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Review

Impacts of Metabolic and Mitochondrial Reprogramming on ADPKD Drug Targets and Repurposing

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Abstract

Autosomal dominant polycystic kidney disease (ADPKD) is a complex disorder characterized by the progressive development of renal cysts and systemic complications, including cardiovascular and metabolic comorbidities. Disease progression is linked to ADPKD-driven metabolic and mitochondrial reprogramming that exacerbates ADPKD pathophysiology by impairing central energetic pathways, including mitochondrial respiration and glucose, lipid, and amino acid metabolism. Recent studies have revealed that caloric intake interventions can attenuate disease progression; however, they are difficult to achieve and likely applicable only to those who are overweight. Therefore, a better understanding of the mechanisms that drive metabolic and mitochondrial reprogramming may foster the identification of novel ADPKD severity-modifying drug targets and/or drugs. Such drugs could synergistically complement the benefits of tolvaptan (the only US Food and Drug Administration (FDA)-approved ADPKD therapeutic), or serve as alternatives to it, as tolvaptan is costly and associated with idiosyncratic hepatotoxicity. Repurposing FDA-approved drugs could accelerate clinical testing and subsequent translation to practice by building on prior work to improve the traditional drug development pipeline. To facilitate identification of repurposed drugs for ADPKD, we review ADPKD-driven metabolic and mitochondrial reprogramming from the perspective of drug target identification for repurposing ADPKD therapeutics.

Keywords: autosomal dominant polycystic kidney disease; ADPKD; polycystic kidney disease; PKD; metabolic reprogramming; mitochondrial dysfunction; cystogenesis; Warburg effect; oxidative phosphorylation; drug repurposing; drug development; tolvaptan; pharmacokinetics; drug metabolism; *in silico*; drug targets; precision medicine

Background

Autosomal dominant polycystic kidney disease (ADPKD), the fourth leading cause of renal replacement therapy, is projected to affect around 12 million individuals worldwide.[1] Its manifestations are characterized by the formation of renal cysts and a subsequent progressive decline in renal function. Cysts seem to originate most often in the distal nephron. As abnormal cystogenesis-promoting epithelial cells proliferate, they separate from the parent nephron, secrete chloride-rich fluid, and alter the extracellular matrix.[2] The underlying cause of this process in most ADPKD cases involves a genetic defect in the *PKD1* (~80% patients with ADPKD) or *PKD2* (~15% patients with ADPKD) genes. These genes encode for polycystins 1 and 2 (PC1/PC2), respectively.[1] Many of their

downstream pathways have been identified; however, so far, no single pathway has been broadly accepted as the principal driver of cystogenesis.

Among pathways involved in renal cystogenesis, the most extensively studied are those associated with metabolic and mitochondrial reprogramming. These pathways can directly modify ADPKD pathophysiology by impairing crucial processes central to normal healthy kidney function.[3] In particular, ADPKD pathogenesis and progression revolve around energetic pathway alterations that impact glucose, amino acid, and lipid metabolism, along with mitochondrial respiration.[3] Genetic defects appear to play a role in these alterations. PC1, for example, directly and indirectly affects mitochondrial structure and function.[4] However, the mechanistic explanation is still not fully understood. Along with changes in other key cellular functions, these alterations can explain why ADPKD patients develop comorbidities associated with metabolic dysfunction, such as central obesity and insulin resistance[5], and the success of dietary interventions for symptomatic management.[3] Understanding metabolic reprogramming is therefore crucial for advancing ADPKD patient care and treatment options.

Tolvaptan became the first and only U.S. Food and Drug Administration (FDA)-approved therapeutic for ADPKD in 2018.[6] It is a vasopressin 2 receptor (V2R) antagonist, suggested to reduce the rate of renal function decline in ADPKD by ~30% on average. However, it is expensive (~$27,906 for a 30-day supply)[7], associated with idiosyncratic hepatotoxicity, and has a limited impact on extrarenal manifestations.[8,9] Alternative candidate therapeutics to tolvaptan have entered preclinical and clinical trials, but none have successfully received FDA approval to date. Because *de novo* drug development is expensive and time-consuming, it may take many years for new ADPKD therapeutics to be approved. High levels of phenotypic, gene locus, and allelic heterogeneity contribute to ADPKD complexity[10], further increasing drug development challenges and creating differences in drug biotransformation between individuals. Both of these challenges can be partially mitigated through drug repurposing. This approach leverages prior studies to reduce development costs and timelines, thereby increasing accessibility in drug research and addressing limitations in current ADPKD treatment options. To foster the identification of ADPKD therapeutics, we review evidence supporting metabolic and mitochondrial reprogramming as targets for ADPKD drug development, and its impact on identifying drug targets and repurposing ADPKD therapeutics.

