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Novel Therapies for Polycystic Kidney Disease

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Summary

Autosomal dominant (AD) polycystic kidney disease (PKD) is a major cause of end-stage renal disease, with neither a cure, nor an approved treatment to slow its progression. In the past decade significant advances have been made in understanding the cellular signaling pathways disrupted in PKD. Understanding the changes in signaling pathways linked to mutations in PKD1 and PKD2 as well as other renal cystic genes led to preclinical trials and Phase II & III human trials to ameliorate PKD progression. Since PKD is a proliferative disease, some treatments are aimed at neoplastic cell proliferation (i.e. src and MAPK inhibition). PKD is also associated with decreased cellular calcium and increased cAMP, so other treatments targeted cellular Ca (i.e. calcimimetics and polycystin 2 agonists) or G-protein linked receptors (i.e. the vasopressin V2 receptor and somatostatin receptor inhibitors). Fluid secretion through the cystic fibrosis transmembrane conductance regulator (CFTR, a chloride channel) also contributes to disease progression and therapies blocking chloride secretion are also possible therapeutic agents. Significantly, the renin- angiotensin system is responsible, at least in part, for PKD associated hypertension, and drugs targeting this pathway are also being evaluated as therapies for ADPKD progression. Assessment of efficacy in humans with ADPKD is complicated by the slow progressive nature of the disease, but the CRISP imaging studies have provided important data on renal cystic enlargement over time. Based on numerous preclinical studies in rodent models, several human clinical trials are currently being performed, suggesting that a treatment to inhibit progression of ADPKD and other renal cystic conditions may be available in the near future.

HepatoRenal FibroCystic (HRFC) diseases include a number of inherited conditions including: polycystic kidney disease-PKD (both autosomal recessive-AR and autosomal dominant-AD), Nephronophthisis-NPHP, Bardet Biedl Syndrome-BBS, Meckel (a.k.a. Meckel-Gruber) Syndrome-MKS and Oro-Facial-Digital Syndrome-OFD1. The number of genes found for these conditions has dramatically increased in the past decade. Identification of the genes and understanding disease pathogenesis in various forms of HRFC disease has fueled the initiation of preclinical trials for treatments using rodent models. As ADPKD is the most prevalent of the renal cystic diseases, it provides the best opportunity to identify efficacious treatments. While the exact mechanisms have not been elucidated by which these mutant proteins actually cause the renal /liver pathology, various forms of cystic disease share many commonalities in pathways and great strides have been made in uncovering contributory pathways. A central common theme is that the protein products for most of these renal cystic genes are found in cilia, basal bodies or centrosomes. Collectively the 30- plus genes causing renal cystic pathology have been called renal ciliopathies [1]. It is currently unclear how these hair-like projections on the apical surface of an epithelial cell actually cause the morphologic changes resulting in cyst formation. However, many different cellular signaling pathways have now been linked to cilia and which have been implicated in renal cyst genesis or progressive enlargement of the cysts. Hallmarks of renal cystic diseases include: a) increased cell proliferation, b) increased apoptosis, c) increased fluid secretion into the cystic space, d) increased connective tissue expression and fibrosis, e) altered state of differentiation, f) inappropriate localization of membrane-bound proteins (transporters and channels), g) altered cellular responses to certain stimuli (i.e. cAMP), and h) altered expression of a diverse group of mRNAs and proteins. This knowledge, albeit incomplete, has provided sufficient data to begin to develop treatments for these renal cystic conditions. In the following sections we will outline the general signaling pathways targeted in HRFC diseases, discuss results from animal studies and the status of human trials.

Growth Factors and Inhibitors of Cell Proliferation

Renal and biliary epithelial proliferation is critical for the formation and expansion of renal cysts. Since early in the disease, cyst burden is a relatively small percentage of total tissue mass, some consider that renal cystic disease is a benign type of neoplasia [2], suggesting that without the fluid, cysts would be small adenomas. Therefore, agents that can be used to treat the cell proliferation in carcinoma might similarly be effective against PKD. Cancer chemotherapies that have been tried in rodent renal cystic disease have focused on growth factors and their receptors (Figure 1) such as EGF receptor tyrosine kinase [3,5] ErbB2 [6,7] and the VEGFR2 [8-12]. Growth factor pathways presumably work through stimulation of Src and therefore Src inhibition can ameliorate PKD cystic pathology in rodent models and the stimulation of MAPK [13].

