

Mechanism-Based Therapeutics for Autosomal Dominant Polycystic Kidney Disease: Recent Progress and Future Prospects

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Key Words

Polycystic kidney disease · Autosomal dominant polycystic kidney disease · *PKD1* · *PKD2* · Therapeutics · mTOR · cAMP · Calcium · ERK

Abstract

Autosomal dominant polycystic kidney disease (ADPKD) is the most common inherited kidney disease, accounting for up to 10% of patients on renal replacement therapy. There are presently no proven treatments for ADPKD and an effective disease-modifying drug would have significant implications for patients and their families. Since the identification of *PKD1* and *PKD2*, there has been an explosion in knowledge identifying new disease mechanisms and testing new drugs. Currently, the three major treatment strategies are to: (1) reduce cAMP levels; (2) inhibit cell proliferation, and (3) reduce fluid secretion. Several compounds shown to be effective in preclinical models have already undergone clinical trials and more are planned. In addition, a whole raft of other compounds have been developed from preclinical studies. The purpose of this paper is to evaluate the results of recent published trials, review current trials and highlight the most promising compounds in the pipeline. There appears to be no shortage of potential candidates, but several key issues need to be addressed to facilitate clinical translation.

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Autosomal dominant polycystic kidney disease (ADPKD) is the most common genetic kidney disease with an estimated prevalence of between 1:400 and 1:1,000 [1]. It is caused by germline mutations in *PKD1* (85%) or *PKD2* (15%) and is the fourth most common cause of end-stage renal disease (ESRD). The cardinal feature of ADPKD is the presence of multiple fluid-filled kidney cysts which enlarge over time. Cyst initiation and expansion is a complex process characterized by abnormalities in tubular cell proliferation, fluid secretion, extracellular matrix formation and cell polarity [2]. In patients with early disease, i.e., estimated glomerular filtration rate (eGFR) >70 ml/min, total kidney volume (TKV) measured by magnetic resonance imaging (MRI) increased by 3.7–9.5% per year and was associated with a change in eGFR of +2.9 to –5.0 ml/min/year [3]. In patients with a baseline TKV of >1,500 cm³, there was a significant correlation with measured GFR decline [3]. *PKD1* kidneys were generally larger than *PKD2* kidneys, and there was a correlation between gender (male sex) and the rate of kidney growth [4]. These findings suggested that TKV could be an early marker of disease activity prior to the later decline in GFR and therefore changes in TKV could be a useful surrogate ‘biomarker’ to identify patients more likely to progress to ESRD and to test the effectiveness of new drugs.

The general approach to discovering new treatments for ADPKD has been largely through targeting the major

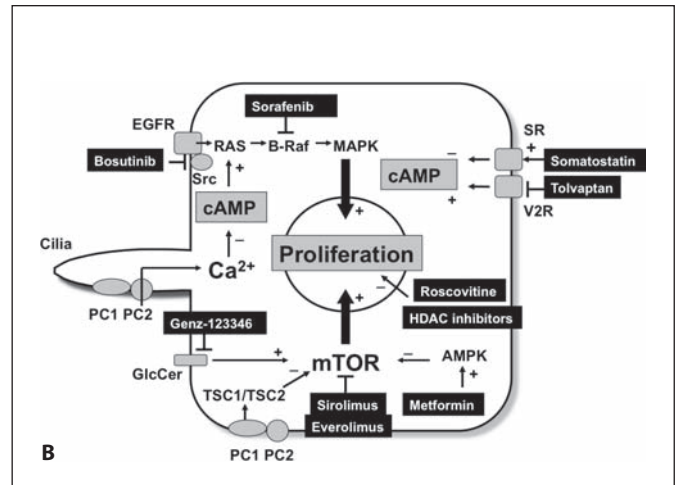
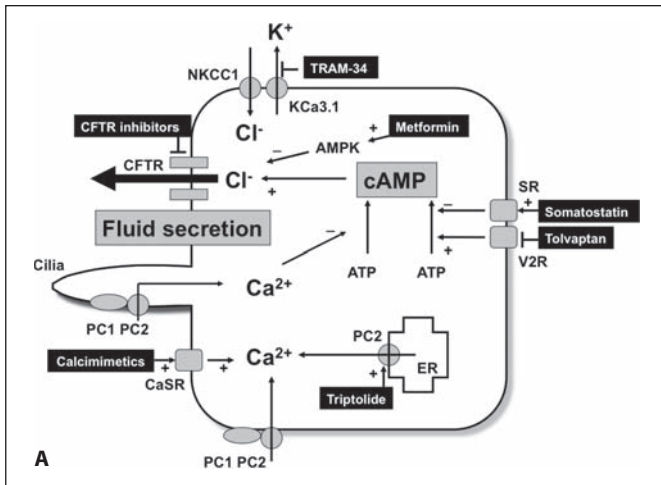


