HHS Public Access

Author manuscript

Adv Drug Deliv Rev. Author manuscript; available in PMC 2021 August 29.

Published in final edited form as:

Adv Drug Deliv Rev. 2020 ; 161-162: 176–189. doi:10.1016/j.addr.2020.08.011.

Targeting and Therapeutic Peptide-Based Strategies for Polycystic Kidney Disease

Jonathan Wang[1], **Nirmalya Tripathy**[1], **Eun Ji Chung**[1,2,3,4,*]

[1]Department of Biomedical Engineering, University of Southern California, Los Angeles, CA, USA

[2]Department of Chemical Engineering and Materials Science, University of Southern California, Los Angeles, CA, USA

[3]Department of Medicine, Division of Nephrology and Hypertension, University of Southern California, Los Angeles, CA, USA

[4]Department of Surgery, Division of Vascular Surgery and Endovascular Therapy, University of Southern California, Los Angeles, CA, USA

Abstract

Polycystic kidney disease (PKD) is characterized by progressive cyst growth and is a leading cause of renal failure worldwide. Currently, there are limited therapeutic options available to PKD patients, and only one drug, tolvaptan, has been FDA-approved to slow cyst progression. Similar to other small molecule drugs, however, tolvaptan is costly, only moderately effective, and causes adverse events leading to high patient dropout rates. Peptides may mitigate many drawbacks of small molecule drugs, as they can be highly tissue-specific, biocompatible, and economically scaled-up. Peptides can function as targeting ligands that direct therapies to diseased renal tissue, or be potent as therapeutic agents themselves. This review discusses various aberrant signaling pathways in PKD and renal receptors that can be potential targets of peptide-mediated strategies. Additionally, peptides utilized in other kidney applications, but may prove useful in the context of PKD, are highlighted. Insights into novel peptide-based solutions that have potential to improve clinical management of PKD are provided.

Keywords

Polycystic kidney disease; Targeted drug delivery; Peptide; Chronic kidney disease

1. Introduction

The kidneys are organs responsible for filtering wastes from the blood, as well as maintaining a balance of blood plasma solutes [1]. One condition affecting proper kidney

*Corresponding author at: Department of Biomedical Engineering, University of Southern California, 1002 Childs Way, MCB 357, Los Angeles, CA, 90089, USA. eunchung@usc.edu.

function is polycystic kidney disease (PKD), which is the most commonly inherited kidney disease, affecting more than 12 million patients worldwide [2, 3]. PKD is characterized by continuous growth of fluid-filled cysts originating from the nephrons, which are the fundamental filtration units of the kidney. Cyst growth leads to massive enlargement and distortion of renal architecture, ultimately reducing filtration function and resulting in end-stage renal disease (ESRD), at which point patients seek dialysis or kidney transplantation [4, 5]. The majority of clinical treatment options focus on symptomatic management, and do not hinder cyst growth. These include a protein restricted diet, blood pressure control, and inhibiting the renin angiotensin aldosterone system (RAS) [6] with a RAS blocker [7]. However, blood pressure management and protein restricted diet ultimately show minimal benefits in delaying the age of ESRD onset due to cyst progression [8].

Recent efforts have focused on the use of drugs already approved by the Food and Drug Administration (FDA) for other diseases that have also shown efficacy in delaying cystogenesis, including pioglitazone, sirolimus, and metformin (Table 1) [9–12]. Despite initial enthusiasm, these drugs have been largely disappointing due to poor tolerability, off-target organ side effects, and/or limited therapeutic efficacy in patients [13]. Similarly, tolvaptan, the only FDA approved drug for autosomal dominant polycystic kidney disease (ADPKD), is difficult to tolerate due to side effects such as nausea and polyuria, and has been found to cause hepatotoxicity in certain patients [14]. Although tolvaptan slows cyst growth and delays the onset of renal failure by an average of ~5 years after 18 years of treatment, like other small molecules investigated for PKD, tolvaptan does not cure the underlying genetic defect of PKD [15]. Currently, no clinical trials exist for therapies that reverse cyst expansion, but emerging anti-micro RNA (anti-miR) [16, 17], clustered regularly interspaced short palindromic repeats (CRISPR) technologies [18], or other gene therapy solutions may provide promise for PKD reversal upon further investigation.

A major bottleneck in the clinical translation of these small molecule therapeutics however is their nonspecific and untargeted nature. Small molecules are classically categorized as organic, lipophilic compounds that have low molecular weight, typically less than 900 g/mol [19, 20]. These characteristics allow them to diffuse throughout the body, chemically interacting with target as well as off-target tissue. Peptides, generally defined as short chains of <50 amino acids, are one class of biologics which can address these issues, [21]. Due to their biologically based origin, they can be tuned to target discrete tissues or pathways, increasing therapeutic efficacy, as well as degrade into biocompatible amino acid constituents [22, 23].

However, peptides are not without their own set of drawbacks as well. Biologics such as peptides have been found to cause immunogenicity and an anti-drug antibody (ADA) response [24, 25], while also exhibiting unfavorable pharmacokinetic properties when compared to small molecules. Furthermore, *in vivo*, peptides encounter proteolytic enzymes and can be rapidly excreted from the body [26], exhibiting plasma half-life as low as a few minutes. Hence, modifications for extending half-life and increasing stability of peptides have been developed, including pegylation [27, 28], terminal modification [29], antibody conjugation (peptibodies) [30], and inducing cyclic and secondary structures [31]. Moreover, peptides can be incorporated into nanomaterials to improve their physiochemical properties

which is currently an active field of research [32–34]. Nanomedicine strategies are just beginning to emerge specifically for PKD, including recent efforts developing an oral nanocapsule strategy to improve the bioavailability of metformin [35].

Nonetheless, applications of peptides towards PKD offers an exciting, untapped area of research and medicine to advance the standard of care for PKD patients [36, 37]. Peptides can function as kidney-targeting ligands to direct small molecules to renal cysts [34, 38]. Additionally, therapeutic peptides can directly reduce cyst growth and exhibit promise for economical large-scale synthesis [39, 40] and long shelf-life [41]. This review outlines the pathogenesis of PKD and offers insights on aberrant pathways and specific cellular targets that may be exploited in targeting diseased, renal cells. Kidney-targeting and therapeutic peptide-based strategies that have shown success in other indications and have potential to be applied in PKD are also discussed.

2. Polycystic kidney disease

2.1. Kidney physiology

The kidneys function to maintain homeostasis in the body, regulating fluid, pH, and ionic balance, as well as removing waste metabolites [42]. The main filtration unit of the kidney is the nephron, which receives unfiltered whole blood from the afferent arteriole and feeds into the glomerulus (Figure 1). The glomerulus is a mass of capillaries functioning as a molecular sieve, where solutes are drawn out of the blood and passed to downstream renal tubule cells for reabsorption of salts, ions, or water. Solutes not reabsorbed back into the blood, which include urea, metabolic waste products, and excess salts are excreted out of the body through collecting ducts which eventually lead to the bladder. The glomerulus is an assembly of four different cell types: the glomerular endothelial cells and podocytes that form a selectively permeable nanoscale barrier for solutes, as well as mesangial cells and parietal epithelial cells that help support the internal and external structure of the glomerulus, respectively [43, 44]. The tubular epithelial cells (Figure 2D) following the glomerulus, which make up the proximal tubule, Loop of Henle, distal tubule, and collecting ducts, are affected by cyst growth in PKD. Hence, the ability to reabsorb solutes from urinary filtrate is compromised.

2.2. Autosomal dominant polycystic kidney disease (ADPKD)

ADPKD is a chronic kidney disease mainly affecting the tubule cells, and is also the most commonly inherited cause of ESRD in adults [45]. The prevalence of ADPKD is estimated between 1:400 to 1:1000 people, and manifests in the form of fluid filled cysts, originating from diseased renal tubular cells that enlarge and destroy healthy nephron architecture and function [46]. ADPKD is diagnosed mainly by past family history, or due to presentation of common symptoms such as hypertension and flank pain, and is typically confirmed by renal ultrasound imaging [47]. Genetic testing is very costly in comparison to ultrasound, and still fail to identify mutations in about 10% of patients, and is therefore not used as a frontline method of diagnosis [48, 49]. What makes new cases of PKD especially tricky to diagnose is that the decrease in kidney function occurs during late stages of cyst formation, when the patient is middle aged. Highly efficient compensatory hyperfiltration by surviving non-cystic

nephrons maintain the glomerular filtration rate (GFR) within a normal range, despite continuous cyst growth and loss of functioning parenchyma [50]. Therefore, even within the same families with the same type of mutation, the age of ESRD and cyst localization can vary greatly [51].

Specifically, ADPKD involves mutations in two genes, PKD1 and PK2, which encode for polycystin-1 (PC1) and polycystin-2 (PC2), respectively [52]. PKD1 mutations account for ~78% of patients, and PKD2 for ~13%, and no mutation is detected in ~9% of cases [53]. Patients with a mutation in PKD1 will reach ESRD by approximately 53 years of age, while PKD2 mutation patients have a much milder phenotype of kidney cysts compared to PKD1, and have a delayed onset of ESRD of ~20 years [54]. The gene products, PC1 and PC2, are essential proteins that are involved in maintaining the differentiated phenotype of renal tubular epithelial cells. Reduction in protein expression below a critical level in either one of these proteins results in loss of planar polarity, increased proliferation and apoptosis, and the development of a secretory phenotype (Figure 2) [46]. PC1 is a transmembrane protein with domains extending into the cytoplasm [52], while PC2 is a transmembrane, calcium-responsive cation channel [55]. In their native state, PC1 and PC2 interact with each other through their C-terminal tails in a 1:3 ratio of PC1 to PC2 to form the polycystin complex (PC) [56]. A number of intracellular localizations of PCs have been studied, but PC complexes residing on the primary cilia of renal epithelial cells are mainly responsible for PKD pathogenesis [57, 58]. Primary cilia are thin extensions of the plasma membrane and in the context of renal epithelial cells, primary cilia play a role in sensing mechanical and chemical extracellular signals and drive intracellular calcium signaling. The aberrant pathways in ADPKD, such as those stemming from primary cilia dysfunction, will be described in detail in section 3 along with peptide targeting and therapeutic solutions focusing on those pathways.

2.3. ARPKD

A related disease to ADPKD is autosomal recessive polycystic kidney disease (ARPKD), which also produces cyst-like structures in the kidneys as well as the liver. This hepatorenal disease is less frequent than ADPKD, and occurs in 1:20,000 people [59], but exhibits a more aggressive progression of cyst growth, with cysts arising mainly from collecting duct cells. The majority of ARPKD patients show disease phenotype as newborn or young children, and neonatal mortality is 25%–35%. Affected fetuses show massively enlarged kidneys, pulmonary hypoplasia, as well as contracted limbs with club feet [60]. In stark contrast to ADPKD, approximately 50% of ARPKD patients that survive the neonatal period progress to ESRD by 10 years of age [61].

In ARPKD, the genes with mutations are the Polycystic Kidney and Hepatic Disease 1 (PKHD1) gene and the DAZ Interacting Zinc Finger Protein 1 (DZIP1L) [62]. DZIP1L encodes a ciliary-transition-zone protein [63], while PKHD1 encodes for the protein fibrocystin, but the specific function and cellular localization of these proteins are not well understood. Histological assessment of ARPKD patients suggests that fibrocystin regulates cell-to-cell adhesion as well as proliferation [60]. Because disease-specific therapies and patient data for ARPKD is currently lacking, our review focuses on the more prevalent

ADPKD. However, many of the downstream pathways and therapeutic targets are shared between ADPKD and ARPKD, and may be opportunities for future ARPKD studies [64].

3. PKD targets for peptide-based intervention

Peptides offer many benefits over other biologics such as proteins, antibodies, and hormones used for therapeutic and targeting applications [65]. Specifically, peptides are relevant for targeting the kidney as they are small enough to access kidney tubule cells through glomerular filtration, usually limited to substances <15 nm in diameter and below 50 kDa [66–68]. Peptides also have the potential to be therapeutically potent, as they can show specificity to certain receptors and therefore reduce undesired off-target effects [69]. Limitations of peptides have included poor metabolic stability and rapid clearance compared to larger biologics, but many of these drawbacks can be improved by the addition of protecting groups onto the N- and C-terminus [70], exchanging L-amino acids with synthetic D-amino acids [31], and cyclization [71], which can minimize enzymatic degradation and unwanted protein adsorption.

Ease of large-scale chemical synthesis of synthetic or naturally occurring peptides is an attractive property for eventual clinical translation [72, 73]. A common method for peptide synthesis is solid phase peptide synthesis (SPPS), where peptides can be constructed stepwise on a solid resin support [74]. Typically, sequences >15 amino acids in length encounter diminishing yields in SPPS, as aggregation and additive coupling errors decrease purity as chain length increases [75]. However, peptide side chain groups can be kept chemically inert through the incorporation of protecting groups to prevent unwanted side reactions that reduce synthesis purity. These side chains can be later deprotected to add imaging agents, small molecule drugs, and allow for specific secondary structure [76–78]. Other synthesis methods include recombinant bacterial expression systems [79] and chemoenzymatic synthesis [80], where peptide bonds are catalyzed by hydrolase. As such, peptide strategies have begun to emerge to target PKD pathways. In this section, we describe the aberrant pathways in PKD and highlight potential targeting and therapeutic peptides applicable to PKD treatment.

3.1. Cellular signaling pathways as PKD targets

Over the last decade, many cellular signaling and metabolic pathways misregulated in PKD have been identified as drivers of cystogenesis [46]. In ADPKD, low levels of the PC on the primary cilia and endoplasmic reticulum (ER) reduce the amount of intracellular calcium available through the PC2 calcium channel. This triggers g-protein coupled activation of calcium-inhibitable adenylyl cyclase 6 (AC-VI) and inhibition of calcium/calmodulin-dependent phosphodiesterase (PDE), causing enhanced accumulation of cyclic AMP (cAMP) and activation of protein kinase A (PKA) [81]. cAMP/PKA signaling regulates a network of downstream pathways that affect cell cycle progression, cell proliferation, energy metabolism, and cell death (Figure 3) [82]. For example, the upregulation of the mitogen-activated protein kinases (MAPK) pathway, and phosphoinositide 3-kinases, protein kinase B, mammalian target of rapamycin (PI3K/AKT/mTOR) pathways through the inhibition of tuberous sclerosis complex proteins (TSC1 and TSC2) drive aerobic glycolysis and cell

cycle progression. The MAPK pathway also drives caspase-dependent cell death [83], even though abnormally increased proliferation in renal tubule cells is the hallmark of PKD [84]. The increased levels of apoptosis can destroy healthy nephron filtration function, while heightened proliferation of cyst lining cells drives cyst progression and expansion [85]. Downregulation of the AMP-activated protein kinase (AMPK) pathway stimulates ion transport through the cystic fibrosis transmembrane conductance regulator (CFTR) and fluid secretion, driving cyst formation [86]. Apart from the PC1 and PC2 transmembrane proteins, a series of cell surface receptors can contribute to increased cAMP and proliferation, including vasopressin receptor (V2R) and Wnt receptors depicted in Figure 3, and discussed in section 3.1.1 and 3.1.3., respectively. In this section, these pathways are reviewed and relevant peptide sequences showing therapeutic promise in PKD (Table 2) are presented.

