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Novel Therapies in *APOL1*-Mediated Kidney Disease: From Molecular Pathways to Therapeutic Options

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Apolipoprotein L1 (*APOL1*) high-risk variants confer an increased risk for the development and progression of kidney disease among individuals of recent African ancestry. Over the past several years, significant progress has been made in understanding the pathogenesis of *APOL1*-mediated kidney diseases (AMKD), including genetic regulation, environmental interactions, immunomodulatory, proinflammatory and apoptotic signaling processes, as well as the complex role of *APOL1* as an ion channel. Collectively, these findings have paved the way for novel therapeutic strategies to mitigate *APOL1*-mediated kidney injury. Precision medicine approaches are being developed to identify subgroups of AMKD patients who may benefit from these targeted interventions, fueling hope for improved clinical outcomes. This review summarizes key mechanistic insights in the pathogenesis of AMKD, emergent therapies, and discusses future challenges.

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The *APOL1* gene resides on chromosome 22 and is part of the *APOL* gene family, present in humans and certain primates. Although the lack of endogenous APOL1 expression in commonly used mouse and rat models has been a barrier to disease modeling and drug discovery efforts, significant progress has been made since the original seminal work by Pollak *et al*. in 2010.[1] G1 and G2 risk alleles define the *APOL1* risk genotypes (G1/G1, G2/G2, G1/G2), whereas the "non-risk" *APOL1* allele is referred to as G0. The *APOL1* G1 allele consists of 2 missense variants in high linkage disequilibrium (*APOL1* p.S342G, rs73885319; *APOL1* p.I384M, rs6091014), whereas the G2 allele is a 2–amino acid deletion (*APOL1* p.delN388/Y389, rs60910145). G1 and G2 alleles exhibit a notably high prevalence in populations of recent African ancestry, likely reflecting the influence of natural selection in West and Central Africa to protect against African trypanosomiasis known as "sleeping sickness." As a result of the slave trade and other migration patterns, *APOL1* high-risk variants are widely disseminated, especially in the Americas.[2] High-risk variants of *APOL1* are found in approximately 10% to 15% of African Americans.[3] In African Americans, carrying 2 high-risk alleles confers a 1.49-fold increased risk of chronic kidney disease and a 1.88-fold risk of end-stage kidney disease compared to those with 0 or 1 risk allele.[4]

AMKD encompasses diverse clinical manifestations characterized by kidney function decline, variable proteinuria levels, and hypertension. A recent large Phenome-Wide Association Study confirmed the association of *APOL1* with primarily kidney and kidney-associated pathologies.[5] Some of the most frequent conditions studied within the spectrum of AMKD include focal segmental glomerulosclerosis (FSGS), to virus-related forms such as HIV-associated nephropathy and COVID-19-associated nephropathy, and the syndrome of solidified or diffuse glomerulosclerosis with low level proteinuria (often mislabeled arterionephrosclerosis or hypertensive nephropathy).[6-9] The role of *APOL1* in conditions such as preeclampsia, sickle cell disease and some autoimmune diseases is not fully understood. Improved knowledge of *APOL1* biology and its therapeutic targeting offers a unique opportunity to treat clinical entities of important public health relevance. In this review, we summarize mechanistic pathways implicated in AMKD and provide an overview of promising emerging therapeutic options.

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APOL1 Expression and Upstream Regulation

The mode of inheritance in AMKD pathogenesis has been a topic of controversy.[10] Although most autosomal

recessive diseases are characterized by loss-of-function mutations, APOL1 is atypical, having a recessive model of inheritance for chronic kidney disease and apparent gain-of-function characteristics.[11] Recent data investigating the use of small molecule inhibitors and antisense oligonucleotides to reduce *APOL1* expression and its downstream effects further support the gain-of-function model.[12,13] The fact that a functional *APOL1* gene is found only in some African primate species and that individuals lacking *APOL1* can still maintain normal kidney function suggests that this gene is not essential for normal kidney development or functioning.[14,15] In theory, inhibiting *APOL1* toxicity should ameliorate kidney disease without major adverse effects. However, caution is warranted until the effects of *APOL1* expression in other systems such as the endothelium, immune cells, and hepatocytes are fully understood. Furthermore, reducing *APOL1* expression may result in deleterious implications in areas endemic for trypanosomiasis.

The expression of *APOL1* is tightly controlled by a complex interplay between genetic and epigenetic factors. Numerous immune and inflammatory pathways have been identified that upregulate *APOL1* expression, including the interferon family, the most extensively studied, interleukin-1β and proteins from the toll-like receptor family.[16-18] The *APOL1* promoter contains regulatory elements that interact with several transcription factors, including STAT2, STAT3, and interferon regulating factors 1, 2, and 3. Interferons and toll-like receptor agonists have been shown to increase *APOL1* expression by up to 200-fold.[16] Comparative promoter analyses have revealed differential effects on *APOL1* expression. Toll-like receptor 3 activation exerts a more pronounced effect than toll-like receptor 4, whereas interferon γ has a greater impact *on APOL1* expression compared to interferon β and α. These findings support the hypothesis that *APOL1* is a cellular immune response gene.

The Janus kinase/signal transducer and activator of transcription (JAK/STAT) pathway, a highly conserved pathway that regulates immunological and adaptative responses, has been well studied in the context of *APOL1* regulation. This pathway consists of 4 JAK members (JAK1–JAK3 and receptor tyrosine kinase 2) and 7 STAT members (STAT1–STAT4, STAT5a, STAT5b, and STAT6), and it is essential for cell maintenance, immune fitness, and tissue repair.[19-21] Extensive activation of the JAK/STAT pathway has been recognized as a critical step in kidney diseases such as diabetic nephropathy and autosomal dominant polycystic kidney disease.[22-26] Most recently, COVID-19-associated nephropathy has been identified as a condition where COVID-19-induced cytokines (predominantly interleukin-6, interleukin-1β, and interleukin-18) are sufficient to activate the JAK/STAT signaling pathway.[26] Interestingly, the amplification of *APOL1* expression in human podocytes and glomerular endothelial cells was seen even when interferon levels were negligible (indicating the presence of interferon-independent mechanisms), but still resulting in podocyte injury and loss. This was rescued by baricitinib (JAK inhibitor), providing a rationale for its use as a therapeutic agent in *APOL1*-induced cellular injury.

