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REVIEW

Nephronophthisis: should we target cysts or fibrosis?

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Abstract Ciliopathy nephronophthisis (NPHP), a common cause of end-stage renal disease (ESRD) in children and young adults, is characterized by disintegration of the tubular basement membrane accompanied by irregular thickening and attenuation, interstitial fibrosis and tubular atrophy, and occasionally cortico-medullary cyst formation. Pharmacological approaches that delay the development of ESRD could potentially extend the window of therapeutic opportunity for this group of patients, generating time to find an appropriate donor or even for new treatments to mature. In this review we provide an overview of compounds that have been tested to ameliorate kidney cysts and/or fibrosis. We also revisit paclitaxel as a potential strategy to target fibrosis in NPHP. At low dosage this chemotherapy drug shows promising results in rodent models of renal fibrosis. Possible adverse events and safety of paclitaxel treatment in pediatric patients would need to be investigated, as would the efficacy, optimum dose, and administration schedule for the treatment of renal fibrosis in NPHP patients. Paclitaxel is an approved drug for human use with known pharmacokinetics, which could potentially be used in other ciliopathies through targeting the microtubule skeleton.

Keywords Kidney · Cysts · Fibrosis · Paclitaxel · Ciliopathy · Cilia · NPHP

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Nephronophthisis

Familial juvenile nephronophthisis (NPHP; MIM 256100) was first described in 1951 [1] and is a leading genetic cause of kidney disease in children and young adults [2]. During the last 15 years, mutations in 19 genes have been identified as causing NPHP, yet less than 50 % of all NPHP cases can be diagnosed using these disease loci [3]. The most commonly identified molecular cause of isolated NPHP is deletion or mutation of the *NPHP1* gene, accounting for approximately 20 % of NPHP cases [3]. NPHP gene products do not share sequence similarities, but they do all localize to the primary cilium–centrosome complex, thereby linking renal cystic disease to primary cilia function [4]. NPHP can also be a feature in other congenital syndromes—the "ciliopathies"—such as Joubert syndrome (MIM 213300), Senior–Løken syndrome (MIM 266900), Bardet–Biedl syndrome (MIM 615993), oro-facial-digital syndrome (MIM 311200) and Meckel–Gruber syndrome (MIM 249000), and presents variably with abnormalities of the retina, kidney, brain, bone, and liver [5]. The occurrence of NPHP is estimated to range from one in 50,000 to one in 900,000 [6], and the median age of NPHP diagnosis is 10 years. The NPHP phenotype presents in three forms, depending on the time of onset of end-stage renal disease (ESRD): infantile, juvenile, and adolescent. Patients develop ESRD approximately 4 years after the initial symptoms [7], and the timespan between the first symptoms, diagnosis, and ESRD is relatively short. Therefore, it would be of great interest to extend the window of therapeutic opportunity.

Current treatment options for NPHP patients are limited to symptomatic treatment of renal failure and include blood pressure control to delay disease progression and renal replacement therapy for ESRD. Pediatric NPHP transplant recipients have excellent outcomes which have been shown to be better than those of the general pediatric transplant population [8].

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Donor kidneys usually function for around 20 years, and NPHP patients will likely require additional transplants [9]. None of the drug-based therapies currently being used in the clinical setting are able to ameliorate disease progression in NPHP kidneys. Pharmacological approaches that delay the development of ESRD could potentially extend the window of therapeutic opportunity for this group of patients, generating time to find an appropriate donor or even for new treatments to mature.

Treating renal cysts?