Common Metabolic Diseases/Disorders Associated with ADPKD

Metabolic syndrome (MetS) describes a cluster of physiological, biochemical, clinical, and metabolic factors that notably increase the risk of cardiovascular diseases and type II diabetes mellitus (DM). Central obesity is the primary risk factor, but MetS diagnostic criteria also include insulin resistance, dyslipidemia, glucose intolerance, hypertension, inflammation, prothrombotic state, and microalbuminuria.[11] ADPKD patients have an increased association with multiple components of MetS, including increased waist circumference, fasting glucose levels, and dyslipidemia.[12,13] Notably, ADPKD patients with DM exhibit worse disease progression than patients with ADPKD alone. These individuals have higher body mass index, greater total kidney volume (TKV), earlier onset of hypertension, increased end-stage renal disease risk, and reduced life expectancy.[14] This increase in MetS components is critical to understand. The risk of developing DM in ADPKD is substantially greater post-transplant, and patients have an approximate threefold increased risk of developing new-onset diabetes after transplantation within the first year compared to non-ADPKD recipients.[15] ADPKD cohorts, however, appear to have a lower incidence of non-transplant-related DM.[16,17] Polycystic lesions may be responsible for the reduced risk by impairing renal gluconeogenesis and insulin degradation, causing hyperinsulinemic blood concentrations that lead to pancreatic beta cell fatigue, suppressing insulin production and release.[16] While studies have reported insulin resistance and hyperinsulinemia[18,19], there remains controversy on whether it is ADPKD-specific or a consequence of general renal disease.[20]

Dietary strategies have established benefits in ADPKD disease management. The prevalence of ADPKD-related metabolic disorders and reprogramming likely explains their efficacy.[3] Daily

caloric restriction (10-40%) in ADPKD mouse models (*Pkd1^RC/RC* and *PKD^cond/cond:Nes^Cre*) slowed kidney growth, improved kidney function, and, notably, in the 40% caloric restriction group, reversed disease progression.[21,22] A clinical trial on weight loss using caloric restriction or intermittent fasting in overweight and obese ADPKD patients showed reduced kidney growth correlated with body weight and visceral adiposity loss. Notably, patients with clinically meaningful weight loss achieved kidney growth cessation.[23] Overall, ADPKD is associated with metabolic derangements, and addressing them through dietary strategies, for example, is beneficial to disease progression.

Metabolic Reprogramming   in ADPKD

Metabolic reprogramming, or alterations in physiological processes in response to disease and stress, is prevalent in ADPKD (Figure 1). Most notable is the Warburg effect, a preferential shift to glycolysis and lactic acid fermentation in the presence of oxygen that drives cystogenesis by promoting flux into biosynthetic pathways and, thus, uncontrolled cell proliferation.[24] *In silico* analysis of human *PKD1* renal cysts identified pathway alterations favoring glucose uptake and lactate production, with key glycolytic enzymes and regulatory genes upregulated, and mitochondrial energy metabolism and pyruvate oxidation pathways downregulated. Additionally, there was increased expression of anoctamin 1, indicating elevated oxidative damage and impairment of antioxidant pathways, such as glutathione metabolism.[25] A chronic progressive model of PKD using heterozygous Han:SPRD (*Cy/+*) rats also had glycolytic gene upregulation and gluconeogenesis-related gene downregulation in cystic kidneys. Treatment with 2-deoxyglucose, a glycolytic inhibitor, attenuated disease progression and improved both renal function and cyst index.[26] ADPKD dysregulates oxidative phosphorylation (OXPHOS), contributing to reactive oxygen species (ROS) generation and oxidative stress.[27] Cystic mice (*Cys1^cpk*) and rats (Han:SPRD-*Cy*) had increased mRNA levels of the renoprotective and oxidative stress marker heme oxygenase (HO)-1, along with reduced antioxidant enzyme mRNAs, proteins, and activity levels.[28] Another study found HO induction mitigated renal cystogenesis in *Cys1^cpk* mice, while inhibition accelerated it, directly connecting oxidative stress to ADPKD pathophysiology.[29] Nitric oxide-related pathways may also increase levels of ROS and oxidative stress in ADPKD. Cystic kidneys of PCK rats exhibited elevated expression of NADPH-oxidase complex-4, likely leading to the observed reduction in endothelial nitric oxide synthase activity, along with upregulated ROS production, DNA damage, protein oxidation, and dysfunction in the mitochondria.[30] Renal oxidative stress increases cell proliferation, extracellular matrix synthesis, inflammatory cell infiltration, and apoptosis.[31] As such, oxidative stress is a likely measure of disease severity. This further highlights the pathogenic role of the Warburg effect in ADPKD cystogenesis and progression by impairing the pentose phosphate pathway (PPP) and mitochondrial respiration.

As noted above, amino acid and lipid metabolism are dysregulated in ADPKD patients. Similar to humans with ADPKD, mouse models of ADPKD demonstrated upregulation in glutaminase 1 (GLS1) GAC, a GLS1 isoform associated with glutaminolysis reliance in cancer, suggesting a similar phenomenon that supports hyperproliferation in ADPKD.[32] Glutamine and glutaminase are important for shuttling ammonia in the urea cycle[33], suggesting GLS1 upregulation in ADPKD may affect the urea cycle. Other key players in the urea cycle include argininosuccinate synthase 1 and arginine. Loss of argininosuccinate synthase 1 was found in both murine and human ADPKD tissue, along with an inverse relationship between arginine levels and cystogenesis[34], further highlighting urea cycle dysregulation in ADPKD. Given that the urea-to-plasma ratio in ADPKD patients is significantly associated with the rate of estimated glomerular filtration rate decline (P=0.02)[35], impairment in the urea cycle may have a pathogenic role in ADPKD progression. Lipid metabolism alterations are common in kidney disease and often present as increased fatty acid (FA) uptake, lipid accumulation, and the formation of lipid droplets.[27] For example, metabolomics identified acetylcarnitine, an important metabolite in mitochondrial *β*-oxidation, as a urine marker in *Pkd1^cko/cko* mice specific to disease progression.[36,37] Another study also demonstrated an intrinsic FA oxidation (FAO) defect in *Pkd1^cko/cko* murine cells lacking glycolysis alterations[38], suggesting ADPKD