Host genetic factors may also affect the expression of *APOL1*. For example, gain-of-function mutations in *TMEM173*, the gene encoding stimulator of interferon genes (STING) can exacerbate the production of interferon, a condition that has been recently described as STING-associated vasculopathy with onset in infancy. Type I IFN triggers a positive feedback loop leading to activation of JAK1 and STAT1/STAT 2, and transcription of proinflammatory IFN-stimulated genes. The recently published case of a patient with *APOL1* G1 and G2 risk alleles with a high interferon state due to STING-associated vasculopathy with onset in infancy, illustrated a human model where a high interferon state can lead to collapsing glomerulopathy.[27]

Several studies continue to explore the role of epigenetic factors, copy number variants and SNPs in APOL1 nephropathy.[28] Genetic modifiers such as SMOC2, DEF1B, UBD, NUDT7, and GSTB1 have also been identified.[29-33] In addition, environmental factors such as air pollution have been implicated in the development of AMKD in patients carrying *APOL1* risk variants, probably due to cellular stress mechanisms.[34-37] In sum, AMKD has diverse clinical manifestations and it is likely that complex epistatic and environmental interactions result in differential pathological cellular programming.

APOL1 Mechanisms of Podocyte Injury

APOL1 as an Ion Channel

One of the most widely accepted proposed mechanisms of *APOL1*-mediated injury centers on its role as an ion channel.[38,39] Conflicting findings have been reported regarding the nature of these channels, especially their anionic or cationic activity. This is related to variability in localization (cellular vs. organelle), model studied (trypanosomal activity vs. podocyte-specific toxicity), and structural or biochemical factors, derived from pH environment, among others.[40-42] Subcellular localization of APOL1 and/or affinity for binding partners have been described but there is a lack of consensus across models.[43-45]

Several studies support the hypothesis that APOL1 forms distinct anion-selective pores in unilamellar

vesicular membranes, promoting chloride influx facilitated by the initial influx of extracellular sodium following its concentration gradient.[46,47] This osmotic imbalance leads to the passive entry of water into the cell, resulting in cell swelling and trypanosome lysis. However, other studies support the cationic nature of the channel, suggesting that trypanosome lysis requires an acidic pH for the initial steps to allow APOL-1 insertion into vacuolar lipid bilayers, to be subsequently transported to the plasma membrane, where it is exposed to a nonacidic pH allowing APOL1 to open pH-sensitive cationic channels, depolarizing the membrane and killing the trypanosome.[48] Another publication supports this view demonstrating that mammalian cells expressing *APOL1* risk variants exhibit increased nonselective cation permeability, resulting in a net efflux of intracellular potassium through the plasma membrane, thereby inducing cell damage through the activation of stress-activated protein kinases, p38, mitogen-activated mitogen kinase, and JNK.[49] These seemingly discordant findings may be reconciled by the proposal that APOL1 ion-channel selectivity is pH-switchable. At pH of 5, APOL1 may promote chloride permeability through anionic channels, whereas at neutral pH, it facilitates potassium permeability.[50] Collectively, the body of evidence suggests that APOL1 channel activity depends on 3 factors that allow APOL1 to associate with pore-forming vesicles: delicate pH fine tuning, presence of negatively charged phospholipids in vesicle membranes, and low ionic strength.

APOL1-Associated Mitochondrial Stress

APOL1-induced mitochondrial dysfunction is believed to contribute to AMKD through various mechanisms.[51] The induction of *APOL1* G1 and G2 expression results in a significant reduction in the maximum oxygen consumption rate and respiratory reserve capacity compared to cells expressing the *APOL1* G0 variant.[52] After being transported to the mitochondria by incompletely understood mechanisms, *APOL1* risk variants form higher-order oligomers within the mitochondria and activate pore opening, resulting in cell toxicity by increasing fatty acid oxidation, and decreased redox homeostasis, disruption of the mitochondrial membrane potential, and cell toxicity.[45] Another possible mechanism underlying *APOL1*-induced mitochondrial dysfunction is the increase in mitochondrial fragmentation (fission), as opposed to fusion. Physiologically, fission helps segregate the most severely damaged mitochondria to preserve the overall health of the mitochondrial network. However, when G1 and G2 variant-induced mitochondrial fission cannot be adequately compensated through mitophagy (possibly due to defective intracellular trafficking), cell death mechanisms are activated.[53–55] Overexpression of *APOL1* G1 and G2 in HEK293 cells promotes mitochondrial fragmentation thought active DRP1. The inhibition of mitochondrial fission using the DRP1 inhibitor, Mdivi-129, appears to preserve mitochondrial morphology, resulting in fewer fragmented mitochondria, and treatment restores cell viability in a dose-dependent manner.[56,57]

APOL1-Associated Endoplasmic Reticulum and Lysosomal Stress

Other organelles that have been implicated in *APOL1*-induced cell damage are lysosomes and the endoplasmic reticulum (ER). *APOL1* risk variants are associated with increased lysosomal permeability and compromised endolysosomal trafficking, suggesting their involvement in cellular perturbations.[58] Insertion of *APOL1* into the lysosomal membrane triggers ion flux into the organelle, leading to osmotic damage and death.[46] Notably, *APOL1* causes lysosomal dysfunction in cultured human renal cells as well as in parasites. The G1 and G2 variants of *APOL1* decrease the number of lysosomes in podocytes, leading to leakage of lysosomal enzymes into the cytoplasm.[59,60]

Recent studies have shown that *APOL1* expression is localized to the ER. In their study using cultured HEK293 cells, Chun *et al*.[61] uncovered a distinct pattern of localization for APOL1 risk variants, primarily within the ER, whereas wild type APOL1 localization predominantly to lipid droplets. Notably, when cells were subjected to treatments promoting lipid droplet formation, a notable shift in the localization of G1 and G2 variants occurred, moving from the ER to the lipid droplets, reducing autophagic flux and cytotoxicity. In addition, factors such as tissue hypoxia,[62] oxidative stress, and chronic inflammation can further amplify ER stress, exacerbating kidney disease progression among those with high-risk *APOL1* variants. Further research efforts are warranted to unravel the complex mechanisms of ER stress, its modulation by *APOL1* variants, and its impact on disease pathogenesis. Consequently, therapeutic approaches targeting ER stress that hold promise for other clinical applications (e.g., cancer and metabolic diseases), could be an important opportunity for drug-repurposing.[63]

