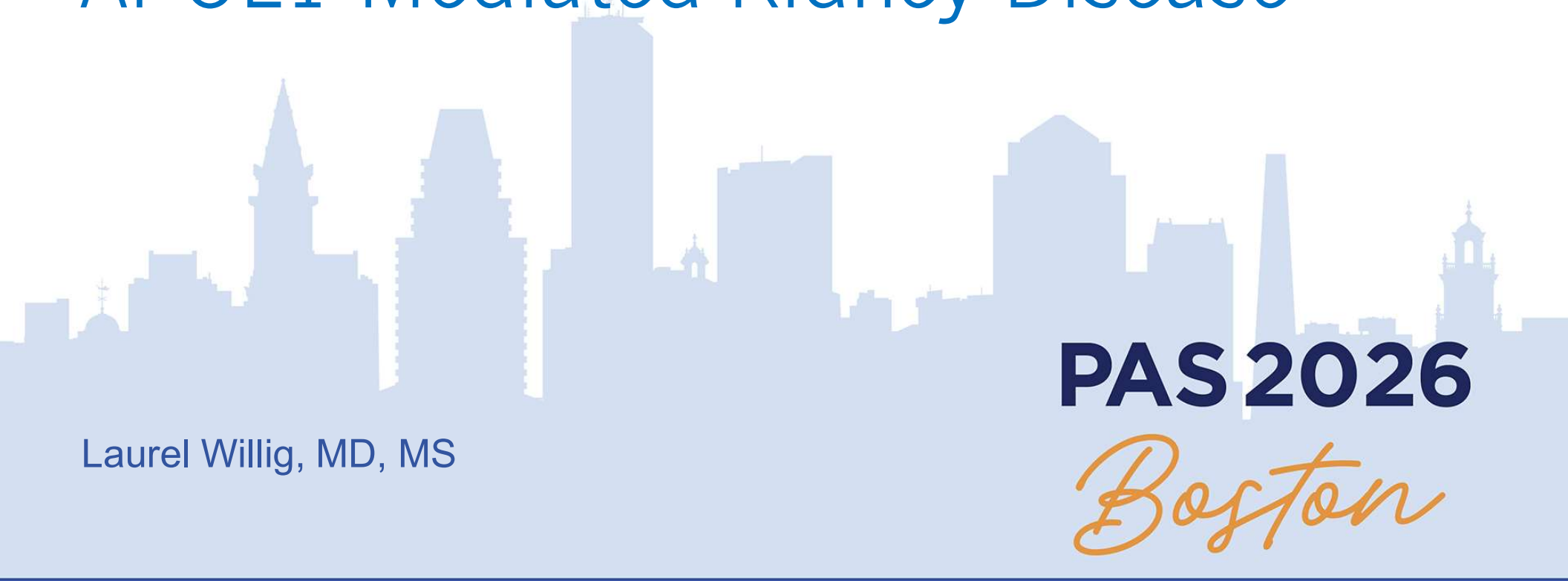
Clinical Management and Treatment of APOL1 Mediated Kidney Disease

Laurel Willig, MD, MS



PAS 2026

Boston

97TH PEDIATRIC ACADEMIC SOCIETIES MEETING

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Disclosure

Laurel Willig, MD, MS

Has documented no financial relationships to disclose or Conflicts of Interest (COIs) to resolve.

PAS

Unapproved or Off Label

Disclosures for
Laurel Willig, MD, MS

Presenter: This presentation ***will*** involve comments or discussion of unapproved or off-label, experimental or investigational use of multiple agents. The only things I am discussing that are **ON** label at least for pediatric patients in any detail are RAAS inhibitors. SGLT2 inhibitors and sparesentan are approved for some uses discussed.

PAS

Inflammatory Imperial Attack

Ion Channel Activation

Inflammatory Response

APOL1 G1/G2

Autophagy

Mitochondrial Dysfunction

Endothelial Injury

Podocyte Destruction

Tubular Injury

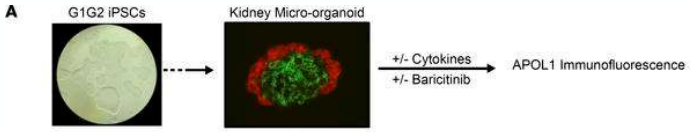
Unsplash Photo: Brian McGowan

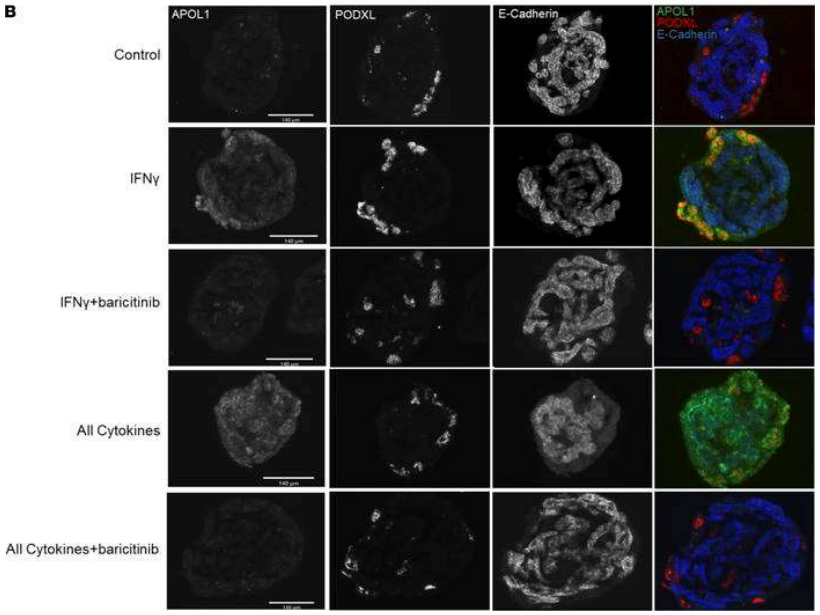
Attacking the Upstream Inflammatory Second Hit: Steroids, Tacrolimus…