mitochondrial reprogramming may be related to mitochondrial dysfunction, rather than a preferential shift to aerobic glycolysis. Reduced FAO often occurs alongside increased *de novo* FA synthesis (FAS) and is associated with rapidly proliferating cells that require membrane production.[37] *Pkd1* mouse embryonic fibroblasts and transcriptomic profiling of human *PKD1* kidneys exhibited a similar phenomenon with increased FAS and preferential glutamine use.[39] These findings suggest FAO impairment in ADPKD may not only highlight mitochondrial dysfunction, but additionally drive hyperproliferation in cystogenesis.
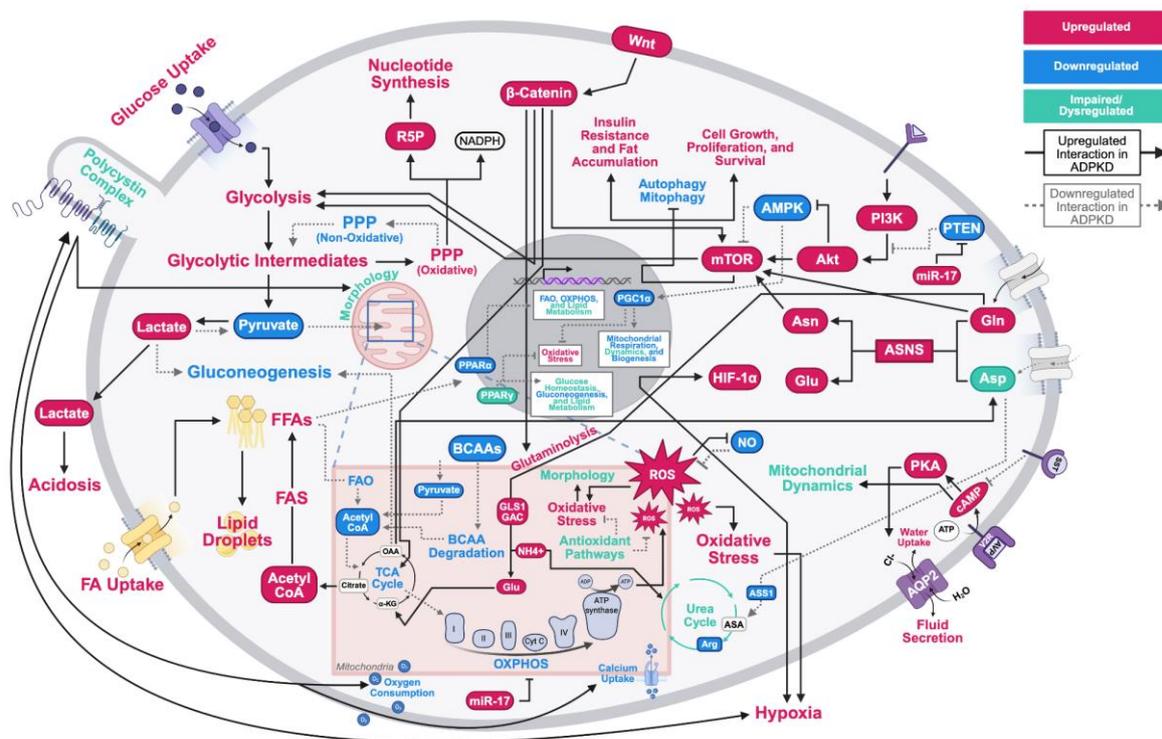
Figure 1. Metabolic and mitochondrial reprogramming in autosomal dominant polycystic kidney disease. This figure shows the interactions and consequences of the alterations discussed in this review. Upregulated molecules and processes are colored in red, and downregulated molecules and processes are colored in blue. Black solid lines denote upregulated interactions in ADPKD, and downregulated interactions are marked with gray dashed lines. *Abbreviations: Akt = protein kinase B; AMPK = adenosine monophosphate-activated protein kinase; Arg = arginine; ASA = argininosuccinic acid; Asn = asparagine; ASNS = Asparagine synthetase; Asp = aspartate; ASS1 = argininosuccinate synthetase 1; ATP = adenine triphosphate; AVP = arginine vasopressin; AQP2 = aquaporin-2; BCAA = branched chain amino acid; cAMP = cyclic adenosine monophosphate; Cl- = chlorine; CoA = carboxylic acid; Cyt C = cytochrome C; FA = fatty acid; FAO = fatty acid oxidation; FAS = fatty acid synthesis; FFA = free fatty acid; Gln = glutamine; GLS1 GAC = Glutaminase C; Glu = glutamate; H2O = water; HIF-1a = hypoxia-inducible factor 1-alpha; miR-17 = microRNA-17; mTOR = mammalian target of rapamycin; NADPH = nicotinamide adenine dinucleotide phosphate; NH4+ = ammonia; NO = nitric oxide; O2 = oxygen; OAA = oxaloacetic acid; OXPHOS = oxidative phosphorylation; PGC1a = peroxisome proliferator-activated receptor gamma coactivator 1-alpha; PI3K = phosphatidylinositol 3-kinase; PKA = protein kinase A; PPAR = peroxisome proliferator–activated receptor; PPP = pentose phosphate pathway; PTEN = phosphatase and tensin homolog; R5P = ribose-5-phosphate; ROS = reactive oxygen species; SST = somatostatin; TCA = tricarboxylic acid; V2R = vasopressin receptor 2; Wnt= wingless-related integration site; a = alpha; a-KG = alpha-ketoglutarate; β = beta; γ = gamma.*

