2). Mutations in either NPHS1 or 2 disrupt the formation of the slit diaphragm, leading to congenital nephrotic syndrome (82,83). Several studies validate this pathogenic mechanism using patient-specific iPSC-derived kidney organoid models (84-87). Two studies demonstrate that a NPHS1 missense mutation results in abnormal NPHS1 localization and impairs slit diaphragm formation in podocytes (84,85). However, a study by Jansen *et al* (86) reports that NPHS2 mutations lead to both a loss of NPHS2 expression levels and the mislocalization of NPHS1, which is a reversible phenotype upon genetic correction. Furthermore, a study by Majmundar *et al* (87) models glomerular developmental abnormalities and an increased rate of apoptosis by introducing a patient-derived nitric oxide synthase 1 adaptor protein variant into human kidney organoids. Collectively, the aforementioned studies highlight the possible utility of kidney organoids in terms of recapitulating the pathological mechanisms of podocytopathies.

Autosomal dominant tubulointerstitial kidney disease (ADTKD). ADTKD, the third most common monogenic kidney disease, causes progressive renal failure via tubular/interstitial injury, and it is attributed to mutations in five genes, namely uromodulin, mucin 1 (*MUC1*), renin (*REN*), SEC61 translocon subunit α 1 and hepatocyte nuclear factor 1-β (*HNF1β*) (88,89).

Kidney organoid models provide a platform for investigating the functional roles of causative genes in ADTKD. A study by Przepiorski *et al* (68), which investigates the role of the *HNF1β* gene, uses CRISPR/Cas9 technology to knock out *HNF1β* in order to observe any downregulation in the expression of markers associated with proximal tubules and thick ascending limbs in the organoids. This demonstrates the regulatory role of genes in nephron segment patterning. Another study by Mae *et al* (90) investigates UB organoids, further revealing that the heterozygous loss of *HNF1β* leads to impaired branching morphogenesis and loss of apicobasal polarity. By contrast, a study by Dvela-Levitt *et al* (91) generates kidney organoids from iPSCs derived from patients with *MUC1* mutations. This recapitulates the pathological hallmark of aberrant mutant protein accumulation, and use this model to identify a small-molecule compound, BRD4780, which directs the mutant protein for degradation via the lysosomal pathway, demonstrating the application of organoids in targeted drug discovery (91).

Autosomal recessive-renal tubular dysgenesis (AR-RTD). AR-RTD is a lethal genetic disorder characterized by the complete absence or severe hypoplasia of proximal tubules, which results from pathogenic mutations in key genes of the renin-angiotensin-aldosterone system (RAAS), including angiotensin-converting enzyme (*ACE*), angiotensin II receptor type 1 (*AGTR1*), autophagy-related and *REN* (92). A study by Pode-Shakked *et al* (93) generated RAAS-deficient kidney organoids by differentiating $ACE^{-/-}$ and $AGTR1^{-/-}$ iPSCs, as well as patient-derived iPSCs with AR-RTD, into kidney organoids. This demonstrates that RAAS-deficient organoids form proximal tubules *in vitro*; however, $AGTR1^{-/-}$ organoids display impaired engraftment at the renal vesicle stage due to insufficient VEGF-A expression levels, suggesting that delayed angiogenesis is a possible mechanism that underlies autosomal recessive renal tubular dysgenesis (93) Additionally, the aforementioned study reveals that, under conventional or hypoxic culture conditions, the loss of RAAS genes does not directly affect proximal tubule patterning in organoids. Following transplantation under the renal capsule of immunodeficient mice, renal vesicle-stage $AGTR1^{-/-}$ organoids have impaired engraftment due to insufficient VEGF-A expression levels and delayed angiogenesis. Hypoxic culture induces the expression of VEGF-A and rescues the engraftment of $AGTR1^{-/-}$ organoids (93). These findings suggest that proximal tubule dysgenesis in AR-RTD is not primarily induced by cell-autonomous tubular defects, but is induced by delayed angiogenesis as a non-cell-autonomous consequence of impaired RAAS signaling.

Nephronophthisis (NPHP). NPHP is an autosomal recessive disorder that is characterized pathologically by disruption of the tubular BM, tubular atrophy, interstitial fibrosis and progression to end-stage kidney disease (94). To investigate its underlying mechanisms, studies focus on the intraflagellar transport 140 (*IFT140*) gene, which encodes a core component of the intraflagellar transport complex A involved in retrograde

ciliary transport (95,96). In a study by Forbes *et al* (51), kidney organoids are generated using patient-derived *IFT140*-mutant iPSCs alongside isogenic gene-corrected control iPSCs. This reveals that mutant organoids have shortened, malformed primary cilia and defects in cellular polarization, whereas genetic correction successfully rescues these abnormal phenotypes, confirming the central role of *IFT140* mutations in NPHP pathogenesis (51).