During the last decade pharmacological intervention for NPHP has focused on renal cysts as target, partly driven by knowledge gained from studies on the proliferative phenotype of autosomal dominant polycystic kidney disease (ADPKD; MIM 173900). Like NPHP, ADPKD is also classified as a ciliopathy; the loss of cilia and cyst development are causally related [10]. Ciliary dysfunction with consequent defective planar cell polarity affecting renal epithelial cells in the kidney is believed to be the fundamental etiology of cystogenesis in ADPKD [11]. The efficacy of various drugs to reduce renal cysts has been extensively investigated, mostly in murine models of ADPKD. One such group of drugs, the cyclin-dependent kinase (CDK) inhibitors, have been shown to ameliorate cyst formation in *cpk* (human ortholog is *PKHD1*, a mouse model for polycystic kidney and hepatic disease, MIM 263200), *jck* (*NEK8/NPHP9*, a NPHP mouse model), and *pkd1* (*PKD1*, an ADPKD mouse model) mice *in vivo* [12, 13]. One possible explanation for the response in the different mouse models is the rescue of cilia by CDK inhibitors, as observed *in vitro* [14]. Similarly, mammalian target of rapamycin (mTOR) inhibitors reverse renal cystogenesis in a rodent model of ADPKD by decreasing proliferation [15]. Inducing cellular calcium release by triptolide treatment in kidney-specific *Pkd1* depletion in mice also slows down the progression of cystic kidney disease [16]. The proto-oncogene *c-myc* is overexpressed in PKD cystic tissue, and antisense oligonucleotide treatment targeting c-myc has been shown to inhibit cyst progression in *cpk* mice [17]. Curcumin has been found to inhibit cystogenesis in a murine *Pkd1*-deletion model, possibly by inhibiting pathways upregulated in ADPKD, such as the transcription factor activator protein-1, nuclear factor-κβ (NF-κB), Wnt/β-catenin signaling, tumor necrosis factor alpha, mitogen-activated protein kinases (MAPKs), early growth response gene-1, hypoxia inducible factor-1, notch-1, and also mTOR-regulated signaling [18]. Furthermore, ginkgolide B inhibits cyst formation and enlargement in a PKD mouse model by inducing cyst cell differentiation and altering the Ras/MAPK signaling pathway to inhibit abnormal proliferation in cyst cells [19]. Trichostatin A, a pan-histone deacetylase (HDAC) inhibitor, and valproic acid, a class I HDAC inhibitor, have been identified as compounds that inhibit cyst formation in zebrafish injected with morpholinos reducing levels of *pkd2* [20]. Finally, short-term effects in a clinical trial of ADPKD patients suggest that patients with low glomerular filtration rates (GFRs) might benefit from treatment with the vasopressin V_2 receptor antagonist tolvaptan [21, 22]. A follow-up of 36 months of tolvaptan treatment in ADPKD patients revealed reduced total kidney volume growth and a reduced rate of kidney tissue decline, providing a potential effective therapy [23].

Or targeting renal fibrosis?

ADPKD is a relatively common disease and is always characterized by cysts. In contrast, NPHP is rare, and the disease usually leads to ESRD in childhood. Moreover, many, if not most NPHP patients do not have renal cysts, an observation that has also been confirmed in NPHP mouse models [24] (Fig. 1). A prominent feature of NPHP is renal fibrosis, characterized by thickening of the tubular basement membranes, tubular atrophy, and interstitial inflammation. The rapid development of ESRD after detection of the disease suggests that the former is the result of an active process, rather than just due to an uninhibited attempt to repair damage [25]. Furthermore, many questions on the etiology of ADPKD versus that of NPHP regarding the balance between cysts versus fibrosis in each disease remain unanswered. Recent data suggest that DNA damage signaling upstream of or concomitant with ciliary dysfunction underlies NPHP [26]. One could argue whether targeting renal cysts is actually the right approach in the clinic for NPHP. We propose that ameliorating fibrosis would be at least an equally relevant approach when designing therapeutic intervention of renal failure in NPHP. Fibrosis ultimately leads to irreversible renal damage; however, the underlying molecular mechanisms are targetable and potentially reversible. While targeting the cystic disease in ADPKD is easily justifiable, we argue that in NPHP targeting fibrosis is more relevant.

Fibrosis development is multi-faceted, and the underlying mechanism is a complex crosstalk of signaling pathways, including inflammatory responses. The principal effector cells of fibrosis are myofibroblasts, which excessively deposit extracellular matrix [27]. Myofibroblasts can be derived from different cell sources, including epithelial or endothelial cells [28]. Tubulointerstitial fibrosis is characterized by increased epithelial-to-mesenchymal transition (EMT) [29], which can be induced by transforming growth factor beta (TGF-β) [30]. It has been shown that children with NPHP have increased urinary secretion of TGF-β, with TGF-β excretion among the highest in groups with different etiologies for pediatric ESRD [31]. Targeting the key fibrosis-promoting molecule TGF-β [32] is one possible strategy to treat fibrosis. Isaka et al.