ADPKD mitochondrial reprogramming is likely influenced heavily by PC1. In HEK293 and LLC-PK$_1$ cell models with modulated PC1 and PC2 expression, oxygen levels controlled the subcellular location and channel activity of polycystin complexes by interacting with Egl-9 Family Hypoxia Inducible Factor 3, the oxygen-sensing prolyl hydroxylase domain containing protein that hydroxylates PC1. Cells lacking PC1 exhibited reduced oxygen consumption and mitochondrial

calcium uptake, indicating that PC1 can directly regulate mitochondrial function in response to changes in cellular oxygen levels.[40] Given that ADPKD-associated cystogenesis aggravates regional hypoxia, pathogenic *PKD1* variants impairing PC1 function may exacerbate hypoxia-related inflammation and ADPKD progression. One study found that tissue oxygenation is inversely correlated with height-adjusted total kidney volume[41], potentially supporting a connection between PC1 and hypoxia. In *Pkd1^{ko/ko}* renal epithelial cells, a PC1 C-terminal fragment containing the cytoplasmic tail (CTT) translocated to the mitochondrial matrix. It restored some mitochondrial phenotypes, further confirming PC1 CTT interaction with both mitochondrial function and cellular metabolism. PC1 also modulates mitochondrial morphology, as demonstrated by studies in *Pkd1* mouse models and *PKD1* ADPKD patients, which found mitochondria had reduced elongation, mass, matrix electron density, and fusion proteins, along with increased mitochondrial network fragmentation, swelling with membrane whorls, and upregulated fission proteins.[4,42] PC2 potentially contributes to the changes in mitochondrial morphology as well, and one study found reduced PC2 expression affected mitochondrial calcium buffering, increasing mitochondrial network fragmentation. The authors proposed that PC2 regulates mitochondrial metabolism at mitochondrial-ER contacts.[43] In another study, truncating *PKD2* mutations altered mitochondrial morphology, resulting in a rounded phenotype and dilated cristae, and resembling the effects of a PC1 deficiency.[44] Overall, it is clear that both PC1 and PC2 have a role in mitochondrial function and may exacerbate ADPKD pathophysiology and progression, as the alterations described are indicators of mitochondrial stress in ADPKD[45], which directly enhances oxidative stress.

Established ADPKD Drug Targets

V2R, the main target for tolvaptan, is upregulated in ADPKD and contributes to cell proliferation, fluid secretion, and cystogenesis. Its activation increases cyclic adenosine monophosphate (cAMP) and protein kinase A, which promote aquaporin 2 membrane localization, increasing water reabsorption and fluid secretion.[46] Tolvaptan antagonizes V2R, reducing cAMP levels and thereby inhibiting cyst epithelial cell proliferation and fluid secretion. However, benefits are largely restricted to patients with rapidly progressing ADPKD (Mayo Class ≥ 1C) or to chronic kidney disease (CKD) patients who begin treatment in an early stage (CKD Stage $\leq$ 3A).[9] As such, alternative safe and effective therapeutics are desperately needed. Encouragingly, advances in understanding the metabolic underpinnings of ADPKD have created opportunities to explore potential drug targets and alleviate some of the challenges in ADPKD drug development. Here, we review both targets currently under development and those that could be studied in future analyses.

The mammalian target of rapamycin (mTOR) signaling pathway and its interactors are promising targets for addressing the consequences of the Warburg effect in ADPKD. The mTOR signaling pathway is hyperactivated in cystic lesions and promotes a metabolic shift from OXPHOS to glycolysis.[47] Increased mTOR activation is also suggested to increase insulin resistance and fat accumulation[48], potentially contributing to the prevalence of MetS in ADPKD. Together, the effects of mTOR upregulation may explain why rapamycin inhibition of mTOR complex 1 (mTORC1) attenuated cystic progression in an ADPKD mouse model.[49] The phosphatidylinositol 3-kinase (PI3K)/protein kinase B pathway activates mTOR, initiating cellular processes, including metabolic reprogramming.[47] As such, dual PI3K/mTOR inhibition may have potential in ADPKD over only rapalog inhibition of mTOR.[50] Asparagine (Asn) synthetase (ASNS) is upregulated in ADPKD and has been implicated in mTOR activation and the Warburg effect through Asn, which can stimulate mTORC1 to boost glycolysis.[51] ASNS inhibition in a slowly progressing ADPKD murine model drastically reduced TKV, proliferation, and cyst expansion, and rescued renal function.[52] Activating adenosine monophosphate-activated protein kinase, which in turn inhibits mTOR signaling and cystic fibrosis transmembrane conductance regulator activity, is another strategy that may be able to reverse the Warburg-like metabolic shift in ADPKD cells and reduce cyst growth.[53–56] Wingless-related integration site (Wnt)/β-catenin signaling is proposed to coordinate metabolic flux consistent with the Warburg effect and activate mTORC1 through interactions with metabolic