Inflammation and *APOL1*

As previously described, inflammatory mechanisms induce the expression of *APOL1*. However, these mechanisms also appear to be involved in the induction and maintenance of *APOL1*-mediated damage. STING is an adjuvant protein on the ER that recognizes the cyclic dinucleotides generated by cyclic GMP-AMP

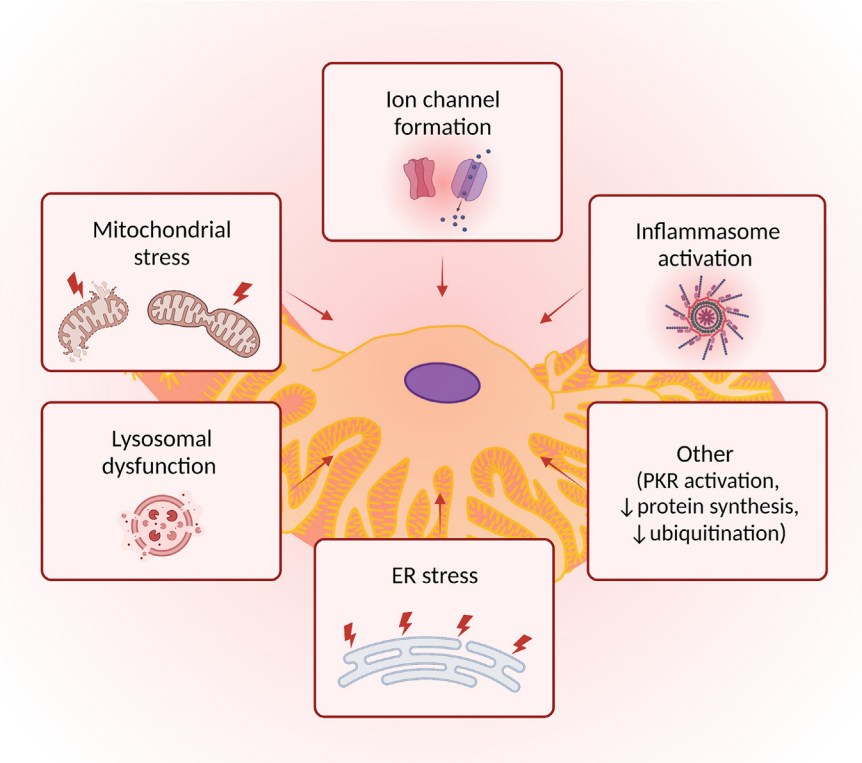

Figure 1. Purported mechanisms of APOL1-induced kidney injury. PKR, protein kinase R.

synthase, that recognizes foreign and host DNA (incremented in states of cellular stress).[64] Once cyclic GMP-AMP synthase senses cytoplasmic dsDNA, it converts GTP and ATP into 2′,3′-cGAMP, which binds and activates STING, promoting the secretion of type I interferons and various proinflammatory cytokines.[65] However, when cyclic GMP-AMP synthase-STING pathway activation exceeds a certain threshold, STING induces necroptosis, apoptosis, and lysosome fragmentation via NOD-like receptor pyrin domain-containing 3 inflammasome-dependent pyroptosis.[66,67] The NOD-like receptor pyrin domain-containing 3 inflammasome is a multiprotein complex that forms part of the innate immune system and activates multiple inflammatory proteins such as interleukin 1β, interleukin-18, and the pore-forming gasdermin D, leading to cellular osmotic imbalance and the release of proinflammatory intracellular contents.[66] Recent studies have identified the STING-NOD-like receptor pyrin domain-containing 3 pathway as a pivotal mechanism underlying *APOL1*-induced cytotoxicity.[68] Emerging small-molecule-based strategies and biologics to therapeutically target cyclic GMP-AMP synthase-STING and NOD-like receptor pyrin domain-containing 3 signaling are gaining interest in several models of chronic inflammation (e.g., cancer and autoimmune disorders), and these findings support its potential value in the treatment of AMKD.

Other Mechanisms

APOL1-mediated cellular injury depends on complex molecular mechanisms that are intricately linked. In addition to those mentioned previously, other mechanisms implicated in AMKD that have been suggested include activation of protein kinase R,[69] which appears during viral infections and inhibits protein synthesis, increased autophagic cell death (mediated by the BCL2-homology 3 domain within the pore-forming domain of *APOL1*),[70] or the alteration of the ubiquitin-proteasome system, which reduces ubiquitin levels prolonging the intracellular retention of proteins (including *APOL1* itself).[31] In addition, *APOL1* G1 and G2 variants have been shown to have high affinity for suPAR activated αvβ3 integrin on podocytes in the progression of chronic kidney disease.[71] These and the aforementioned mechanisms are summarized in Figure 1.

Emerging Therapies in AMKD

Drug discovery has traditionally relied on well-characterized disease targets, high-throughput screening methods to test large compound libraries, and prior experimental data.[72,73] Nonetheless, the emergence of novel technologies such as genomics, proteomics, and bioinformatics to generate and analyze large-scale data sets, enabled the identification of new mechanistic pathways and therefore more precise options such as peptide-based inhibitors, oligonucleotides,

Table 1. Recent and ongoing APOL1 therapeutic trials

NCT number	Drug	Mechanism of action	Status	Phase	Completion
NCT04340362	VX-147	APOL1 channel blocker (small molecule inhibitor)	Completed	Phase 2	December 2021
NCT05312879			Recruiting	Phase 2/3	June 2026
NCT05324410	VX-840	APOL1 channel blocker (small molecule inhibitor)	Completed	Phase 1	November 2022
NCT04269031	AZD2373	APOL1 antisense oligonucleotide	Completed	Phase 1	August 2021
NCT05351047			Active, not recruiting	Phase 1	July 2023
NCT05237388	Baricitinib	Janus Kinase-STAT Inhibition	Recruiting	Phase 2	March 2026

APOL1, apolipoprotein L1; STAT, signal transducer and activator of transcription.
Search of clinicaltrials.gov was performed on July 19, 2023.

or gene therapies.[74–76] These modalities have been extensively described in other fields such as oncology and rheumatology. The rapid development of drug repurposing methods, systems biology, and artificial intelligence in nephrology is supporting the emergence of novel approaches to tackle AMKD.[77–79] Given the number of potential mechanisms that contribute to *APOL1*-mediated renal injury, it is not surprising that different approaches are currently being explored. A summary of phase 1 to 3 clinical trials for AMKD since its discovery is presented in Table 1. A brief discussion of these emerging agents (Figure 2) will be discussed below.

