

Small molecule inhibition of APOL1 reverses albuminuria in a chronic mouse model of APOL1 kidney disease



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Introduction

Two coding variants in the APOL1 gene (G1 and G2) confer a greater risk for progressive, proteinuric kidney disease in individuals of African ancestry. Available therapies do not address the causal genetic driver of disease, highlighting the need for novel efficacious APOL1-targeted treatments. We have previously shown that pharmacologic inhibition of APOL1 pore function ameliorates albuminuria in an acute mouse model of APOL1 kidney disease (AKD). Here we describe the development of a novel chronic AKD mouse model heterozygous for the APOL1 G1/G2 variants. Continuous increased APOL1 expression was achieved by infecting mice with an adeno-associated virus (AAV) engineered to express interferon- γ (IFN γ), resulting in elevated uACR and glomerulosclerosis. Oral administration of a small molecule APOL1 inhibitor, MZ-302, robustly reversed established IFN γ -induced albuminuria and kidney injury in APOL1 G1/G2 transgenic mice.

IFN γ induces albuminuria in APOL1 G1/G2 HET mice

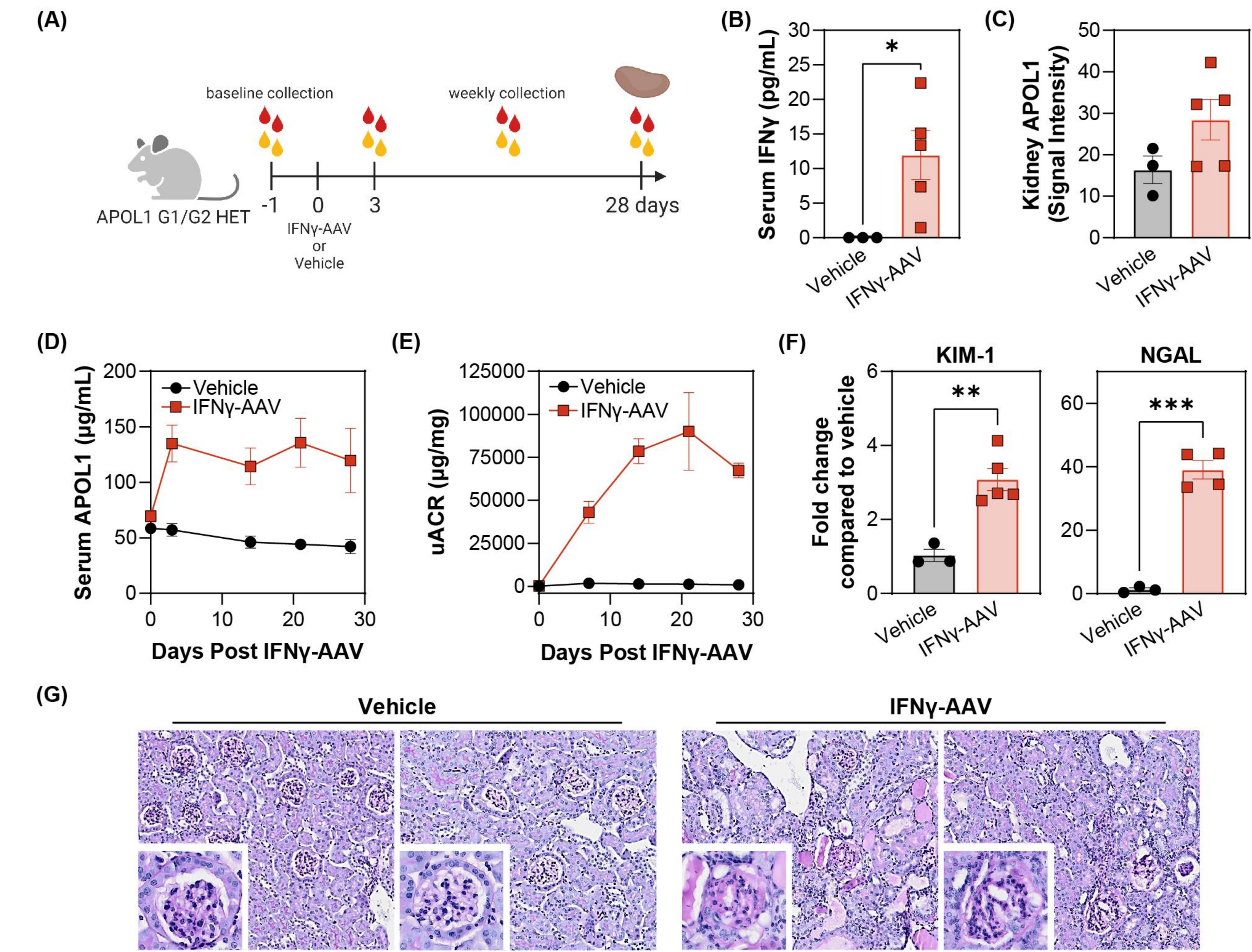


Figure 1. APOL1 transgenic mice were generated using a bacterial artificial chromosome (BAC) containing APOL1 and its upstream and downstream genomic regions. Mice were provided by Taconic Biosciences Inc on behalf of Merck Sharp & Dohme LLC, Rahway, NJ. Administration of IFN γ -AAV in APOL1 G1/G2 HET mice led to sustained APOL1 induction, elevated uACR, and glomerulosclerosis. (A) Schematic highlighting the administration of IFN γ -AAV and urine/tissue collections. (B) Terminal serum levels of IFN γ from mice. An unpaired t-test was performed (* $p=0.0450$). (C) Quantified western blot of normalized APOL1 levels from mouse kidneys. (D) Serum levels of APOL1 from mice dosed with IFN γ -AAV or vehicle (PBS). (E) uACR in APOL1 G1/G2 HET mice. (F) Kidney injury markers, KIM-1 and NGAL, were evaluated by qPCR from mouse kidney tissue homogenates. An unpaired t-test was conducted (** $p=0.0027$ and *** $p=0.0001$). (G) PAS staining of mouse kidneys. Error bars represent the SEM for all experiments.