transcription factors such as cellular myelocytomatosis oncogene, peroxisome proliferator–activated receptor (PPAR) δ, and PPARγ.[57] Transcriptomic profiling of *PKD1* ADPKD renal cortical patient tissue samples demonstrated substantial Wnt pathway upregulation specific to cystic cells, and that the free CTT of PC1 physically interacts with β-catenin to inhibit Wnt signaling. The authors suggested that ADPKD-related loss of PC1-CTT β-catenin inhibition causes epithelial cells to revert to a less differentiated phenotype associated with proliferation and cyst formation[58], directly connecting aberrant Wnt/β-catenin signaling to cystogenesis.

PPARα, a transcription factor vital for OXPHOS, is a potent target for addressing ADPKD-related mitochondrial dysfunction.[59,60] Studies have noted reduced PPARα levels in CKD, aging kidneys, and ADPKD, which impair FAO, leading to lipid accumulation in the kidney and worsened renal fibrosis.[61–63] Researchers are also exploring inducing PPARγ signalling to target lipid metabolism, glucose homeostasis, and oxidative stress.[64] PPARγ coactivator 1-α (PGC-1α), a key regulator of mitochondrial biogenesis and function, is downregulated in ADPKD and linked to several PKD and cilia-related genes.[65] One study found that reduced PGC-1α was associated with increased mitochondrial superoxide and reduced antioxidative effect, suggesting that inducing PGC-1α activity may reduce oxidative stress in ADPKD.[66] Another avenue for rescuing mitochondrial function is the microRNA (miR)-17 family, which is upregulated in both human and murine ADPKD models.[67] ADPKD mouse models have shown anti-*miR*-17 oligonucleotides can rescue OXPHOS defects and attenuate disease progression regardless of variant location (*Pkd1* or *Pkd2)* or type (null or hypomorphic).[59,68] Finally, the hormone somatostatin inhibits intracellular cAMP production and, in part, could regulate cellular energy turnover, which is heavily altered in ADPKD.[69] Targeting somatostatin may additionally improve mitochondrial function, as cAMP signaling is involved in mitochondrial dynamics like fusion, fission, motility, and mitophagy.[70] These drug targets may offer the opportunity to mitigate ADPKD metabolic and mitochondrial reprogramming, and advance options for patients.

ADPKD Impact on Drug Development and Metabolism

Traditional drug development is an extensive process that can take up to 17 years and $2-3 billion, with approval rates around 11%.[71] These associated costs and low approval rates create a barrier to entrance for designing novel therapeutics, further confounded in ADPKD by heterogeneity and limited research support (Figure 2). As such, drug repurposing has emerged as a strategic alternative. It leverages computational tools and prior studies to provide new indications for therapeutics, increasing approval rates to ~30% and reducing time and costs as low as 3 years and $300 million, respectively (Figure 3).[71] Tolvaptan is an example of the potential of drug repurposing in ADPKD, as it was originally indicated for hypervolemic or euvolemic hyponatremia from the syndrome of inappropriate antidiuretic hormone, chronic heart failure, or cirrhosis.[72] In one drug repurposing study from our lab, we prioritized 16 drug repurposing candidates and 29 drug targets, including many related to metabolic and mitochondrial pathways. We also demonstrated that protein interactions within oxidoreductase activity were involved in modulating drug metabolism activity, specifically within the cytochrome P450 (CYP450) family.[73] Many repurposed candidates proposed by the field target cellular metabolism, a key driver of cystogenesis in ADPKD (Table 1). Given the high level of metabolic and overall dysregulation in ADPKD, precision medicine approaches that account for its metabolic heterogeneity are essential as the field advances.

Hepatic and renal dysfunction can have significant consequences on drug metabolism and excretion, leading to the toxic accumulation of the drug and its metabolites.[74] This is particularly relevant in ADPKD, as 81.7% of adult patients develop hepatic cysts[75] that can cause hepatomegaly, loss of liver parenchyma, and lower quality of life in advanced stages.[76] Patients with renal disease commonly exhibit altered pharmacokinetics due to decreased renal excretion. They are particularly susceptible to volume of distribution and clearance changes, potentially requiring adjustments in dosing regimens to avoid adverse events.[77] Chronic renal failure has been shown to affect hepatic, renal, and intestinal mechanisms of drug metabolism and transport with a 40-85% downregulation