APOL1 Small Molecule Inhibitors

Small molecules are a class of pharmacological agents that exhibit high specificity and potency in targeting enzymes or protein-protein interactions of disease-relevant pathways.[78] With their relatively low molecular weight and favorable physicochemical properties, small molecule inhibitors possess the ability to penetrate cellular membranes and enable access to intracellular components. These inherent characteristics offer significant advantages for therapeutic intervention by mitigating off-target effects and minimizing toxicity to normal cells. In addition, harnessing the modulatory potential of small molecule inhibitors holds great promise in advancing personalized medicine, particularly in the context of AMKD, because individual patients may exhibit distinct molecular drivers of disease within the spectrum of AMKD.[26,49,53,68] Moreover, the oral bioavailability of many small molecule inhibitors enables convenient administration.

A novel small molecule inhibitor on *APOL1* channel called VX-147 or inaxaplin demonstrated promising results in reducing proteinuria in patients with *APOL1*-associated FSGS in a recently published phase 2a study.[12] After demonstration of efficacy in preclinical models (a reduction of cationic influx in vitro and a reduction of proteinuria in a transgenic APOL1 mouse model), inaxaplin was administered during 13 weeks to 16 participants who had 3 *APOL1* high-risk variants, biopsy-proven FSGS, and estimated glomerular filtration rate $\geq$27 ml/min per 1.73 m^2. Among the 13 participants who were adherent to the treatment threshold, the mean change from the baseline urinary

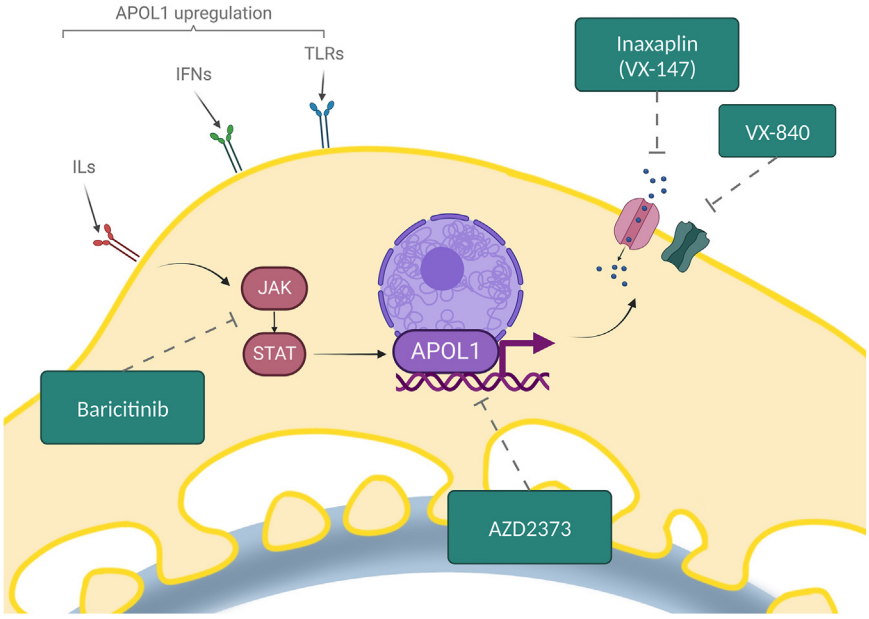

Figure 2. Mechanism of action of current APOL1 therapeutic agents in development.

protein-to-creatinine ratio at week 13 was −47.6% (95% confidence interval, −60.0 to −31.3). Furthermore, in an analysis that included all 16 participants regardless of adherence to therapy, reductions were similar to those in the primary analysis in all but 1 participant. The drug showed a substantial decrease in proteinuria, even in patients receiving standard-of-care treatment. However, there are some limitations to note. In addition to statistical limitations and biases inherent to the single arm, small sample study design, most patients had FSGS with subnephrotic range proteinuria, and secondary FSGS could not be ruled out. Furthermore, baseline and concomitant therapy for FSGS were variable during the treatment phase and it remains unclear whether longer duration of inaxaplin would persistently suppress proteinuria. A larger phase 2/3 inaxaplin AMKD study (NCT05312879), not limited to FSGS, is currently actively enrolling. In addition, another small molecule inhibitor (VX-840) is currently being studied by the same sponsor (phase 1 completed in November 2022).

Recently, small molecule inhibitor, MZ-301 has been developed to potentially block *APOL1* electrophysiological currents in response to a voltage ramp in HEK293 cells expressing *APOL1* G2.[80] *APOL1*-mediated ion currents measured in HEK293 cells were noted to decrease in the presence of incremental doses of MZ-301, eventually rescuing them from *APOL1*-mediated cytotoxicity. Furthermore, MZ-301 was described to inhibit *APOL1*-dependent cytotoxicity *in vitro* in human immortalized podocytes, which translated into urine albumin-to-creatinine ratio reductions in *APOL1* G2 mutant mice.

Antisense Oligonucleotides

Oligonucleotide therapeutics, such as those based on antisense oligonucleotides (ASOs), small interfering RNA, microRNA, aptamers, and decoys, are promising agents that have gained importance during the past decades in nephrology and other fields.[81-83] *APOL1* ASOs are oligonucleotide analogs that modify expression of specific RNAs and can alter protein synthesis. ASOs bind to select mRNA sequences and can cause RNase H1-mediated degradation (ceasing synthesis of the protein), splicing defects, or interfere with gene expression. In a recent study, a generation 2.5 *APOL1* ASO (IONIS-APOL1$_{Rx}$) was selected as the APOL1 clinical candidate based on its consistent and potent activity *in vitro* as well as *in vivo* in genomic *APOL1*-transgenic mice. Subcutaneous administration of IONIS-APOL1$_{Rx}$ to *APOL1* G1-transgenic mice resulted in dose-dependent reductions in kidney and liver *APOL1* mRNA, preventing dose-dependent interferon-induced proteinuria.[84] The agent was used in a first-in-human, single ascending dose, phase I study (NCT04269031), to evaluate the safety and assess the pharmacokinetics of escalating single doses of a subcutaneously administered ASO (ION532, also known as AZD2373), with results pending. Another phase I study (NCT05351047) is ongoing.