3.1.1. cAMP and calcium dependent pathway—In PKD, an increase in cAMP levels stimulates cyst progression, which is led by a decrease in intracellular calcium and increased V2R signaling [85, 87–89]. cAMP is nucleotide second messenger, important for multiple cellular processes such as cell differentiation, DNA synthesis, and cell proliferation [90, 91]. cAMP stimulates cyst growth by promoting epithelial cell proliferation via B-Raf/MEK/ERK pathway activation [91, 92] and by transepithelial fluid secretion, which regulates chloride secretion through CFTR [93, 94]. Intracellular cAMP levels are regulated by adenylyl cyclases (AC), where AC catalyzes cAMP formation cAMP from ATP, and PDEs degrade cAMP to AMP. A study by Igarashi *et al.* studied the role of PC complexes in regulating cAMP in the primary cilia, and showed that the loss of primary cilia results in AC activation and increased cAMP levels, driving cyst growth in PKD [95].

One peptide that has shown efficacy to reduce pathways downstream of cAMP in a polycystic kidney disease rat (PCK) is the B-type natriuretic peptide (BNP) (SPKMVQGSGCFGRKMDRISSSSGLGCKVLRRH), a naturally occurring peptide responsible for blood pressure reduction [96]. Delivery *in vivo* stimulated cyclic GMP (cGMP) production and enhanced intracellular calcium levels, counteracting the effects of increased cAMP in PKD. While the crosstalk between cAMP and cGMP is not well understood in PKD, BNP led to decreased fibrosis, hypertension and vasopressin, thus offsetting PKD pathogenesis [97]. At the endpoints of this study, kidney histology revealed a 40% reduced cystic index in BNP-treated rats compared to PCK controls, and total kidney weight per body weight (TKW/BW) ratio was reduced by 1.9%, suggesting BNP could be a novel treatment for PKD.

Building on this study, a V2R antagonist peptide was used to treat PKD by reducing intracellular cAMP [98]. Ciolek et al. used mambaquaretin-1 (RPSFCNLPVKPGPC-NGFFSAFYYSQKTNKCHSFTYGGCKGNANRFSTLEKCRRTCVG), which was originally identified and purified from the venom of the green mamba snake and found to selectively inhibit major signaling pathways in PKD including both cAMP production and MAPK activity. When mambaquaretin-1 was synthesized by SPSS and administered daily for 99 days to CD1-pcy/pcy mice, a juvenile model of PKD, cystic index was reduced by 28% compared to controls, and the average number of cysts was decreased by 33% without causing toxicity (Figure 4). However, increased urine outflow was observed in a dose-

dependent manner with reduced urine osmolality, suggesting an aquaretic effect similar to inhibiting V2R by antagonists such as tolvaptan.

Somatostatin is another peptide hormone that can inhibit downstream intracellular cAMP levels. It is naturally secreted in a broad range of mammalian tissues, including the pancreas, hypothalamus, and from portions of the central nervous system [99]. As somatostatin receptors are highly expressed in the kidney and liver, somatostatin analogs have the potential to slow cystogenesis in both organs in ADPKD patients. In pioneering work, Epstein et al. demonstrated the efficacy of long-acting somatostatin (octreotide long-acting release (LAR)) for ADPKD patients [100]. In this randomized, placebo-controlled clinical trial, patients were intramuscularly treated every 28 days for 6 months with 40 mg of octreotide-LAR, a synthetic analog of somatostatin encapsulated into microspheres for long-acting release, followed by estimated glomerular filtration rate (eGFR) measurements and kidney volume evaluation via computed tomography (CT). Twelve out of 13 patients tolerated somatostatin well and showed decreased kidney volume of 71 ± 107 mL ($P < 0.05$) compared to those receiving the placebo (162 ± 114 mL; $P < 0.010$), as well as decreased cystic volume (3.0 ± 6.5% vs. 5.6 ± 5.8%). However, no significant changes in GFR was found, prompting further clinical trials.

In the follow up ALADIN trial (A Long-Acting somatostatin on Disease progression in Nephropathy due to ADPKD), 79 patients with eGFR >40 ml/min/1.73m^2 (healthy eGFR is approximately 90 ml/min/1.73m^2) were randomized to receive subcutaneous injections of octreotide-LAR or the placebo every 4 weeks for 3 years [101]. After 1 year, the increase in the total kidney volume (TKV) was reduced by 2/3rd with octreotide-LAR compared to the placebo. Over the 3 years of the ALADIN trial, the placebo group doubled in TKV compared to the octreotide group, but was not statistically significant due to a wide range of patient responses. Hence, the effects of octreotide treatment attenuated over time and a larger study may be needed to fully assess its therapeutic benefits. A follow up study, ALADIN 2, is currently recruiting additional patients in Italy. ALADIN 2 is similar to ALADIN except that patients with severely hindered eGFR of 15–40 ml/min/1.73 m^2 that may also benefit from treatment are being recruited. These clinical trials of peptides to reduce cAMP levels in PKD present promising new avenues for inhibiting cyst growth.

3.1.2. mTOR pathway—The mTOR signaling pathway serves a critical role in regulating several biological processes including cell metabolism, growth, proliferation, and survival. Dysregulation of mTOR complexes, mTORC1 or mTORC2, or overactivation of mTORC1 has been implicated in PKD development [11]. mTORC1 is inhibited by the tuberous sclerosis complex proteins TSC1 and TSC2, and thus, loss-of-function mutations of either TSC1 or TSC2 lead to kidney cyst formation [102, 103]. PC1 plays an vital role in stabilizing the TSC1/TSC2 complex and increased mTOR signaling has been described in multiple PKD models [104, 105], suggesting that PC1 is linked to mTOR expression. mTORC1 activation is linked to the S6 kinase (S6K)-dependent pathway which stimulates lipid synthesis and enhanced glycolysis [106]. mTOR and S6 kinase, a downstream effector of mTOR, has been found to localize to cyst-lining epithelial cells from PKD1 knockout mice, linking loss of PC1 function to heightened mTOR activity [107]. Prominent mTORC1 inhibitors currently in PKD clinical trials include rapamycin itself, analogues such as

sirolimus and everolimus [108], as well as metformin, a known AMP-activated protein kinase (AMPK) activator that also downregulates S6K phosphorylation [109, 110]. Currently, no mTOR peptide inhibitors have been tested for PKD, but in 2017, the first polypeptide named small regulatory polypeptide of amino acid response (SPAR) (MGAKAPRGPKVAQWAMETAVIGV-VVVLFVVTVAITCVLCCFSCDSRAQDPQGGPGRSFTVATFRQEASLFTGPVRHAQPV PS AQDFWTFM) was found to suppress mTORC1 activity by analyzing and transcribing cytosolic RNA sequences previously thought to be non-coding [111, 112].

Therapeutic peptides demonstrate immense potential in the treatment of PKD as they can offer potent mTOR inhibition and anti-proliferative effects. Li et al. reported a Smac-mimetic peptide to induce TNF-α pathway-dependent cystic renal epithelial cell death [113]. Smac-mimetics are synthetic, cell membrane permeable peptides consisting of the 4 N-terminal amino acids of Smac, a protein naturally found in mitochondria that antagonizes cellular inhibitor of apoptosis protein 1 (cIAP1) and cellular inhibitor of apoptosis protein 2 cIAP2, which is related to downstream effects of mTOR-activated overproliferation [114]. In a PKD1 knockout murine model, upon intraperitoneal administration of Smac-mimetic peptides in lactating mothers on day 3 and 5 after birth of their litters, slowed cyst expansion and cell death of cystic epithelial cells was specifically observed in the kidney tissue of their pups, with no effects on neighboring healthy renal tubule cells. The Smac-mimetic peptide promoted degradation of cIAP1 in renal epithelial cells, and in combination with TNF-α, activated receptor interacting serine/threonine kinase 1 (RIPK1) dependent cell death complex, and degradation of the caspase-8 inhibitor, Fas-associated death domain-like interleukin-1-beta-converting enzyme-inhibitory protein long form (FLIP), in cystic renal epithelial cells.

Xueying Lin and colleagues established a zebrafish ADPKD model by transcription activator-like effector nucleases (TALEN) mediated gene editing to study the effect of autophagy in ADPKD which is directly controlled by the mTOR energy sensing and proliferative pathways. Beclin 1 has been reported to induce autophagy by binding to the autophagy inhibitor, GAPR-1, and was modified with a HIV transactivator of transcription 1 (Tat-1) protein domain to promote cell membrane permeability. The authors demonstrated that by activating autophagy with a specific autophagy inducer via a partial sequence of Beclin 1 (267–284), cystogenesis is reduced and renal function can be restored [115]. As a combinatorial strategy for ADPKD therapeutics, treatment with autophagy activators and mTOR-dependent rapamycin may be a promising strategy to attenuate cyst formation and restore kidney function.

3.1.3. Wnt signaling pathway—Both known wingless integration 1 (Wnt) signaling pathways are involved in formation of kidney cysts; activation of the canonical, β-catenin-dependent pathway drives renal cell nuclear changes (Figure 3) towards an undifferentiated, proliferative state, while activation of the noncanonical pathway alters planar cell polarity [116–118], compared to normal renal tubular cells that divide parallel to the tubular lumen axis. In PKD, alterations in planar cell polarity due to Wnt signaling leads to aberrant orientation of cell division and contributes to cysts sprouting from the main tubule lumen [119–121]. Although canonical Wnt signaling is essential for normal kidney maturation

during development, pathological activation of the canonical Wnt pathway in PKD destabilizes the PC complex and results in severe cystogenesis [122]. Loss of cilial PC complex function has also been correlated with a substantial increase in canonical Wnt pathway activation [123]. While no studies have investigated peptides in the context of Wnt signaling in PKD, many Wnt peptide inhibitors have been investigated in the context of cancer and may provide efficacy in PKD. For example, stapled peptides investigated by Dietrich et al. (RRWPRXILDXHVRRVWR), were found to inhibit β-catenin dependent Wnt signaling [124]. Incorporation of cationic and amphipathic properties found in classes of cell penetrating peptides (CPPs) motivated the sequence design of these synthetic peptides, and allowed improved passage through the cell membrane and access to cytosolic β-catenin. The macrocyclic peptide (RKYLYERFWWCG) has been found to inhibit Wnt signaling through direct interaction with Wnt surface protein [125]. Both may be effective peptide treatments for PKD.

3.1.4. Notch signaling pathway—Notch signaling has also been reported to be a central pathway in PKD development, as it regulates cellular processes such as proliferation [126]. Specifically, Notch3 is a receptor that has been found to be upregulated in the epithelial lining of cysts in both PKD murine models as well as human ADPKD-derived cysts [127]. Furthermore, a study using 3D cultures of primary human ADPKD cells demonstrated inhibition of Notch3 via gamma secretase resulted in reduced cyst proliferation *in vitro* [127]. Thus, targeting Notch3 signaling may result in an effective therapeutic strategy to arrest cyst growth in PKD.

Like Wnt signaling, no peptides have been developed to inhibit Notch signaling specifically in the context of PKD, but peptide-based strategies have been demonstrated against the Notch signaling pathway in other contexts. For instance, a library of 5–15 amino acid length, synthetic peptides were developed by Lin et al. to target Notch receptors 1–4, of which Notch3 is most relevant to PKD. Out of a library of 155 peptides, 15 short synthetic peptide sequences bound to Notch3 receptors, the key receptor in PKD, and induced apoptosis in HCC2429 lung carcinoma cells and HeLa cells [128]. These peptides exhibited a secondary structure containing a core with a β-pleated sheet, three disulfide bonds, and a series of loops [129], which allows for efficient and selective binding to Notch3 [130]. These peptides may be used as a targeting ligand in the context of PKD, and also provide additional benefits by inducing apoptosis in overproliferative cells in cyst epithelia.

3.2. Receptor targets in PKD

Receptor-mediated targeting presents an opportunity to achieve enhanced therapeutic efficiency and reduced off-target effects compared to current therapeutics in PKD [131, 132]. Receptors including megalin and cubilin, folate, and vasopressin V2R receptors are overexpressed in PKD and presents a strategy for binding to target cells [34, 133–136]. The binding to these target receptors may also cause downstream effects, including triggering endocytosis and associated cellular pathways, some of which may be therapeutically beneficial. This section will highlight the receptor targets which may be exploited for delivering PKD peptide and small molecule prodrug therapies (Table 3) and discuss the design insights and origins of these candidates.

3.2.1. Megalin and cubilin receptors—For PKD therapy, ligands with a high affinity for megalin and cubilin receptors provide an opportunity for kidney-targeted delivery of drugs and biologics. These endocytic receptors are expressed on the apical surface of proximal tubule epithelial cells and mediates renal-tubular reabsorption of proteins and several filtered ligands [137]. Cubilin is an intrinsic factor-cobalamin receptor (460 kDa) and interacts with megalin through an alpha-helical amino terminus [137]. Megalin is a low-density lipoprotein (~600 kDa) with a large extracellular domain which allows endocytic trafficking of ligands [138]. Of note, megalin is a key contributor to the reabsorption of albumin [139], and albumin peptide fragments and synthetic albumin-like-peptides can allow for enhanced megalin binding and cell internalization [140, 141]. Therefore, megalin-binding peptides may serve as front runners for selective renal targeting and enhancing uptake of peptide-conjugated payloads.

Binding to megalin as well as cubilin has been shown to regulate the endocytic trafficking of several ligands including lipoproteins, carrier proteins, hormones, and drugs in renal epithelial cells [142]. While relatively few kidney-targeting peptides are available, the synthetic peptide $(KKEEE)_3K$ [143], which was previously found to target the kidneys through the megalin receptor, has been explored in multiple, recent studies [143–145]. In addition to $(KKEEE)_3K$, related peptide sequences have been produced via Fmoc SPSS, including $(KKEE)_5K$, $(KKQQQ)_3K$ [145], and $(KKEEE)_2K$ [146], to elucidate effects of peptide size, charge, and payload in relation to kidney targeting. Generally, these studies found acidic, negatively-charged peptides are not as efficiently reabsorbed by megalin and are more readily excreted, demonstrated by highly negative peptides, D_8 and $(DSS)_4$. Slightly positively-charged sequences investigated in these series of experiments, ranging between 0 to +10.0 mV zeta potential [147], was found to have higher kidney accumulation compared to negatively-charged counterparts. The underlying cause may be due to the affinity of more positively-charged peptides to the negatively-charged surface of renal proximal tubule cells, facilitating further interaction with the megalin receptor [148]. However, using highly-charged peptides like lysine (K) and glutamic acid (E) may confer undesirable properties, including aggregation and immune responses which remain to be full elucidated. Like nanoparticles, and small molecules to a lesser extent, highly-charged peptides may adsorb serum proteins and molecules of the complement immune system, causing toxicity [149]. Nonetheless, the sequence of specific amino acids still plays a role, as when comparing equally-charged peptide sequences with amino acid substitutions, renal uptake can be nullified. For example, substitution of lysine (K) with arginine (R) to synthesize (RREEE)3R preserves the number of positively-charged amino acids, but showed a 45% reduction in kidney uptake as well as faster urinary clearance [145].

Taking into account these design considerations, Lenhart et al. later demonstrated the potential of the $(KKEEE)_3K$ peptide to target diseased kidneys in a juvenile cystic kidney (JCK) mouse model. Renal localization of dye-labeled $(KKEEE)_3K$, as well as a shorter, related sequence $(KKEEE)_2K$ was investigated. Although the shorter, less negatively-charged sequence was hypothesized to improve renal accumulation [145], after 4 hours post-intravenous administration, >90% of the fluorescence signal was found in the kidneys of wild type and JCK mice for both peptides (Figure 5) [150]. In contrast, the free dye

accumulated equally in the liver and kidney. Both peptide-dye conjugates co-localized with megalin and aquaporin 1 (AQ1), markers of proximal tubule cells. Interestingly, slightly better renal retention was observed for the longer $(KKEEE)_3K$ sequence, although not statistically significant. This may suggest the zwitterionic nature of peptides may affect renal retention. Additionally, $(KKEEE)_3K$ has been incorporated into micelle nanoparticles to take advantage of the increased half-life and multifunctionally offered by nanocarriers [32, 151], and was found to have higher kidney accumulation compared to untargeted micelles in wild type mice [144, 147].