Epidermal Growth Factor Receptor (EGFR)

While there was a dramatic improvement in PKD pathology with the EGFR tyrosine kinase (TK) inhibitors in studies conducted in a few rodent models, the treatment did not succeed in the orthologous

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PCK rat model of ARPKD [14]. In addition, very early treatment of rodent PKD models with EGF (in cpk [15] and bpk [16] mice) was actually beneficial. EGFR TK inhibitors also have side-effect profiles that made this treatment potentially unsuitable for long term use at normal antineoplastic dosages. However, combined with other agents, it may be possible to use these agents at a more reduced dosage. ErbB2, a truncated EGFR- like protein, has been very valuable in treating breast cancer, and may ameliorate renal cystic pathology. Generally, care must be taken when using anti- neoplastic drugs for PKD as they would probably be needed for a very prolonged period of therapy (i.e. decades) and historically drugs approved for use in cardiovascular and renal diseases have been required to have low side effect profiles.

Human trial: Pfizer Inc has just initiated a Clinical trial for their receptor kinase inhibitor Bosutinib (SKI-606, Table 1). This trial was initially designed to target Src (based on Sweeney et al., 13), and the increase in MAPK activation. While this kinase inhibitor is not necessarily specific [17], some of the other kinases it inhibits have also been associated with PKD.

Vascular Endothelial Growth Factor (VEGF): Another recent approach for treating cancer, including renal cell carcinoma, is to block angiogenesis. It is known that renal epithelial cells in PKD have an increased expression of VEGF, possibly secondary to the reduction in renal blood flow associated with disease progression in ADPKD [described in the CRISP Study, 18]. Alternatively, VEGF could directly stimulate vascular cell proliferation and targeting it may inhibit cell growth. Inhibiting VEGF- induced angiogenesis could reduce blood flow to cystic regions of the kidney, impeding the cyst growth. VEGF-R2 antagonists and other anti-angiogenesis approaches have been successful at inhibiting rodent renal cystic progression in both liver and kidney [11,12]. Human VEGF polymorphisms may also contribute to the development of CKD [8]. While these findings are intriguing, it should be noted that blocking the VEGFR2 in 2-3 week mice actually stimulated the development of renal cysts [19]. The exact mechanism of VEGF-induced progression of cystic disease is unclear but may be via stimulation of hypoxia inhibitory factor-HIF and ERK [20]. It is unclear at this time, if any anti-angiogenesis clinical trials for PKD are being pursued.

Tumor necrosis factor-alpha (TNF-α): utilizes a different pathway from other growth factors discussed above. It appears that TNF-α disrupts polycystin 2 through increased expression of FIP2, a scaffolding protein that binds polycystin 2 in murine PKD2+/- kidneys [21]. Treating pkd2+/- embryonic kidneys with TNF-α stimulated cyst formation and inhibition of TNF-α was effective at preventing cystic disease in postnatal pkd2+/- mice [22,23]. TNF-α administration has also been associated with significant amelioration of renal cystic pathology in a non-orthologous murine model of ARPKD [24]. At present, it is unclear what role TNF-α plays in the development or progression of polycystic kidney disease in rodent models, or human forms of PKD.

Oncogenes: Renal cystic epithelial cells over-express several oncogenes, including *c-myc*. The fact that *c-myc* transgenic mice develop cystic kidneys [25] suggests that this oncogene (and/or others) may contribute to PKD progression in inherited forms of cystic disease. Treatment of the cpk murine model of ARPKD with a morpholino antisense oligonucleotide to *c-myc* was able to slow the progression of the renal pathology [26]. An antisense oligonucleotide approach has not been further explored.