Fig. 1. Schematic illustration of the major signaling pathways involved in the pathogenesis of ADPKD and the targets of candidate drugs. The ‘secretory’ pathways (A) and the ‘proliferative’ pathways (B). AMPK = AMP-activated protein kinase; CaSR = calcium-sensing receptor; CFTR = cystic fibrosis transmembrane regulator; ER = endoplasmic reticulum; GlcCer = glucosylceramide;

HDAC = histone deacetylase; KCa3.1 = endothelial Ca^{2+} -activated K^+ -channel; MAPK = mitogen-activated protein kinase; mTOR = mammalian target of rapamycin; NKCC1 = Na-K-Cl cotransporter; PC = polycystin; SR = somatostatin receptor; TSC = tuberous sclerosis; V2R = vasopressin V2 receptor.

signaling pathways dysregulated in ADPKD. These in turn are being clarified by functional studies of the ADPKD proteins, polycystin-1 (PC-1) and polycystin-2 (PC-2). PC-1 and PC-2 have been shown to form a protein complex via their C-terminal tails [5]. This ‘polycystin complex’ appears to interact with multiple other protein partners which in turn enable it to regulate multiple signaling pathways critical for the maintenance of normal tubular structure and function during embryonic development and throughout adult life [6]. PC-1 and PC-2 have been localized to multiple subcellular compartments including primary cilia, cell-cell junctions, focal adhesions and the endoplasmic reticulum where there is evidence that they play a functional role. The polycystin complex is likely to function as a mechanosensor in primary cilia and mediate flow-dependent Ca^{2+} entry [7]. In addition, it could sense the force of coupling between cells or at cell-matrix attachments through homophilic and heterophilic interactions [8]. PC-2 can clearly function as a non-selective calcium channel and has been adopted as ‘TRPP2’ into the transient receptor potential (TRP) channel superfamily [6]. PC-2 can act independently of PC1 in left-right axis determination during development, and this could be an ER-specific function at the embryonic node [9].

The major aberrant signaling pathways implicated in ADPKD pathogenesis are Ca^{2+} , cAMP and mammalian target of rapamycin (mTOR) [1, 10, 11]. A decrease in in-

tracellular Ca^{2+} levels could have pleiotropic effects on gene regulation but could also increase cAMP levels by altering the activity of Ca^{2+} -dependent adenylate cyclases (V and VI) and/or phosphodiesterases [12]. Renal cAMP levels are elevated in many PKD models, and there is a general consensus that it plays a major role in cyst formation. Cystic cells have a characteristic pro-mitogenic response to cAMP in vitro which can be reversed by restoring intracellular Ca^{2+} [12–14]. In addition, cAMP can stimulate fluid secretion into the cyst lumen by activating the apically located Cl^- channel, cystic fibrosis transmembrane conductance regulator (CFTR) [15, 16]. The mTOR pathway is upregulated in kidneys of patients with ADPKD [17]. The TSC2 protein tuberlin functions by inhibiting basal mTOR activity. Tuberlin binding to PC1 may be lost in ADPKD resulting in mTOR activation [17]. Loss of cilia function (e.g. IFT88) is also associated with mTOR activation suggesting that other cilia signals could exhibit a tonic inhibition on this key enzyme under normal conditions [18].