3.2.2. Folate receptor—The folate receptor is highly expressed on the apical brush border of renal proximal tubules, and functions to reabsorb filtered folate, a vitamin crucial for cell division and metabolism [152–159]. Very recently, folate-targeting approaches have received attention as a kidney-specific carrier for PKD therapy as folate receptors are highly expressed on renal cysts *in vivo* [160, 161]. Weimbs et al. investigated a folate-conjugated rapamycin (FC-rapa) and showed inhibition of mTOR activity in the kidneys of a Pkd1flox/_: Nestin-Cre murine model at a dose of 0.6 μmol/kg/day [161]. Both FC-rapa and free rapamycin treatment groups were found to reduce the progression of PKD to a similar degree; however, FC-rapa demonstrated significantly less hepatotoxicity [161]. Although folate receptors are expressed in several tissues, expression is orders of magnitude higher in the kidneys [162], and hence, FC-rapa was found to preferentially accumulate in both healthy and polycystic kidneys and showed the highest mTOR inhibition in cystic cells. Notably, because supratherapeutical levels of folate have been shown to cause adverse effects such as ferroptosis (iron dependent cell death) [163], dose must be taken into account during the development of renal-targeting solutions via the folate receptor.

While folate is not a peptide, many peptides have been developed to efficiently bind the folate receptor. The peptide sequence MHTAPGWGWRLS, identified through phage display, exhibited an equilibrium dissociation constant (K_d) of 300 nM [164]. Through computational docking experiments, the peptide was found to bind to the surface of the receptor instead of docking into the folate binding pocket. While this K_d was weaker than that of folate itself ($K_d \approx 1$ nM), one way to improve peptide binding affinity includes altering the stereochemistry of the peptide, as reported by Zhou et al. [165]. In addition to folate-targeting peptides, conjugating peptides to folate can improve the binding affinity of folate beyond normal levels. For instance, the binding affinity of peptide-conjugated folate, GF-folate-IQ, to the folate receptor was found to be 0.18 nM [166]. This strategy may offer both high binding to the folate receptor and a direct conjugation strategy for many therapeutics relevant to PKD.

3.2.3. Vasopressin V2 receptor—Vasopressin V2 receptor antagonists have emerged as a potential therapeutic strategy against disease progression in PKD [167]. These receptors are usually localized to the basolateral side of collecting duct cells in the kidneys, and its activation initiates key homeostatic effects of vasopressin such as water reabsorption from the filtrate. Vasopressin binding to its V2 receptor activates an intracellular cascade, which in turn activates adenyl cyclase and induces cAMP generation as mentioned above. This results in increased gene expression and stimulates the aquaporin water channel AQP-2,

which ultimately allows reabsorption of water from urine, as well as a PKA-dependent positive feedback expression of the V2R. Consequently, urine volume decreases while urine osmolality increases. Failure of V2 receptor binding causes inability to concentrate urine, thus results in concentrated fluid in the renal cysts.

Given the crucial role of vasopressin in PKD pathogenesis, studies have found that treatment with V2 receptor antagonists can reduce cystic burden in orthologous animal models of human PKD by reducing renal cAMP levels [87, 168]. These studies eventually motivated development of the V2 receptor antagonist, tolvaptan, which received FDA approval in 2018 [169]. In the first seminal clinical trial, the Tolvaptan Efficacy and Safety in Management of Autosomal Dominant Polycystic Kidney Disease and Its Outcomes (TEMPO) 3:4, tolvaptan, as compared with placebo, slowed the increase in total kidney volume and the decline in kidney function.

Despite these outcomes, this first generation, small molecule drug also has undesirable drawbacks. Patients treated with tolvaptan exhibit adverse events related to aquaresis (excretion of dilute urine) and liver toxicity, which led to a higher discontinuation rate (23% dropout rate vs. 14% in the placebo group). Deranged liver function tests detected in clinical trials were found to be potentially life-threatening, and additional, major side effects include dry mouth, polyuria, hypernatremia, nausea/vomiting, and abdominal pain/cramps [170]. Notably, expected therapeutic outcomes have also been lackluster, as perfect adherence to tolvaptan treatment for 18 years is predicted to delay the time to ESRD by only 4.9 years [15]. The oral bioavailability of tolvaptan is expected to be 42% [171], and these drawbacks of off-target side effects and limited therapeutic efficacy calls for opportunities in precision medicine using strategies such as peptide targeting and therapeutics.

As mentioned, among aberrant signaling pathways in PKD, cAMP overexpression driven by upregulated V2 receptor and vasopressin production are highly prevalent [172]. As disease progresses, the V2 receptor is also overexpressed in a positive feedback loop due to stimulation of downstream cAMP pathways [173]. Therefore, a highly promising strategy to target the diseased cells in PKD would be to direct therapeutic payloads to cells overexpressing V2R. Jung et al. utilized the peptide vasopressin analogue desmopressin (dDAVP) conjugated with nine D-arginines (dDAVP-9r), YFQNCPdRGGGGGRRRRRRRRR, utilized as a peptide delivery platform for siRNA delivery against aquaporins to collecting duct cells [174]. *In vitro*, Madin-Darby Canine Kidney (MDCK) cells and pig epithelial-like kidney cells (LLC-PK1) exhibited an order of magnitude higher binding when incubated with FITC-siRNA/dDAVP-9r compared to FITC-siRNA alone or FITC-siRNA/9r. As expected, no substantial differences in cellular uptake between FITC-siRNA/9r and FITC-siRNA/dDAVP-9r were found in monkey kidney (Cos-7) cells, which are negative for V2 receptors, indicating that targeting the V2 receptor was essential for cellular uptake of the payload siRNA [175].

3.2.4. Epidermal growth factor receptor—One of the abnormalities in PKD pathogenesis is the mis-localization of epidermal growth factor receptors (EGFR) in cyst lining epithelium, resulting in increased activity of EGFR in cystic tissues [176]. Hence, although the EGFR pathway is highly studied in the context of cancer, this pathway can also

be used as a ligand target in PKD [177]. EGFR is a transmembrane protein and plays a central role in regulating cell proliferation, cell survival, and plays a crucial role in embryonic kidney development [178]. Seven highly effective EGFR binding ligands have been identified to trigger such canonical downstream effects: EGF, transforming growth factor-α (TGF-α), heparin-binding epidermal growth factor (HB-EGF), amphiregulin (AREG), betacellulin, epiregulin, and epigen [179]. Binding of each of these to EGFR triggers a wide variety of downstream effects in renal cells, including changes to inflammation, cell cycle state, and fibrosis [180], and hence, peptide ligand concentrations must be carefully considered to limit such adverse effects. Furthermore, studies assessing immunogenicity of peptides will be crucial before clinical translation.

Richards *et al.* showed that inducing expression of a modified, inactive form of EGFR could block the overexpression in EGFR-specific tyrosine kinase activity that accompanies renal cyst growth, leading to an improvement in kidney function and a significant decrease in collecting duct cyst burden [181]. Hence, these results suggest that changes in EGFR expression may drive cyst formation in the collecting ducts, and that therapeutics targeting the tyrosine kinase activity of EGFR may be therapeutic in PKD. Ahsan et al. synthesized the peptide Disruptin (SVDNPHVC), which was found to dimerize with EGFR causing its degradation and downregulation [182]. Although applied to throat, neck, and lung squamous cell cancers, it is important to note that intraperitoneal injection of Distruptin into mice bearing EGFR-driven human tumor xenografts did not affect adjacent healthy tissue, and only caused apoptosis in overproliferative, cancer cells. Hence, in the context of PKD, this peptide strategy may target cystic regions overexpressing EGFR without disturbing healthy nephrons that show baseline levels of EGFR.

3.2.5. Galectin-3—Galectin-3 is a β-galactoside-binding lectin expressed in the ureteric bud and collecting duct of the nephron during embryonic development [183]. It is also overexpressed in human ARPKD and in cyst epithelia, and is correlated to disease severity in ADPKD [184]. Galectin-3 has been hypothesized to be primarily localized to the cytoplasm; however, there is evidence that it localizes to the nucleus, cell surface, and is secreted in serum and urine [183]. Therefore, cell surface galectin-3 is a potential target for peptide ligands, while serum and urine galectin-3 may be a potential biomarker for PKD [185]. Phage display was previously performed to identify three highly specific, short peptide sequences for binding to galectin-3: G3-A9 (PQNSKIPGPTFLDPH), G3-A9 (SMEPALPDWWWKMFK) and G3-C12 (ANTPCGPYTHDCPVKR) [186]. High expression of galectin-3 in BT549 mammary gland cells corresponded to high peptide binding efficiency, compared to the negative controls, prostate carcinoma cells (PC-3 M) and human breast (MDA-MB-435), that have lower galectin-3 expression, demonstrating target specificity. Although initially investigated for renal carcinoma, these highly specific peptides ($K_d \approx$ 17–80 nM) have potential to target cystic epithelia expressing galectin-3.

3.3 Tubule-targeting peptides

Some kidney targeting peptides may not target PKD specific phenotypes, but can target specific segments of the nephron and may be used as a strategy to prevent ESRD in younger patients in which kidney architecture is still relatively non-cystic [187, 188]. Bidwell et al.

utilized an elastin-like polypeptide (ELP) conjugated to a seven amino acid length sequence, CLPVASC named the kidney targeting peptide (KTP), and demonstrated kidney accumulation that is 5-fold higher than an untargeted ELP and 5-fold higher compared to other peripheral organs in swine [189]. Intrarenal distribution showed association of this KTP ELP around the glomerulus and surrounding proximal and distal tubules. This is the shortest peptide sequence to date to produce such accumulation increases above controls, which may be beneficial for conjugating active pharmaceutical compounds while not hindering their therapeutic efficacy.

Odermatt et al. reported a method of screening phage-display libraries *ex vivo* on intact kidney tubules using microdissection, vs. traditional monolayer-plated cells [190]. The linear peptide ligand, ELRGDMAAL, was found to selectively bind cortical collecting ducts (CCD) compared to other parts of the nephron such as the distal convoluted tubules, glomerulus, proximal convoluted tubules (PCT). Peptide sequences containing this motif exhibited 16-fold higher binding to CCD compared with PCT in wild type rats upon intravenous injection. Using this same microdissection screening method, Odermatt et al. found that peptides with a motif $K(X_3)TNHP$ showed twice as much binding to PCT compared to CCD. Tunable uptake within different nephron cell types may be useful in applications for ARPKD drug delivery, where cysts arise in both the tubule cells and collecting ducts.

Recently, Jung et al. took a machine learning approach to predict the tissue-specific targeting ability of peptides, saving time and cost over traditional phage display [191, 192]. In this approach, prior to *in vitro* studies, candidate peptide sequences can be given a prediction score representing their affinity to various organs. Two sequences demonstrated especially high prediction scores for the kidney, PKNGSDP and DSHKDLK, based on support vector machine (SVM) and artificial neural network (ANN) methods. The authors conclude that these sequences recognize cellular markers present on glomerular endothelial cells. Although, no *in vivo* studies have been performed to verify kidney localization in PKD mice models, these nephron-segment-specific peptides present an opportunity for future prodrug, nanoparticle, and peptide targeting studies.

4. Conclusion

This review focuses on cellular and molecular signaling pathways involved in the PKD progression, which can be exploited for designing effective renal-targeted, peptide-based therapeutics. The only currently available treatment, tolvaptan, experiences many of the drawbacks of typical small-molecule drugs, such as poor delivery, low bioavailability, and/or lack of specific targeting. Hence, targeting using peptide-based ligands and therapeutics specific to PKD cellular pathways, such as cAMP dysfunction and renal cell overproliferation, may be used to overcome these challenges. With future improvements in peptide-based technologies paired with the growing understanding of PKD molecular pathogenesis, the development of PKD-specific peptides will likely emerge as a powerful treatment strategy.

Acknowledgements

The authors would like to acknowledge the financial support from the University of Southern California (USC) Alfred Manning Institute (AMI) fellowship awarded to JW, the National Heart, Lung, and Blood Institute (NHLBI, R00HL124279) and NIH New Innovator Award (DP2-DK121328) awarded to EJC. JW and NT contributed to this work equally.

Abbreviations

ALADIN	a long-acting somatostatin on disease progression in nephropathy due to PKD
AC	adenylyl cyclase
AMPK AMP	activated protein kinase
AREG	amphiregulin
ADA	anti-drug antibody
anti-miR	anti-micro RNA
AQ1	aquaporin 1
ANN	artificial neural network methods
ADPKD	autosomal dominant polycystic kidney disease
ARPKD	autosomal recessive polycystic kidney disease
BNP B	type natriuretic peptide
AC-VI	calcium-inhibitable adenylyl cyclase 6
cIAP1	cellular inhibitor of apoptosis protein 1
CRISPR	clustered regularly interspaced short palindromic repeats
CCD	cortical collecting ducts
cAMP	cyclic adenosine monophosphate
cGMP	cyclic GMP
CFTR	cystic fibrosis transmembrane conductance regulator
DZIP1L	DAZ interacting zinc finger protein 1
ELP	elastin-like polypeptide
ER	endoplasmic reticulum
ESRD	end-stage renal disease
ELISA	enzyme-linked immunosorbent assay
EGFR	epidermal growth factor receptors

eGFR	estimated glomerular filtration rate
ERK	extracellular signal-regulated kinase
FLIP	Fas-associated death domain-like interleukin-1-beta-converting enzyme-inhibitory protein long form
FDA	Food and Drug Administration
GFR	glomerular filtration rate
GSK3β	glycogen synthase kinase 3 β
HB-EGF	heparin-binding epidermal growth factor
KTP	kidney targeting peptide
LAR	long-acting release
mTOR	mammalian target of rapamycin
MAPK	mitogen-activated protein kinases pathway
PDE	phosphodiesterase
PI3K/AKT/mTOR	phosphoinositide 3-kinases, protein kinase B, mammalian target of rapamycin
PKHD1	polycystic kidney and hepatic disease 1
PKD	polycystic kidney disease
PC	polycystin complex
PC1	polycystin-1
PC2	polycystin-2
PKA	protein kinase A
PCT	proximal convoluted tubules
PCK	rat rat model of polycystic kidney disease
Ras	rat sarcoma
RIPK1	receptor interacting serine/threonine kinase 1
RAS	renin angiotensin aldosterone system
S6K	S6 kinase
Src	sarcoma
SPAR	small regulatory polypeptide of amino acid response
SPPS	solid phase peptide synthesis

SVM	support vector machine
SPR	surface plasmon resonance
TEMPO	tolvaptan efficacy and safety in management of autosomal dominant polycystic kidney disease and its outcomes
TKV	total kidney volume
TKW/BW	total kidney weight per body weight
Tat-1	transactivator of transcription 1
TALEN	transcription activator-like effector nucleases
TGF-α	transforming growth factor-α
TSC1	tuberous sclerosis complex protein 1
TSC2	tuberous sclerosis complex protein 2
TNFα	tumor necrosis factor α
V2R	vasopressin receptor
VEGF	vessel endothelial growth factor
B-Raf	v-raf murine sarcoma viral oncogene homolog B
Wnt	wingless integration 1

References

[1]. Kumaran GK, Hanukoglu I, Identification and classification of epithelial cells in nephron segments by actin cytoskeleton patterns, The FEBS Journal, 287 (2020) 1176–1194. [PubMed: 31605441]

[2]. Willey C, Kamat S, Stellhorn R, Blais J, Analysis of Nationwide Data to Determine the Incidence and Diagnosed Prevalence of Autosomal Dominant Polycystic Kidney Disease in the USA: 2013–2015, Kidney Dis (Basel), 5 (2019) 107–117. [PubMed: 31019924]

[3]. Chapman AB, Devuyst O, Eckardt K-U, Gansevoort RT, Harris T, Horie S, Kasiske BL, Odland D, Pei Y, Perrone RD, Pirson Y, Schrier RW, Torra R, Torres VE, Watnick T, Wheeler DC, Conference P, Autosomal-dominant polycystic kidney disease (ADPKD): executive summary from a Kidney Disease: Improving Global Outcomes (KDIGO) Controversies Conference, Kidney Int, 88 (2015) 17–27. [PubMed: 25786098]

[4]. Kalluri HV, Hardinger KL, Current state of renal transplant immunosuppression: Present and future, World J Transplant, 2 (2012) 51–68. [PubMed: 24175197]

[5]. Grantham JJ, Autosomal Dominant Polycystic Kidney Disease, New England Journal of Medicine, 359 (2008) 1477–1485.