Drug	Phase	Company (Institution)	Condition Assessment	ClinicalTrials.gov Identifier	Reference for **Results**
Tolvaptan (Vasopressin V2 Receptor Antagonist)	TEMPO 2/4 TEMPO 3/4	International (Otsuka Pharma)	ADPKD Kidney Volume	NCT00413777 NCT00428948	57
Sirolimus (mTOR inhibitor)	Phase 3 SUISSE Study	University of Zurich	ADPKD Kidney Volume	NCT00346918	42
	Phase 2 SIRENA Study	Mario Negri Inst.	ADPKD Kidney Volume	NCT00491517	41
	Phase 1-2	Cleveland Clinic	ADPKD GFR	NCT00286156	
	Phase 2-3	Mayo Clinic (Wyeth)	ADPKD Liver Volume		39
Everolimus (mTOR inhibitor)	Phase 3	Multicenter (Novartis)	ADPKD Kidney Volume	NCT00414440	43
Octreotide (Somatostatin	Phase 3	Mario Negri Inst.	ADPKD Kidney Volume	NCT00309283	61
Agonist)	Phase 2-3	Mayo Clinic (Novartis)	ADPKD-PLD Liver / Kidney Volume, eGFR	NCT00426153	60
Lanreotide (Somatostatin Agonist)	Phase 2-3	Radbound Univ. (Netherlands)	ADPKD-PLD Liver Volume	NCT00565097 NCT00771888	63
ACE inhibitor / ARBs	Phase 3 HALT-PKD	NIDDK	ADPKD Kidney Volume	NCT00283686	
Pravastatin (a statin)	Phase 3	Univ. of Colorado	ADPKD Kidney Volume	NCT00456365	
Tripotolide (polycystin 2 mimic)	Phase 2	Nanjing University	ADPKD Kidney Volume eGFR	NCT00801268	
Bosutinib (kinase inhibitor)	Phase 2	Pfizer	ADPKD	NCT01233869	
Water Intake		Kyorin University	ADPKD Kidney Volume & GFR	NCT01348035	**56**

Table 1: Current Human Clinical Trials for Assessing Efficacy for ADPKD.

Cyclin-dependent kinase (cdk) Inhibitors: Another line of study has targeted the antineoplastic capabilities of cdk inhibitors that trigger increased apoptosis in neoplastic cells (Figure 1). Disruption of the cdk-linked cell proliferation in PKD progression has been evaluated in several rodent models. Roscovitine, caused a long-lasting inhibition of the renal pathology progression in rodent PKD [27]. Because of long-lasting effects of cdk-inhibitors, they may only need to be used periodically [28], potentially making their use in treating PKD more feasible. Treatment with roscovitine also caused an increase in cystic epithelial differentiation back toward normal suggestive that it was acting on basic epithelial abnormalities associated with HRFC disease [29]. However, there are no human clinical trials at this time with roscovitine or any other cdk-inhibitor.

mTOR Inhibitors: The mTOR (mammalian target of rapamycin) signaling complex integrates growth factor signaling pathways with cellular energy supplies. For example EGF and insulin like growth factor signaling pathways may act in concert with or through the mTOR pathway (Figure 1). mTOR inhibitors are immuno-suppressive drugs used in transplant patients and are familiar to most nephrologists. This class of drug is also used as a chemotherapetic agent to treat renal cell carcinoma, especially those resistant to other treatments [30] .mTOR inhibitors also appear to have an anti-proliferative affect on renal epithelial cells, including renal cystic epithelia [31]. mTOR inhibitors have been used to treat a number of rodent models of PKD and have almost consistently been found to be efficacious [32-38]. However, in later stages of ADPKD, when renal function may be more limited, mTOR inhibitors may display their nephrotoxicity, precluding their further use.