- Little evidence for improved clinical status with immunosuppression
  - Small cases series in patients with collapsing FSGS show poor outcomes with immunosuppression
- No clinical trials of immunosuppression in APOL1 mediated renal diseases in adults or children
- Use should be limited to those patients whose triggers are diseases that require/respond to immunosuppression (i.e. lupus)

Unsplash Photo: Brian McGowan

Attacking the Upstream Inflammatory Second Hit: Baricitinib



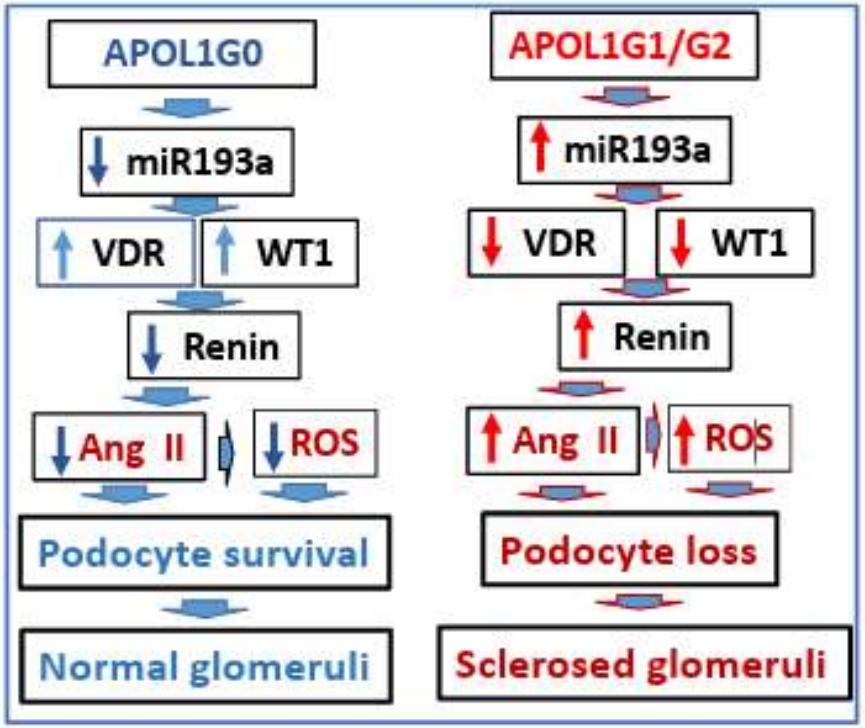


Nystrom, SE et al, 2022 and Olabisi, OA et al, 2024

- (JAK- STAT) signaling seems to drive the cytokine reaction seen APOL1 mediated kidney disease
- Blocking Jak-STAT blocks APOL1 synthesis
- Findings have led to development of the JUSTICE Trial, phase 2 clinical trial in APOL1 mediated hypertensive and FSGS disease
  - Age: 18-70
  - Endpoint: UACR reduction
  - Enrollment: 25 from each kidney disease

Unsplash photo: Eugene Chystiakov

The Supporting Cast: Renin Angiotensin Aldosterone System (RAAS) Inhibitors

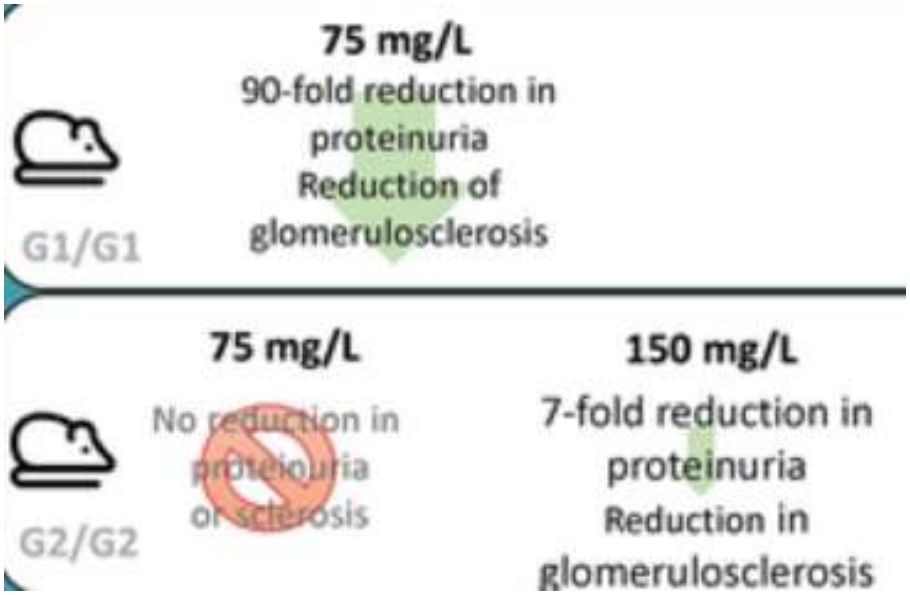


Kumar, V et al, 2024

- RAAS is upregulated in podocytes expressing high risk APOL1 genotypes
- Difference may be mediated by miR193a, a suppressor of WT1 translation

Unsplash photo: Eugene Chystiakov

The Supporting Cast: Renin Angiotensin Aldosterone System (RAAS) Inhibitors



- No difference in ACE levels between the genotypic groups
- Timing of RAAS initiation did not change effect
- Effect not solely attributable to blood pressure control

Sula Karruci, E, et al, 2024

Unsplash photo: Eugene Chystiakov

The Supporting Cast: Sparsentan

Table 2. General and baseline characteristics of patients by genetic and treatment groups