JAK/STAT Pathway Blockade

As described above, JAK/STAT plays a critical role in activating proinflammatory cell programs and its inhibition could efficiently decrease *APOL1*-associated cellular toxicity, which has been tested in preclinical models with promising results. A phase 2 trial (JUSTICE, NCT05237388) is currently recruiting to evaluate the efficacy of baricitinib, a JAK inhibitor approved for the treatment of rheumatoid arthritis and alopecia areata, in patients with AMKD. STAT3 inhibition using next-generation ASOs, including 2.5 ASO (e.g., AZD9150) has been explored for other clinical indications. STAT3 binds mRNA and silences gene expression through blocking translation or recruiting RNase H enzymes, which degrade the DNA-RNA heteroduplex.[19,20] AZD9150 is currently being studied in leukemia and lymphoma due to its proapoptotic and cell regulatory effects.[85,86]

Future Directions and Considerations

Extensive studies have shed light on cellular pathways activated by *APOL1* risk variants in cellular, animal, and human studies; however, several gaps remain. Evidence that less than 30% of individuals with 2 high-risk *APOL1* variants develop AMKD warrants careful exploration to further define "second hits" and clarify patient populations that should undergo genetic screening. This will influence ongoing initiatives to potentially reduce adverse kidney and transplant outcomes, support the development of noninvasive biomarkers that could potentially anticipate the onset of kidney disease, provide risk-stratification algorithms and advance precision-based therapeutic approaches.

There are still other unresolved questions in developing *APOL1* therapeutics. There is uncertainty regarding the impact of circulating *APOL1* on the kidneys and consequently a lack of clarity regarding the relative efficacy of reducing systemic *APOL1* levels versus inhibiting the function of mutant APOL1 protein. The multiple upstream regulatory and downstream pathogenic signaling cascades may also require potentially divergent therapeutic approaches in certain AMKD subpopulations. Safety will be a concern, especially in regions endemic for trypanosomiasis and where prolonged therapy may be required. Small molecule inhibitors can lead to off-target effects and prolonged genetic alterations. Advances are also required in improving kidney-specific drug delivery to reduce the potential for off-target effects of APOL1 inhibitors.

In summary, significant progress has been made in understanding the cellular injury mechanisms of *APOL1* risk variants and the development of new therapies for AMKD. More work will be needed in molecular subphenotyping, precision-based targeted approaches, and careful investigation of the efficacy and safety profile of emerging therapies.