Human trials: In transplant ADPKD patients receiving sirolimus, the cystic kidney volume was reduced [33] and sirolimus treatment reduced ADPKD cystic liver volume [39]. In another study, eight early ADPKD patients were treated for 6 months with an ARB plus sirolimus while the control group received just the ARB. The sirolimus arm of the study had a beneficial effect on limiting renal enlargement [40]. A similar study found a similar reduction in cystic enlargement but also documented preservation of normal appearing parenchyma [41]. Additional Human Phase III clinical trials using either sirolimus/rapamycin or everolimus have now been published (Table 1). While preclinical and a few clinical report found mTOR inhibitors to be effective at limiting cyst expansion, two new trials, one with sirolimus [42] and the other everolimus [43] showed no statistically significant benefit. When everolimus was used at the dose utilized for transplant patients, there was some amelioration of renal cystic pathology, however there were a significant number of adverse events and patient withdrawals from the study [42]. When sirolimus was used at a dosage lower than that used for transplant, there was no evidence of efficacy [43]. It is presently unclear whether mTOR inhibitors will ultimately be tried further. However, in light of preclinical data and some clinical trial findings, a lower dose used in a longer trial or at another phase of the disease (i.e. later, when the kidneys develop a tubulointerstitial fibrosis with an inflammatory infiltrate) may warrant further study. However given the propensity for higher dose therapy to cause ischemic damage and fibrosis, it is likely that this class of agents will be relegated to limited use as a "salvage" therapy in patients in which progression to end-stage renal disease is highly likely.

Adenylyl Cyclase, cAMP and Calcium

The autosomal dominant PKD proteins, polycystins 1 & 2, were clearly implicated in the cilia associated generation of an increase in ionized calcium associated with the bending of the cilia in epithelial cells [44]. Cellular calcium is known to be lower than normal in PKD cells and adding calcium back normalizes the cell phenotype [45]. Polycystin 2 is a functional calcium channel associated with cilia and
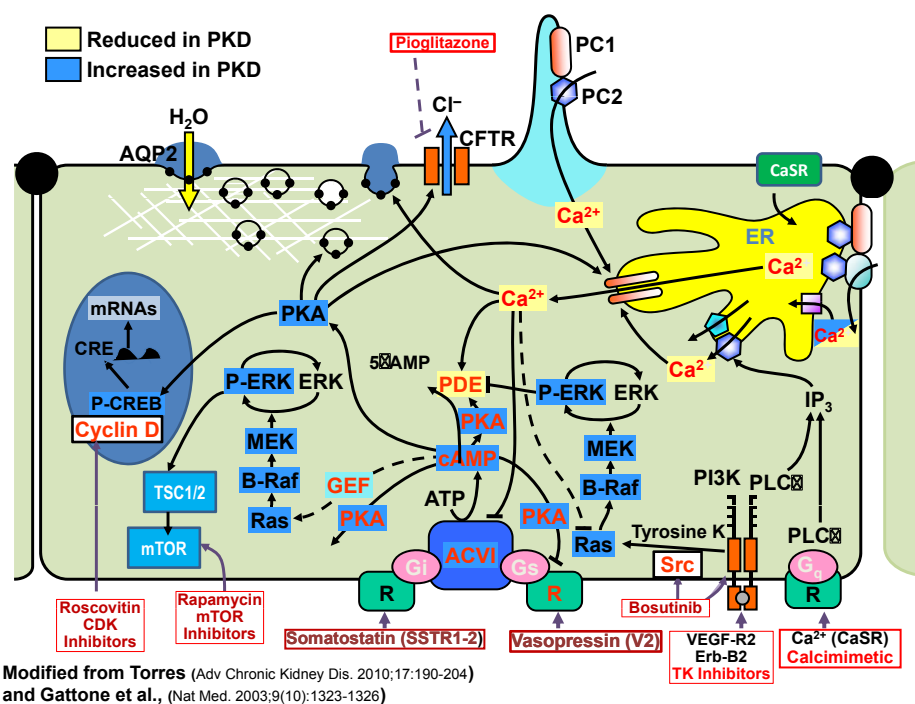

Figure 1:

endoplasmic reticulum. Among the many actions of cellular calcium in renal epithelial cells is inhibition of adenylyl cyclase (responsible for the generation of cyclic adenosine monophosphate (cAMP) from ATP) and the calcium dependence of a phosphodiesterase critical for the degradation of cAMP to its noncyclic form (Figure 1). G protein receptors can act to either stimulate adenylyl cyclase (Gs-linked receptors) generation of cAMP or inhibit the adenylyl cyclase (Gi-linked receptors). Low cell calcium leads to reduced cAMP degradation and over-stimulation of Gs linked G-protein receptors causing an increase in cellular cAMP. In PKD, both increased production and decreased degradation of cAMP contribute to increased cellular cAMP which stimulates cystic disease progression.