Patient Characteristics	Podocyte Gene Variants				*COL4A3–5* Variants		*APOL1* High-Risk Genotypes	
	All		Recessive *NPHS2* Disease					
	Sparsentan (*n*=13)	Irbesartan (*n*=18)	Sparsentan (*n*=9)	Irbesartan (*n*=6)	Sparsentan (*n*=11)	Irbesartan (*n*=14)	Sparsentan (*n*=9)	Irbesartan (*n*=5)
Age at informed consent, yr, mean (SD)	26 (13)	36 (15)	26 (15)	32 (13)	41 (12)	42 (11)	36 (13)	32 (22)
Age group, yr, *n* (%)								
<18	6 (46)	2 (11)	4 (44)	1 (17)	0 (0)	0 (0)	1 (11)	2 (40)
≥18	7 (54)	16 (89)	5 (56)	5 (83)	11 (100)	14 (100)	8 (89)	3 (60)
Sex, *n* (%)								
Male	4 (31)	5 (28)	3 (33)	2 (33)	5 (45)	6 (43)	5 (56)	3 (60)
Female	9 (69)	13 (72)	6 (67)	4 (67)	6 (55)	8 (57)	4 (44)	2 (40)
Race, *n* (%)[a]								
Asian	0 (0)	1 (6)	0 (0)	0 (0)	1 (9)	3 (21)	0 (0)	0 (0)
Black or African American	2 (15)	1 (6)	2 (22)	1 (17)	0 (0)	1 (7)	7 (78)	2 (40)
Other	0 (0)	1 (6)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	3 (60)
White	12 (92)	15 (83)	8 (89)	5 (83)	10 (91)	10 (71)	2 (22)	0 (0)
BMI, kg/m^2, mean (SD)	24 (5)	25 (5)	24 (5)	23 (4)	29 (6)	26 (5)	34 (7)	34 (9)
BMI group, kg/m^2, *n* (%)								
<27	9 (69)	11 (61)	6 (67)	4 (67)	5 (46)	8 (62)	1 (11)	1 (20)
≥27	4 (31)	7 (39)	3 (33)	2 (33)	6 (55)	5 (39)	8 (89)	4 (80)
eGFR, ml/min per 1.73 m^2								
Mean (SD)[b]	75 (43)	74 (47)	80 (42)	109 (69)	54 (26)	53 (20)	59 (26)	47 (8)
Median (IQR)	56 (47, 93)	62 (46, 75)	79 (53, 93)	123 (32, 141)	47 (40, 67)	46 (40, 55)	50 (41, 66)	44 (42, 50)
UPCR, g/g								
Mean (SD)	4.9 (2.4)	4.2 (2.3)	5.0 (2.9)	4.5 (3.1)	3.2 (1.5)	2.8 (1.5)	2.7 (1.8)	2.7 (1.6)
Median (IQR)	4.5 (3.5–5.3)	3.7 (2.9–5.2)	3.7 (3.5–5.7)	3.9 (2.9–6.7)	2.6 (2.0–4.2)	2.6 (1.9–4.5)	1.8 (1.6–3.2)	2.1 (1.9–2.3)

APOL1, apolipoprotein L1; *COL4A3–5*, collagen type 4 α3, α4, and α5; BMI, body mass index; CKD-EPI, CKD Epidemiology Collaboration; IQR, interquartile range; *NPHS2*, podocin; UPCR, urine protein-to-creatinine ratio.

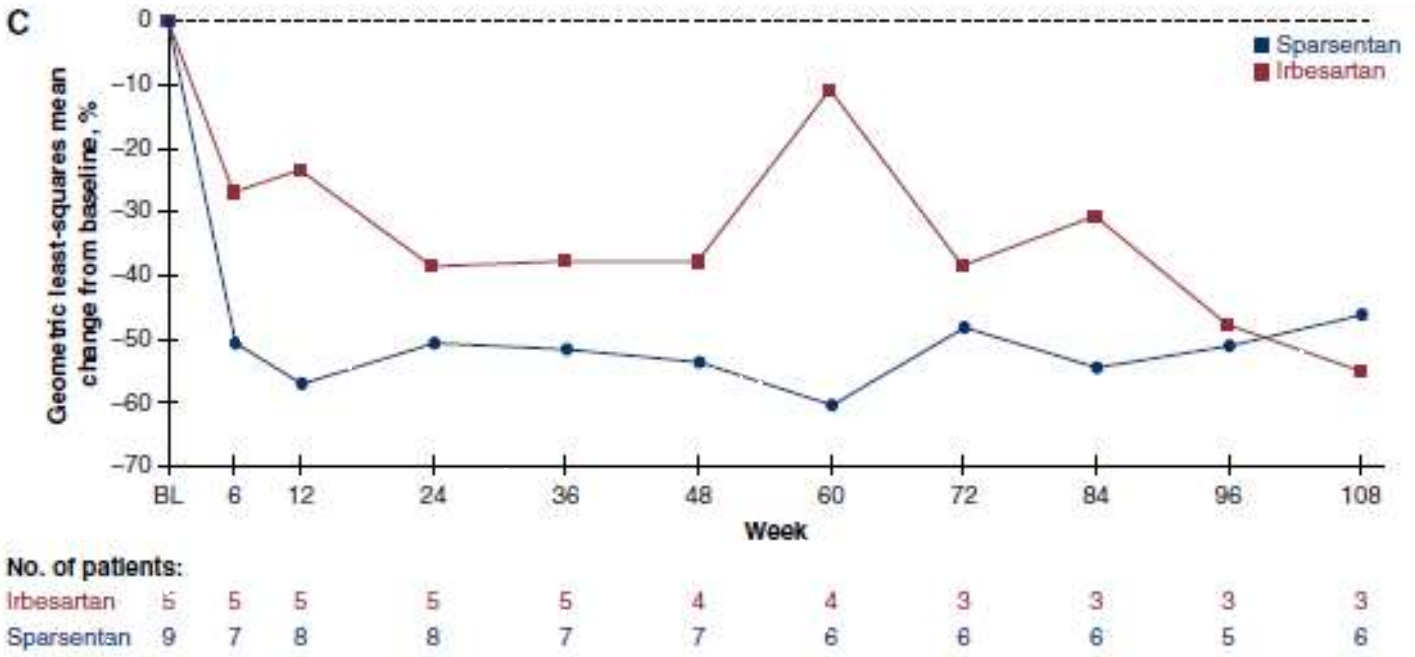
[a]Race was reported by the patients; patients could have selected more than one race.