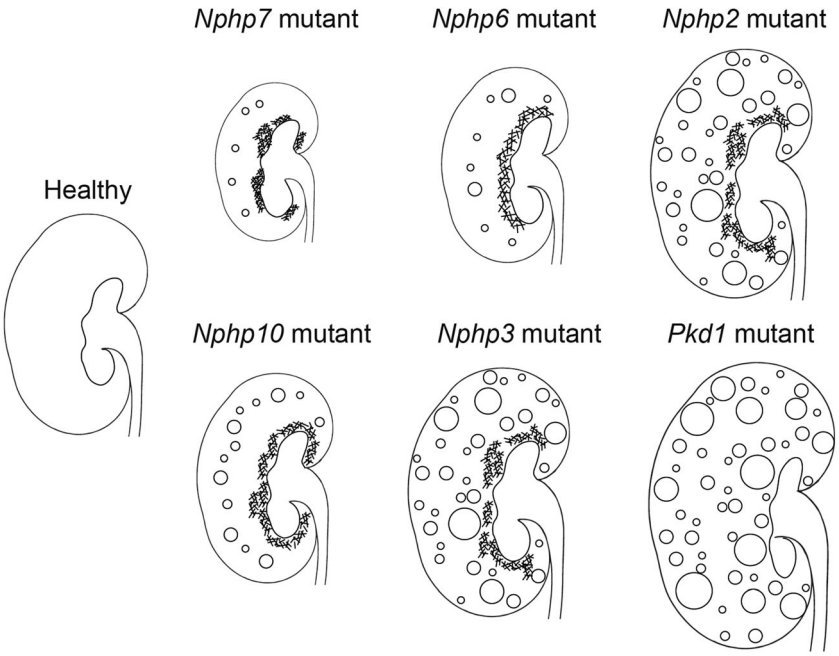

Fig. 1 Different mouse kidney models for renal cysts and fibrosis. Schematic overview of renal degeneration of *Nphp7* (*Glis2*), *Nphp6* (*Cep290*), *Nphp3* (*pcy*), *Nphp2* (*Inv*), *Nphp10* (*Sdccag8*), and *Pkd1* mutant mice, which are characterized by varying levels of interstitial fibrosis (*xxxx*) and renal cysts (*circles*) when compared to healthy kidneys. *Nphp7*, *Nphp6*, and *Nphp10* mutant mice kidneys are smaller, display more fibrosis, and do not display excessive cyst development. The more cystic models, such as *Nphp2* and *Nphp3*, show enlarged kidneys, similar to *Pkd1* mutant kidneys. *NPHP* Familial juvenile nephronophthisis, *PKD* polycystic kidney disease

reported that antisense TGF-β oligodeoxynucleotides were able to block interstitial fibrosis in an unilateral ureteral obstruction (UUO) animal model [33]. Angiotensin II, among other signaling molecules, upregulates TGF-β expression. Angiotensin converting enzyme inhibitors (ACEi) and angiotensin II receptor blockers (ARBs) are used extensively in various renal diseases to prevent the progression of fibrosis by inhibiting proteinuria [34, 35] and have been proven to be safe in children [36]. Blocking angiotensin production through the use of ACEi or ARBs leads to an increased expression of renin, and these increased levels may partly offset the downregulation of TGF-β production by ACEi and ARBs, given that TGF-β expression is upregulated by angiotensin-independent signaling of renin to the (pro)renin receptor. Therefore, combined interventions aimed at key regulators of TGF-β expression might be one of the more effective therapeutic approaches [37].