G-Protein Receptors – Parathyroid Hormone receptor (PTHR1): Two of the main G-protein linked receptors in the kidney are the PTH1R for parathyroid hormone and the V2R vasopressin receptor. PTH is an important hormone in all forms of chronic kidney disease (CKD) since serum concentrations increase quite early as renal function is diminishing. Treatments to reduce the secretion of PTH include phosphate binders and calcium sensory receptor (CaSR) agonist. The PTH1R is found in multiple tubule segments and treatment of the Cy/+ rat model of ADPKD with a calcimimetic, R-568, late in the disease inhibited late stage progression of the cystic kidney as well as the elevated PTH levels from CKD-induced secondary hyperparathyroidism [47]. However, there are conflicting reports on the efficacy of R-568 in other rodent models and different stages of renal cystic disease [48,49]. In the pcy mouse model of NPH, R568 ameliorated the cystic pathology and decreased renal cAMP level [49]. Notably many chronic kidney disease patients, including those with various renal cystic diseases are placed on calcimimetics to control secondary hyperparathyroidism. Therefore, if calcimimetics help control cystic disease progression, especially late in disease, there may be an additional benefit to prescribing calcimimetics as CKD develops in those with PKD. At this time there does not appear to be a clinical trial planned for the use of calcimimetics for PKD.

Gs Linked-Protein Receptor – Vasopressin Receptor (V2R): A major Gs-linked receptor in kidney is the vasopressin receptor (V2R) on collecting ducts, a major tubule segment in many, if not most, autosomal recessive forms of renal cystic disease (i.e. ARPKD, NPHP, MKS etc.). The use of the vasopressin V2R antagonist OPC31260 and OPC41061 (Tolvaptan) has been shown to be efficacious in four rodent models of renal cystic disease, with three of these models being orthologous to human renal cystic diseaseS [pcy-NPHP3 and pkd2ws25/- mice and Pck-PKHD1 rats, 50-53]. Crossing the PCK rat with the Brattleboro rat that lack vasopressin, almost totally inhibits cyst formation [54]. This last study reinforces the potential importance of vasopressin and its V2R in HRFC / PKD progression. The V2R normally causes the collecting duct to be permeable to the tubular fluid /primitive urine, causing water movement from the lumen of the collecting duct to the interstitium, making urine more concentrated. However, most, if not all, forms of renal cystic disease are associated with a urine concentration defect so the increased water loss may help trigger a compensatory increase in vasopressin secretion to stimulate water reabsorption by the kidney. If rats are made to drink excessively to compensate for the water loss, AVP secretion is suppressed, inhibiting both the stimulation of V2R and cystic disease [55].

Human trials: Currently, patients with PKD are encouraged to drink a sufficient amount of water to curb thirst. A clinical study sought to have ADPKD patients drink sufficiently to lower their urine osmolarity, however, lowering urine osmolarity appears to have been the major goal without assessing the effect on disease progression [56]. A small Open Label Phase III Clinical trial evaluated the tolvaptan's efficacy in inhibiting the ADPKD disease progression (renal cystic enlargement) and found that treatment limited cyst growth and kidney enlargement [57]. Currently a placebo controlled Phase III / IV (Tempo ¾) clinical trial is underway, evaluating the efficacy of tolvaptan. Tolvaptan, a vasopressin V2 receptor antagonist is currently being used in a large Phase III/IV clinical Trial ending in 2012 (Table 1).

Gi Linked-Protein Receptor –Somatostatin Receptors: A major class of Gi-linked receptor family are the somatostatin receptors (SSTs) that act to inhibit adenylyl cyclase and cAMP generation (Figure 1). The somatostatin agonist Octreotide was shown to be effective in a small group of patients in 2005 [58], which then spurred significant interest in its evaluation in an animal model system [59].

Human trials: Recent clinical trials have found SST agonists to be efficacious in ameliorating the growth of liver in ADPKD / PLD (polycystic liver disease) [60-63]. Data thus far has clearly found Octreotide to be safe and effective in treating polycystic liver disease.