MZ-302 reverses albuminuria and kidney injury in the APOL1 G1/G2 chronic model

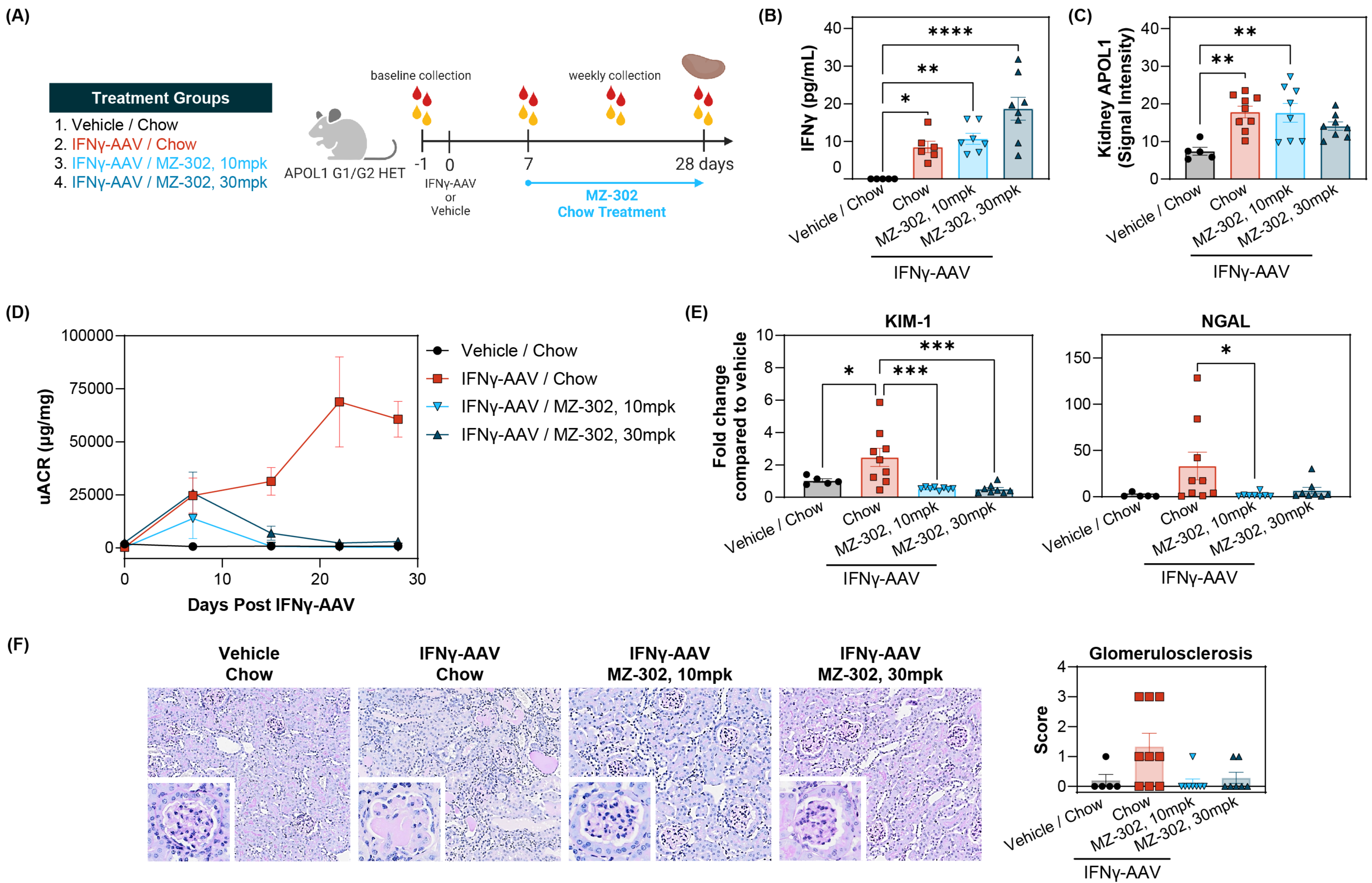


Figure 2. Oral administration of a small molecule APOL1 inhibitor, MZ-302, robustly reversed established IFN γ -induced albuminuria and kidney injury in APOL1 G1/G2 transgenic mice. (A) Schematic highlighting the administration of IFN γ -AAV, MZ-302, and urine/tissue collections. (B) Terminal serum levels of IFN γ from mice. A one-way ANOVA with a Dunnett's multiple comparison test was performed (* $p=0.0470$, ** $p=0.0089$, and **** $p<0.0001$). (C) Quantified western blot of normalized APOL1 levels from kidneys. A one-way ANOVA with a Tukey's multiple comparison test was performed (** $p<0.01$). (D) uACR assessment over time. (E) Kidney injury markers, KIM-1 and NGAL, were evaluated by qPCR from kidney tissue homogenates. A one-way ANOVA with a Dunnett's multiple comparison test was performed (* $p<0.05$ and *** $p<0.001$). (F) Histological assessment of kidneys by PAS staining and corresponding glomerulosclerosis scoring. IFN γ -AAV / Chow mice had a greater number of glomerular and tubular lesions than Vehicle / Chow or IFN γ -AAV / MZ-302 treatment groups. Error bars represent the SEM for all experiments.

Conclusions

- We have developed a novel chronic AKD mouse model heterozygous for the APOL1 G1/G2 variants, where administration of IFN γ -AAV led to sustained APOL1 induction, elevated uACR, and glomerulosclerosis.
- Oral administration of a small molecule APOL1 inhibitor, MZ-302, robustly reversed established IFN γ -induced albuminuria and kidney injury in a chronic mouse model of AKD.
- These findings support the continued development of precision APOL1-targeted small molecule therapies for patients with AKD.