[6]. Levin A, Hemmelgarn B, Culleton B, Tobe S, McFarlane P, Ruzicka M, Burns K, Manns B, White C, Madore F, Moist L, Klarenbach S, Barrett B, Foley R, Jindal K, Senior P, Pannu N, Shurraw S, Akbari A, Cohn A, Reslerova M, Deved V, Mendelssohn D, Nesrallah G, Kappel J, Tonelli M, Guidelines for the management of chronic kidney disease, Canadian Medical Association Journal, 179 (2008) 1154. [PubMed: 19015566]

[7]. Torra R, Recent advances in the clinical management of autosomal dominant polycystic kidney disease, F1000Res, 8 (2019) F1000 Faculty Rev-1116.

[8]. Klahr S, Breyer JA, Beck GJ, Dennis VW, Hartman JA, Roth D, Steinman TI, Wang SR, Yamamoto ME, Dietary protein restriction, blood pressure control, and the progression of polycystic kidney disease. Modification of Diet in Renal Disease Study Group, Journal of the American Society of Nephrology, 5 (1995) 2037. [PubMed: 7579052]

[9]. Müller R-U, Benzing T, Management of autosomal-dominant polycystic kidney disease—state-of-the-art, Clinical Kidney Journal, 11 (2018) i2–i13. [PubMed: 30581561]

[10]. Walz G, Budde K, Mannaa M, Nürnberger J, Wanner C, Sommerer C, Kunzendorf U, Banas B, Hörl WH, Obermüller N, Arns W, Pavenstädt H, Gaedeke J, Büchert M, May C, Gschaidmeier H, Kramer S, Eckardt K-U, Everolimus in Patients with Autosomal Dominant Polycystic Kidney Disease, New England Journal of Medicine, 363 (2010) 830–840.

[11]. Kim H-J, Edelstein CL, Mammalian target of rapamycin inhibition in polycystic kidney disease: From bench to bedside, Kidney Res Clin Pract, 31 (2012) 132–138. [PubMed: 26894018]

[12]. Zhou X, Fan LX, Sweeney WE Jr., Denu JM, Avner ED, Li X, Sirtuin 1 inhibition delays cyst formation in autosomal-dominant polycystic kidney disease, J Clin Invest, 123 (2013) 3084–3098. [PubMed: 23778143]

[13]. Weimbs T, Shillingford JM, Torres J, Kruger SL, Bourgeois BC, Emerging targeted strategies for the treatment of autosomal dominant polycystic kidney disease, Clinical Kidney Journal, 11 (2018) i27–i38. [PubMed: 30581563]

[14]. Sans-Atxer L, Joly D, Tolvaptan in the treatment of autosomal dominant polycystic kidney disease: patient selection and special considerations, Int J Nephrol Renovasc Dis, 11 (2018) 41–51. [PubMed: 29430193]

[15]. Chebib FT, Perrone RD, Chapman AB, Dahl NK, Harris PC, Mrug M, Mustafa RA, Rastogi A, Watnick T, Yu ASL, Torres VE, A Practical Guide for Treatment of Rapidly Progressive ADPKD with Tolvaptan, Journal of the American Society of Nephrology, 29 (2018) 2458. [PubMed: 30228150]

[16]. Lee EC, Valencia T, Allerson C, Schairer A, Flaten A, Yheskel M, Kersjes K, Li J, Gatto S, Takhar M, Lockton S, Pavlicek A, Kim M, Chu T, Soriano R, Davis S, Androsavich JR, Sarwary S, Owen T, Kaplan J, Liu K, Jang G, Neben S, Bentley P, Wright T, Patel V, Discovery and preclinical evaluation of anti-miR-17 oligonucleotide RGLS4326 for the treatment of polycystic kidney disease, Nature Communications, 10 (2019) 4148.

[17]. Yheskel M, Patel V, Therapeutic microRNAs in polycystic kidney disease, Curr Opin Nephrol Hypertens, 26 (2017) 282–289. [PubMed: 28399020]

[18]. Cruz NM, Freedman BS, CRISPR Gene Editing in the Kidney, American journal of kidney diseases : the official journal of the National Kidney Foundation, 71 (2018) 874–883. [PubMed: 29606501]

[19]. Smith A, Manoli H, Jaw S, Frutoz K, Epstein AL, Khawli LA, Theil F-P, Unraveling the Effect of Immunogenicity on the PK/PD, Efficacy, and Safety of Therapeutic Proteins, J Immunol Res, 2016 (2016) 2342187–2342187. [PubMed: 27579329]

[20]. Mallick P, Taneja G, Moorthy B, Ghose R, Regulation of drug-metabolizing enzymes in infectious and inflammatory disease: implications for biologics-small molecule drug interactions, Expert Opinion on Drug Metabolism & Toxicology, 13 (2017) 605–616. [PubMed: 28537216]

[21]. Tesauro D, Accardo A, Diaferia C, Milano V, Guillon J, Ronga L, Rossi F, Peptide-Based Drug-Delivery Systems in Biotechnological Applications: Recent Advances and Perspectives, Molecules, 24 (2019) 351.

[22]. Accardo A, Tesauro D, Morelli G, Peptide-based targeting strategies for simultaneous imaging and therapy with nanovectors, Polymer Journal, 45 (2013) 481–493.

[23]. Trac NT, Chung EJ, Peptide-based targeting of immunosuppressive cells in cancer, Bioactive Materials, 5 (2020) 92–101. [PubMed: 31956738]

[24]. Shankar G, Arkin S, Cocea L, Devanarayan V, Kirshner S, Kromminga A, Quarmby V, Richards S, Schneider CK, Subramanyam M, Swanson S, Verthelyi D, Yim S, American S Association of Pharmaceutical, Assessment and reporting of the clinical immunogenicity of therapeutic proteins and peptides-harmonized terminology and tactical recommendations, The AAPS journal, 16 (2014) 658–673. [PubMed: 24764037]

[25]. Rosenberg AS, Sauna ZE, Immunogenicity assessment during the development of protein therapeutics, Journal of Pharmacy and Pharmacology, 70 (2018) 584–594. [PubMed: 28872677]

[26]. Potter LR, Yoder AR, Flora DR, Antos LK, Dickey DM, Natriuretic peptides: their structures, receptors, physiologic functions and therapeutic applications, Handb Exp Pharmacol, (2009) 341–366. [PubMed: 19089336]

[27]. Harris JM, Chess RB, Effect of pegylation on pharmaceuticals, Nature Reviews Drug Discovery, 2 (2003) 214–221. [PubMed: 12612647]

[28]. Swierczewska M, Lee KC, Lee S, What is the future of PEGylated therapies?, Expert Opin Emerg Drugs, 20 (2015) 531–536. [PubMed: 26583759]

[29]. Stanley TL, Chen CY, Branch KL, Makimura H, Grinspoon SK, Effects of a growth hormone-releasing hormone analog on endogenous GH pulsatility and insulin sensitivity in healthy men, The Journal of clinical endocrinology and metabolism, 96 (2011) 150–158. [PubMed: 20943777]

[30]. Wang Y-MC, Krzyzanski W, Doshi S, Xiao JJ, Pérez-Ruixo JJ, Chow AT, Pharmacodynamics-Mediated Drug Disposition (PDMDD) and Precursor Pool Lifespan Model for Single Dose of Romiplostim in Healthy Subjects, The AAPS Journal, 12 (2010) 729–740. [PubMed: 20963535]

[31]. Agersø H, Seiding Larsen L, Riis A, Lövgren U, Karlsson MO, Senderovitz T, Pharmacokinetics and renal excretion of desmopressin after intravenous administration to healthy subjects and renally impaired patients, British journal of clinical pharmacology, 58 (2004) 352–358. [PubMed: 15373927]

[32]. Chin DD, Wang J, Mel de Fontenay M, Plotkin A, Magee GA, Chung EJ, Hydroxyapatite-binding micelles for the detection of vascular calcification in atherosclerosis, Journal of Materials Chemistry B, 7 (2019) 6449–6457. [PubMed: 31553027]

[33]. Zavaleta C, Ho D, Chung EJ, Theranostic Nanoparticles for Tracking and Monitoring Disease State, SLAS Technology: Translating Life Sciences Innovation, 23 (2017) 281–293.

[34]. Zhou P, Sun X, Zhang Z, Kidney-targeted drug delivery systems, Acta Pharmaceutica Sinica B, 4 (2014) 37–42. [PubMed: 26579362]

[35]. Wang J, Hallows K, Chung E, Sun-159 Oral Nanocapsule Formulation for Polycystic Kidney Disease, Kidney International Reports, 5 (2020) S266.

[36]. Gurevich EV, Gurevich VV, Therapeutic potential of small molecules and engineered proteins, Handb Exp Pharmacol, 219 (2014) 1–12. [PubMed: 24292822]

[37]. Di L, Strategic approaches to optimizing peptide ADME properties, The AAPS journal, 17 (2015) 134–143. [PubMed: 25366889]

[38]. McGaraughty S, Davis-Taber RA, Zhu CZ, Cole TB, Nikkel AL, Chhaya M, Doyle KJ, Olson LM, Preston GM, Grinnell CM, Salte KM, Giamis AM, Luo Y, Sun V, Goodearl AD, Gopalakrishnan M, Lacy SE, Targeting Anti-TGF-β Therapy to Fibrotic Kidneys with a Dual Specificity Antibody Approach, J Am Soc Nephrol, 28 (2017) 3616–3626. [PubMed: 28827403]

[39]. Wang J, Masehi-Lano JJ, Chung EJ, Peptide and antibody ligands for renal targeting: nanomedicine strategies for kidney disease, Biomaterials Science, 5 (2017) 1450–1459. [PubMed: 28516997]

[40]. Nastase MV, Zeng-Brouwers J, Wygrecka M, Schaefer L, Targeting renal fibrosis: Mechanisms and drug delivery systems, Advanced Drug Delivery Reviews, 129 (2018) 295–307. [PubMed: 29288033]

[41]. Böttger R, Hoffmann R, Knappe D, Differential stability of therapeutic peptides with different proteolytic cleavage sites in blood, plasma and serum, PLoS One, 12 (2017) e0178943–e0178943. [PubMed: 28575099]

[42]. Blantz RC, Deng A, Miracle CM, Thomson SC, Regulation of kidney function and metabolism: a question of supply and demand, Trans Am Clin Climatol Assoc, 118 (2007) 23–43. [PubMed: 18528487]

[43]. Scott RP, Quaggin SE, Review series: The cell biology of renal filtration, J Cell Biol, 209 (2015) 199–210. [PubMed: 25918223]

[44]. Zhuo JL, Li XC, Proximal nephron, Compr Physiol, 3 (2013) 1079–1123. [PubMed: 23897681]

[45]. Loftus H, Ong ACM, Cystic kidney diseases: many ways to form a cyst, Pediatr Nephrol, 28 (2013) 33–49. [PubMed: 22736301]

[46]. Torres VE, Harris PC, Autosomal dominant polycystic kidney disease: the last 3 years, Kidney international, 76 (2009) 149–168. [PubMed: 19455193]

[47]. Magistroni R, Corsi C, Martí T, Torra R, A Review of the Imaging Techniques for Measuring Kidney and Cyst Volume in Establishing Autosomal Dominant Polycystic Kidney Disease Progression, Am J Nephrol, 48 (2018) 67–78. [PubMed: 30071518]

[48]. Chebib FT, Torres VE, Recent Advances in the Management of Autosomal Dominant Polycystic Kidney Disease, Clinical Journal of the American Society of Nephrology, 13 (2018) 1765. [PubMed: 30049849]

[49]. Lee K-B, Genetic diagnosis of autosomal dominant polycystic kidney disease: linkage analysis versus direct mutation analysis, Kidney Res Clin Pract, 35 (2016) 67–68. [PubMed: 27366659]

[50]. Franz KA, Reubi FC, Rate of functional deterioration in polycystic kidney disease, Kidney International, 23 (1983) 526–529. [PubMed: 6405076]

[51]. Hwang Y-H, Conklin J, Chan W, Roslin NM, Liu J, He N, Wang K, Sundsbak JL, Heyer CM, Haider M, Paterson AD, Harris PC, Pei Y, Refining Genotype-Phenotype Correlation in Autosomal Dominant Polycystic Kidney Disease, J Am Soc Nephrol, 27 (2016) 1861–1868. [PubMed: 26453610]

[52]. Harris PC, Torres VE, Genetic mechanisms and signaling pathways in autosomal dominant polycystic kidney disease, The Journal of Clinical Investigation, 124 (2014) 2315–2324. [PubMed: 24892705]

[53]. Rossetti S, Consugar MB, Chapman AB, Torres VE, Guay-Woodford LM, Grantham JJ, Bennett WM, Meyers CM, Walker DL, Bae K, Zhang Q, Thompson PA, Miller JP, Harris PC, Comprehensive Molecular Diagnostics in Autosomal Dominant Polycystic Kidney Disease, Journal of the American Society of Nephrology, 18 (2007) 2143. [PubMed: 17582161]

[54]. Hateboer N, v Dijk MA, Bogdanova N, Coto E, Saggar-Malik AK, Millan JLS, Torra R, Breuning M, Ravine D, Comparison of phenotypes of polycystic kidney disease types 1 and 2, The Lancet, 353 (1999) 103–107.

[55]. xe Gonz, lez-Perrett S, Kim K, Ibarra C, Damiano AE, Zotta E, Batelli M, Harris PC, Reisin IL, Arnaout MA, Cantiello HF, Polycystin-2, the Protein Mutated in Autosomal Dominant Polycystic Kidney Disease (ADPKD), is a Ca2+-Permeable Nonselective Cation Channel, Proc Natl Acad Sci U S A, 98 (2001) 1182–1187. [PubMed: 11252306]

[56]. Yu Y, Ulbrich MH, Li M-H, Buraei Z, Chen X-Z, Ong ACM, Tong L, Isacoff EY, Yang J, Structural and molecular basis of the assembly of the TRPP2/PKD1 complex, Proc Natl Acad Sci U S A, 106 (2009) 11558–11563. [PubMed: 19556541]

[57]. Hildebrandt F, Benzing T, Katsanis N, Ciliopathies, New England Journal of Medicine, 364 (2011) 1533–1543.