Fibrosis signaling involves connective tissue growth factor (CTGF), epidermal growth factor (EGF), and platelet-derived growth factor (PDGF), as well as their receptors, making them likewise targets for intervention of fibrosis. Targeting CTGF, EGF, and PDGF pathways in renal disease progression has been extensively reviewed recently [38, 39]. Yokoi et al. reported that antisense treatment resulting in CTGF reduction ameliorated fibrosis in a 7-day UUO mouse model [40], and Wang et al. found that treatment with antibody FG-3019 targeting CTGF reduced matrix deposition in 14-day UUO mice [41]. Molecular inhibition of EGF by Gefitinib [42] and Erlotinib [43] similarly reduces fibrosis. A knockout mouse model of the EGF receptor reduces interstitial fibrosis after kidney injury [43]. Inhibition of PDGF by imatinib [44] and trapidil [45], as well as targeting PDGF with antibody and knockout of *Pdgf*, reduce renal interstitial fibrosis [46]. In addition, a selective p38 MAPK inhibitor FR167653 and extracellular signal-regulated protein kinase kinase (MEK) inhibitor decreased the degree of renal fibrosis in an *Nphp2* mouse model, although it did not extend the overall life span [47]. Collectively these studies support possible medical intervention of fibrotic pathways for the treatment of both injury-related and nephronophthisis-related renal fibrosis.

The role of mutations affecting primary cilia function (e.g. NPHP) in the initiation and/or progression of fibrosis initiation is not yet understood. Downstream ciliary signaling or signaling of cilia proteins with extra-ciliary functions could play a role in fibrosis. Recent reports describe a link with replication stress and enhanced DNA damage response (DDR) signaling and NPHP, suggesting that replication stress and DDR could be an underlying mechanism of NPHP development [14, 26, 48–50]. Increased CDK activity causing replication stress and DDR can be rescued by a CDK1/2 inhibitor [14]; however, whether CDK inhibition can rescue fibrosis remains to be investigated. One study has shown that the cilium is lost during EMT, although it is required for the initiation of the transition [51]. In the pro-fibrotic tissue environment, EMT and cilium loss are thought to require two triggers: (1) disassembly of cellular contacts and (2) TGF-β exposure [51]. Molecular mechanisms of EMT have been reviewed by Lamouille and collegues, who also list cilia-signaling ligands, such as canonical Wnt, Hh, and Notch signaling, as potential regulators of EMT and further report that crosstalk between pathways (enhanced in cilia) regulating EMT accelerates the transition [52]. Interestingly, HDAC inhibitors ameliorate fibrosis via TGF-β suppression in models of diabetic nephropathy (DN), focal segmental glomerulosclerosis (FSGS), and tubulointerstitial

injury [53–55]. These same HDAC inhibitors rescue primary cilia by inhibiting ciliary resorption [56]; however, no direct link of cilia to DN, FSGS, or tubulointerstitial injury has been described. The applications of HDAC inhibitors in kidney disease have been reviewed by Brilli et al. [57]. In conclusion, while HDAC inhibitors may stabilize renal cilia as well as suppress fibrosis, this promising approach has not been intensively tested in humans, let alone children, and may be a long way off from testing in NPHP patients.

The key fibrosis molecule TGF-β activates fibrotic signaling when TGF-β/Smad signaling is upregulated in the nucleus following microtubule destabilization [58]. Smad proteins cannot enter the nucleus while bound to microtubules; therefore it follows that pro-fibrotic gene transcription will be blocked by stabilizing microtubules (Fig. 2) [58]. The ciliary axoneme also requires stabilized microtubules to avoid resorption, and taxol/paclitaxel treatment facilitates α-tubulin acetylation and consequent stabilization [59]. Microtubule-stabilizing agents could be the common denominator in treating both cysts and fibrosis. Interestingly, paclitaxel has been examined in several cystic and fibrotic rodent models (Tables 1, and 2).

Reviving paclitaxel?

One possibly interesting approach to revisit with regard to NPHP patients is paclitaxel (taxol), which is derived from the bark of the Pacific yew tree. This natural-source anti-cancer drug was first discovered in the USA in 1971 and is one of the most well-known drugs used in cancer chemotherapy [67]. Paclitaxel and comparable tubulin-active taxane analogs stabilize GDP-bound tubulin in microtubules, inhibit depolymerization, alter the normal equilibrium between tubulin dimers and microtubules, and promote cells to accumulate in G_0 or mitosis and consequently undergo apoptosis if used at higher dosages (Fig. 2) [68, 69]. There is limited clinical experience with the short-term use of taxanes in pediatric oncology [70]. Three phase I clinical trials using taxanes to treat refractory solid tumors have been reported [71, 72], and one phase II trial has studied recurrent solid tumors [73]. The phase I trials determined the maximum tolerable dose as 350 mg/m^2/day; the (dose-limiting) toxicities included neutropenia [71], acute neurotoxicities (transient coma, somnolence, agitation), and delayed neurotoxicities (paresthesia, dysesthesia, exCitation, headache, and ileus) [72]. Additional pulmonary, dermatologic, and infectious side effects, as well as edema, were significant.