Chloride secretion: The Cystic Fibrosis Transmembrane Regulator (CFTR) chloride channel is thought to be a major factor in the secretion associated with the development and enlargement of renal cysts (Figure 1). PKA and cAMP are involved in the regulation of CFTR activity [64]. CFTR inhibition is another recent focus of research for agents that inhibit renal cystic disease. Small molecule inhibitors of CFTR inhibited the development of PKD in a rodent model [65,66]. PPAR-gamma activators have been shown to inhibit vasopressin mediated chloride transport via CFTR [67] and have been shown to inhibit renal cystic disease in rat models of PKD [68-70]. Interestingly, renal cystic disease appears to be less severe in humans who inherited both ADPKD and cystic fibrosis [71,72] further implicating the CFTR chloride channel in the secretion of cyst fluid and contributing to the progression of PKD. There are no clinical trials as yet for the use of CFTR inhibitors or PPAR-gamma agonists for the treatment of human forms of renal cystic disease. AMP activating protein kinase (AMPK) inhibits both mTOR and CFTR. Additionally, AMPK stimulating drugs like Metformin are already in use in for the treatment of diabetes. A recent study using Metformin disease in two mouse models of ADPKD found it to be efficacious in inhibiting the progression of cystic [73]. PPAR gamma agonists and AMPK stimulating drugs are already available hypoglycemic agents for diabetes. Since all current clinical trials exclude diabetic patients with ADPKD, there may be an opportunity to treat diabetics with ADPKD with either PPAR gamma agonists or Metformin as they may be efficacious for both the diabetes as well as the renal cystic disease.

Enhance Cellular Calcium: A basic abnormality in most forms of cystic disease is a low cell calcium concentration. Treating with a calcium channel blocker has been shown to make the renal cystic disease worse in a rat model [74]. Several preclinical trials that inhibited the cystic disease also up-regulate cellular Ca. Triptolide directly stimulates the intracellular calcium release through the polycystin 2 associated calcium channel and has been found to inhibit cyst development in murine PKD models [75-77].

Phosphodiesterase Degradation of cAMP: Cyclic AMP is a second messenger whose cellular half-life is regulated by both its generation by adenylyl cyclase and its degradation to AMP by phosphodiesterase-PDE [78]. The use of G-protein receptor targeting was discussed

earlier. The collecting duct form of phosphodiesterase-PDE is calcium dependent so the reduction in calcium ions in cystic epithelial cells may cause a reduced activity of PDE leading to a longer half-life of cAMP. New phosphodiesterase (PDE) activators inhibit *in vitro* cyst formation by MDCK cells. This inhibition appears to be due, at least in part, to inhibition of chloride secretion into the cysts by the CFTR chloride channel [79]. Protein kinase A (PKA) is activated by cAMP, therefore, treatments aimed at G-protein receptors would affect PKA stimulated pathways. The increased cAMP amplify the response by PKA sensitive pathways in renal cells including: vasopressin stimulated- synthesis and phosphorylation of aquaporin 2, stimulation of Na-K-2Cl, ENaC and urea transporter 1; parathyroid hormone receptor 1 inhibition of NHE3; and adrenergic stimulation of renin secretion. PKA also phosphorylates CREB (cAMP response element binding protein) that can activate transcription by binding to CRE (cAMP response element in the promoter region of genes). Cystic kidneys have an increased amount of CREB-1 [78]. Increased CREB-1 activity could activate or inhibit the transcription of numerous additional genes that can change the cellular phenotype even further. Notably, inhibition of the vasopressin V2R in PKD2^ws25/- mice led to a reduction in cAMP as well as a reduction in mRNA misexpression of V2R and AQP2 mRNA, genes who have CRE in their promoter regions [52]. This supports the idea that increased PKA phosphorylation may play a role in the abnormal gene expression that is so evident in various rodent models and human PKD [80]. Aside from reducing excessive stimulation of Gs-linked G-protein receptors, another approach to limiting the influence of cAMP and over activity of PKA is to increase cAMP degradation. Mice with disruption of PKA activity had a decrease in age related renal lesions and other changes associated "with healthy aging" [81]. Therefore, excessive activity of PKA appears to play a role in progression of PKD, but may also stimulate premature aging of non-cystic kidney. PKA can also phosphorylate Src which can stimulate the MAPK cascade and as stated earlier, Src inhibition slowed PKD progression in both bpk and PCK rodent models of ARPKD [13].