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REFERENCES

1. Genovese G, Friedman DJ, Ross MD, et al. Association of trypanolytic ApoL1 variants with kidney disease in African Americans. *Science*. 2010;329:841–845. https://doi.org/10.1126/science.1193032
2. Nadkarni GN, Gignoux CR, Sorokin EP, et al. Worldwide frequencies of APOL1 renal risk variants. *N Engl J Med*. 2018;379:2571–2572. https://doi.org/10.1056/NEJMc1800748
3. Friedman DJ, Kozlitina J, Genovese G, Jog P, Pollak MR. Population-based risk assessment of APOL1 on renal disease. *J Am Soc Nephrol*. 2011;22:2098–2105. https://doi.org/10.1681/ASN.2011050519
4. Foster MC, Coresh J, Fornage M, et al. APOL1 variants associate with increased risk of CKD among African Americans. *J Am Soc Nephrol*. 2013;24:1484–1491. https://doi.org/10.1681/ASN.2013010113
5. Bajaj A, Ihegword A, Qiu C, et al. Phenome-wide association analysis suggests the APOL1 linked disease spectrum primarily drives kidney-specific pathways. *Kidney Int*. 2020;97:1032–1041. https://doi.org/10.1016/j.kint.2020.01.027
6. Yusuf AA, Govender MA, Brandenburg JT, Winkler CA. Kidney disease and APOL1. *Hum Mol Genet*. 2021;30:R129–R137. https://doi.org/10.1093/hmg/ddab024
7. Wu H, Larsen CP, Hernandez-Arroyo CF, et al. AKI and collapsing glomerulopathy associated with COVID-19 and APOL 1 high-risk genotype. *J Am Soc Nephrol*. 2020;31:1688–1695. https://doi.org/10.1681/ASN.2020050558
8. Pollak MR, Genovese G, Friedman DJ. APOL1 and kidney disease. *Curr Opin Nephrol Hypertens*. 2012;21:179–182. https://doi.org/10.1097/MNH.0b013e32835012ab
9. Friedman DJ, Pollak MR. APOL1 nephropathy: from genetics to clinical applications. *Clin J Am Soc Nephrol*. 2021;16:294–303. https://doi.org/10.2215/CJN.15161219
10. Bruggeman LA, O'Toole JF, Sedor JR. APOL1 polymorphisms and kidney disease: loss-of-function or gain-of-function? *Am J Physiol Ren Physiol*. 2019;316:F1–F8. https://doi.org/10.1152/ajprenal.00426.2018
11. Dummer PD, Limou S, Rosenberg AZ, et al. APOL1 kidney disease risk variants: an evolving landscape. *Semin Nephrol*. 2015;35:222–236. https://doi.org/10.1016/j.semnephrol.2015.04.008
12. Egbuna O, Zimmerman B, Manos G, et al. Inaxaplin for proteinuric kidney disease in persons with two APOL1 variants. *N Engl J Med*. 2023;388:969–979. https://doi.org/10.1056/NEJMoa2202396
13. Friedman DJ, Ma L, Freedman BI. Treatment potential in APOL1-associated nephropathy. *Curr Opin Nephrol Hypertens*. 2022;31:442–448. https://doi.org/10.1097/MNH.0000000000000816
14. Johnstone DB, Shegokar V, Nihalani D, et al. APOL1 null alleles from a rural village in India do not correlate with glomerulosclerosis. *PLoS One*. 2012;7:e51546. https://doi.org/10.1371/journal.pone.0051546
15. Vanhollebeke B, Truc P, Poelvoorde P, et al. Human Trypanosoma evansi infection linked to a lack of apolipoprotein L-I. *N Engl J Med*. 2006;355:2752–2756. https://doi.org/10.1056/NEJMoa063265
16. Nichols B, Jog P, Lee JH, et al. Innate immunity pathways regulate the nephropathy gene apolipoprotein L1. *Kidney Int*. 2015;87:332–342. https://doi.org/10.1038/ki.2014.270
17. Wang DP, Yu ZX, He ZC, et al. Apolipoprotein L1 is transcriptionally regulated by SP1, IRF1 and IRF2 in hepatoma cells. *FEBS Lett*. 2020;594:3108–3121. https://doi.org/10.1002/1873-3468.13887
18. O'Toole JF, Bruggeman LA, Madhavan S, Sedor JR. The cell biology of APOL1. *Semin Nephrol*. 2017;37:538–545. https://doi.org/10.1016/j.semnephrol.2017.07.007
19. Pace J, Paladugu P, Das B, He JC, Mallipattu SK. Targeting STAT3 signaling in kidney disease. *Am J Physiol Ren Physiol*. 2019;316:F1151–F1161. https://doi.org/10.1152/ajprenal.00034.2019
20. Hu X, Li J, Fu M, Zhao X, Wang W. The JAK/STAT signaling pathway: from bench to clinic. *Signal Transduct Target Ther*. 2021;6:402. https://doi.org/10.1038/s41392-021-00791-1
21. Villarino AV, Kanno Y, O'Shea JJ. Mechanisms and consequences of Jak-STAT signaling in the immune system. *Nat Immunol*. 2017;18:374–384. https://doi.org/10.1038/ni.3691
22. Woroniecka KI, Park AS, Mohtat D, Thomas DB, Pullman JM, Susztak K. Transcriptome analysis of human diabetic kidney disease. *Diabetes*. 2011;60:2354–2369. https://doi.org/10.2337/db10-1181
23. Lu TC, Wang ZH, Feng X, et al. Knockdown of Stat3 activity in vivo prevents diabetic glomerulopathy. *Kidney Int*. 2009;76:63–71. https://doi.org/10.1038/ki.2009.98
24. Berthier CC, Zhang H, Schin M, et al. Enhanced expression of Janus kinase-signal transducer and activator of transcription pathway members in human diabetic nephropathy. *Diabetes*. 2009;58:469–477. https://doi.org/10.2337/db08-1328
25. Brosius FC 3rd, He JC. JAK inhibition and progressive kidney disease. *Curr Opin Nephrol Hypertens*. 2015;24:88–95. https://doi.org/10.1097/MNH.0000000000000079
26. Nystrom SE, Li G, Datta S, et al. JAK inhibitor blocks COVID-19 cytokine-induced JAK/STAT/APOL1 signaling in glomerular cells and podocytopathy in human kidney organoids. *JCI Insight*. 2022;7. https://doi.org/10.1172/jci.insight.157432
27. Abid Q, Best Rocha A, Larsen CP, et al. APOL1-associated collapsing focal segmental glomerulosclerosis in a patient with stimulator of interferon genes (STING)-associated vasculopathy with onset in infancy (SAVI). *Am J Kidney Dis*. 2020;75:287–290. https://doi.org/10.1053/j.ajkd.2019.07.010

28. Langefeld CD, Comeau ME, Ng MCY, et al. Genome-wide association studies suggest that APOL1-environment interactions more likely trigger kidney disease in African Americans with nondiabetic nephropathy than strong APOL1-second gene interactions. *Kidney Int*. 2018;94:599–607. https://doi.org/10.1016/j.kint.2018.03.017

29. Chaudhary NS, Armstrong ND, Hidalgo BA, et al. SMOC2 gene interacts with APOL1 in the development of end-stage kidney disease: a genome-wide association study. *Front Med (Lausanne)*. 2022;9:971297. https://doi.org/10.3389/fmed.2022.971297

30. Vy HMT, Lin BM, Gulamali FF, et al. Genome-wide epistatic interaction between DEF1B and APOL1 high-risk genotypes for chronic kidney disease. *Clin J Am Soc Nephrol*. 2022;17:1522–1525. https://doi.org/10.2215/CJN.03610322

31. Zhang JY, Wang M, Tian L, et al. UBD modifies APOL1-induced kidney disease risk. *Proc Natl Acad Sci U S A*. 2018;115:3446–3451. https://doi.org/10.1073/pnas.1716113115

32. Divers J, Ma L, Brown WM, et al. Genome-wide association study for time to failure of kidney transplants from African American deceased donors. *Clin Transpl*. 2020;34:e13827. https://doi.org/10.1111/ctr.13827

33. Bodonyi-Kovacs G, Ma JZ, Chang J, et al. Combined effects of GSTM1 null allele and APOL1 renal risk alleles in CKD progression in the African American study of kidney disease and hypertension trial. *J Am Soc Nephrol*. 2016;27:3140–3152. https://doi.org/10.1681/ASN.2015050487

34. Chen TK, Coresh J, Daya N, et al. Race, APOL1 risk variants, and clinical outcomes among older adults: the ARIC study. *J Am Geriatr Soc*. 2021;69:155–163. https://doi.org/10.1111/jgs.16797

35. Tamrat R, Peralta CA, Tajuddin SM, Evans MK, Zonderman AB, Crews DC. Apolipoprotein L1, income and early kidney damage. *BMC Nephrol*. 2015;16:14. https://doi.org/10.1186/s12882-015-0008-6

36. Hung AM, Shah SC, Bick AG, et al. APOL1 risk variants, acute kidney injury, and death in participants with African ancestry hospitalized with COVID-19 from the Million Veteran Program. *JAMA Intern Med*. 2022;182:386–395. https://doi.org/10.1001/jamainternmed.2021.8538

37. Paranjpe I, Chaudhary K, Paranjpe M, et al. Association of APOL1 risk genotype and air pollution for kidney disease. *Clin J Am Soc Nephrol*. 2020;15:401–403. https://doi.org/10.2215/CJN.11921019