Paclitaxel and related taxanes have the ability to promote microtubule assembly [68], which has been shown to inhibit PKD progression [61]. The results of many different studies (Table 1) lead to the conclusion that paclitaxel has limited effectiveness as a therapeutic agent in the treatment of slowly progressing cystic kidneys; in contrast, rapidly progressive forms of PKD in rodent models benefit from therapy with paclitaxel [62]. Treating NPHP with high-dose paclitaxel would cause cell death and potentially worsen interstitial fibrosis and overall renal function. However, low-dose taxol ameliorates renal fibrosis *in vivo* (Table 2) [64, 65]. Low-dose paclitaxel was found to be more renoprotective than taurine in unilateral ureteral obstruction (UUO) rats [65]. Paclitaxel also blocks Toll-like receptor 4 (TLR-4) and thereby

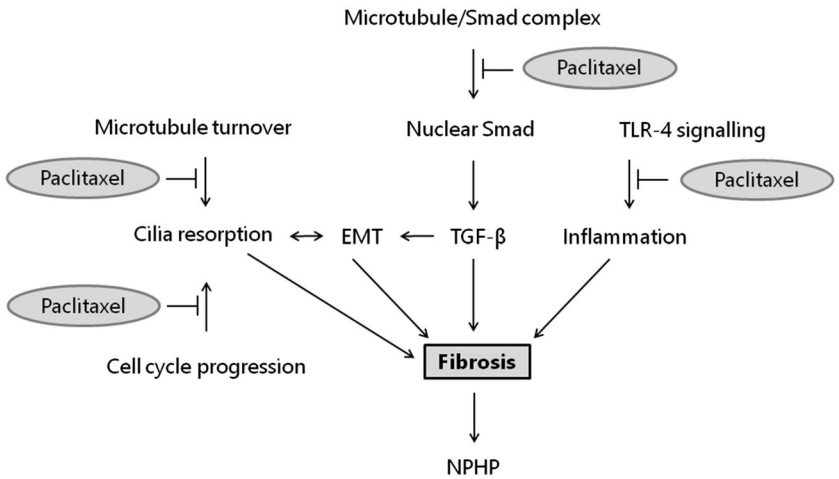

Fig. 2 Paclitaxel inhibits renal fibrosis by interfering with several pathophysiological routes in NPHP. It blocks Toll-like receptor 4 (TLR-4) and thereby inhibits inflammation. It stabilizes microtubules and prevents Smad signaling in the nucleus which, in turn, upregulates transforming growth factor beta (*TGF-β*) transcription. TGF-β subsequently induces epithelial-to-mesenchymal transition (EMT), contributing to tubulointerstitial fibrosis. Paclitaxel prevents cilia resorption via two mechanisms: by inhibiting microtubule turnover and by arresting the cell cycle. The loss of cilia is linked to EMT. The loss of cilia and its downstream signaling are involved in regulating nephronophthisis (NPHP). All four pathways which are targeted by paclitaxel contribute to fibrosis development, which leads to the clinical phenotype NPHP