of hepatic and intestinal CYP450 metabolism, along with interference in phase II reactions and drug transporters like P-glycoprotein and organic anion transporting polypeptide.[78] ADPKD-specific effects on hepatic and renal drug metabolism and transporter-mediated drug expression are not well characterized, but are likely, as CKD has been shown to change the protein expression and activity of kidney and liver drug metabolism enzymes and transporters.[79] One study on early- and late-stage ADPKD human kidney samples found significant reductions in several drug metabolism enzymes. In the end-stage group, organic anion transporter (OAT) 1, OAT3, and organic cation transporter 2 were below the limit of quantification.[80] These changes could contribute to tolvaptan hepatotoxicity, as demonstrated by an ADPKD ex-situ perfused rat liver study that found decreased hepatobiliary clearance and greater hepatocellular concentrations of tolvaptan within their prediction model.[81] Impaired renal function has additionally been associated with changes in absorption, plasma protein binding, and drug distribution, along with altered liver and gut drug metabolism and transport pathways. As such, the FDA recommends that renal function effects are characterized early in drug development to avoid later-stage issues in dosing, efficacy, and safety.[82] While currently understudied, ADPKD alterations in drug metabolism are likely and could explain some of the challenges in finding safe and effective therapeutic options.
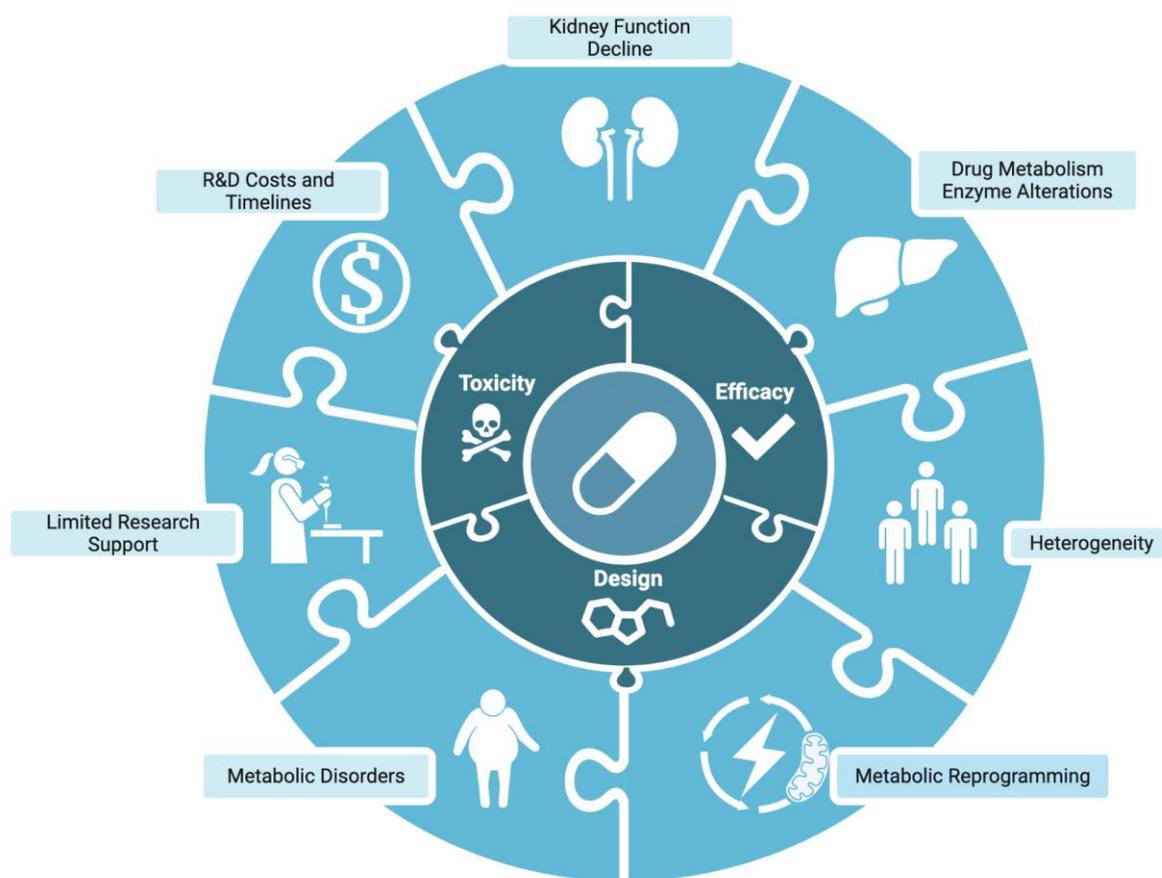
Figure 2. Overview of complications in autosomal dominant polycystic kidney disease (ADPKD) drug development. Like a puzzle, ADPKD pathophysiology and external influences combine to complicate therapeutic design, efficacy, and toxicity. This creates obstacles in developing efficacious and safe therapeutic options for ADPKD patients.
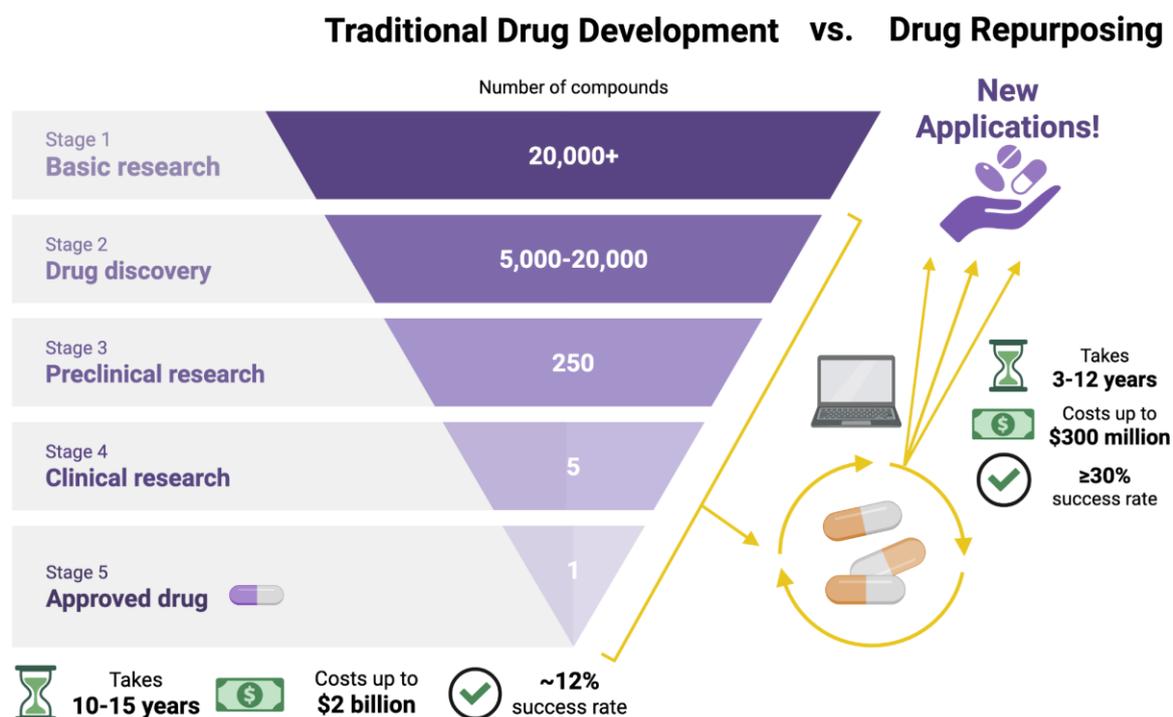
Figure 3. Traditional drug development compared to drug repurposing. Drug repurposing leverages prior studies and computational tools to reduce the time and costs associated with *de novo* development. While traditional drug development can take 10-15 years and up to $2 billion, drug repurposing takes 3-12 years and up to $300 million. Drug repurposing also increases approval rates from 12% to over 30%.