[58]. Abou Alaiwi WA, Lo ST, Nauli SM, Primary cilia: highly sophisticated biological sensors, Sensors (Basel), 9 (2009) 7003–7020. [PubMed: 22423203]

[59]. Sweeney WE, Avner ED, Molecular and cellular pathophysiology of autosomal recessive polycystic kidney disease (ARPKD), Cell and Tissue Research, 326 (2006) 671–685. [PubMed: 16767405]

[60]. Bergmann C, Genetics of Autosomal Recessive Polycystic Kidney Disease and Its Differential Diagnoses, Frontiers in pediatrics, 5 (2018) 221–221. [PubMed: 29479522]

[61]. Sweeney WE Jr., Avner ED, Pathophysiology of childhood polycystic kidney diseases: new insights into disease-specific therapy, Pediatr Res, 75 (2014) 148–157. [PubMed: 24336431]

[62]. Ward CJ, Hogan MC, Rossetti S, Walker D, Sneddon T, Wang X, Kubly V, Cunningham JM, Bacallao R, Ishibashi M, Milliner DS, Torres VE, Harris PC, The gene mutated in autosomal recessive polycystic kidney disease encodes a large, receptor-like protein, Nat Genet, 30 (2002) 259–269. [PubMed: 11919560]

[63]. Lu H, Galeano MCR, Ott E, Kaeslin G, Kausalya PJ, Kramer C, Ortiz-Brüchle N, Hilger N, Metzis V, Hiersche M, Tay SY, Tunningley R, Vij S, Courtney AD, Whittle B, Wühl E, Vester U, Hartleben B, Neuber S, Frank V, Little MH, Epting D, Papathanasiou P, Perkins AC, Wright GD, Hunziker W, Gee HY, Otto EA, Zerres K, Hildebrandt F, Roy S, Wicking C, Bergmann C, Mutations in DZIP1L, which encodes a ciliary-transition-zone protein, cause autosomal recessive polycystic kidney disease, Nat Genet, 49 (2017) 1025–1034. [PubMed: 28530676]

[64]. Halvorson CR, Bremmer MS, Jacobs SC, Polycystic kidney disease: inheritance, pathophysiology, prognosis, and treatment, Int J Nephrol Renovasc Dis, 3 (2010) 69–83. [PubMed: 21694932]

[65]. Morrow T, Felcone LH, Defining the difference: What Makes Biologics Unique, Biotechnol Healthc, 1 (2004) 24–29.

[66]. Choi HS, Liu W, Misra P, Tanaka E, Zimmer JP, Itty Ipe B, Bawendi MG, Frangioni JV, Renal clearance of quantum dots, Nat Biotechnol, 25 (2007) 1165–1170. [PubMed: 17891134]

[67]. Longmire M, Choyke PL, Kobayashi H, Clearance properties of nano-sized particles and molecules as imaging agents: considerations and caveats, Nanomedicine (Lond), 3 (2008) 703–717. [PubMed: 18817471]

[68]. Ruggiero A, Villa CH, Bander E, Rey DA, Bergkvist M, Batt CA, Manova-Todorova K, Deen WM, Scheinberg DA, McDevitt MR, Paradoxical glomerular filtration of carbon nanotubes, Proc Natl Acad Sci U S A, 107 (2010) 12369–12374. [PubMed: 20566862]

[69]. Bruno BJ, Miller GD, Lim CS, Basics and recent advances in peptide and protein drug delivery, Therapeutic Delivery, 4 (2013) 1443–1467. [PubMed: 24228993]

[70]. John H, Maronde E, Forssmann WG, Meyer M, Adermann K, N-terminal acetylation protects glucagon-like peptide GLP-1-(7–34)-amide from DPP-IV-mediated degradation retaining cAMP- and insulin-releasing capacity, European journal of medical research, 13 (2008) 73–78. [PubMed: 18424366]

[71]. Weber SJ, Greene DL, Hruby VJ, Yamamura HI, Porreca F, Davis TP, Whole body and brain distribution of [3H]cyclic [D-Pen2,D-Pen5] enkephalin after intraperitoneal, intravenous, oral and subcutaneous administration, The Journal of pharmacology and experimental therapeutics, 263 (1992) 1308–1316. [PubMed: 1469637]

[72]. Craik DJ, Fairlie DP, Liras S, Price D, The Future of Peptide-based Drugs, Chemical Biology & Drug Design, 81 (2013) 136–147. [PubMed: 23253135]

[73]. Sharma AR, Kundu SK, Nam J-S, Sharma G, Priya Doss CG, Lee S-S, Chakraborty C, Next Generation Delivery System for Proteins and Genes of Therapeutic Purpose: Why and How?, BioMed Research International, 2014 (2014) 327950. [PubMed: 25126554]

[74]. Fields GB, Introduction to peptide synthesis, Curr Protoc Protein Sci, Chapter 18 (2002) Unit-18.11.

[75]. Isidro-Llobet A, Kenworthy MN, Mukherjee S, Kopach ME, Wegner K, Gallou F, Smith AG, Roschangar F, Sustainability Challenges in Peptide Synthesis and Purification: From R&D to Production, The Journal of Organic Chemistry, 84 (2019) 4615–4628. [PubMed: 30900880]

[76]. Amblard M, Fehrentz J-A, Martinez J, Subra G, Methods and protocols of modern solid phase peptide synthesis, Molecular Biotechnology, 33 (2006) 239–254. [PubMed: 16946453]

[77]. He R, Finan B, Mayer JP, DiMarchi RD, Peptide Conjugates with Small Molecules Designed to Enhance Efficacy and Safety, Molecules, 24 (2019) 1855.

[78]. Petrou C, Sarigiannis Y, 1 - Peptide synthesis: Methods, trends, and challenges, in: Koutsopoulos S (Ed.) Peptide Applications in Biomedicine, Biotechnology and Bioengineering, Woodhead Publishing 2018, pp. 1–21.

[79]. Löfblom J, Bacterial display in combinatorial protein engineering, Biotechnology Journal, 6 (2011) 1115–1129. [PubMed: 21786423]

[80]. Yazawa K, Numata K, Recent advances in chemoenzymatic peptide syntheses, Molecules, 19 (2014) 13755–13774. [PubMed: 25191871]

[81]. Ye H, Wang X, Constans MM, Sussman CR, Chebib FT, Irazabal MV, Young WF Jr., Harris PC, Kirschner LS, Torres VE, The regulatory 1α subunit of protein kinase A modulates renal cystogenesis, Am J Physiol Renal Physiol, 313 (2017) F677–F686. [PubMed: 28615245]

[82]. Torres VE, Harris PC, Strategies targeting cAMP signaling in the treatment of polycystic kidney disease, J Am Soc Nephrol, 25 (2014) 18–32. [PubMed: 24335972]

[83]. E.J. L, Cell Proliferation and Apoptosis in ADPKD, Springer, Singapore, 2016.

[84]. Fragiadaki M, Lannoy M, Themanns M, Maurer B, Leonhard WN, Peters DJ, Moriggl R, Ong AC, STAT5 drives abnormal proliferation in autosomal dominant polycystic kidney disease, Kidney Int, 91 (2017) 575–586. [PubMed: 28104302]

[85]. Hanaoka K, Guggino WB, cAMP Regulates Cell Proliferation and Cyst Formation in Autosomal Polycystic Kidney Disease Cells, Journal of the American Society of Nephrology, 11 (2000) 1179. [PubMed: 10864573]

[86]. Li X, Polycystic Kidney Disease, Codon Publications, Brisbane, 2015.

[87]. Gattone VH, Wang X, Harris PC, Torres VE, Inhibition of renal cystic disease development and progression by a vasopressin V2 receptor antagonist, Nature Medicine, 9 (2003) 1323–1326.

[88]. Starremans PG, Li X, Finnerty PE, Guo L, Takakura A, Neilson EG, Zhou J, A mouse model for polycystic kidney disease through a somatic in-frame deletion in the 5′ end of Pkd1, Kidney Int, 73 (2008) 1394–1405. [PubMed: 18385665]

[89]. Yamaguchi T, Pelling JC, Ramaswamy NT, Eppler JW, Wallace DP, Nagao S, Rome LA, Sullivan LP, Grantham JJ, cAMP stimulates the in vitro proliferation of renal cyst epithelial cells by activating the extracellular signal-regulated kinase pathway[1], Kidney Int, 57 (2000) 1460–1471. [PubMed: 10760082]

[90]. Yamaguchi T, Pelling JC, Ramaswamy NT, Eppler JW, Wallace DP, Nagao S, Rome LA, Sullivan LP, Grantham JJ, cAMP stimulates the in vitro proliferation of renal cyst epithelial cells by activating the extracellular signal-regulated kinase pathway11See Editorial by Grande, p. 1770, Kidney International, 57 (2000) 1460–1471. [PubMed: 10760082]

[91]. Yamaguchi T, Nagao S, Wallace DP, Belibi FA, Cowley BD, Pelling JC, Grantham JJ, Cyclic AMP activates B-Raf and ERK in cyst epithelial cells from autosomal-dominant polycystic kidneys, Kidney International, 63 (2003) 1983–1994. [PubMed: 12753285]

[92]. Parker E, Newby LJ, Sharpe CC, Rossetti S, Streets AJ, Harris PC, O'Hare MJ, Ong ACM, Hyperproliferation of PKD1 cystic cells is induced by insulin-like growth factor-1 activation of the Ras/Raf signalling system, Kidney Int, 72 (2007) 157–165. [PubMed: 17396115]

[93]. Brill SR, Ross KE, Davidow CJ, Ye M, Grantham JJ, Caplan MJ, Immunolocalization of ion transport proteins in human autosomal dominant polycystic kidney epithelial cells, Proc Natl Acad Sci U S A, 93 (1996) 10206–10211. [PubMed: 8816777]

[94]. Hanaoka K, Devuyst O, Schwiebert EM, Wilson PD, Guggino WB, A role for CFTR in human autosomal dominant polycystic kidney disease, American Journal of Physiology-Cell Physiology, 270 (1996) C389–C399.

[95]. Choi Y-H, Suzuki A, Hajarnis S, Ma Z, Chapin HC, Caplan MJ, Pontoglio M, Somlo S, Igarashi P, Polycystin-2 and phosphodiesterase 4C are components of a ciliary A-kinase anchoring protein complex that is disrupted in cystic kidney diseases, Proc Natl Acad Sci U S A, 108 (2011) 10679–10684. [PubMed: 21670265]

[96]. Vickery S, Price CP, John RI, Abbas NA, Webb MC, Kempson ME, Lamb EJ, B-type natriuretic peptide (BNP) and amino-terminal proBNP in patients with CKD: relationship to renal function and left ventricular hypertrophy, American journal of kidney diseases : the official journal of the National Kidney Foundation, 46 (2005) 610–620. [PubMed: 16183415]

[97]. Holditch SJ, Schreiber CA, Harris PC, LaRusso NF, Ramirez-Alvarado M, Cataliotti A, Torres VE, Ikeda Y, B-type natriuretic peptide overexpression ameliorates hepatorenal fibrocystic disease in a rat model of polycystic kidney disease, Kidney Int, 92 (2017) 657–668. [PubMed: 28416225]

[98]. Ciolek J, Reinfrank H, Quinton L, Viengchareun S, Stura EA, Vera L, Sigismeau S, Mouillac B, Orcel H, Peigneur S, Tytgat J, Droctové L, Beau F, Nevoux J, Lombès M, Mourier G, De Pauw E, Servent D, Mendre C, Witzgall R, Gilles N, Green mamba peptide targets type-2 vasopressin receptor against polycystic kidney disease, Proceedings of the National Academy of Sciences, 114 (2017) 7154.

[99]. Ampofo E, Nalbach L, Menger MD, Laschke MW, Regulatory Mechanisms of Somatostatin Expression, International journal of molecular sciences, 21 (2020) 4170.

[100]. Ruggenenti P, Remuzzi A, Ondei P, Fasolini G, Antiga L, Ene-Iordache B, Remuzzi G, Epstein FH, Safety and efficacy of long-acting somatostatin treatment in autosomal-dominant polycystic kidney disease, Kidney Int, 68 (2005) 206–216. [PubMed: 15954910]

[101]. Anthony L, Freda PU, From somatostatin to octreotide LAR: evolution of a somatostatin analogue, Curr Med Res Opin, 25 (2009) 2989–2999. [PubMed: 19842996]

[102]. Fantus D, Rogers NM, Grahammer F, Huber TB, Thomson AW, Roles of mTOR complexes in the kidney: implications for renal disease and transplantation, Nature Reviews Nephrology, 12 (2016) 587–609. [PubMed: 27477490]

[103]. Henske EP, Jóźwiak S, Kingswood JC, Sampson JR, Thiele EA, Tuberous sclerosis complex, Nature Reviews Disease Primers, 2 (2016) 16035.

[104]. Shillingford JM, Murcia NS, Larson CH, Low SH, Hedgepeth R, Brown N, Flask CA, Novick AC, Goldfarb DA, Kramer-Zucker A, Walz G, Piontek KB, Germino GG, Weimbs T, The mTOR pathway is regulated by polycystin-1, and its inhibition reverses renal cystogenesis in polycystic kidney disease, Proceedings of the National Academy of Sciences, 103 (2006) 5466.

[105]. Shillingford JM, Piontek KB, Germino GG, Weimbs T, Rapamycin Ameliorates PKD Resulting from Conditional Inactivation of <em>Pkd1</em&gt, Journal of the American Society of Nephrology, 21 (2010) 489. [PubMed: 20075061]

[106]. Düvel K, Yecies JL, Menon S, Raman P, Lipovsky AI, Souza AL, Triantafellow E, Ma Q, Gorski R, Cleaver S, Vander Heiden MG, MacKeigan JP, Finan PM, Clish CB, Murphy LO, Manning BD, Activation of a metabolic gene regulatory network downstream of mTOR complex 1, Mol Cell, 39 (2010) 171–183. [PubMed: 20670887]

[107]. Saigusa T, Bell PD, Molecular pathways and therapies in autosomal-dominant polycystic kidney disease, Physiology (Bethesda), 30 (2015) 195–207. [PubMed: 25933820]

[108]. Thoreen CC, Kang SA, Chang JW, Liu Q, Zhang J, Gao Y, Reichling LJ, Sim T, Sabatini DM, Gray NS, An ATP-competitive mammalian target of rapamycin inhibitor reveals rapamycin-resistant functions of mTORC1, J Biol Chem, 284 (2009) 8023–8032. [PubMed: 19150980]

[109]. Larsson O, Morita M, Topisirovic I, Alain T, Blouin M-J, Pollak M, Sonenberg N, Distinct perturbation of the translatome by the antidiabetic drug metformin, Proceedings of the National Academy of Sciences, 109 (2012) 8977.

[110]. Hallows KR, McCane JE, Kemp BE, Witters LA, Foskett JK, Regulation of Channel Gating by AMP-activated Protein Kinase Modulates Cystic Fibrosis Transmembrane Conductance Regulator Activity in Lung Submucosal Cells, Journal of Biological Chemistry, 278 (2003) 998–1004.