Table 1 Paclitaxel studies in rodent models of cystic kidney disease

Rodent model	Human ortholog	Dose paclitaxel	Observed effect	Reference
C57BL/6 J-*cpk/cpk* mice	*PKHD1*	150 μg/week (maximum of 28 weeks)	Prolonged survival (170 days), minimal loss of renal function, limited collecting-duct cyst enlargement, attainment of adult size	[60]
C57BL/6 J-*cpk/cpk* mice	*PKHD1*	50 μg/every other week (maximum of 17 weeks)	Increased survival, fewer/smaller cysts, more (hypertrophied) nephrons and fibrosis	[61]
C57BL/6 J-*cpk/cpk* mice	*PKHD1*	150 μg/week (maximum of 8 weeks)	Prolonged survival (>40 days), decreased relative kidney weight, increased interstitial fibrosis	[62]
Orpk mice	*IFT88*	10 μg/g body weight/week (approx.200 μg/week) (7 weeks)	No effect on PKD progression	[63]
DBA/2FG-*pcy/pcy* mice	*NPHP3*	100–150 μg/week (9–11 week)	No effect on increased kidney weight or serum urea nitrogen level, premature death	[62]
Han:SPRD-*Cy/Cy* 7-10day old rats	*PKDR1*	0.15–15 mg/kg/week (approx. 1.5–150 μg/week (maximum of 1.5 weeks)	Severe side effects, premature death	[62]
Han:SPRD-*Cy/+* male rats	*PKDR1*	7, 15, or 27 mg/kg/week (approx. 438, 3750, 6750 μg/week) (6 weeks)	Inconsistent effect on relative kidney weight, no effect on serum urea nitrogen concentration, increased mortality at higher dosages	[62]

PKD, Polycystic kidney disease

inhibits inflammation (Fig. 2) [74], which significantly contributes to fibrotic signaling [25]. TLR-4 is present on renal epithelial cells, including cells of the proximal tubule and collecting ducts. CD14 is expressed at high levels in macrophages and monocytes and at low levels in nonmyeloid cells, including cells of the kidney and liver, where it is membrane-bound through glycosyl phosphatidylinositol linkage. Under normal conditions, CD14 facilitates the binding of lipopolysaccharides to TLR-4 to stimulate the innate immune response. However, TLR-4 signaling can also be activated by interaction with extracellular matrix (ECM) degradation products. In PKD, CD14 expression is upregulated and levels of the proteolytically shed CD14 variant increase, indicative of immunological activation or cell injury. Consequently, the renal tubule-derived CD14 is able to activate TLR-4 signaling either locally or in more distal segments of the nephron, long before the infiltration of inflammatory cells. Additionally, proteolytically shed CD14 is found in the urine of both recessive PKD and ADPKD patients, where, in the case of male ADPKD patients, the levels correlate with kidney volume. Thus, CD14 could be a potential biomarker for the early progression of PKD [75].

Ciliary architecture and function closely rely on the microtubule cytoskeleton. Loss of NPHP protein function causes disturbance of microtubule organizing centers at the centrosomes, possibly leading to defective cilia, mitotic spindles, and transport. Taxol treatment leads to suppressed tubule dynamics, which blocks ciliary absorption before entering the cell cycle, and blocks TGF-β expression (Fig. 2) [58, 76]. Intracellular transport of ECM proteins, such as matrix metalloproteinase-9, along stabilized microtubules is decreased by paclitaxel [77]. There are many factors which could play a role in inhibiting fibrosis by blocking microtubule dynamics. Microtubules are involved in many cellular processes, including cilium formation, maintenance of cell polarity, intracellular transport, mitosis, differentiation, and migration [78–80]. Treatments which could inhibit microtubule dynamics may prevent such pathological processes as hyperproliferation, TGF-β expression, EMT (Fig. 2), and senescence, all of which contribute to renal fibrosis. There is only limited clinical experience with taxanes in pediatric oncology, and as

Table 2 Paclitaxel studies in rodent models of renal fibrosis

Rodent model	Dose paclitaxel	Observed effect	Reference
UUO[a] Wistar rats	2× week 0.3 mg/kg (approx.90 μg 2× week) (1 or 2 weeks)	Ameliorate renal tubulointerstitial fibrosis	[64]
UUO[a] rats	2× week 0.3 mg/kg (approx. 48 μg 2× week) (4 weeks)	Preservation of nephrons, 53 % less necrosis and fibrosis, longer renal tubules	[65]
5/6 nephrectomy of male Wistar rats	2× week 0.3 mg/kg (approx. 90 μg 2× week) (8 weeks)	Reduced progression of glomerular injury and interstitial fibrosis, improved kidney function	[66]

[a] UUO, Unilateral ureteral obstruction

administration of these drugs for the prevention of fibrosis in patients with NPHP would require an extensive timeframe, possible damaging effects of long-term use of these anti-mitotic agents on growth and development should be considered.