MAP Kinase Cell Proliferation Pathway: Whether stimulated by growth factors or excessive cAMP, PKD-associated cellular proliferation still progresses through the mitogen activated proliferation kinase (MAPK) cascade (Figure 1). This cascade involves as series of kinases associated with cell proliferation, which is stimulated by several pathways such as growth factor receptor and Ras. Ras can phosphorylate Raf kinase which can then phosphorylate and activate MEK, which, in turn, phosphorylates and activates ERK (extracellular signal-regulated kinases). Renal phospho-ERK is elevated in essentially all rodent forms of PKD and correlates well with the proliferation of PKD epithelia and renal progression. Inhibition of ERK also inhibits the progression of PKD in rodents [82]. The MAPK pathway can also phosphorylate c-myc, a transcription factor that is elevated in PKD as described earlier. B-Raf participates in this cascade and B-Raf inhibition using Sorafenib also inhibited cyst growth in cultured cystic cells [83]. Curcumin, found in the spice tumeric, has antioxidant properties and, in cultures, reduced cyst formation by MDCK cells and embryonic kidney [84]. This treatment reduced much of the MAPK cascade (B-Raf, p-MEK & p-ERK). Strikingly the MAPK cascade is critical to the proliferation of the cystic epithelial cells in cystic disease. Most therapies that have been effective in preclinical trials have also demonstrated a reduced activation of the MAPK pathway.

ACE inhibition, ARBs and Statins

ACE & ARBs: The hypertension in ADPKD appears to be, at least in part, renin dependent and renal cystic epithelial cells exhibit significant renin immunostaining [85]. Angiotensin converting enzyme (ACE) inhibition has also ameliorated the cystic disease in the Cy/+ rat model [86]. The hypertension in ADPKD has been associated with an increased serum renin leading to the use of ACE inhibitors and angiotensin receptor blockers (ARBs) to treat PKD-associated hypertension. In the PCK rat, an orthologous model of ARPKD, liver over-expresses ACE and has increased AII which was thought to be secondary to the increased TGF-β expression [87]. When PCK rats were treated with lisinopril, the proliferation, apoptosis and renal pathology was ameliorated with the elimination of the model's proteinuria [88]. The current HALT PKD study supported by the NIH (Table 1) is comparing the affects of an ACE inhibitor alone or in combination with an ARB in patients with ADPKD. However, a major aim of the HALT study is the tighter regulation of ADPKD-associated hypertension, and its effect on PKD progression. Another major class of drugs used to treat hypertension are calcium channel blockers-CCB. Since renal cystic epithelial cells have a reduced cellular calcium concentration, these agents need to be further investigated for their use in PKD since treatment of the Cy/+ rat with CCB accelerated the progression of the renal cystic disease [74]. There are many approaches for treating the hypertension associated with PKD which have been extensively studied and that data reviewed [89]. The control of blood pressure should effect both disease progression and development of renal demise.

Statins (HMG CoA reductase inhibitors): Serum lipid reduction has had a beneficial effect on various forms of chronic kidney disease and were shown to reduce the severity of the renal cystic disease in the Cy/+ rat model of PKD [90,91]. A 4 week trial of simvastatin increased effective renal plasma flow and GFR, apparently by an increased vasodilator effect of acetylcholine [92]. However, a two year clinical study using pravostatin had no significant effect on kidney function or urinary protein excretion in patients with ADPKD [93]. However, currently there is another clinical trial planned with pravastatin in ADPKD patients (Table 1).

Glycolipids in PKD: A number of years ago, a basic abnormality in cellular lipids was found in the cystic kidney of the cpk mouse with rapidly progressive ARPKD [94]. Very recently, it was found that glucosylceramide synthatase inhibitors had a profound inhibitory effect on the cystic disease in several rodent models of PKD [95]. This represents a very novel target for therapies for renal cystic diseases.