[111]. Matsumoto A, Clohessy JG, Pandolfi PP, SPAR, a lncRNA encoded mTORC1 inhibitor, Cell Cycle, 16 (2017) 815–816. [PubMed: 28319435]

[112]. Matsumoto A, Pasut A, Matsumoto M, Yamashita R, Fung J, Monteleone E, Saghatelian A, Nakayama KI, Clohessy JG, Pandolfi PP, mTORC1 and muscle regeneration are regulated by the LINC00961-encoded SPAR polypeptide, Nature, 541 (2017) 228–232. [PubMed: 28024296]

[113]. Fan LX, Zhou X, Sweeney WE Jr., Wallace DP, Avner ED, Grantham JJ, Li X, Smac-mimetic-induced epithelial cell death reduces the growth of renal cysts, Journal of the American Society of Nephrology : JASN, 24 (2013) 2010–2022. [PubMed: 23990677]

[114]. Silke J, Meier P, Inhibitor of apoptosis (IAP) proteins-modulators of cell death and inflammation, Cold Spring Harb Perspect Biol, 5 (2013) a008730. [PubMed: 23378585]

[115]. Zhu P, Sieben CJ, Xu X, Harris PC, Lin X, Autophagy activators suppress cystogenesis in an autosomal dominant polycystic kidney disease model, Human Molecular Genetics, 26 (2016) 158–172.

[116]. Benzing T, Simons M, Walz G, Wnt Signaling in Polycystic Kidney Disease, Journal of the American Society of Nephrology, 18 (2007) 1389. [PubMed: 17429050]

[117]. McNeill H, Planar Cell Polarity and the Kidney, Journal of the American Society of Nephrology, 20 (2009) 2104. [PubMed: 19762494]

[118]. Carroll TJ, Yu J, The kidney and planar cell polarity, Curr Top Dev Biol, 101 (2012) 185–212. [PubMed: 23140630]

[119]. Fischer E, Legue E, Doyen A, Nato F, Nicolas J-F, Torres V, Yaniv M, Pontoglio M, Defective planar cell polarity in polycystic kidney disease, Nature Genetics, 38 (2006) 21–23. [PubMed: 16341222]

[120]. Patel V, Li L, Cobo-Stark P, Shao X, Somlo S, Lin F, Igarashi P, Acute kidney injury and aberrant planar cell polarity induce cyst formation in mice lacking renal cilia, Human Molecular Genetics, 17 (2008) 1578–1590. [PubMed: 18263895]

[121]. Wallingford JB, Mitchell B, Strange as it may seem: the many links between Wnt signaling, planar cell polarity, and cilia, Genes & Development, 25 (2011) 201–213. [PubMed: 21289065]

[122]. Qian C-N, Knol J, Igarashi P, Lin F, Zylstra U, Teh BT, Williams BO, Cystic Renal Neoplasia Following Conditional Inactivation of Apc in Mouse Renal Tubular Epithelium, Journal of Biological Chemistry, 280 (2005) 3938–3945.

[123]. Corbit KC, Shyer AE, Dowdle WE, Gaulden J, Singla V, Reiter JF, Kif3a constrains β-catenin-dependent Wnt signalling through dual ciliary and non-ciliary mechanisms, Nature Cell Biology, 10 (2008) 70–76. [PubMed: 18084282]

[124]. Dietrich L, Rathmer B, Ewan K, Bange T, Heinrichs S, Dale TC, Schade D, Grossmann TN, Cell Permeable Stapled Peptide Inhibitor of Wnt Signaling that Targets β-Catenin Protein-Protein Interactions, Cell Chemical Biology, 24 (2017) 958–968.e955. [PubMed: 28757184]

[125]. Otero-Ramirez ME, Matoba K, Mihara E, Passioura T, Takagi J, Suga H, Macrocyclic peptides that inhibit Wnt signalling via interaction with Wnt3a, RSC Chemical Biology, 1 (2020) 26–34.

[126]. Formica C, Peters DJM, Molecular pathways involved in injury-repair and ADPKD progression, Cellular Signalling, 72 (2020) 109648. [PubMed: 32320858]

[127]. Idowu J, Home T, Patel N, Magenheimer B, Tran PV, Maser RL, Ward CJ, Calvet JP, Wallace DP, Sharma M, Aberrant Regulation of Notch3 Signaling Pathway in Polycystic Kidney Disease, Scientific reports, 8 (2018) 3340–3340. [PubMed: 29463793]

[128]. Lin L, Mernaugh R, Yi F, Blum D, Carbone DP, Dang TP, Targeting specific regions of the Notch3 ligand-binding domain induces apoptosis and inhibits tumor growth in lung cancer, Cancer Res, 70 (2010) 632–638. [PubMed: 20068176]

[129]. Domenga V, Fardoux P, Lacombe P, Monet M, Maciazek J, Krebs LT, Klonjkowski B, Berrou E, Mericskay M, Li Z, Tournier-Lasserve E, Gridley T, Joutel A, Notch3 is required for arterial identity and maturation of vascular smooth muscle cells, Genes & Development, 18 (2004) 2730–2735. [PubMed: 15545631]

[130]. Pelay-Gimeno M, Glas A, Koch O, Grossmann TN, Structure-Based Design of Inhibitors of Protein-Protein Interactions: Mimicking Peptide Binding Epitopes, Angewandte Chemie International Edition, 54 (2015) 8896–8927. [PubMed: 26119925]

[131]. Batrakova EV, Gendelman HE, Kabanov AV, Cell-mediated drug delivery, Expert Opin Drug Deliv, 8 (2011) 415–433. [PubMed: 21348773]

[132]. Chandana M, Manasi D, Jagat RK, Sanjeeb KS, Receptor Mediated Tumor Targeting: An Emerging Approach for Cancer Therapy, Current Drug Delivery, 8 (2011) 45–58. [PubMed: 21034422]

[133]. Dolman MEM, Harmsen S, Storm G, Hennink WE, Kok RJ, Drug targeting to the kidney: Advances in the active targeting of therapeutics to proximal tubular cells, Advanced Drug Delivery Reviews, 62 (2010) 1344–1357. [PubMed: 20719242]

[134]. Birn H, Nielsen S, Christensen EI, Internalization and apical-to-basolateral transport of folate in rat kidney proximal tubule, American Journal of Physiology-Renal Physiology, 272 (1997) F70–F78.

[135]. Sudimack J, Lee RJ, Targeted drug delivery via the folate receptor, Advanced Drug Delivery Reviews, 41 (2000) 147–162. [PubMed: 10699311]

[136]. Cu Y, LeMoëllic C, Caplan MJ, Saltzman WM, Ligand-modified gene carriers increased uptake in target cells but reduced DNA release and transfection efficiency, Nanomedicine: Nanotechnology, Biology and Medicine, 6 (2010) 334–343.

[137]. Christensen EI, Birn H, Megalin and cubilin: synergistic endocytic receptors in renal proximal tubule, American Journal of Physiology-Renal Physiology, 280 (2001) F562–F573. [PubMed: 11249847]

[138]. Saito A, Pietromonaco S, Loo AK, Farquhar MG, Complete cloning and sequencing of rat gp330/“megalin,” a distinctive member of the low density lipoprotein receptor gene family, Proc Natl Acad Sci U S A, 91 (1994) 9725–9729. [PubMed: 7937880]

[139]. Cui S, Verroust PJ, Moestrup SK, Christensen EI, Megalin/gp330 mediates uptake of albumin in renal proximal tubule, American Journal of Physiology-Renal Physiology, 271 (1996) F900–F907.

[140]. Vegt E, Eek A, Oyen WJG, de Jong M, Gotthardt M, Boerman OC, Albumin-derived peptides efficiently reduce renal uptake of radiolabelled peptides, Eur J Nucl Med Mol Imaging, 37 (2010) 226–234. [PubMed: 19722105]

[141]. Zhai XY, Nielsen R, Birn H, Drumm K, Mildenberger S, Freudinger R, Moestrup SK, Verroust PJ, Christensen EI, Gekle M, Cubilin- and megalin-mediated uptake of albumin in cultured proximal tubule cells of opossum kidney, Kidney International, 58 (2000) 1523–1533. [PubMed: 11012887]

[142]. Christensen EI, Birn H, Megalin and cubilin: multifunctional endocytic receptors, Nature Reviews Molecular Cell Biology, 3 (2002) 258–267.

[143]. Wischnjow A, Sarko D, Janzer M, Kaufman C, Beijer B, Brings S, Haberkorn U, Larbig G, Kübelbeck A, Mier W, Renal Targeting: Peptide-Based Drug Delivery to Proximal Tubule Cells, Bioconjugate Chemistry, 27 (2016) 1050–1057. [PubMed: 26999755]

[144]. Wang J, Poon C, Chin D, Milkowski S, Lu V, Hallows KR, Chung EJ, Design and in vivo characterization of kidney-targeting multimodal micelles for renal drug delivery, Nano Research, 11 (2018) 5584–5595.

[145]. Janzer M, Larbig G, Kübelbeck A, Wischnjow A, Haberkorn U, Mier W, Drug Conjugation Affects Pharmacokinetics and Specificity of Kidney-Targeted Peptide Carriers, Bioconjugate Chemistry, 27 (2016) 2441–2449. [PubMed: 27617593]

[146]. Huang Y, Jiang K, Zhang X, Chung EJ, The Effect of Size, Charge, and Peptide Ligand Length on Kidney Targeting by Small, Organic Nanoparticles, Bioengineering & Translational Medicine, n/a (2020).

[147]. Yi Huang KJ, Zhang Xuting, and Chung Eun Ji, Size and Charge Effects of Small, Organic Nanoparticles on Kidney Targeting, BioTM, under review, (2020).

[148]. Yang NJ, Hinner MJ, Getting across the cell membrane: an overview for small molecules, peptides, and proteins, Methods Mol Biol, 1266 (2015) 29–53. [PubMed: 25560066]

[149]. Moussa EM, Panchal JP, Moorthy BS, Blum JS, Joubert MK, Narhi LO, Topp EM, Immunogenicity of Therapeutic Protein Aggregates, Journal of Pharmaceutical Sciences, 105 (2016) 417–430. [PubMed: 26869409]

[150]. Lenhardt S, McAlexander A, Virtue A, Fieles W, Skedzielewski T, Rambo M, Trinh H, Cheng S-H, Hong H, Isidro-Llobet A, Nadin A, Geske R, Klein J-L, Lee D, Jucker BM, Hu E, In Vivo Imaging of Small Molecular Weight Peptides for Targeted Renal Drug Delivery: A Study in Normal and Polycystic Kidney Diseased Mice, Journal of Pharmacology and Experimental Therapeutics, (2019) jpet.119.257022.

[151]. Chin DD, Poon C, Trac N, Wang J, Cook J, Joo J, Jiang Z, Sta Maria NS, Jacobs RE, Chung EJ, Collagenase-Cleavable Peptide Amphiphile Micelles as a Novel Theranostic Strategy in Atherosclerosis, Advanced Therapeutics, n/a (2020) 1900196.

[152]. Chu H, Shillingford JM, Reddy JA, Westrick E, Nelson M, Wang EZ, Parker N, Felten AE, Vaughn JF, Xu L-C, Lu YJ, Vlahov IR, Leamon CP, Detecting Functional and Accessible Folate Receptor Expression in Cancer and Polycystic Kidneys, Molecular Pharmaceutics, 16 (2019) 3985–3995. [PubMed: 31356752]

[153]. Chung EJ, Hallows KR, “First do no harm”: kidney drug targeting to avoid toxicity in ADPKD, American Journal of Physiology-Renal Physiology, 315 (2018) F535–F536. [PubMed: 29846111]

[154]. Birn H, Spiegelstein O, Christensen EI, Finnell RH, Renal Tubular Reabsorption of Folate Mediated by Folate Binding Protein 1, Journal of the American Society of Nephrology, 16 (2005) 608. [PubMed: 15703271]

[155]. Birn H, The kidney in vitamin B12 and folate homeostasis: characterization of receptors for tubular uptake of vitamins and carrier proteins, American Journal of Physiology-Renal Physiology, 291 (2006) F22–F36. [PubMed: 16760376]

[156]. Sandoval RM, Kennedy MD, Low PS, Molitoris BA, Uptake and trafficking of fluorescent conjugates of folic acid in intact kidney determined using intravital two-photon microscopy, American Journal of Physiology-Cell Physiology, 287 (2004) C517–C526. [PubMed: 15102609]

[157]. Wu K-C, Lu Y-H, Peng Y-H, Tsai T-F, Kao Y-H, Yang H-T, Lin C-J, Decreased Expression of Organic Cation Transporters, Oct1 and Oct2, in Brain Microvessels and its Implication to MPTP-

Induced Dopaminergic Toxicity in Aged Mice, Journal of Cerebral Blood Flow & Metabolism, 35 (2014) 37–47. [PubMed: 25248837]

[158]. Collins JF, Novel insights into intestinal and renal folate transport. Focus on "Apical membrane targeting and trafficking of the human proton-coupled folate transporter in polarized epithelia", American Journal of Physiology-Cell Physiology, 294 (2008) C381–C382. [PubMed: 18057122]

[159]. Hilgenbrink AR, Low PS, Folate Receptor-Mediated Drug Targeting: From Therapeutics to Diagnostics, Journal of Pharmaceutical Sciences, 94 (2005) 2135–2146. [PubMed: 16136558]

[160]. Shillingford JM, Leamon CP, Vlahov IR, Weimbs T, Folate-conjugated rapamycin slows progression of polycystic kidney disease, J Am Soc Nephrol, 23 (2012) 1674–1681. [PubMed: 22859856]

[161]. Kipp KR, Kruger SL, Schimmel MF, Parker N, Shillingford JM, Leamon CP, Weimbs T, Comparison of folate-conjugated rapamycin versus unconjugated rapamycin in an orthologous mouse model of polycystic kidney disease, American Journal of Physiology-Renal Physiology, 315 (2018) F395–F405. [PubMed: 29717938]

[162]. Knight SF, Kundu K, Joseph G, Dikalov S, Weiss D, Murthy N, Taylor WR, Folate receptor-targeted antioxidant therapy ameliorates renal ischemia-reperfusion injury, J Am Soc Nephrol, 23 (2012) 793–800. [PubMed: 22282594]

[163]. Martin-Sanchez D, Ruiz-Andres O, Poveda J, Carrasco S, Cannata-Ortiz P, Sanchez-Niño MD, Ruiz Ortega M, Egido J, Linkermann A, Ortiz A, Sanz AB, Ferroptosis, but Not Necroptosis, Is Important in Nephrotoxic Folic Acid-Induced AKI, J Am Soc Nephrol, 28 (2017) 218–229. [PubMed: 27352622]

[164]. Kamen BA, Capdevila A, Receptor-mediated folate accumulation is regulated by the cellular folate content, Proceedings of the National Academy of Sciences, 83 (1986) 5983.

[165]. Zhou N, Luo Z, Luo J, Fan X, Cayabyab M, Hiraoka M, Liu D, Han X, Pesavento J, Dong C-Z, Wang Y, An J, Kaji H, Sodroski JG, Huang Z, Exploring the Stereochemistry of CXCR4-Peptide Recognition and Inhibiting HIV-1 Entry with d-Peptides Derived from Chemokines, Journal of Biological Chemistry, 277 (2002) 17476–17485.

[166]. Dharmatti R, Miyatake H, Nandakumar A, Ueda M, Kobayashi K, Kiga D, Yamamura M, Ito Y, Enhancement of Binding Affinity of Folate to Its Receptor by Peptide Conjugation, International Journal of Molecular Sciences, 20 (2019).

[167]. van Gastel MDA, Torres VE, Polycystic Kidney Disease and the Vasopressin Pathway, Annals of Nutrition and Metabolism, 70(suppl 1) (2017) 43–50. [PubMed: 28614813]

[168]. Torres VE, Wang X, Qian Q, Somlo S, Harris PC, Gattone VH, Effective treatment of an orthologous model of autosomal dominant polycystic kidney disease, Nature Medicine, 10 (2004) 363–364.