The major treatment strategies currently being tested can be divided into three categories: (1) reduce cAMP levels; (2) inhibit cell proliferation, and (3) reduce fluid secretion [2] (fig. 1). Several compounds shown to be effective in preclinical models have been tested in clinical trials and more are planned. In addition, a whole raft of newer compounds have been developed which generally

Table 1. Completed clinical trials for ADPKD

| Study drugs | Study design | Treatment duration months | Eligibility (renal function) | Patient, n (recruitment/completion) | Outcomes | Side effects | Ref. | Clinical trials Gov identifier |
|--------------------------|--|---------------------------|---|-------------------------------------|--|---|------|--------------------------------|
| Sirolimus | Single center, randomized, open-label (phase 2/3) | 18 | eGFR >70 | 100/96 | TKV and GFR: no significant change | Oral mucositis, diarrhea, peripheral edema, hyperlipidemia | 24 | NCT00346918 |
| Sirolimus (SIRENA study) | Single center, randomized, open-label, crossover (phase 2) | 6 | eGFR >40 | 21/15 | TKV and GFR: no significant change | Aphthous stomatitis, acne, and peripheral edema | 22 | NCT00491517 |
| Everolimus | Multicenter, randomized, double-blind, placebo-controlled (phase 3) | 24 | eGFR 30–89 | 433/329 | TKV and GFR: no significant change; improved Δ TKV in first year (+5.03 vs. + 8.22% with placebo) | Acne, stomatitis, angioedema, hyperlipidemia, folliculitis, leukopenia, proteinuria | 23 | NCT00414440 |
| Ocreotide | Single center, randomized, double-blind, placebo-controlled, crossover (phase 2/3) | 12 | No eGFR criteria (baseline eGFR 20–124) | 42/42 | Significant reduction in Δ TKV (+0.25 vs. +8.61% with placebo) and Δ TLV (–4.95 vs. +0.92% with placebo); GFR: no significant change | Diarrhea, injection site granuloma | 30 | NCT00426153 |
| Landreotide | Single center, randomized, double-blind, placebo-controlled (phase 2/3) | 6 | Not on dialysis (baseline creat. 8–173 μ mol/l) | 54/53 | Significant improvement in Δ TKV (–2.5 vs. +3.4% with placebo) and Δ TLV (–2.9 vs. + 1.6% with placebo); creat.: no significant change | Loose stool, nodules on the injection site | 31 | NCT00565097 |

eGFR = Estimated glomerular filtration rate; TKV = total kidney volume; TLV = total liver volume; Δ = change.

target one or more of these strategies. The purpose of this paper is to evaluate the results of recent published trials, review current trials and highlight the most promising compounds in the pipeline.

Drugs That Have Completed Clinical Trials

mTOR Inhibitors

mTOR inhibitors have been shown to inhibit cell proliferation and cyst growth in a number of orthologous and non-orthologous models and were therefore regarded as a potential treatment for ADPKD [17, 19, 20]. These findings were supported by a retrospective observational study showing that rapamycin treatment after renal transplantation was more effective than cyclosporine in limiting native kidney enlargement in ADPKD patients [17]. In another retrospective study, treatment with the sirolimus regimen for an average of 19.4 months was associated with an $11.9 \pm 0.03\%$ reduction in polycystic liver volume compared to conventional treatment in 7 ADPKD patients who had received kidney transplants [21].

Nonetheless, recent clinical trials using mTOR inhibitors in ADPKD patients have been disappointing (table 1). In the SIRENA study, 21 patients with eGFR >40 ml/min were randomized to a 6-month treatment with sirolimus (starting dose 3 mg/day; target blood trough levels 10–15 ng/ml) or conventional therapy in a crossover study [22]. In the 15 patients who completed the study, no significant differences in TKV or eGFR between sirolimus and conventional treatment were found, although the increase in cyst volume was less after sirolimus and renal parenchymal volume increased (possibly due to less cystic compression) [22]. Two larger clinical trials have also not reported benefits in TKV or eGFR with longer treatment durations [23, 24]. In the study by Serra et al. [24] in 100 early-stage ADPKD patients (eGFR >70 ml/min/1.73 m²), sirolimus treatment (target dose, 2 mg/day) for 18 months did not significantly alter TKV or eGFR compared to the control group receiving standard care. The median increase in TKV over 18 months was 99 (interquartile range 43–173) cm³ in the sirolimus group and 97 (interquartile range 37–181) cm³ in the control group [24].

In a second study, 433 ADPKD patients (eGFR 20–89 ml/min/1.73 m²) were randomized to receive everolimus (2.5 mg b.d.) or placebo over a 2-year period [23]. The annual increase in TKV was significantly less in the everolimus group compared to placebo (102 vs. 157 ml, $p = 0.02$) in the first year, but failed to reach significance by the second year. In addition, there was a smaller increase in parenchymal volume in the everolimus group (56 vs. 93 ml, $p = 0.11$) and loss of eGFR was more rapid than the placebo group at 2 years (–8.9 vs. –7.7 ml/min, $p = 0.15$) [23]. It appears that everolimus treatment resulted in the dissociation between changes in TKV and eGFR (smaller kidney but worse renal function). Compared to the sirolimus study, there was a much higher dropout rate in the everolimus-treated group (33%) with a predictable side-effect profile.