[b]eGFR was determined using the CKD Epidemiology Collaboration equation for patients ≥16 years of age and the modified Schwartz formula for patients <16 years of age at screening.

Yee, J, et al, 2026

Unsplash photo: Eugene Chystiakov

The Supporting Cast: Sparsentan



Yee, J, et al, 2026

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The Supporting Cast: Sparsentan

Table 3 - Time-weighted urine protein-to-creatinine ratio change from baseline by genetic and treatment groups

Type of Variant/Genotype	Time-Averaged Change from Baseline, % (95% CI)		Relative Change, % (95% CI)	*P* Value
	Sparsentan	Irbesartan		
Podocyte gene variants	−53.4 (−63.7 to −40.3)	−21.5 (−36.8 to −2.6)	−32.5 (−52.7 to −3.9)	0.03
COL4A3–5 variants	−59.7 (−70.3 to −45.5)	−23.1 (−41.8 to 1.6)	−44.9 (−63.6 to −16.5)	0.01
APOL1 high-risk genotypes	−54.3 (−76.6 to −10.9)	−33.8 (−71.2 to 52.2)	−27.3 (−78.1 to 141.2)	0.57

APOL1, apolipoprotein L1; CI, confidence interval; *COL4A3–5*, collagen type 4 α3, α4, and α5.

Yee, J, et al, 2026

Unsplash photo: Eugene Chystiakov

The Supporting Cast: Sparsentan

Table 4 - Changes in eGFR by genetic and treatment groups

eGFR Change from Baseline to Week 108	Podocyte Gene Variants		*COL4A3–5* Variants		*APOL1* High-Risk Genotypes	
	Sparsentan (*n*=8)	Irbesartan (*n*=11)	Sparsentan (*n*=9)	Irbesartan (*n*=10)	Sparsentan (*n*=6)	Irbesartan (*n*=3)
Mean (SD), ml/min per 1.73 m^2	−20 (29)	−17 (13)	−12 (11)	−10 (8)	−7 (6)	−11 (11)
Median (IQR), ml/min per 1.73 m^2	−7 (−48 to −2)	−13 (−27 to −8)	−8 (−17 to −4)	−11 (−15 to −2)	−8 (−12 to −1)	−7 (−23 to −3)

APOL1, apolipoprotein L1; *COL4A3–5*, collagen type 4 α3, α4, and α5; IQR, interquartile range.

Yee, J, et al, 2026

Unsplash photo: Eugene Chystiakov

The Supporting Cast: SGLT2 Inhibitors

- No clinical trials specifically in APOL1 disease
- Small case series shows a 40% reduction in proteinuria in Alport syndrome and FSGS
- No evidence that dapagliflozin as standard dosing decreased proteinuria or glomerulosclerosis in transgenic mice with G1/G1 or G2/G2 phenotype