Table 1. Repurposed autosomal dominant polycystic kidney disease (ADPKD) drugs with their targets and clinical trial outcomes. Drugs in this table were repurposed for molecular targets discussed in this review. Original indications were found using the U.S. Food and Drug Administration (FDA) Drugs@FDA search tool. As shown, metabolic reprogramming is being extensively studied as a therapeutic target with promising results. Conclusive evidence of a successful repurposed drug targeting ADPKD metabolic reprogramming is still lacking.

Drug Class	Molecular Target / MOA	Drug Compound	Original Indication	Results	Clinical Trials / Relevant DOIs
Vaptans					
	V2R / Antagonist	Tolvaptan	Hypervolemic or euvolemic hyponatremia	Tolvaptan significantly reduced the rate of TKV growth and eGFR decline (P<0.001) compared to the placebo. Patients in the tolvaptan group had a higher frequency of aquaresis- and hepatic-related adverse events.	TEMPO (NCT00428948); REPRISE (NCT02160145); doi:10.1056/NEJMoa120551; doi:10.1056/NEJMoa1710030
		Lixivaptan	Euvolemic hyponatremia	Terminated early by sponsor due to concerns about commercial potential and hepatic safety.	ACTION (NCT04064346); ALERT (NCT04152837)
Rapalogs					

mTORC1 / Antagonist		Everolimus	Advanced renal cell carcinoma after failure of sunitinib or sorafenib treatment	Everolimus significantly slowed TKV increase (P=0.02) in the first year but was associated with a significantly greater decline in eGFR (P=0.004) compared with placebo.	NCT00414440; doi:10.1056/NEJMoa1003491
		Sirolimus	Prophylaxis of organ rejection in renal transplant patients	Sirolimus treatment increased TKV and TCV and did not significantly affect eGFR. Incidence of gastrointestinal adverse events in treated patients was high (94%). SIRENA-II was terminated early due to increased adverse events and ESRD progression in treated participants. A later study found that low-dose oral sirolimus is associated with ovarian toxicity, menstrual cycle disturbances, and ovarian cysts.	SIRENA-II (NCT01223755); NCT00346918; doi:10.2215/CJN.09900915; doi:10.1056/NEJMoa0907419; doi:10.1093/ndt/gfp280; doi:10.1371/journal.pone.0045868
Polyunsaturated Fatty Acids					
PPAR family / Agonist		Gamolenic acid	Atopic dermatitis/eczema; Asthma; Rheumatoid arthritis	Identified as a potential ADPKD treatment option in a drug repurposing study. Reduced cyst size in renal epithelial cells grown in a 3D-gel matrix.	doi:10.1016/j.ebiom.2019.11.046
		Icosapent ethyl / Eicosapentaenoic acid (EPA)	Hypertriglycidemia	Part of a larger clinical trial investigating the use of calcium channel blockers for the treatment of hypertension in ADPKD patients. EPA administration over 2 years did not have a significant effect on renal function decline or kidney enlargement.	NCT00541853; doi:10.1093/ndt/gfn144
Fibrates					
PPAR-α / Agonist		Fenofibrate	Hypertriglyceridemia; Primary hypercholesterolemia; Mixed dyslipidemia	In a preclinical trial on Pkd1^RC/RC mice, treatment with fenofibrate reduced TKV by 26.9%, TCV by 60.9%, liver fibrosis by 40%, and cyst proliferation by 71.6% compared to the control group.	doi:10.1152/ajprenal.00352.2017
Thiazolidinediones					
PPAR-γ / Agonist		Pioglitazone	T2DM	Low-dose pioglitazone was associated with reduced TKV growth rate compared to the placebo; however, the study was underpowered. Due to	NCT02697617; doi:10.1093/ckj/sfaa232