Cystinosis. Cystinosis is an autosomal recessive lysosomal storage disorder caused by mutations in the cystinosin, lysosomal cystine transporter gene, which encodes the protein cystinosin (97). The major characteristic of cystinosis is the accumulation of cystine in lysosomes, which leads to progressive renal tubular damage and multiple organ dysfunction (98).

A study by Hollywood *et al* (98) differentiates kidney organoids from iPSCs derived from patients with cystinosis, recapitulating key disease phenotypes. For example, cystine crystal accumulation was observed in the proximal tubular cells of the organoids, accompanied by lysosomal dysfunction, elevated oxidative stress and impaired levels of autophagy. Electron microscopy and molecular analyses further revealed features of mitochondrial dysfunction and increased rates of apoptosis of renal tubular epithelial cells in the organoids, demonstrating the successful modeling of progressive injury processes observed in patient kidneys (98) (Table II).

4. Emerging applications, limitations and translational challenges

Overview of emerging applications. Kidney organoid technology demonstrates multifaceted application potential, including disease modeling, toxicological safety assessment, personalized medicine, organ transplantation, organ-on-chip development and extracellular vesicle (EV)-associated research (99).

Two transplantation models promote vascularization and maturation of kidney organoids. A study by van den Berg *et al* (48) first transplanted organoids under the renal capsule of immunodeficient mice,. Subsequently, a study by Koning *et al* (100) used intracoelomic transplantation into chicken embryos to study vasculogenesis in kidney organoids. These transplantation studies demonstrated that *in vivo* engraftment promotes the vascularization and maturation of kidney organoids. In the renal subcapsular transplantation model, van den Berg *et al* (48) showed that transplanted organoids developed host-derived vascularization, fenestrated endothelial cells and podocyte foot processes, and exhibited selective permeability to dextran and albumin, suggesting the formation of a functional glomerular filtration barrier. In the intracoelomic transplantation model, Koning *et al* (100) demonstrated vascular integration and improved maturation of kidney organoids in the chicken embryo environment. Together, these findings indicate that transplantation can enhance vascularization, glomerular maturation and epithelial organization in kidney organoids.

The study by Lim *et al* (101) was the first to combine collagen scaffold encapsulation with minimally invasive intrarenal injection, overcoming the shortcomings of traditional subcapsular or abdominal transplantation that require surgical exposure. Furthermore, the method avoids the problems of uneven distribution and low survival rate that occurs with simple cell injection. This study (101) demonstrates that this method not only preserves the structural integrity of organoids, but it also promotes their functional integration into the host kidney, providing a feasible preclinical model for future organoid-based kidney regeneration therapy.

Microfluidic technology, via the construction of microphysiological systems with dynamic fluidic microenvironments, provides kidney organoids with a culture platform that more closely mimics *in vivo* conditions, notably enhancing organoid vascularization, maturation and functional simulation capabilities. This technology is able to simulate fluid shear stress and intraluminal pressure within nephrons, promoting the polarization and functional maturation of renal tubular epithelial cells (102). Through multi-chamber designs, it enables spatial coupling of the glomerular filtration barrier with tubular structures, simulating the urine-formation process (103). Additionally, in disease modeling, microfluidic systems successfully recapitulate drug-induced nephrotoxicity (104) and the cyst-expansion mechanisms in genetic diseases such as ADPKD (105). In drug screening, its integrated high-throughput detection systems allow real-time monitoring of organoid responses to drugs, which notably improves the precision of nephrotoxicity assessments (106). Furthermore, connecting kidney organoid chips with other organ chips provides a novel platform for studying systemic diseases and multi-organ interactions (107). However, despite their advantages, current microfluidic platforms have several technical bottlenecks that limit their broader application, including: i) Chip material (polydimethylsiloxane) adsorption of hydrophobic drugs causing dosing inaccuracy; ii) inconsistent flow shear stress across replicates due to bubble formation; iii) limited imaging depth (typically <200 μm) for thick organoids; and iv) a lack of standardized protocols for organoid loading and perfusion. Moreover, common failure points involve organoid detachment, leakage at chip interfaces and microbial contamination during long-term culture (>7 days). Therefore, these issues must be addressed prior to the widespread adoption of this technology.