These studies have raised several important questions. Firstly, although changes in TKV (measured by CT or MRI) had been proposed as a rational biomarker for disease progression before GFR decline [3, 25], these results question whether it is a sufficiently sensitive predictive tool when used in isolation [26, 27]. Secondly, even if the trial had been positive, the side-effect profile (in the everolimus study) would have made lifelong treatment unrealistic [28]. Thirdly, it appears that murine models (which generally develop earlier and more severe disease) do not always predict therapeutic outcome in human disease (which is slower and more chronic in nature). Finally, it is possible that the use of mTOR inhibitors given in earlier disease at higher doses and for longer periods might have worked. The dose of sirolimus required to inhibit mTOR in kidney tubular cells, may be higher than for peripheral blood mononuclear cells and this could have led to a negative outcome in that study [29]. Future options to explore for the future use of mTOR inhibitors could include analogues with a better side-effect profile and/or better renal penetration or the use of lower doses (to minimize side effects) in combination with a second agent.

Somatostatin

Somatostatin could theoretically improve both autosomal-dominant polycystic liver disease (PCLD) and ADPKD due to its ability to inhibit cAMP signaling in cholangiocytes and tubular epithelial cells [30]. In a randomized, double-blind, placebo-controlled trial, the long-lasting somatostatin analogue octreotide was given to ADPKD and PCLD patients for 1 year [30] (table 1). In the octreotide group (<40 mg every 28 days), changes in liver volume were significantly lower com-

pared to the placebo group (–4.95 vs. +0.92%, $p = 0.048$). Similarly, TKV remained stable as compared to a significant increment in the control group (+0.25 vs. +8.6%, $p = 0.045$) [30]. However, there was no significant difference in the loss of GFR between the octreotide and the placebo groups (–5.1 vs. –7.2%, $p = 0.98$). Nevertheless, patients in the octreotide group reported subjective benefits such as less pain and increased physical activity. Major side effects were diarrhea and impaired glucose tolerance.

In a similarly designed trial using lanreotide for 6 months, the percent increase in liver volume was –2.9% in patients treated with lanreotide (120 mg every 28 days for 24 weeks) compared to +1.6% in the placebo group [31]. Interestingly, the increment in TKV was +3.4% in the placebo group as compared to –1.5% in those treated with lanreotide (a difference of 4.9% at 6 months). These data suggest that somatostatin analogues are effective in reducing the growth of both liver and kidney cysts. Whether they will be as effective for retarding the decline of eGFR will be the subject of future trials (see below).

Drugs in Current Clinical Trials

Somatostatin

The efficacy of somatostatin on TKV is being studied in a randomized placebo-controlled trial over 36 months (table 2).

Tolvaptan

Arginine vasopressin stimulates cAMP production in the distal nephron and collecting ducts by acting on vasopressin V2 receptors [32]. Vasopressin V2 receptor antagonists (OPC-31260 and tolvaptan) have been effective in reducing cAMP levels in kidney epithelial cells and cystogenesis in several PKD models [33–35]. A number of clinical studies investigating the effect of tolvaptan in ADPKD have been completed or are currently active under the Tolvaptan Efficacy and Safety in Management of PKD and Outcomes (TEMPO) program [36]. The results from phase-2 studies suggest that tolvaptan is well-tolerated in most ADPKD patients at a dose to control urine osmolality <300 mOsm/kg [36] with water diuresis and thirst as predictable side effects. A large multicenter randomized placebo-controlled trial with tolvaptan in patients with a TKV of >750 ml will report in 2012 [36]. It is worth noting that V2 receptors are not expressed in the liver and therefore V2 receptor antagonists are unlikely to be effective for PLD [30].