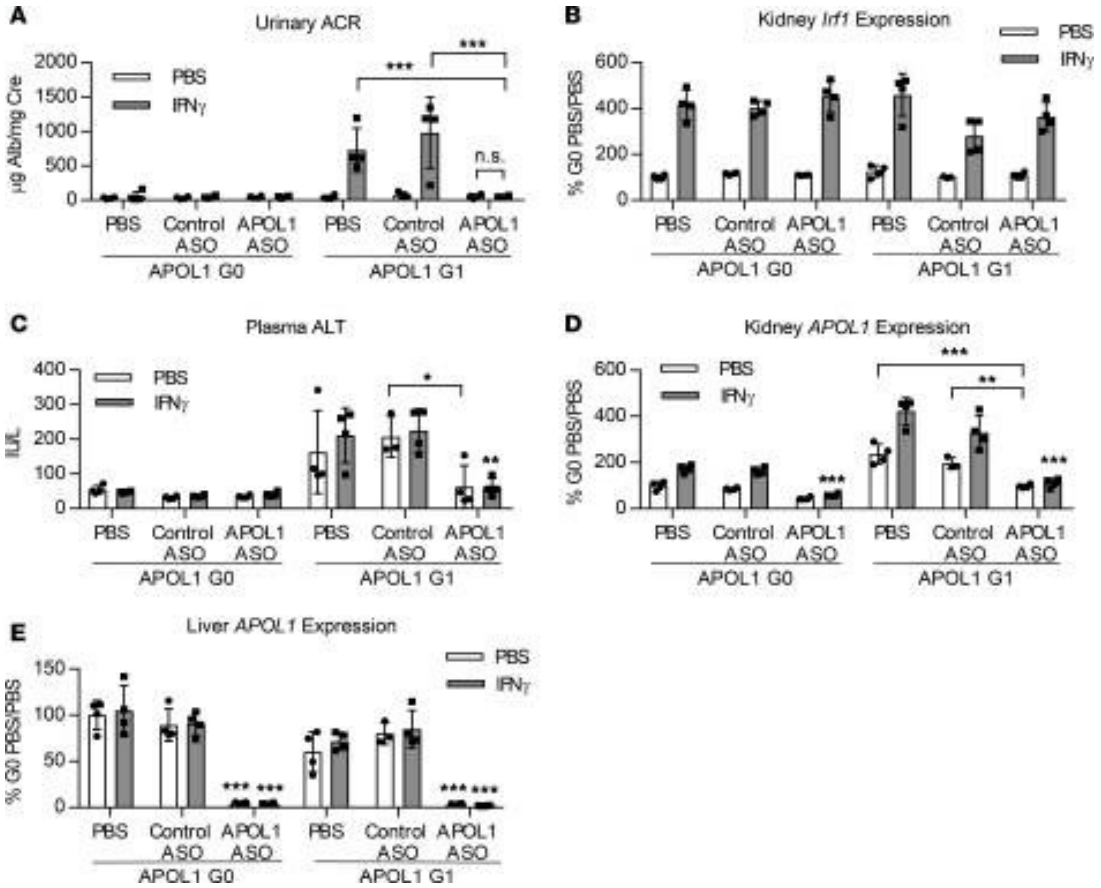
Sula Karruci, E, et al, 2024

Boeckhaus J, et al, 2021

StarWars.com free background

Altering the Force: AZD2373 (opemalirsen) an Antisense oligonucleotide (ASO) inhibitor of *APOL1*

- AZD2373 reduces proteinuria through decreased APOL1 expression in G0 and G1 transgenic mice
- There is a Phase 2B trial of AZD2373 (NCT06824987)
  - Ages 18-65 years
  - Design: Randomized, double blinded to 3 arms
  - Enroll: 96



Aghajan, M et al, 2019 and Clinical Trials, 2026

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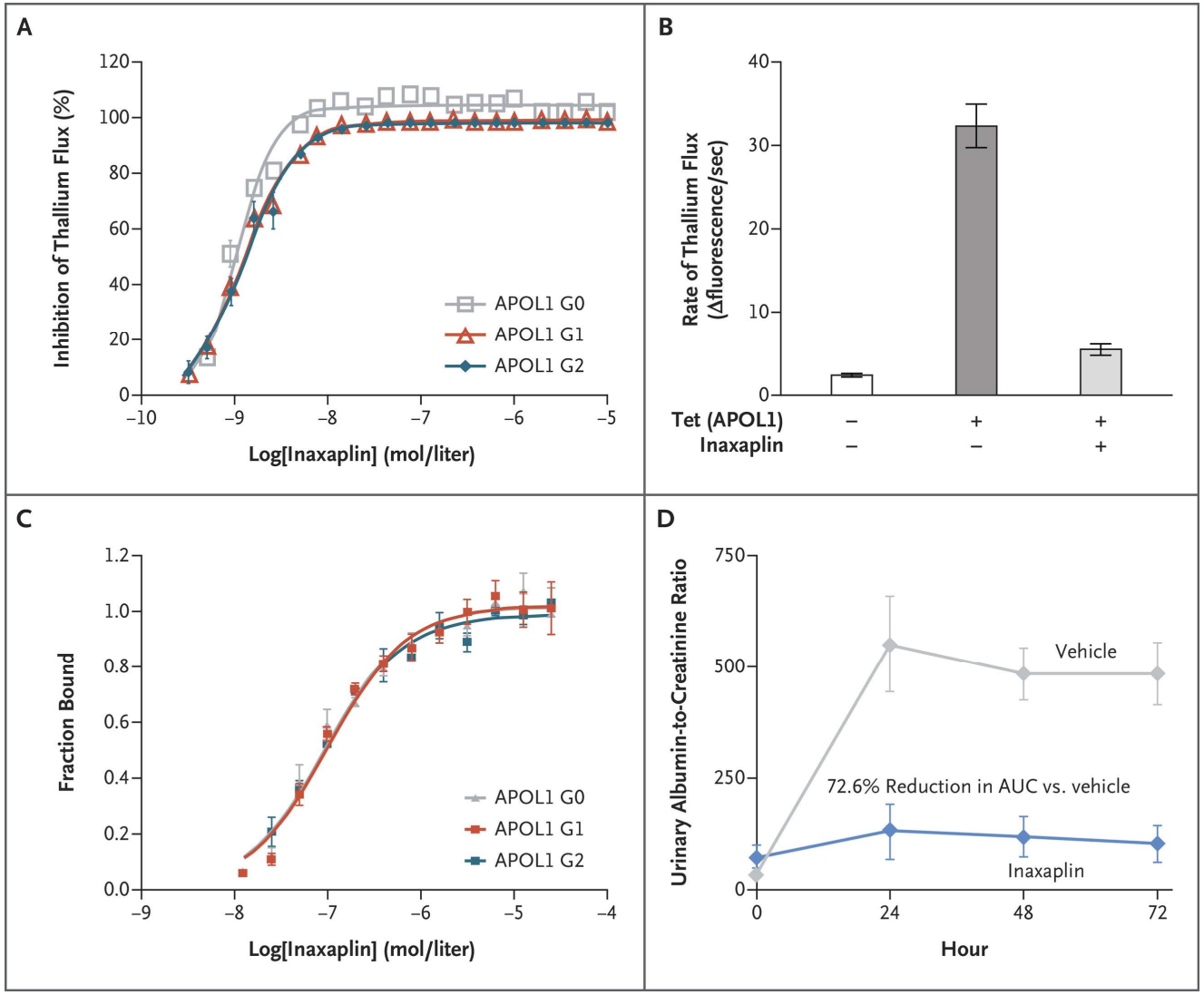
The Exhaust Port: Inaxaplin's Preclinical data



Egbuna, O, et al, 2023

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The Exhaust Port: Inaxaplin's Clinical 2a Trial

Table 2. Mean Percent Change from the Baseline Urinary Protein-to-Creatinine Ratio at Week 13.*

Variable	Total (N=13)	Participants with Nephrotic-Range Proteinuria (N=3)	Participants with Subnephrotic-Range Proteinuria (N=10)
Mean urinary protein-to-creatinine ratio			
At baseline	2.21±0.95	3.47±1.07	1.84±0.52
At wk 13	1.27±0.73	1.83±0.58	1.10±0.71
Geometric percent change from baseline at wk 13 (95% CI)	−47.6 (−60.0 to −31.3)	−47.7 (−70.1 to −8.5)	−47.5 (−63.4 to −24.6)

* Plus–minus values are means ±SD. Baseline and week 13 assessments of the urinary protein-to-creatinine ratio for each of the participants were calculated as the mean of three first-morning void measurements obtained within a 7-day window. The efficacy analysis set included all the participants who completed inaxaplin treatment and had at least 80% adherence to treatment. CI denotes confidence interval.