Two birds with one stone: targeting both cysts and fibrosis

Patients with NPHP or ADPKD would benefit the most from interventions aimed at reducing both renal cysts and fibrosis. Calcimimetic R-568 and octreotide normalize intracellular calcium and cAMP levels and inhibit the progression of renal cysts. This same treatment inhibits the development of renal fibrosis equally well in *pcy* mice and pck rats (orthologous to *NPHP3* and *PKHD1*/fibrocystin respectively) [81, 82]. In a randomized clinical trial, the long-acting somatostatin analog octreotide slowed down disease progression in patients with polycystic kidney and liver disease [83]. Rapamycin (mTOR inhibitor) has been found to reduce cyst enlargement and fibrosis in *pcy* mice during late-stage treatment and ameliorated renal function [84]. In addition, a 10 nM rapamycin treatment of zebrafish injected with *nphp2* (*INVS*) and *nphp6* (*CEP290*) morpholinos reduced the increase of kidney size significantly [85]. Furthermore, rapamycin-loaded microspheres inhibited local fibrotic response in UUO mice by inhibiting mTOR activity [86]. mTOR inhibitors have also been tested in several large-scale clinical trials. Disappointingly, in humans with ADPKD, different rapamycin and everolimus dosages have not revealed a clear-cut benefit in terms of total kidney volume or GFR [87–91]. The potential effects of mTOR inhibitors in ADPKD patients remain to be determined. However, in a retrospective study of patients with ADPKD who had been transplanted and subsequently received rapamycin as an immunosuppressant, their native kidneys showed reduced cyst sizes [92]. Folate conjugation of rapamycin inhibited mTOR activity exclusively in the kidneys of PKD mice, suggesting renal efficacy and decreased side effects when applied to ADPKD patients [93]. Everolimus, an orally available single agent mTOR inhibitor, is already in use for treatment of subependymal giant astrocytomas in children with tuberous sclerosis complex [94]. Finally, the vasopressin receptor antagonist OPC-31260 and tolvaptan ameliorate fibrosis and cystogenesis in pck rats and *pcy* mice [95, 96]. Clinical trials for humans with ADPKD have reported beneficial effects of tolvaptan on renal cysts, but did not include analysis of renal fibrosis.

Concluding remarks

Unfortunately, treatment options for pediatric patients with NPHP are limited at the present time; however, there may be possibilities to extend the window of therapeutic opportunity for these juvenile patients. Understanding how fibrosis is initiated and propagated upon functional loss of NPHP (and to a lesser extent ADPKD) gene products needs to be further elucidated. It is also entirely unclear whether pro-fibrotic cellular changes are a consequence of ciliary function or whether they are a response to extraciliary functions of these gene products. We propose paclitaxel as a potential therapeutic agent for NPHP, albeit the appropriate timing and dosage of paclitaxel are currently unknown. It would be very interesting to investigate the administration of low-dose paclitaxel in an early stage of a NPHP animal model such as *Cep290* gene trap mice [97] to establish efficacy in delaying renal failure.

Assuming NPHP symptoms are not fully reversible and having acquired extensive data from cystic and fibrotic kidney animal models that show the benefits of low-dose paclitaxel treatment, coupled with the fact that paclitaxel being an approved drug for human use with known pharmacokinetics, an exploratory phase II trial of low-dose paclitaxel treatment in NPHP patients soon after the first symptoms appear or diagnosis is made, with a primary endpoint of time to progression of ESRD, may be warranted. Possible adverse events upon paclitaxel treatment in pediatric patients would need to be investigated. Research will determine the efficacy, optimum dose, and administration schedule for renal fibrosis treatment in children and young adults with NPHP.

Complimentary to such a strategy, the treatment of other ciliopathies with low-dose microtubule stabilizing agents, such as paclitaxel and HDAC inhibitors, should be explored, since these drugs also stabilize microtubules in the cilium. Several lines of evidence suggest that stabilizing microtubules and the cilium will lead to promising results *in vivo*, as discussed in this review. However, the window of opportunity to prevent rapid loss of renal function in ciliopathies will generally present in childhood. Therefore, the safety of these anti-proliferative drugs for the growing and developing child is a major issue that should be resolved before this alternative therapy can be offered to NPHP patients.

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Conflict of interest The authors declare that they have no conflict of interest.

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