EVs are heterogeneous membrane-enclosed nanoparticles that mediate intercellular communication and participate in both physiological and pathophysiological conditions in the kidney (108). EVs derived from stem cells, especially MSCs, which are adult stem cells found in tissues such as bone marrow, adipose tissue, umbilical cord, placenta and dental pulp, have demonstrated notable regenerative potential in various models of acute and chronic kidney injury (109,110).

Critical appraisal of kidney organoid models. Kidney organoids have notably revolutionized renal research and, when combined with gene-editing techniques, are a valuable research model. This model uses genome-wide screening to investigate the underlying mechanisms of genetic diseases, facilitates drug and toxicity screening on personalized human-derived platforms, and serves as a key tool for deciphering renal morphogenesis and functional maintenance (111,112). However, several constraints limit clinical translation. Compared with conventional animal models, kidney organoids provide a human genetic background and greater compatibility with

Table II. Guidance for model selection: Matching differentiation strategy to disease application.

Disease category	Representative diseases	Recommended differentiation strategy	Key model characteristics	(Refs.)
Ciliopathies with cystogenesis	ADPKD and ARPKD	Classic multi-stage; assembly/co-culture strategies to model collecting duct-derived cystogenesis	Cyst formation upon cAMP induction; collecting duct integration for ARPKD	(45,46,50, 54,55,61)
Glomerular basement membrane diseases	Alport syndrome	Classic multi-stage; nephron subtype induction (glomerular enrichment)	Abnormal type IV collagen expression levels; podocyte foot process effacement	(80,81)
Podocytopathies/slit diaphragm disorders	Congenital nephrotic syndrome (NPHS1 and 2)	Classic multi-stage; ventral mesoderm (for increased podocyte purity)	Nephrin/podocin mislocalization; impaired slit diaphragm formation	(84-87)
Tubular transport disorders	Gitelman syndrome (SLC12A3)	Optimized/simplified; nephron subtype induction (PT enrichment)	Reduced NCCT expression; electrolyte transport defects requiring functional validation, such as thiazide-sensitive NaCl uptake, ion flux and transepithelial transport assays	(66,67)
DNA repair-associated tubulointerstitial disease	Karyomegalic interstitial nephritis (FAN1)	Classic or optimized protocol	Increased H2A.X expression after mitomycin C treatment; Ki67 was assessed to evaluate cell proliferation and viability	(73)
Lysosomal storage disorders	Fabry disease and cystinosis	Classic or optimized protocol	Gb3 deposition (Fabry); cystine crystals (cystinosis); oxidative stress	(64,65, 69,98)
Nephron segment patterning disorders	ADTKD (HNF1B and MUC1)	Classic multi-stage; ureteric bud organoid assembly	Reduced proximal tubule markers, such as LTL, CUBN and AQP1, and thick ascending limb markers, such as uromodulin and SLC12A1/NKCC2; branching defects	(68,90,91)
RAAS-related developmental defects	AR-RTD (ACE and AGTR1)	Classic protocol followed by transplantation	Delayed angiogenesis; impaired engraftment after transplantation	(93)
Ciliopathy with tubular atrophy	Nephronophthisis (IFT140)	Classic or optimized protocol	Shortened primary cilia; defective cellular polarization	(51)

ADPKD, autosomal dominant polycystic kidney disease; ARPKD, autosomal recessive polycystic kidney disease; ADTKD, autosomal dominant tubulointerstitial kidney disease; AR-RTD, autosomal recessive renal tubular dysgenesis; PT, proximal tubule; RAAS, renin-angiotensin-aldosterone system; NCCT, sodium chloride cotransporter; cAMP, cyclic adenosine monophosphate; NPHS1, nephrin; NPHS2, podocin; SLC12A3, solute carrier family 12 member 3; FAN1, FANCD2/FANCI-associated nuclease 1; Gb3, globotriaosylceramide; HNF1B, hepatocyte nuclear factor-1β; MUC1, mucin 1; ACE, angiotensin-converting enzyme; AGTR1, angiotensin II receptor type 1; IFT140, intraflagellar transport 140.

high-throughput screening. However, they lack key aspects of systemic physiology, including hemodynamic forces, endocrine regulation and immune interactions (111,112) For drug screening, organoids enable rapid phenotypic readouts such as cyst growth and protein mislocalization, but have lower scalability compared with 2D cultures. Reproducibility remains a major concern. Independent differentiations of the same hiPSC line yield organoids with up to 30-40% variability in nephron progenitor numbers (44). In addition, scalability for drug screening is limited by manual handling; bioreactor-based expansion does improve yield, although this process also introduces shear stress artifacts.