Egbuna, O, et al, 2023

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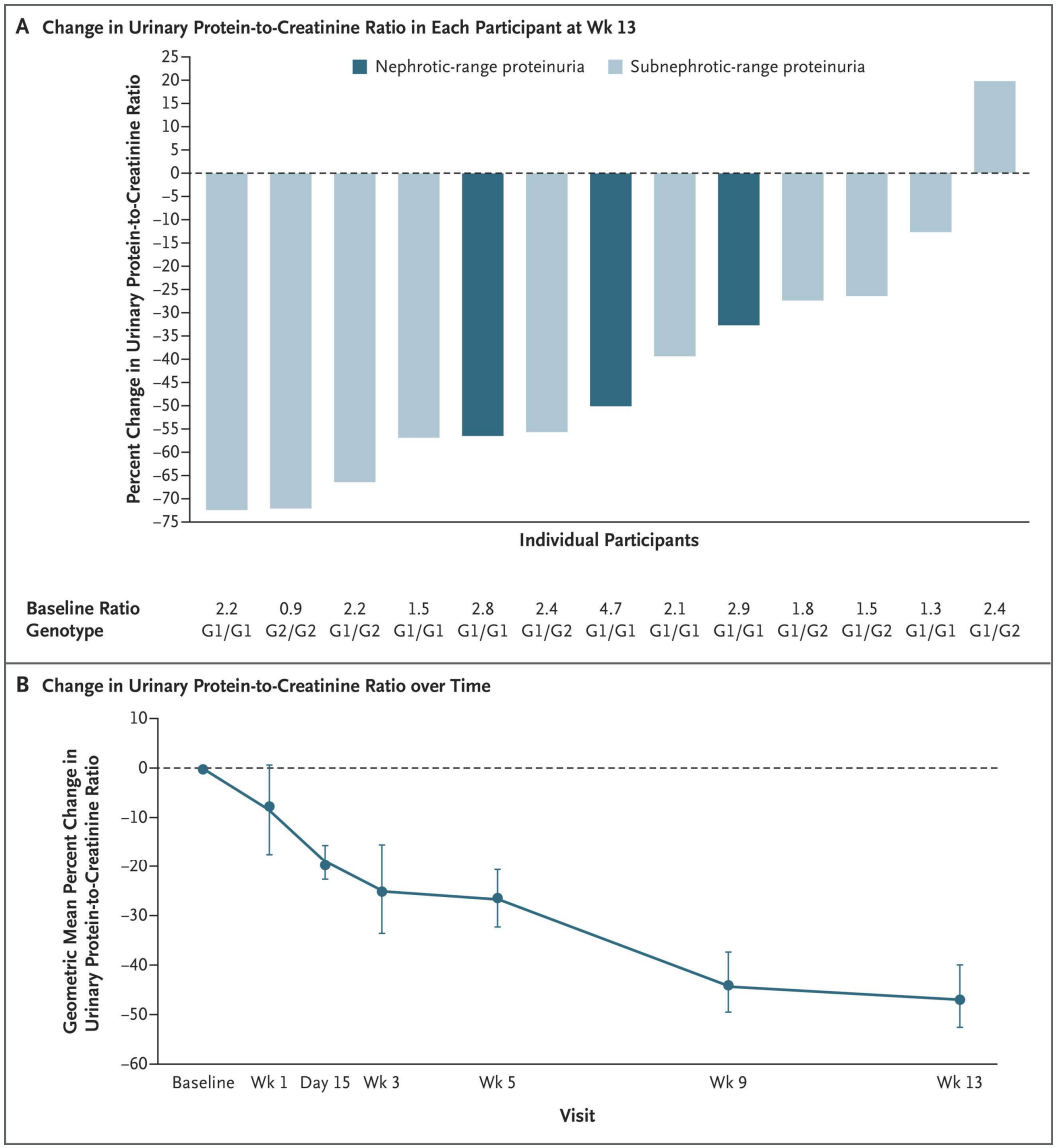
The Exhaust Port: Inaxaplin's Clinical 2a Trial

Egbuna, O, et al, 2023



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The Exhaust Port: Inaxaplin's Clinical 2a Trial

Egbuna, O, et al, 2023

Table 3. Adverse Events.*

Event	Total (N=16)	Participants with Nephrotic-Range Proteinuria (N=3)	Participants with Subnephrotic-Range Proteinuria (N=13)
Any adverse event†	15 (94)	3 (100)	12 (92)
Adverse events according to severity			
Mild	7 (44)	1 (33)	6 (46)
Moderate	8 (50)	2 (67)	6 (46)
Severe	0	0	0
Life-threatening	0	0	0
Serious adverse event‡	1 (6)	0	1 (8)
Adverse event leading to treatment discontinuation	0	0	0
Adverse event occurring in ≥2 participants			
Headache	4 (25)	1 (33)	3 (23)
Back pain	3 (19)	0	3 (23)
Nausea	3 (19)	1 (33)	2 (15)
Decrease in blood bicarbonate level	2 (12)	0	2 (15)
Diarrhea	2 (12)	1 (33)	1 (8)
Dizziness	2 (12)	0	2 (15)
Dyspepsia	2 (12)	0	2 (15)
Fatigue	2 (12)	0	2 (15)

* The safety analysis included all the participants who received at least one dose of inaxaplin.
† Adverse events that were considered by the investigator as being possibly related to inaxaplin occurred in three participants: headache in one participant in the nephrotic-range group and in one in the subnephrotic-range group and headache, abdominal distension, dyspepsia, and back pain in one participant in the subnephrotic-range group.
‡ Two serious adverse events occurred in one participant: deep-vein thrombosis and uterine leiomyoma. Neither event was considered by the investigator to be related to inaxaplin.