Table 2. Ongoing clinical trials for ADPKD

| Study drugs | Study design | Treatment duration months | Eligibility (renal function) | Estimated enrollment | Outcome measures | Estimated completion date | Clinical trials Gov identifier |
|--|---|---------------------------|---|----------------------|---|---------------------------|--------------------------------|
| Pravastatin ¹ | Randomized, double-blind, placebo-controlled (phase 3) | 36 | normal | 100 | TKV (MRI) LV mass index Urinary albumin excretion endothelial-dependent vasodilation | April 2011 | NCT00456365 |
| Bosutinib | Multicenter, randomized, double-blind, placebo-controlled (phase 2) | 24 | TKV ≥ 750 cm ³ and eGFR ≥ 60 | 275 | Safety endpoints Annualized rate (%) of TKV and rate of eGFR decline | March 2018 | NCT01233869 |
| Tolvaptan (TEMPO 3/4 Trial) | Multicenter, double-blind, placebo-controlled, parallel-arm (phase 3) | 36 | TKV ≥ 750 cm ³ and eGFR ≥ 60 | 1,500 | Renal volume Hypertension, renal pain, albuminuria and renal function | March 2012 | NCT00428948 |
| Lisinopril and Telmisartan (HALT PKD) ¹ | Multicenter, randomized, double-blind, placebo-controlled (phase 3) | 48–72 | eGFR >60 (study A); eGFR 25–60 (study B) | 1,018 | Study A: TKV Study B: Time to 50% reduction of baseline eGFR, ESRD (initiation of dialysis or preemptive transplant), or death | April 2013 | NCT00283686 |
| Somatostatin | Randomized, single-blind, placebo-controlled (phase 3) | 36 | GFR >40 | 78 | TKV, renal intermediate and parenchymal volume (MRI) | June 2011 | NCT00309283 |
| Triptolide | Randomized, open-label (phase 2) | 36 | GFR >30 | 150 | TKV and eGFR | June 2011 | NCT00801268 |

eGFR = Estimated glomerular filtration rate; LV = left ventricle; TKV = total kidney volume; TLV = total liver volume.
¹ Not mechanism-based studies.

Increasing water intake could be beneficial in ADPKD by suppressing plasma arginine vasopressin levels. This strategy was effective in the PCK rat model [37]. A pilot study has shown that decreased urine osmolarity can be achieved in ADPKD patients by increased water intake [38].

HALT-PKD Studies

Standard blood pressure control remains a practical recommendation for PKD patients not only for kidney protection but also for limiting the extrarenal complications of ADPKD. Hypertensive subjects have a greater annual increase in kidney volume than normotensive subjects [39, 40] and an increased prevalence of left ventricular hypertrophy, ischemic heart disease and stroke [41]. Although the renin-angiotensin-aldosterone system is activated in ADPKD patients with cyst expansion, data from late-stage ADPKD patients (mean serum creatinine 3.0 mg/dl) suggest that the role of angiotensin-converting enzyme (ACE) inhibitors in slowing kidney disease progression remains uncertain [42]. The potential benefits of rigorous ($\leq 110/75$ mm Hg) versus standard ($\leq 130/80$

mm Hg) blood pressure control with combination lisinopril and telmisartan versus lisinopril monotherapy on kidney disease progression in ADPKD is being examined in the ongoing HALT-PKD study [40]. TKV (as assessed by MRI) and eGFR will be used as outcome measures in this study, which will recruit both early (eGFR >60 ml/min/1.73 m²)- and advanced (eGFR 25–60 ml/min/1.73 m²)-stage ADPKD patients.

Pravastatin

Hypertension and cardiovascular disease are common in patients with ADPKD. An ongoing phase-3 trial is being conducted to assess the effect of pravastatin treatment on renal and cardiovascular disease outcomes in children and young adults aged 8–22 years with ADPKD who are receiving lisinopril [43]. It is hoped that early intervention will be effective in reducing cardiovascular morbidity and mortality in ADPKD.