38. Beckerman P, Bi-Karchin J, Park AS, et al. Transgenic expression of human APOL1 risk variants in podocytes induces kidney disease in mice. *Nat Med*. 2017;23:429–438. https://doi.org/10.1038/nm.4287

39. Datta S, Kataria R, Zhang JY, et al. Kidney disease-associated APOL1 variants have dose-dependent, dominant toxic gain-of-function. *J Am Soc Nephrol*. 2020;31:2083–2096. https://doi.org/10.1681/ASN.2020010079

40. Daneshpajouhnejad P, Kopp JB, Winkler CA, Rosenberg AZ. The evolving story of apolipoprotein L1 nephropathy: the end of the beginning. *Nat Rev Nephrol*. 2022;18:307–320. https://doi.org/10.1038/s41581-022-00538-3

41. Scales SJ, Gupta N, De Maziere AM, et al. Apolipoprotein L1-specific antibodies detect endogenous APOL1 inside the endoplasmic reticulum and on the plasma membrane of podocytes. *J Am Soc Nephrol*. 2020;31:2044–2064. https://doi.org/10.1681/ASN.2019080829

42. Vanwalleghem G, Fontaine F, Lecordier L, et al. Coupling of lysosomal and mitochondrial membrane permeabilization in trypanolysis by APOL1. *Nat Commun*. 2015;6:8078. https://doi.org/10.1038/ncomms9078

43. Madhavan SM, O'Toole JF, Konieczkowski M, Ganesan S, Bruggeman LA, Sedor JR. APOL1 localization in normal kidney and nondiabetic kidney disease. *J Am Soc Nephrol*. 2011;22:2119–2128. https://doi.org/10.1681/ASN.2011010069

44. Ma L, Shelness GS, Snipes JA, et al. Localization of APOL1 protein and mRNA in the human kidney: nondiseased tissue, primary cells, and immortalized cell lines. *J Am Soc Nephrol*. 2015;26:339–348. https://doi.org/10.1681/ASN.2013091017

45. Shah SS, Lannon H, Dias L, et al. APOL1 kidney risk variants induce cell death via mitochondrial translocation and opening of the mitochondrial permeability transition pore. *J Am Soc Nephrol*. 2019;30:2355–2368. https://doi.org/10.1681/ASN.2019020114

46. Perez-Morga D, Vanhollebeke B, Paturiaux-Hanocq F, et al. Apolipoprotein L-I promotes trypanosome lysis by forming pores in lysosomal membranes. *Science*. 2005;309:469–472. https://doi.org/10.1126/science.1114566

47. Vanhollebeke B, Pays E. The function of apolipoproteins L. *Cell Mol Life Sci*. 2006;63:1937–1944. https://doi.org/10.1007/s00018-006-6091-x

48. Thomson R, Finkelstein A. Human trypanolytic factor APOL1 forms pH-gated cation-selective channels in planar lipid bilayers: relevance to trypanosome lysis. *Proc Natl Acad Sci U S A*. 2015;112:2894–2899. https://doi.org/10.1073/pnas.1421953112

49. Olabisi OA, Zhang JY, VerPlank L, et al. APOL1 kidney disease risk variants cause cytotoxicity by depleting cellular potassium and inducing stress-activated protein kinases. *Proc Natl Acad Sci U S A*. 2016;113:830–837. https://doi.org/10.1073/pnas.1522913113

50. Bruno J, Pozzi N, Oliva J, Edwards JC. Apolipoprotein L1 confers pH-switchable ion permeability to phospholipid vesicles. *J Biol Chem*. 2017;292:18344–18353. https://doi.org/10.1074/jbc.M117.813444

51. Ma L, Divers J, Freedman BI. Mechanisms of injury in APOL1-associated Kidney Disease. *Kidney Dis Transplant*. 2019;103:487–492. https://doi.org/10.1097/TP.0000000000002509

52. Ma L, Chou JW, Snipes JA, et al. APOL1 renal-risk variants induce mitochondrial dysfunction. *J Am Soc Nephrol*. 2017;28:1093–1105. https://doi.org/10.1681/ASN.2016050567

53. Ogata M, Hino S, Saito A, et al. Autophagy is activated for cell survival after endoplasmic reticulum stress. *Mol Cell Biol*. 2006;26:9220–9231. https://doi.org/10.1128/MCB.01453-06

54. Youle RJ, van der Bliek AM. Mitochondrial fission, fusion, and stress. *Science*. 2012;337:1062–1065. https://doi.org/10.1126/science.1219855

55. Archer SL. Mitochondrial dynamics–mitochondrial fission and fusion in human diseases. *N Engl J Med*. 2013;369:2236–2251. https://doi.org/10.1056/NEJMra1215233

56. Ma L, Ainsworth HC, Snipes JA, et al. APOL1 kidney-risk variants induce mitochondrial fission. *Kidney Int Rep*. 2020;5:891–904. https://doi.org/10.1016/j.ekir.2020.03.020

57. Kim H, Lee JY, Park KJ, Kim WH, Roh GS. A mitochondrial division inhibitor, Mdivi-1, inhibits mitochondrial fragmentation and attenuates kainic acid-induced hippocampal cell death. *BMC Neurosci*. 2016;17:33. https://doi.org/10.1186/s12868-016-0270-y

58. Kruzel-Davila E, Shemer R, Ofir A, et al. APOL1-mediated cell injury involves disruption of conserved trafficking processes. *J Am Soc Nephrol*. 2017;28:1117–1130. https://doi.org/10.1681/ASN.2016050546

59. Lan X, Jhaveri A, Cheng K, et al. APOL1 risk variants enhance podocyte necrosis through compromising lysosomal membrane permeability. *Am J Physiol Ren Physiol*. 2014;307:F326–F336. https://doi.org/10.1152/ajprenal.00647.2013

60. Kruzel-Davila E, Bavli-Kertselli I, Ofir A, et al. Endoplasmic reticulum-translocation is essential for APOL1 cellular toxicity. *iScience*. 2022;25:103717. https://doi.org/10.1016/j.isci.2021.103717

61. Chun J, Zhang JY, Wilkins MS, et al. Recruitment of APOL1 kidney disease risk variants to lipid droplets attenuates cell toxicity. *Proc Natl Acad Sci U S A*. 2019;116:3712–3721. https://doi.org/10.1073/pnas.1820414116