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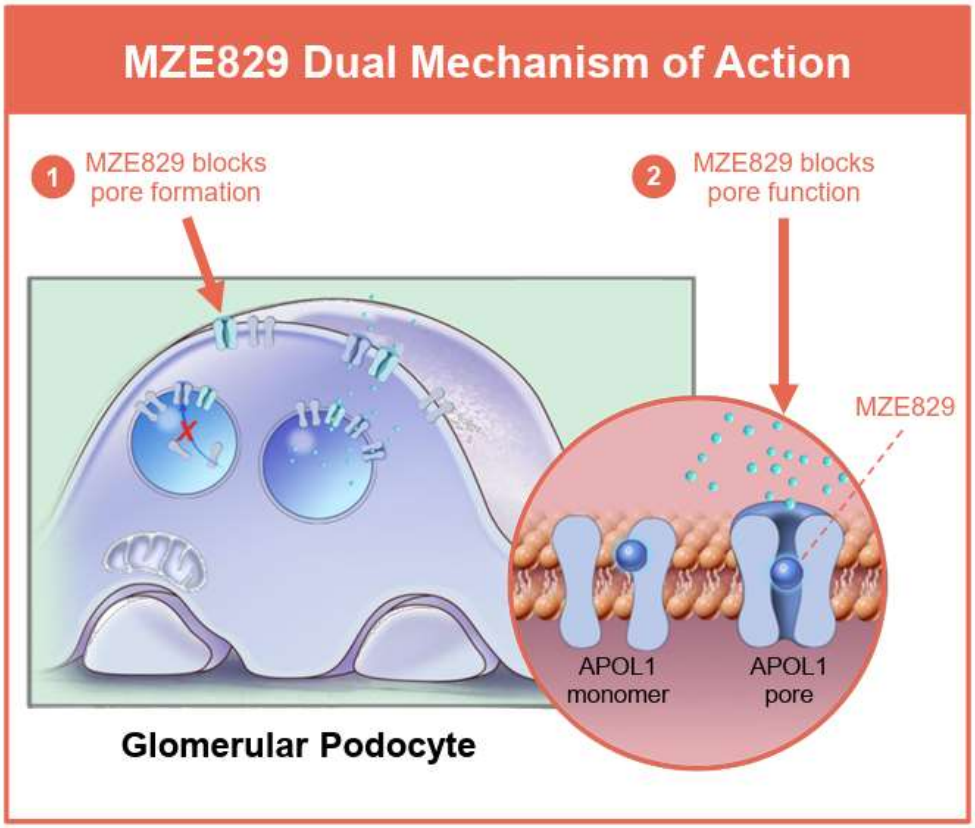
The Exhaust Port: Future Inaxiplan Trials

- Amplitude Trial (NCT05312879)
  - Adaptive Phase 2/3
  - Design: Randomized, double-blind, placebo controlled
  - Population: Age 10-65yrs
  - Enrollment: ~466
  - Outcome: Change in albuminuria
- Other small molecule ion channel blockers are in the works but are pre-IND

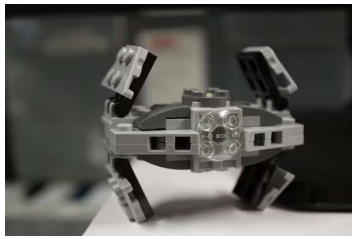
ClinicalTrials.gov

MZE829: Dual Mechanism Small Molecule Inhibitor



- Oral, dual-mechanism small-molecule inhibitor of APOL1 that blocks pore formation and channel function
- Phase 2 – HORIZON trial (NCT06830629)
  - Design: Open-label basket trial across broad AMKD phenotypes
  - Topline results: (Week 12):35.6% mean reduction in UACR overall≥30% UACR reduction in ~50% of patients
  - FSGS subgroup: ~61.8% mean UACR reduction

ClinicalTrials.gov and Maze Therapeutics website, 2026



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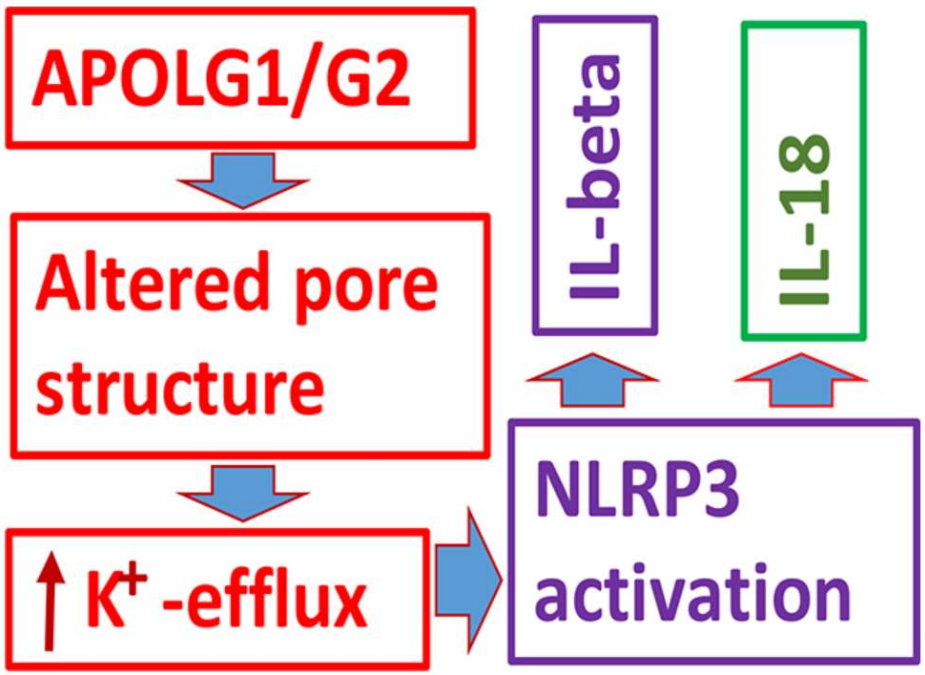
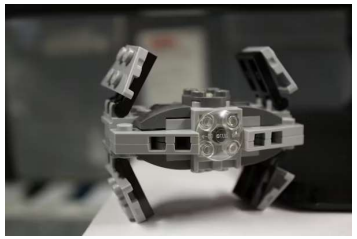
Other Death Star Controls: Inflammasome