Bosutinib (SKI-606)

Inhibition of Src activity with the Src/Abl tyrosine kinase inhibitor SKI-606 resulted in a reduction in renal

Table 3. Candidate drugs for ADPKD tested in preclinical studies

| Compounds | Signaling pathways | Models | Results | Ref. |
|--|--|--|--|------------|
| Vasopressin V2R antagonist | Inhibit cAMP-stimulated fluid secretion and cell proliferation | pcy mice PCK rat Pkd2 ^{WS25/-} | Decreased renal cystic index; decreased proliferation; improved renal function | 33–35 |
| Triptolide | Restore intracellular Ca ²⁺ signaling and inhibit cell proliferation | Pkd1 ^{-/-} mice (from E10.5) Pkd1 ^{lox/-} ;Ksp-Cre mice Pkd1 ^{lox/lox} ;Mx1Cre mice | Decreased renal cystic index; decreased proliferation; improved renal function | 11, 47, 48 |
| Roscovitine | Inhibit cyclin-dependent kinases (cdk) and cell proliferation | cpk mice jck mice | Decreased renal cystic index; decreased proliferation and apoptosis; improved renal function | 45 |
| Glucosylceramide inhibitor | Inhibit glycosphingolipid synthesis; inhibit Akt-mTOR signaling | Pkd1 conditional knockout mice (Pkd1 ^{tm1Gztn} allele); jck and pcy mice | Decreased renal cystic index; decreased proliferation and apoptosis | 49 |
| Sorafenib | Raf-inhibitor; inhibit cell proliferation | ADPKD cells in 3D culture | Decreased cyst growth in 3D culture | 52 |
| Pioglitazone Rosiglitazone | PPAR- γ receptor agonist; inhibit CFTR-driven fluid secretion; inhibit mTOR and ERK | PCK rat | Decreased liver and renal cystic index; decreased proliferation and fibrosis | 55, 56 |
| Metformin | AMPK agonist; inhibit mTOR and CFTR chloride channel | Pkd1 ^{lox/-} ;Ksp-Cre mice | Decreased renal cystic index; decreased proliferation | 69 |
| CFTR inhibitors Tetrazolo-CFTRinh-172 Ph-GlyH-101 | Inhibit CFTR | Pkd1 ^{lox/-} ;Ksp-Cre mice | Decreased renal cyst number, kidney weights and serum urea and creatinine concentrations | 61 |
| KCa3.1 potassium channel blocker TRAM-34 | Inhibit K ⁺ efflux; indirectly inhibit CFTR | MDCK and ADPKD cells in 3D culture | Inhibit Cl ⁻ currents and cyst formation in 3D culture | 63 |
| HDAC inhibitors Trichostatin A (TSA) Valproic acid (VPA) | Inhibit HDAC, modify chromatin and gene expression | Pkd1 ^{lox/lox} ;Pkh1-Cre mice Pkd2 ^{-/-} mouse embryos Zebrafish pkd2 morphants | Improved cystic index, blood urea nitrogen, and percentage of cyst formation | 67, 68 |
| Calcimimetics R-568 | Stimulate calcium-sensing receptor to increase intracellular Ca ²⁺ | Male Cy/+ rat | Improved kidney weight, cystic index, fibrosis score and blood urea nitrogen | 70 |

AMPK = AMP-activated protein kinase; CFTR = cystic fibrosis transmembrane regulator; mTOR = mammalian target of rapamycin; PPAR- γ = peroxisome proliferator-activated receptor γ .

cyst formation and biliary ductal abnormalities in the bpk and PCK rodent models. This was associated with reduced activation of EGF receptor, B-Raf and ERK [44]. A phase-2 trial is being conducted to test the safety and efficacy of Src inhibition in ADPKD patients.

Drugs in Preclinical Studies

Roscovitine

Roscovitine, a cyclin-dependent kinase (CDK) inhibitor, has been shown to initiate cell cycle arrest, reduce apoptosis and inhibit cystic disease in the jck and cpk

mouse models of PKD [45] (table 3). The molecule has a long-lasting effect and can be given as pulse treatment. Roscovitine has been reported to suppress cAMP and aquaporin 2 in the cystic kidneys of jck mice [46]. Its effectiveness in orthologous models has not yet been established.

Triptolide

Triptolide is a natural compound derived from the traditional Chinese medicine Lei Gong Teng. It was found to bind PC2 in vitro, restores cytosolic Ca²⁺ release (in a PC2-dependent manner) and leads to growth arrest in Pkd1^{-/-} murine kidney epithelial cells [11]. It has moderate

effects on cyst burden in *Pkd1*^{-/-} mice, kidney-specific *Pkd1*^{fllox/-};Ksp-Cre mice and an interferon-inducible *Pkd1*-floxed model [11, 47, 48]. These studies suggest triptolide could be a potential treatment for ADPKD. A phase-2 trial of triptolide for ADPKD is currently ongoing in China (table 2).