62. Grampp S, Kruger R, Lauer V, et al. Hypoxia hits APOL1 in the kidney. *Kidney Int*. 2023;104:53–60. https://doi.org/10.1016/j.kint.2023.03.035

63. Cybulsky AV. The intersecting roles of endoplasmic reticulum stress, ubiquitin- proteasome system, and autophagy in the pathogenesis of proteinuric kidney disease. *Kidney Int*. 2013;84:25–33. https://doi.org/10.1038/ki.2012.390

64. Zhang H, You QD, Xu XL. Targeting stimulator of interferon genes (STING): a medicinal chemistry perspective. *J Med Chem*. 2020;63:3785–3816. https://doi.org/10.1021/acs.jmedchem.9b01039

65. Zhang S, Zheng R, Pan Y, Sun H. Potential therapeutic value of the STING inhibitors. *Molecules*. 2023;28. https://doi.org/10.3390/molecules28073127

66. Couillin I, Riteau N. STING signaling and sterile inflammation. *Front Immunol*. 2021;12:753789. https://doi.org/10.3389/fimmu.2021.753789

67. Decout A, Katz JD, Venkatraman S, Ablasser A. The cGAS-STING pathway as a therapeutic target in inflammatory diseases. *Nat Rev Immunol*. 2021;21:548–569. https://doi.org/10.1038/s41577-021-00524-z

68. Wu J, Raman A, Coffey NJ, et al. The key role of NLRP3 and STING in APOL1-associated podocytopathy. *J Clin Invest*. 2021:131. https://doi.org/10.1172/JCI136329

69. Okamoto K, Rausch JW, Wakashin H, et al. APOL1 risk allele RNA contributes to renal toxicity by activating protein kinase R. *Commun Biol*. 2018;1:188. https://doi.org/10.1038/s42003-018-0188-2

70. Wan G, Zhaorigetu S, Liu Z, Kaini R, Jiang Z, Hu CA. Apolipoprotein L1, a novel Bcl-2 homology domain 3-only lipid-binding protein, induces autophagic cell death. *J Biol Chem*. 2008;283:21540–21549. https://doi.org/10.1074/jbc.M800214200

71. Hayek SS, Koh KH, Grams ME, et al. A tripartite complex of suPAR, APOL1 risk variants and alphavbeta3 integrin on podocytes mediates chronic kidney disease. *Nat Med*. 2017;23:945–953. https://doi.org/10.1038/nm.4362

72. Hughes JP, Rees S, Kalindjian SB, Philpott KL. Principles of early drug discovery. *Br J Pharmacol*. 2011;162:1239–1249. https://doi.org/10.1111/j.1476-5381.2010.01127.x

73. Jenwitheesuk E, Horst JA, Rivas KL, Van Voorhis WC, Samudrala R. Novel paradigms for drug discovery: computational multitarget screening. *Trends Pharmacol Sci*. 2008;29:62–71. https://doi.org/10.1016/j.tips.2007.11.007

74. Moffat JG, Vincent F, Lee JA, Eder J, Prunotto M. Opportunities and challenges in phenotypic drug discovery: an industry perspective. *Nat Rev Drug Discov*. 2017;16:531–543. https://doi.org/10.1038/nrd.2017.111

75. Plenge RM, Scolnick EM, Altshuler D. Validating therapeutic targets through human genetics. *Nat Rev Drug Discov*. 2013;12:581–594. https://doi.org/10.1038/nrd4051

76. Tautermann CS. Current and future challenges in modern drug discovery. *Methods Mol Biol*. 2020;2114:1–17. https://doi.org/10.1007/978-1-0716-0282-9_1

77. Reilly DF, Breyer MD. The use of genomics to drive kidney disease drug discovery and development. *Clin J Am Soc Nephrol*. 2020;15:1342–1351. https://doi.org/10.2215/CJN.11070919

78. Liu GH, Chen T, Zhang X, Ma X, Shi H. Small molecule inhibitors targeting the cancers. *MedCommComm (2020)*. 2022;3:e181. https://doi.org/10.1002/mco2.181, 2022.

79. Zhou Y, Castonguay P, Sidhom EH, et al. A small-molecule inhibitor of TRPC5 ion channels suppresses progressive kidney disease in animal models. *Science*. 2017;358:1332–1336. https://doi.org/10.1126/science.aal4178

80. Assimon V, Bronner S, Yu C, et al. MZ-301 Is a Small Molecule Inhibitor of APOL1 Pore Function That Attenuates Albuminuria in a Mouse Model of APOL1-Mediated Kidney Disease. ASN Kidney Week 2022 Poster FR-PO318. Accessed September 12, 2023. https://www.asn-online.org/education/kidneyweek/archives/KW22Abstracts.pdf

81. Carton-Garcia F, Saande CJ, Meraviglia-Crivelli D, Aldabe R, Pastor F. Oligonucleotide-based therapies for renal diseases. *Biomedicines*. 2021;9:303. https://doi.org/10.3390/biomedicines9030303

82. Dhuri K, Bechtold C, Quijano E, et al. Antisense oligonucleotides: an emerging area in drug discovery and development. *J Clin Med*. 2020;9:2004. https://doi.org/10.3390/jcm9062004

83. Li H, Wang C, Che R, et al. A potential therapy using antisense oligonucleotides to treat autosomal recessive polycystic kidney disease. *J Clin Med*. 2023:12. https://doi.org/10.3390/jcm12041428

84. Aghajan M, Booten SL, Althage M, et al. Antisense oligonucleotide treatment ameliorates IFN-gamma-induced proteinuria in APOL1-transgenic mice. *JCI Insight*. 2019;4:e126124. https://doi.org/10.1172/jci.insight.126124

85. Shastri A, Choudhary G, Teixeira M, et al. Antisense STAT3 inhibitor decreases viability of myelodysplastic and leukemic stem cells. *J Clin Invest*. 2018;128:5479–5488. https://doi.org/10.1172/JCI120156

86. Hong D, Kurzrock R, Kim Y, et al. AZD9150, a next-generation antisense oligonucleotide inhibitor of STAT3 with early evidence of clinical activity in lymphoma and lung cancer. *Sci Transl Med*. 2015;7:314ra185. https://doi.org/10.1126/scitranslmed.aac5272