Key limitations and challenges. Firstly, the cells generated by kidney organoids are mostly immature, possessing embryonic or fetal characteristics, and fail to form the mature cell types that are unique to adult kidneys (112,113). The epithelial cells within organoids primarily express development-associated genes and often show limited expression or maturation of functional proteins associated with kidney diseases, such as NPHS1, NPHS2, COL4A3-5, SLC12A3 and uromodulin. Targeted induction protocols are required to promote the further maturation of organoids, which enables the construction of a research model that more closely mimics the physiological characteristics of adult kidneys (44).

Secondly, batch-to-batch variations, residual off-target cells and individual variability during maturation can lead to misleading conclusions when comparing patient-derived organoids with isogenic control organoids (44,114). This heterogeneity notably undermines the reliability of research results and presents a critical factor limiting their precise application.

Thirdly, key cell types, such as vascular endothelial cells and immune cells, are absent in kidney organoids derived from hPSCs; however, these cells perform crucial roles in the maintenance of renal physiological functions and pathological processes (for example, inflammation and injury repair) (114-116). This deficiency has notable limitations for investigations into the interactions between renal cells and immune cells, which especially hinders the *in vitro* modeling of complex diseases such as infectious and autoimmune nephropathies (114,116).

Fourthly, kidney organoids lack the macroanatomical structures that are similar to those of natural kidneys and more complex organ tissue architectures. This prevents them from simulating core renal functions, such as tubular reabsorption and renal filtration (114), making it difficult to recapitulate the physiological functional characteristics of adult kidneys.

The functional validation of kidney organoids has been insufficiently addressed in numerous studies (44,111-113,116,117). Beyond morphological assessment, critical parameters also require systematic evaluation. Electrophysiological properties, including transepithelial resistance and ion channel activity, remain largely uncharacterized. Electrolyte transport could be measured via an assessment of Na^+/K^+-ATPase activity (namely, ouabain-sensitive ATP hydrolysis) (117) and by evaluating glucose uptake or reabsorption (105). Vascularization could be assessed morphologically by calculating the $CD31^+$ vascular area fraction and functionally by evaluating fluorescent tracer perfusion. Transcriptomic maturity should be benchmarked using principal component analysis, comparing organoid transcriptomes to both fetal (12-20 weeks) and adult kidney reference datasets; a maturity score closer to that of the adult kidney indicates an improved differentiation (44). Long-term stability over weeks to months in culture or after transplantation also requires systematic reporting. These functional benchmarks are essential for validating organoid utility in disease modeling and drug screening (Table III).

Bioengineering solutions to overcome limitations. Organoids-on-chip are able to optimize nutrient exchange via shear stress, and compared with static culture, they are more likely to induce organoids to form structures resembling mature kidneys (102,118). This technology has a wide range of applications, for example, it can be used to study vascularization (providing key support for drug testing), and can simulate glomerular filtration function through the co-culture of podocytes and endothelial cells (103,104).

Although organoids-on-chip offer notable advantages over traditional research platforms, they are still not able to fully replicate the physiological complexity of human kidneys and currently face several challenges, including limited standardization, poor reproducibility, chip material-related limitations and microfluidic designs that may not fully accommodate the size, 3D architecture and long-term perfusion requirements of kidney organoids. These limitations complicate organoid integration, stable perfusion, long-term culture and imaging-based analysis at different tissue depths (119).

As a cutting-edge technology, 3D bioprinting has a potential for developing kidney organoids. Through enabling the precise positioning of cells and biomaterials, 3D bioprinting may construct larger-scale, more complex kidney-like tissues, suggesting a potential for the development of preclinical models (120). A key advantage of this method is its capacity for high-throughput production, which ensures consistent cell numbers, high viability and reduced inter-organoid variability (121). By leveraging iPSCs, bioprinting platforms have been demonstrated to generate kidney constructs with improved uniformity and expression of lineage-specific markers, including NPHS1, NPHS2 and WT1 for podocytes; LTL, E-cadherin and AQP1 for tubular epithelial cells; and CD31/PECAM1 and VE-cadherin/CDH5 for endothelial cells (122). Furthermore, the technology allows the modulation of biophysical parameters, such as cell number and tissue size, to improve the modelling of renal functional and physiological characteristics (121). This strategy not only mitigates patient-derived heterogeneity, but it also establishes stable, reproducible models that are suitable for high-throughput screening and comparative studies (118).