| | | | | concerns over side effects with higher doses and preclinical data showing maximal efficacy at a low dose, the study did not examine higher dosages. | |
| | | Rosiglitazone | | In human cystic epithelial cell culture models, rosiglitazone reduced the expression of fibrotic markers and cell proliferation. Male heterozygous Han:SPRD rats treated with rosiglitazone had improved kidney-to-body weight ratios and delayed ADPKD progression. | doi:10.1152/ajprenal.00194.2015 |

Biguanides

	AMPK / Agonist	Metformin	Malaria; T2DM	Metformin treatment was well tolerated in ADPKD patients. Changes in htTKV (p=0.9) and eGFR (p=0.2) were not statistically significant, but eGFR decline was reduced in the metformin group compared to placebo (-0.41±1.81 vs -3.35±1.70 mL/min/1.73 m^2). Starting kidney size, hypertension, and disease stage may have influenced this difference.	TAME-PKD (NCT02656017); IMPEDE-PKD (NCT04939935); NCT02903511; doi:10.34067/KID.0004002020; doi:10.1053/j.ajkd.2021.06.026

Glucose Analogs

	Glycolysis / Antagonist	2-deoxy-d-glucose (2DG)	Cancer	In a preclinical Pkd1^(ΔC/flox)TmCre murine model, 2DG administration restored AMPK activation, reduced kidney-to-body weight ratio, and was associated with improved kidney function preservation. Mice treated with 2DG additionally had reduced cyst expansion in both distal tubules and collecting ducts.	doi:10.1681/ASN.2015030231

Somatostatin Analogs

	SSTR1-5 / Agonist	Octreotide	Acromegaly; Thyrotrophinomas	Octreotide-LAR significantly decreased TKV growth in both studies after one year (P=0.002, P=0.04) and at three years in ALADIN (P=0.04). ALADIN found the octreotide-LAR group had reduced eGFR decline, while ALADIN 2 found a higher rate of	ALADIN (NCT00309283); ALADIN 2 (NCT01377246); doi:10.1016/S0140-6736(13)61407-5; doi:10.1371/journal.pmed.1002777

			eGFR decline compared to the placebo (11.3% vs 7.0%). Octreotide treatment was associated with cholelithiasis and cholecystitis adverse events.	
		Lanreotide	Acromegaly; Gastroenteropancreatic neuroendocrine tumors	Lanreotide treatment significantly lowered the percent change in htTKV (P=0.02), with a 24% reduction in htTKV growth rate compared to the placebo. There was a high incidence of adverse events in the treatment group, leading 10% of patients to withdraw from the study. 28% of treated patients experienced serious adverse events. An interim analysis of DIPAK-1 concluded somatostatin analog use is associated with an increased risk of hepatic cyst infection.	DIPAK-1 (NCT01616927); doi:10.1001/jama.2018.15870; doi:10.1007/s40264-016-0486-x
		Pasireotide	Acromegaly; Cushing's disease	In patients with ADPKD/ADPLD with severe liver involvement, pasireotide-LAR treatment was associated with a significant decrease in TLV (P<0.001) and TKV (P=0.02). Adverse events were most commonly related to hyperglycemia, and 19/32 (59%) of treated patients developed diabetes compared to 1/15 (7%) of patients in the placebo group (P<0.001).	NCT01670110; doi:10.2215/CJN.13661119

Abbreviations: ADPKD = autosomal dominant polycystic kidney disease; ADPLD = autosomal dominant polycystic liver disease; AMPK = adenosine monophosphate-activated protein kinase; eGFR = estimated glomerular filtration rate; ESRD = end-stage renal disease; htTKV = height-adjusted total kidney volume; LAR = long-acting release; mTORC1 = mammalian target of rapamycin complex 1; PPAR = peroxisome proliferator–activated receptor; SSTR = somatostatin receptor; T2DM = type-2 diabetes mellitus; TCV = total cyst volume; TKV = total kidney volume; TLV = total liver volume; V2R = vasopressin 2 receptor.

Conclusions, Limitations, and Future Directions

Here, we outlined the metabolic and mitochondrial alterations associated with ADPKD, in relation to potential drug targets and the challenges in drug development. Further exploration is critical for understanding ADPKD pathophysiology and uncovering promising mechanisms for pharmacological evaluation. While there are numerous ADPKD models that offer many benefits, they do not fully capture the complexity of ADPKD pathophysiology, translatability to humans, and resources for model generation and upkeep.[83] Moving forward, *in silico* drug repurposing methods leveraging genomic, structural, and phenotypic data, combined with improved drug screening efficiency through options like high-throughput organoid drug screening, may help identify context-

specific therapies and improve translational success.[84] Techniques such as network/graph theory, molecular docking, and large language models offer promising avenues to refine target selection and predict off-target effects, potentially avoiding pitfalls seen with mTOR inhibitors and others. This, coupled with better characterization of metabolic and mitochondrial alterations, could improve outcomes for ADPKD patients.

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