Glucosylceramide Inhibitors

A new approach to treating PKD may be by modifying renal glycosphingolipid metabolism. Inhibition of glucosylceramide (GlcCer) synthesis with Genz-123346 was shown to suppress cystogenesis in several mouse models including *Pkd1* conditional knockouts, *jck* and *pcy* by inhibiting Akt-mTOR-mediated proliferation and apoptosis [49]. GlcCer synthase inhibitors have been well tolerated in clinical trials for Gaucher's disease, so they may prove to be suitable for further clinical development as lifelong treatments for ADPKD [50, 51].

Sorafenib

B-Raf plays a central role in cAMP-dependent activation of ERK activity and cell proliferation in human ADPKD cyst epithelia [12]. Sorafenib is a nonselective Raf inhibitor that blocks cAMP-dependent activation of B-Raf and ERK signaling. It has been reported to block stimulated proliferation and 3D cyst growth of human ADPKD cystic cells [14, 52]. Sorafenib has been approved for the treatment of advanced renal cell and hepatocellular carcinomas and may therefore prove to be effective for both kidney and liver cystic disease [53].

Thiazolidinediones

Pioglitazone and rosiglitazone are PPAR- γ (peroxisome-proliferator-activated receptor- γ) agonists that were initially developed for the treatment of type-2 diabetes mellitus. However, they have been shown to have many other effects [54] including moderate effects on cystic disease in several PKD models [55–58].

Several potential mechanisms of action have been proposed. In an MDCK subclone with principal cell features (MDCK-C7), rosiglitazone decreased CFTR mRNA and vasopressin-stimulated Cl⁻ secretion [59]. Similarly, pioglitazone inhibits kidney and liver cyst growth in the PCK rat by inhibiting CFTR-driven ion and fluid secretion [55, 56]. Maternally administered pioglitazone increased postnatal survival of *Pkd1*^{-/-} embryos with an associated reduction in renal cystic burden possibly by restoring Wnt/ β -catenin signaling [57]. In the MDCK cyst model, rosiglitazone exerted potent inhibitory effects on cyst expansion by blocking proliferation and disrupting

both planar and apicobasal polarity, the latter by altering Cdc42 localization and activation [60]. In the Han:SPRD rat, rosiglitazone delayed renal failure but at the expense of cardiac enlargement probably due to excessive rosiglitazone-mediated renal sodium reabsorption [58]. Overall, these results suggest that PPAR γ agonists have moderate anti-cystogenic properties. Their future development as treatments for human ADPKD are however likely to be limited by the increasing recognition of their cardiotoxicity (heart failure, cardiac death) in certain patient subgroups.

Small-Molecule CFTR Inhibitors

Screening of 32 analogues of the thiazolidinone and glycine hydrazide classes of small-molecule CFTR inhibitors in the MDCK cyst model led to the identification of two highly effective compounds (Tetrazolo-CFTRinh-172; Ph-GlyH-101) [61]. Further testing in *Pkd1*^{fllox/-};Ksp-Cre mice showed that they could inhibit cyst growth and preserve renal function without apparent effects on cell proliferation indicating that an anti-secretory strategy could be an alternative or parallel approach to anti-proliferative therapies [61]. One potential concern in the use of these compounds in man is the development of a cystic fibrosis-like pulmonary disease. However, this seems unlikely as the concentration of CFTR inhibitors is much lower in the lung than the kidney at least in rodents [62].

KCa3.1 Potassium Channel Blockers

In addition to being activated directly by cAMP, CFTR is also indirectly regulated by KCa3.1 channels since these maintain a negative intracellular membrane potential by mediating K⁺ efflux and thus driving apical Cl⁻ secretion [63]. TRAM-34, a specific KCa3.1 potassium channel blocker, has been shown to inhibit in vitro ADPKD cyst growth and could be an alternative to CFTR inhibitors to block fluid secretion [63]. Of interest, the orally active KCa3.1 inhibitor Senicapoc (ICA-17043) has been shown to be safe in phase-2 clinical trials in sickle cell anemia patients and is also being evaluated as a potential new treatment for asthma [64, 65].