The integration of patient-derived iPSCs, genome editing, reporter lines, microfluidic devices and 3D bioengineering approaches is expanding the utility of kidney organoids for disease modeling and preclinical drug evaluation (107,111-114,117-124). Reporter lines can facilitate lineage tracing, cell-type identification and real-time monitoring of organoid differentiation; examples include SIX2-based reporters for nephron progenitor cells, WT1- or NPHS1-based reporters for podocyte-lineage cells, and PECAM1/CD31- or CDH5-based reporters for endothelial cells. In parallel, patient-derived iPSCs and gene-edited isogenic controls allow

Table III. Proposed assessment metrics for kidney organoid quality evaluation.

Metric category	Specific assay	Target	(Refs.)
Transcriptomic maturity	Principal component analysis comparing organoid transcriptome of fetal (12-20 weeks of age) vs. adult kidney	Closer clustering with adult human kidney transcriptomic profiles indicates greater transcriptomic maturity	(44)
Glomerular filtration proxy	FITC-inulin clearance in microfluidic device	Detectable selective filtration/ permeability assessed using FITC-inulin, dextran or albumin tracer assays in organoid-on-chip or transplantation-based models	(103)
Transporter activity	Na^+/K^+-ATPase activity; organic cation transporter 2/multidrug and toxin extrusion 2-K uptake/efflux assays	Expression of a functional transporter and polarity; inhibitor-sensitive activity	(104-106, 117)
Vascularization efficiency	$CD31^+$ area fraction quantified using confocal microscopy	Increased $CD31^+$ vascular area fraction compared with static controls	(46,48, 100,102)
Long-term stability	Histology, immunofluorescence staining, vascular perfusion/tracer assays and graft retention analysis after transplantation	Maintained graft survival, vascular integration and tissue architecture at representative follow-up points, such as 2-4 weeks and, when applicable, up to 12 weeks after transplantation	(48,100, 101)

disease-associated phenotypes to be modeled in a human genetic background, whereas microfluidic and bioengineering platforms can provide dynamic culture conditions and more standardized tissue construction (107,111-114,117-124). Together, these approaches may improve the analysis of pathological endpoints related to drug efficacy and toxicity and support more individualized disease modeling.

Translational challenges and standardization. Translating kidney organoids to clinical applications requires overcoming several hurdles. Good Manufacturing Practice compliance demands xeno-free, defined media and stringent quality control release criteria. Regulatory barriers are substantial, since guidance from the Food and Drug Administration on organoid-based products remains in its early phase. Furthermore, scalability is limited by manual handling; in addition, although bioreactor-based expansion improves yield, it also introduces shear stress artifacts. Quantitative benchmarking is suggested to be mandated for preclinical studies. Proposed metrics include organoid size distribution (target coefficient of variation <20%), cell type proportions by single-cell RNA-sequencing (>80% kidney lineage) and functional assays, such as FITC-inulin clearance for glomerular filtration or Na^+/K^+-ATPase activity for proximal tubule function. These benchmarks may facilitate cross-laboratory comparisons and accelerate clinical translation.

Emerging applications: modeling viral kidney disease. As well as hereditary disorders, kidney organoids are also applied to model viral nephropathies. SARS-CoV-2 infection of kidney organoids recapitulates viral entry, replication and cytopathic effects, primarily targeting proximal tubular cells via ACE2, with enhanced organoid maturation improving viral replication modeling (123). Similarly, BK polyomavirus, a major cause of nephropathy in transplant recipients, induces nuclear enlargement characteristic of BK virus nephropathy in kidney tubuloids, and such models enable antiviral compound testing (124). These applications expand the use of kidney organoids beyond genetic disorders, highlighting their potential in infectious disease modeling and drug development.

5. Conclusion

Despite challenges in standardization, maturity and scalability, kidney organoids have the potential to support personalized medicine by enabling patient-specific disease modeling, genotype-informed therapeutic testing and individualized drug-response assessment. From 'modeling diseases in a dish' to 'designing tailored therapies for patients', kidney organoids may improve the understanding of genetic kidney diseases and support the development of individualized therapeutic interventions.

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Competing interests

The authors declare that they have no competing interests.

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