Summary of Therapies That are Most Likely to Progress of Human PKD Use

While there are a number of different pathways that are being explored for drugs for use in humans, it is not yet clear with strategy will result in therapies with acceptable long-term side effects. At present the leading candidate therapies aim to lower intra cellular cAMP. Vasopressin V2R antagonists and the SSTR agonists both are in clinical trials that are providing evidence of efficacy and are likely to be the first possible therapeutic agents to be used in ADPKD patients. As there are no vasopressin 2 receptors in liver and there is limited data on efficacy of SSTR in the kidney, there may need to be combination treatments to achieve efficacy in both principal organs affected in HRFC diseases like ADPKD. The most recent, disappointing, clinical studies with mTOR inhibitors suggest that pathway may not be enthusiastically supported for further clinical trials. The results of the clinical study clearly

point toward an incomplete understanding of this pathways role in PKD. Antineoplastic agents have an inherent problem for long-term usage since many tissues in the body utilize the targeted pathways for normal function and cell renewal. Antineplastic agents can also cause unacceptable side-effects in long term usage, unless they could be used intermittently as has been proposed for roscovitine. ACE-inhibitors, ARBs and calcimimetics are all used in ADPKD and CKD patients at present and if they have beneficial affects, their usage may be expanded to non-hypertensive patients and earlier stages of CKD. Targeting the CFTR runs the risk of generating some cystic fibrosis-like symptoms, however, there is considerable experience with PPAR-γ agonists and Metformin in diabetic patients and this may be a therapeutic option for treating the hyperglycemia in diabetic PKD patients who are presently excluded as a group from the ADPKD clinical trials.

Establishing Surrogate BioMarkers for Treatment Efficacy

PKD causes chronic kidney disease (CKD) which usually leads to the need for renal replacement therapy. However, CKD by definition is a prolonged process that takes decade to develop in PKD. As nephrons become dysfunctional by the developing cystic pathology, other nephrons compensate to retain a relatively normal renal function [96]. A number of factors can impact the progression of the PKD CKD including the presence of hypertension [97,98]. But pathological renal cystic enlargement is a feature that can be relatively easily assessed thanks to the data from the ongoing CRISP studies [99-102]. Renal enlargement has now become a central surrogate biomarker for treatment efficacy in all of current clinical trials (Table 1). However this biomarker has not yet been accepted by the Food and Drug Administration (FDA). At present eGFR is another biomarker that may be considered for FDA acceptance of clinical trial efficacy [103].

The CRISP Study has provided a wealth of information on renal cystic enlargement in ADPKD. Aside from the evaluation of cystic renal enlargement, the study has documented the differences between PKD1 and PKD2 disease is a difference in the number of cysts [100] and the changes in renal function, and renal blood flow with disease progression [18,101,102]. Still, renal size and/or cyst volume changes over time still appear to be the best biomarkers for PKD progression [104,105], at least while the kidneys are enlarging the most, i.e. young to middle age adults. Inhibition of renal enlargement is an excellent biomarker for treatment efficacy during the developmental phase of ADPKD. However, renal size eventually plateaus years before the development of azotemia. It may be difficult to develop biomarkers for initiating a treatment after the kidneys have already approached their maximal size. In a few studies in the pcy mouse model, it was possible to obtain positive treatment efficacy when treatment was initiated after the kidney enlargement was already about maximal [37,51]. Renal cystic enlargement may not be the best biomarker in patients with very large kidneys at the start of the trial. Renal blood flow changes may be a possibility biomarker in those circumstances and needs to be assessed in later stages of human ADPKD. In addition, *in vivo* imaging technology may need to develop the ability to assess functional parenchyma versus fibrosis in the regions between cysts. It is also critical that biomarker development research aims for validation based on criteria accepted by the FDA. Clearly, more biomarkers are needed for the assessment of chronic kidney diseases, including PKD.

In summary, basic scientific understanding of signaling pathways altered in PKD have allowed for the rapid identification of promising therapeutic interventions in PKD. Additional future promising avenues are gene therapy approaches, agents that might act as chemotherapy for cystic epithelia that leaves normal kidney cells intact and agents that inhibit fibrosis in kidneys. While the efforts to find a curative agent have not yielded fruit, clearly promising drug therapies that inhibit disease progression will be available in the near term.

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