HDAC Inhibitors

HDAC inhibitors have been shown to exert potent anticancer activities inducing cell cycle arrest and apoptosis by inducing the accumulation of hyperacetylated histones and modifications of specific chromatin domains [66]. Trichostatin A (TSA), a pan-HDAC (histone deacetylase) inhibitor, was found to inhibit cyst formation in

pkd2-deficient zebrafish and *Pkd2*^{-/-} mouse embryos [67, 68]. Further testing showed that a class I HDAC inhibitor, valproic acid could suppress kidney cyst formation in *Pkd1* mutant mice by inhibiting proliferation and apoptosis [67].

Metformin

Metformin, an activator of AMP-kinase (AMPK), has been shown to reduce renal cystogenesis in two murine models [69]. It is interesting to note that both CFTR and mTOR are negatively regulated by AMPK-mediated phosphorylation. Metformin is already widely used in the treatment of type-2 diabetes mellitus. Although the potential risk of lactic acidosis precludes its use in late-stage ADPKD, it may play a role in the early-stage ADPKD if future clinical trials prove positive.

Calcimimetics

Defective intracellular Ca²⁺ regulation due to mutations in PC-1 and PC-2 may alter cAMP signaling in favor of proliferation [70]. The calcimimetic R-568, an allosteric modulator of the calcium-sensing receptor, was shown to inhibit the late-stage increase in renal cystic volume and development of interstitial fibrosis in the Han:SPRD rat [70]. However, R-568 had no effect on cystic burden in two other models, the *Pkd2*^{WS25/-} mouse and the PCK rat [71]. A significant reduction in renal fibrosis was detected in the PCK rat suggesting a possible benefit in late-stage ADPKD [71].

Overall Perspectives

In 1841, Pierre Rayer, one of the first physicians to recognize the pathological features of polycystic kidney disease (PKD), wrote that ‘The cystic degeneration of the kidney, where it can be detected or recognized during life, is an illness without cure’. 170 years later, the first clinical trials attempting to alter the natural history of this disease have recently been reported. Despite the negative results from the first trials with mTOR inhibitors, there remains great optimism that discovery of an effective treatment for ADPKD is just a matter of time. Indeed, there is now a long list of potential treatments for ADPKD arising from a wealth of preclinical studies. Nonetheless, there remain several hurdles that need to be overcome. First of all, the early trials have indicated the need for additional or better biomarkers for disease progression apart from MRI [72]. Arguably, there is also a need to develop experimental models that better mimic human disease. There is a need to systematically compare and contrast different models to find ones that most closely mirror human disease but in a time-efficient manner. Thirdly, combination or pulse therapies may need to be tested to maximize treatment benefits while minimizing side effects. Since the majority of patients are well prior to the onset of ESRD, the emphasis must be to develop a safe and effective lifelong treatment. Finally, more careful genetic and phenotypic definition of patient subgroups could help select those who respond better to different treatments.

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Editorial Comment

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The review by Chang and Ong provides readers with a comprehensive and up-to-date critical appraisal of mechanisms and treatment of autosomal dominant polycystic kidney disease (ADPKD). It is quite impressive how far and how quickly the understanding of the pathophysiology of this condition is impacting on therapies to slow progression of this relatively rare but important and potentially devastating kidney condition. It seems that ADPKD may be a 3-hit condition, a monogenic disorder triggered by mutations to genes coding for PC1 or PC2 with a second hit allowing the expression of the phenotype, but also additional mutations to modifying genes such as HNF-1 β may affect the severity of the phenotypic expression. The range of therapies highlighted in the review and based on successful preclinical, experimental observations cautions nephrologists that rodent/murine models of chronic kidney disease (CKD) do not always successfully translate into humans with the corresponding condition. The review also cautions

against the putative value of surrogate markers of disease in nephrology; total kidney volume (TKV) in ADPKD was thought to correlate with function, yet interventions affecting TKV do not seem to translate into an improved rate of decline of glomerular filtration rate. Lessons for nephrologists from the ADPKD story so far are: (1) translation from the laboratory to the bedside can, with concerted effort, take place relatively quickly in CKD, (2) animal models of disease do not always accurately reflect the human equivalent, and (3) biomarkers and surrogate markers of disease should not be the target of interventions instead the hard endpoints of CKD progression and end-stage renal disease should be kept in focus. Finally, most clinical trials target a single ADPKD pathway. Perhaps progression in this condition will require a multitargeted approach. The ADPKD polypill combines a range of inhibitors of cell proliferation and transduction pathways: multitargeted therapy for a multigenetic disease?