[169]. Blair HA, Tolvaptan: A Review in Autosomal Dominant Polycystic Kidney Disease, Drugs, 79 (2019) 303–313. [PubMed: 30689194]

[170]. Patra S, Kumar B, Harlalka KK, Jain A, Bhanuprakash HM, Sadananda KS, Basappa H, Santhosh K, Rajith KS, Bharathi KS, Manjunath CN, Short term efficacy and safety of low dose tolvaptan in patients with acute decompensated heart failure with hyponatremia: a prospective observational pilot study from a single center in South India, Heart Views, 15 (2014) 1–5. [PubMed: 24949180]

[171]. Bhatt PR, McNeely EB, Lin TE, Adams KF, Patterson JH, Review of Tolvaptan's Pharmacokinetic and Pharmacodynamic Properties and Drug Interactions, J Clin Med, 3 (2014) 1276–1290. [PubMed: 26237603]

[172]. Rinschen MM, Schermer B, Benzing T, Vasopressin-2 receptor signaling and autosomal dominant polycystic kidney disease: from bench to bedside and back again, J Am Soc Nephrol, 25 (2014) 1140–1147. [PubMed: 24556353]

[173]. Torres VE, Vasopressin antagonists in polycystic kidney disease, Semin Nephrol, 28 (2008) 306–317. [PubMed: 18519091]

[174]. Jung HJ, Lim J-S, Choi H-J, Lee MS, Kim J-H, Kim S-Y, Kim S, Kim E, Kwon T-H, Vasopressin V2R-Targeting Peptide Carrier Mediates siRNA Delivery into Collecting Duct Cells, PLoS One, 7 (2012) e40010. [PubMed: 22761946]

[175]. Rothbard JB, Kreider E, VanDeusen CL, Wright L, Wylie BL, Wender PA, Arginine-Rich Molecular Transporters for Drug Delivery: Role of Backbone Spacing in Cellular Uptake, Journal of Medicinal Chemistry, 45 (2002) 3612–3618. [PubMed: 12166934]

[176]. Zheleznova NN, Wilson PD, Staruschenko A, Epidermal growth factor-mediated proliferation and sodium transport in normal and PKD epithelial cells, Biochim Biophys Acta, 1812 (2011) 1301–1313. [PubMed: 20959142]

[177]. Nicholson RI, Gee JMW, Harper ME, EGFR and cancer prognosis, European Journal of Cancer, 37 (2001) 9–15. [PubMed: 11165124]

[178]. Melenhorst Wynand BWH, Mulder Gemma M, Xi Q, Hoenderop Joost GJ, Kimura K, Eguchi S, van Goor H, Epidermal Growth Factor Receptor Signaling in the Kidney, Hypertension, 52 (2008) 987–993. [PubMed: 18981331]

[179]. Singh B, Carpenter G, Coffey RJ, EGF receptor ligands: recent advances, F1000Research, 5 (2016) F1000 Faculty Rev-2270.

[180]. Rayego-Mateos S, Rodrigues-Diez R, Morgado-Pascual JL, Valentijn F, Valdivielso JM, Goldschmeding R, Ruiz-Ortega M, Role of Epidermal Growth Factor Receptor (EGFR) and Its Ligands in Kidney Inflammation and Damage, Mediators Inflamm, 2018 (2018) 8739473–8739473. [PubMed: 30670929]

[181]. Richards WG, Sweeney WE, Yoder BK, Wilkinson JE, Woychik RP, Avner ED, Epidermal growth factor receptor activity mediates renal cyst formation in polycystic kidney disease, The Journal of Clinical Investigation, 101 (1998) 935–939. [PubMed: 9486961]

[182]. Ahsan A, Ramanand SG, Bergin IL, Zhao L, Whitehead CE, Rehemtulla A, Ray D, Pratt WB, Lawrence TS, Nyati MK, Efficacy of an EGFR-specific peptide against EGFR-dependent cancer cell lines and tumor xenografts, Neoplasia (New York, N.Y.), 16 (2014) 105–114.

[183]. Dong R, Zhang M, Hu Q, Zheng S, Soh A, Zheng Y, Yuan H, Galectin-3 as a novel biomarker for disease diagnosis and a target for therapy (Review), Int J Mol Med, 41 (2018) 599–614. [PubMed: 29207027]

[184]. Ozkurt S, Dogan I, Ozcan O, Fidan N, Bozaci I, Yilmaz B, Bilgin M, Correlation of serum galectin-3 level with renal volume and function in adult polycystic kidney disease, International Urology and Nephrology, 51 (2019) 1191–1197. [PubMed: 31012038]

[185]. Chiu MG, Johnson TM, Woolf AS, Dahm-Vicker EM, Long DA, Guay-Woodford L, Hillman KA, Bawumia S, Venner K, Hughes RC, Poirier F, Winyard PJD, Galectin-3 associates with the primary cilium and modulates cyst growth in congenital polycystic kidney disease, Am J Pathol, 169 (2006) 1925–1938. [PubMed: 17148658]

[186]. Zou J, Glinsky VV, Landon LA, Matthews L, Deutscher SL, Peptides specific to the galectin-3 carbohydrate recognition domain inhibit metastasis-associated cancer cell adhesion, Carcinogenesis, 26 (2005) 309–318. [PubMed: 15528216]

[187]. Kelleher CL, McFann KK, Johnson AM, Schrier RW, Characteristics of hypertension in young adults with autosomal dominant polycystic kidney disease compared with the general U.S. population*, American Journal of Hypertension, 17 (2004) 1029–1034. [PubMed: 15533729]

[188]. Wyss PP, Lamichhane SP, Abed A, Vonwil D, Kretz O, Huber TB, Sarem M, Shastri VP, Renal clearance of polymeric nanoparticles by mimicry of glycan surface of viruses, Biomaterials, 230 (2020) 119643. [PubMed: 31812275]

[189]. Bidwell GL, Mahdi F, Shao Q, Logue OC, Waller JP, Reese C, Chade AR, A kidney-selective biopolymer for targeted drug delivery, American Journal of Physiology-Renal Physiology, 312 (2016) F54–F64. [PubMed: 27784692]

[190]. Odermatt A, AudigÉ A, Frick C, Vogt B, Frey BM, Frey FJ, Mazzucchelli L, Identification of Receptor Ligands by Screening Phage-Display Peptide Libraries Ex Vivo on Microdissected Kidney Tubules, Journal of the American Society of Nephrology, 12 (2001) 308–316. [PubMed: 11158220]

[191]. Jung E, Lee NK, Kang S-K, Choi S-H, Kim D, Park K, Choi K, Choi Y-J, Jung DH, Identification of tissue-specific targeting peptide, Journal of Computer-Aided Molecular Design, 26 (2012) 1267–1275. [PubMed: 23104667]

[192]. Pasqualini R, Rouslahti E, Organ targeting in vivo using phage display peptide libraries, Nature, 380 (1996).

[193]. Holditch SJ, Schreiber CA, Harris PC, LaRusso NF, Ramirez-Alvarado M, Cataliotti A, Torres VE, Ikeda Y, B-type natriuretic peptide overexpression ameliorates hepatorenal fibrocystic disease in a rat model of polycystic kidney disease, Kidney Int, 92 (2017) 657–668. [PubMed: 28416225]

[194]. Lenhard SC, McAlexander A, Virtue A, Fieles W, Skedzielewski T, Rambo M, Trinh H, Cheng S-H, Hong H, Isidro-Llobet A, Nadin A, Geske R, Klein J-L, Lee D, Jucker BM, Hu E, In Vivo Imaging of Small Molecular Weight Peptides for Targeted Renal Drug Delivery: A Study in Normal and Polycystic Kidney Diseased Mice, Journal of Pharmacology and Experimental Therapeutics, 370 (2019) 786.

[195]. Ahsan A, Ramanand SG, Bergin IL, Zhao L, Whitehead CE, Rehemtulla A, Ray D, Pratt WB, Lawrence TS, Nyati MK, Efficacy of an EGFR-specific peptide against EGFR-dependent cancer cell lines and tumor xenografts, Neoplasia, 16 (2014) 105–114. [PubMed: 24709418]

[196]. Suzuki K, Susaki H, Okuno S, Yamada H, Watanabe HK, Sugiyama Y, Specific Renal Delivery of Sugar-Modified Low-Molecular-Weight Peptides, Journal of Pharmacology and Experimental Therapeutics, 288 (1999) 888.

[197]. Geng Q, Sun X, Gong T, Zhang Z-R, Peptide-Drug Conjugate Linked via a Disulfide Bond for Kidney Targeted Drug Delivery, Bioconjugate Chemistry, 23 (2012) 1200–1210. [PubMed: 22663297]

[198]. Bidwell GL 3rd, Mahdi F, Shao Q, Logue OC, Waller JP, Reese C, Chade AR, A kidney-selective biopolymer for targeted drug delivery, Am J Physiol Renal Physiol, 312 (2017) F54–F64. [PubMed: 27784692]

[199]. K.A.Y. Betts J. Gordon, Wise James A., Johnson Eddie, Poe Brandon, Kruse Dean H., Korol Oksana, Johnson Jody E., Womble Mark, DeSaix Peter, Anatomy and Physiology, OpenStax, Houston, Texas, 2013.

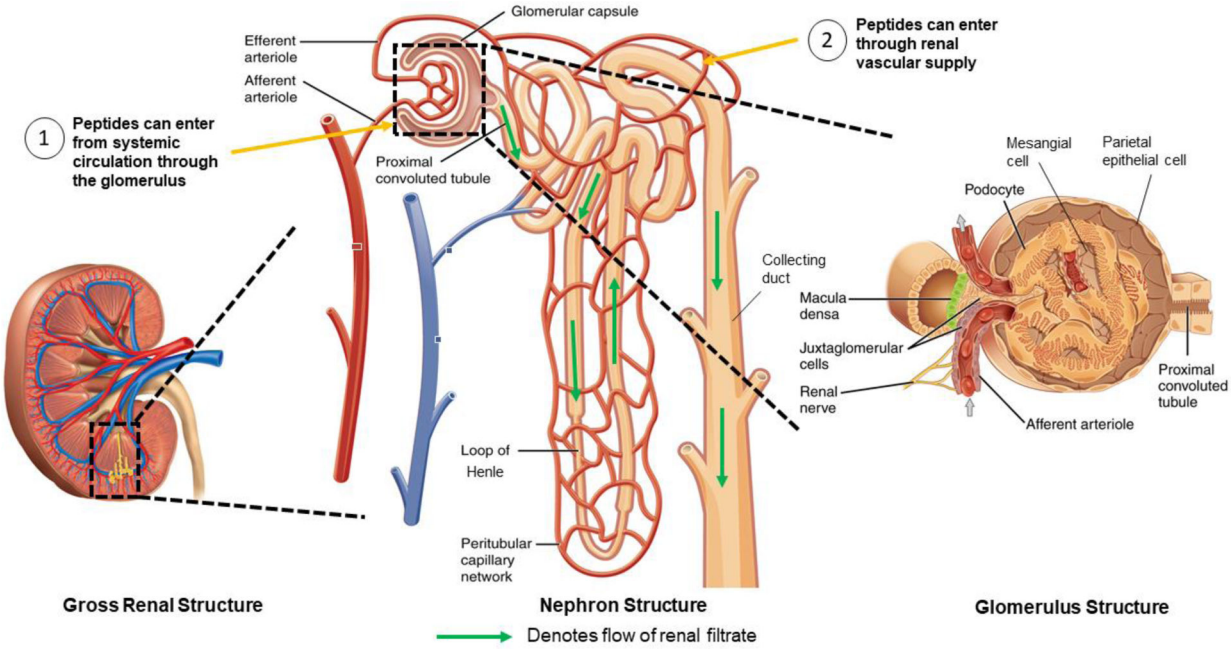

Figure 1.
Structure and cellular makeup of the nephron. Adapted and reprinted from ref. [199].

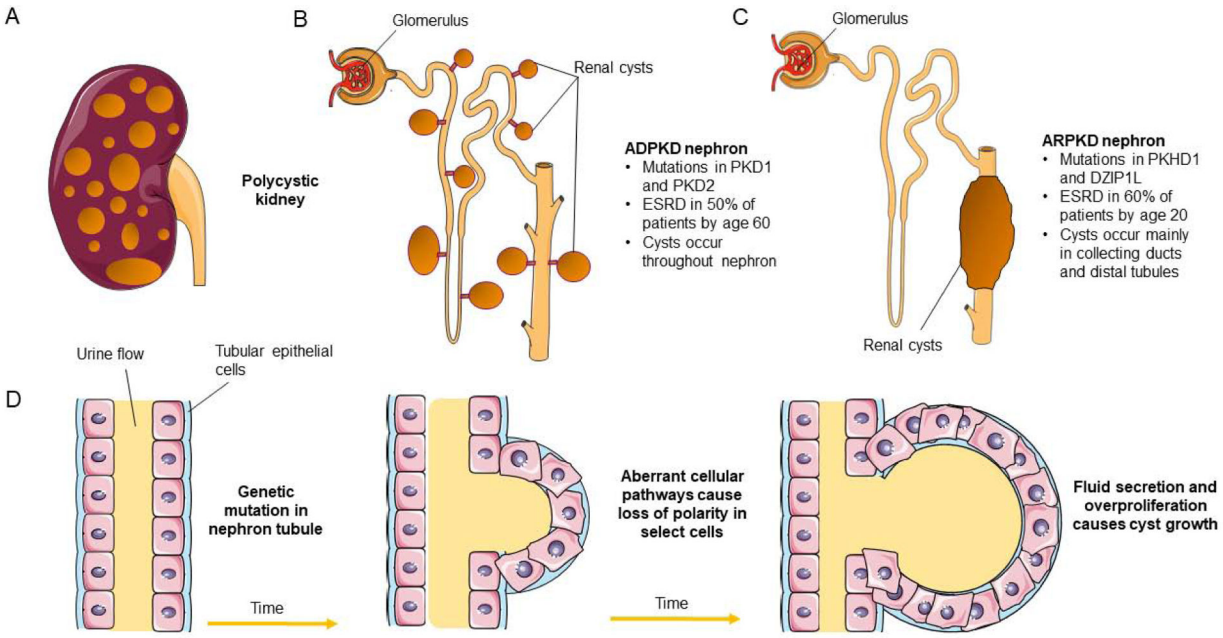

Figure 2.

A) Polycystic kidney disease (PKD) is the most common form of inherited kidney disease and is characterized by cyst growth in kidney parenchyma. B) Autosomal dominant PKD (ADPKD) is caused by mutations in the genes PKD1 and PKD2, affecting their respective protein products polycystin 1 (PC1) and polycystin 2 (PC2). C) Autosomal recessive PKD (ARPKD) is caused by mutations in polycystic kidney and hepatic disease 1 (*PKHD1*) and *DZIP1L* which encodes fibrocystin and DAZ-interacting protein 1-like protein, respectively. D) In kidney tubules or collecting ducts, germline mutations in a few renal cells initiates cystogenesis. As time progresses, loss of planar polarity causes sprouting of cysts from the tubule axis. Fluid secretion and overproliferation continues to drive cyst enlargement until neighboring healthy parenchyma is compressed and filtration function is decreased.

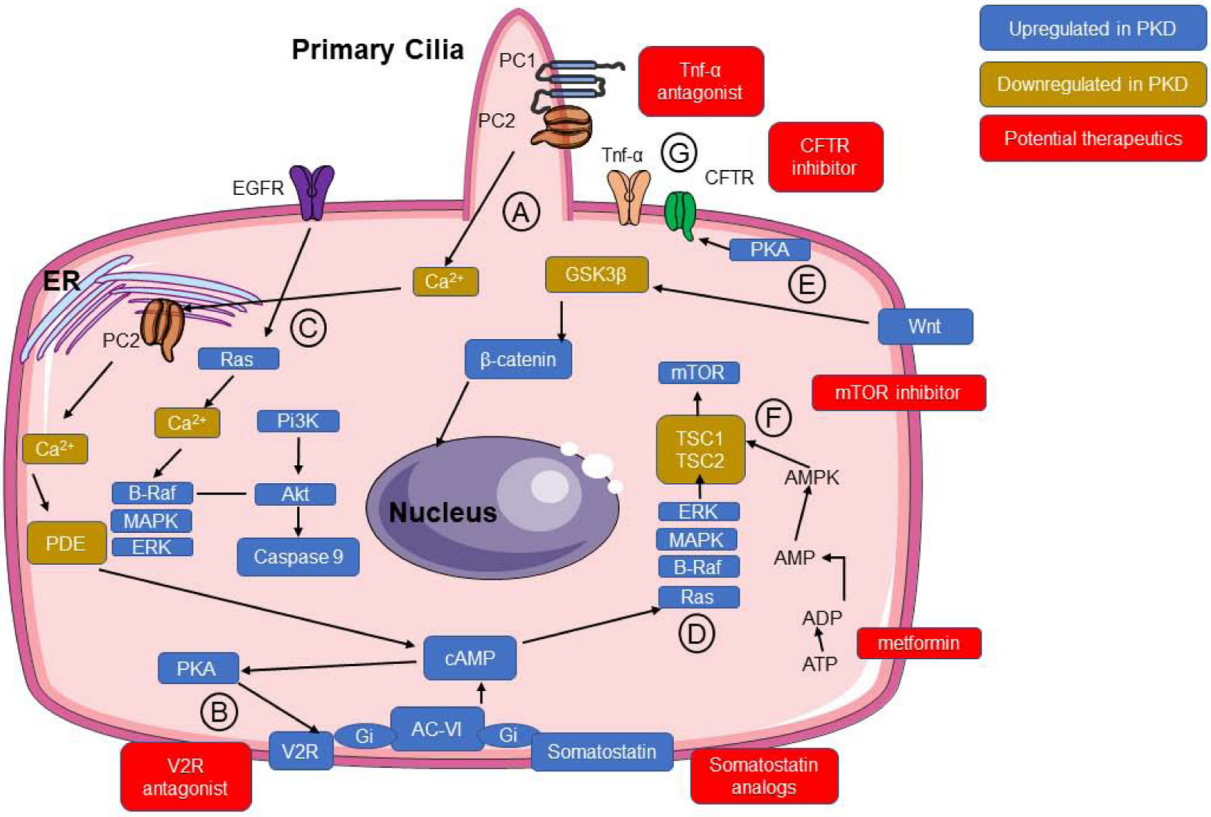

Figure 3.

Cellular pathways involved in ADPKD pathogenesis within a renal epithelial cell. A) PC1 or PC2 loss of function on the primary cilia and ER impairs the calcium transient response, resulting in intracellular cAMP accumulation by preventing PDE degradation of cAMP. B) V2R activation is a major source of cAMP production in the cell through g-protein coupled activation of AC-VI. C) Ras dependent EGFR activation also lowers intercellular calcium. D) The response to abnormally increased cAMP levels leads to an activation of B-Raf/MAP2K1/ERK and inhibition of TSC1 and TSC2, driving the cell towards aerobic glycolysis and cell cycle progression. E) Other alterations include loss of planar cell polarity through Wnt dysregulation, and downstream β-catenin-dependent nuclear changes can drive cell de-differentiation into a proliferative phenotype. F) Master regulators of cellular energy metabolism, including the AMPK and mTOR pathways are mis-regulated, further enhancing proliferation. G) Altered CFTR behavior generates a secretory cell phenotype, in contrast to the normal absorptive phenotype, while TNF-α is an upregulated inflammatory mediator of the PKD phenotype. Proteins and receptors upregulated in PKD are highlighted in blue, and those downregulated are highlighted in yellow. Potential therapeutic targets have been listed in red next to the relevant receptor or misregulated protein.

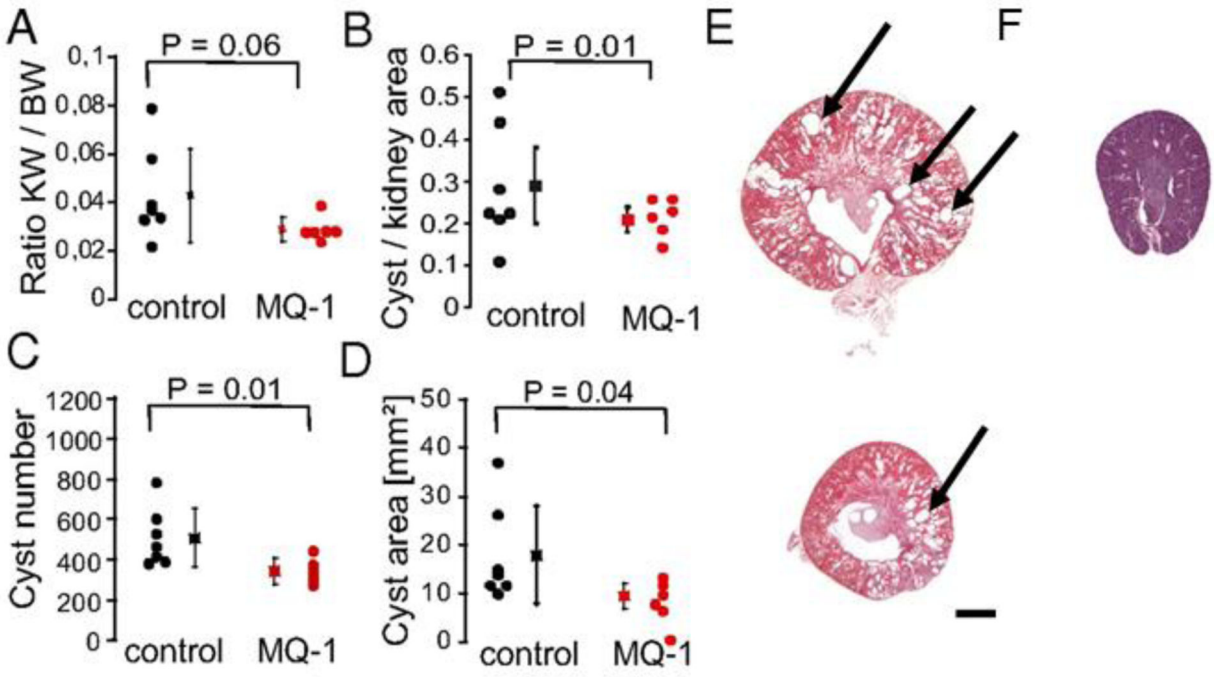

Figure 4.

Therapeutic effect of mambaquaretin-1 (MQ-1) in pcy mice. A) Ratio of kidney weight to body weight (KW/BW), B) ratio of cyst area to kidney area, C) cyst number, D) cyst area, and E) representative H&E-stained sections from kidneys of top: nontreated pcy mice and bottom: treated with mambaquaretin-1. n = 6–7. Cysts appear as voids throughout healthy tissue, and large individual cysts have been marked with arrows. F) Representative H&E-stained section from a wild type mouse. Scale bar, 2 mm. Adapted and reprinted with permission from United States National Academy of Sciences [98].

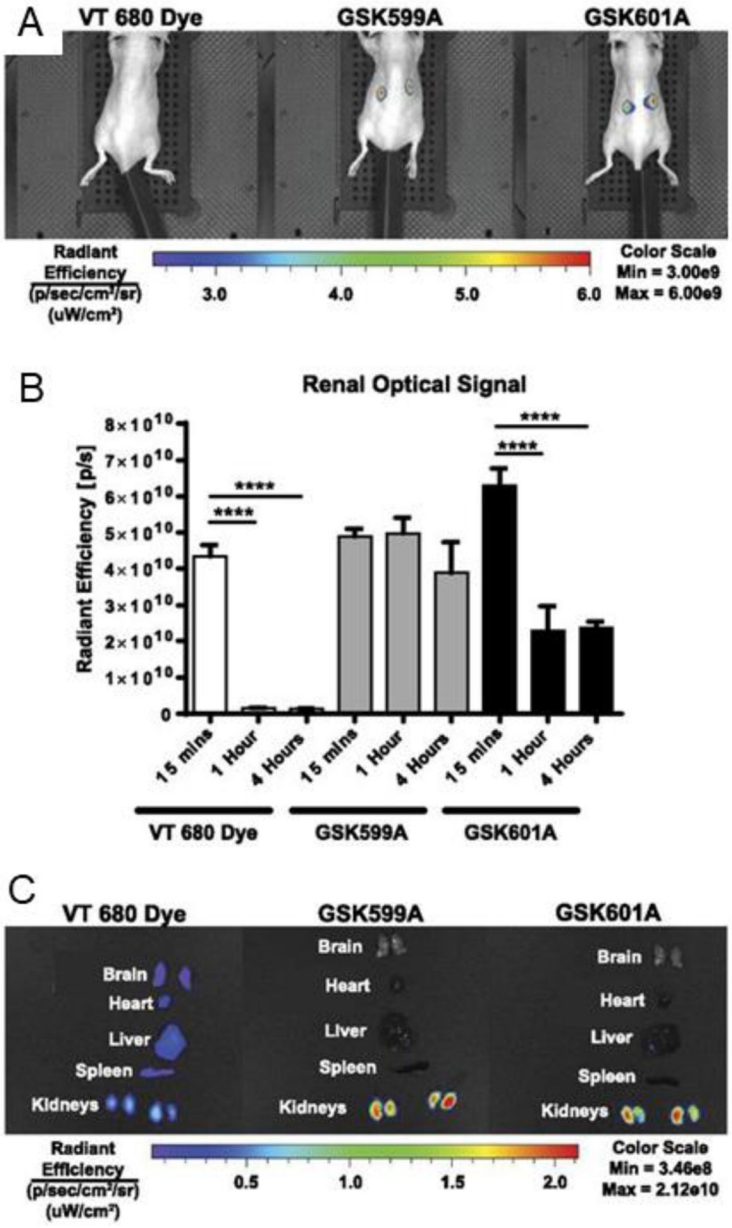

Figure 5.

Biodistribution of kidney targeting peptides. A) *In vivo* and *ex vivo* biodistribution of control VivoTag 680 dye, $(KKEEE)_2K$ (GSK599A), and $(KKEEE)_3K$ (GSK601A) 4 hours post-injection to JCK mice. B) Renal signal at 15 minutes, 1 hour, and 4 hours post-injection. n = 4–6 (****P < 0.0001). C) Ex vivo organ optical signals in groups treated with VivoTag 680 dye vs. those treated with GSK599A and GSK601. Reprinted and modified with permission from ASPET [194].

Table 1.

Clinical trials for PKD.

Interventions	Phases	Company/Sponsor	ClinicalTrials.gov Identifiers
KD019 (Tesevatinib)	Phase1/2	Kadmon Corporation, LLC	NCT01559363, NCT03203642, NCT02616055
Rapamune	Phase 1/2	The Cleveland Clinic	NCT00286156
Bosutinib	Phase 2	Pfizer	NCT01233869
Lixivaptan	Phase 2	Palladio Biosciences	NCT03487913
Metformin	Phase 2	University of Maryland, Baltimore, University of Southern California, United States Department of Defense, University of Colorado, Denver	NCT02903511, NCT02656017
Pasireotide LAR	Phase 2	Mayo Clinic	NCT01670110
Pioglitazone	Phase 2	Indiana University	NCT02697617
Pravastatin	Phase 2	University of Southern California, University of Southern California, National Institute of Diabetes and Digestive and Kidney Diseases	NCT03273413, NCT04284657, NCT00456365
Tolvaptan MR vs Tolvaptan IR	Phase 2	Otsuka	NCT01210560, NCT01451827
Bardoxolone methyl capsules	Phase 2/3	Reata Pharmaceuticals	NCT03918447, NCT03366337
Rapamycin	Phase 2/3	Yale university	NCT00920309
Venglustat GZ402671	Phase 2/3	Genzyme, a Sanofi Company	NCT03523728
Lisinopril,Telmisartan	Phase 3	National Institute of Diabetes and Digestive and Kidney Diseases	NCT01885559, NCT00283686
Spironolactone	Phase 3	University of Colorado, Denver	NCT01853553
Tolvaptan	Phase 3	Otsuka	NCT01214421, NCT02160145, NCT00428948, NCT02251275, NCT00413777
Curcumin	Phase 4	University of Colorado, Denver	NCT02494141

Table 2.

Therapeutic peptides for polycystic kidney disease.

Peptide	Type	Major Findings	Reference
Somatostatin (FCDWKTCT)	Therapeutic	Clinical trial with octreotide-LAR, a somatostain analogue; patients had lower kidney volume but no change in eGFR compared to controls	[100]
Smac-mimetic (4 N-terminal amino acids of Smac)	Therapeutic	Pkd1-floxed mouse model treated with Smac mimetic demonstrated cystic index reduction and kidney weight reduction	[113]
Tat-Beclin-1 peptide (amino acids 267–284 of Beclin-1)	Therapeutic	Beclin-1 peptide treatment to PKD zebrafish reduced cyst burden through mTOR pathway	[115]
B-type natriuretic peptide (SPKMVQGSGC-FGRKMDRISSS-SGLGCKVLRRH)	Therapeutic	Upregulated BNP production in the PKD rat model reduced cyst progression	[193]
Mambaquaretin-1 (RPSFCNLPVKPGPCNG-FFSAFYYSQKTNKCHS-FTYGGCKGNANRFST-LEKCRRTCVG)	Therapeutic	CD1-pcy/pcy mice, a juvenile model of PKD, showed less cysts after treatment with the peptide	[98]

Table 3.

Targeting peptides for polycystic kidney disease.

Peptide	Targets	Major Findings	Reference
$(KKEEE)_3K$ family	Megalin receptor	In polycystic JCK mice, $(KKEEE)_3K$ peptide found in cortex of kidneys	[194]
Desmopressin-conjugated D-arginine (dDAVP-9r)	Upregulated V2R	(dDAVP-9r) delivered siRNA payload to V2R in the kidneys	[174]
Disruptin (SVDNPHVC)	Upregulated EGFR	Disruptin is specific to upregulated EGFR cancer phenotypes	[195]
Library of 5–15 AA length synthetic peptides	Upregulated Notch3 receptors	Identified peptide sequences with specific binding to Notch receptors 1–4 to inhibit tumor growth	[128]
PKNGSDP and DSHKDLK	Glomerular endothelium	Machine learning prediction of sequences from phage display input data	[191]
AVP Peptide (CYFQNCPRG)	Proximal Tubule Cell	Specific renal delivery of sugar-modified low-molecular-weight peptides to proximal tubule cells	[196]
G3-C12 (ANTPCGPYTHDCPVKR)	Proximal Tubule Cell	IV injection of G3-C12 peptide accumulated in proximal renal tubule cells	[197]
CLPVASC	Proximal Tubule Cell	CLPVASC showed high kidney specificity to human podocytes, proximal tubule epithelial, and glomerular microvascular endothelial cells	[198]