Jha, A, et.al, 2020

- K+ efflux stimulates NLRP3 activation
- Glyburide seems to blunt this effect but only at high doses
- NLRP3 inhibitors are active area of study with one specifically, AZD4144, being studied in kidney disease



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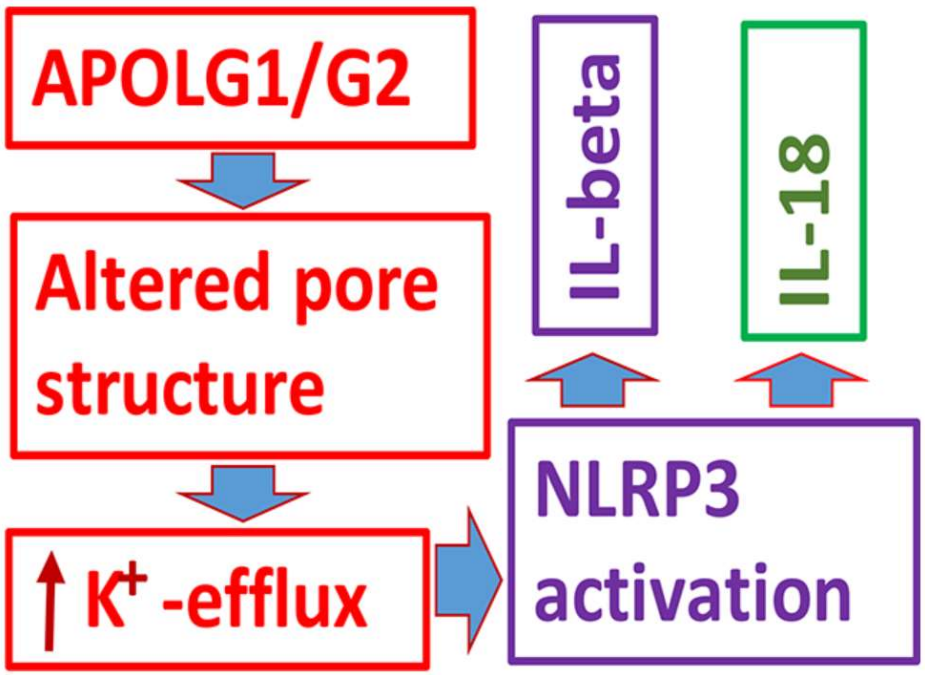

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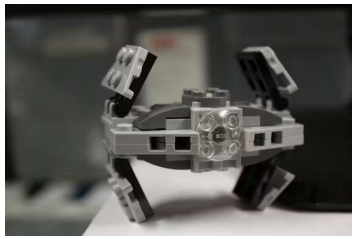
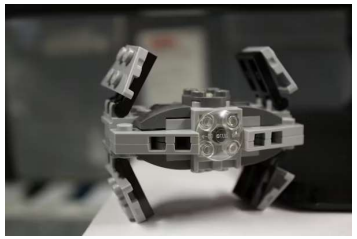


Unsplash: Joel Dryzcimski

Other Death Star Controls: Mitochondrial Function/Metabolic Programming

Therapy / Intervention	Mechanism (mitochondrial)	APOL1 model studied	Key reference (first author, year)
Mdivi-1 (Drp1 inhibitor)	Inhibits mitochondrial fission by blocking Drp1 → preserves mitochondrial network integrity, cristae structure, and cell viability	Human podocytes and renal tubular cells expressing APOL1 G1/G2; APOL1 overexpression models	Ma et al 2020
Elamipretide (SS-31)	Stabilizes cardiolipin and mitochondrial cristae; improves ETC efficiency and ATP generation	APOL1 models not yet directly tested, but proposed based on APOL1-induced cardiolipin-dependent mitochondrial injury	Shankland, et al, 2023
Nac	Increases Glutathione leading to antioxidant and anti-inflammatory effects	APOL1 risk variants biologically implicated, but not directly trialed in APOL1-genotyped cohorts	Shankland, et al, 2023



Unsplash: Joel Dryzcimski

Other Death Star Controls: Abnormal Autophagy

- APOL1 high risk variants induce mTOR activation in podocytes
- Rapamycin has been shown in transgenic G2 mouse models by Shah, et al to decrease proteinuria and improve histologic outcomes of podocytes
- mTOR inhibits autophagy and so rapamycin may increase autophagy and clear APOL1 oligodimers
- However, this rapamycin mouse model suggested instead that it prevented podocyte cell cycle entry
- Notably previous studies in FSGS showed mTOR inhibitors to be deleterious to podocytes

The Rebellion's Tactile Plan (for now)

- APOL1 genotype all non steroid responsive nephrotic syndrome pediatric and adult patients
- Lifestyle modifications
- Maximize use of clinically available antiproteinuric agents
  - RAAS blockade vs sparsentan
- Suspect soon first line treatment may be ion channel inhibitors like inaxiplan or potentially JAK-stat inhibitors

The New Republic: What We Need to Build It

- Better Risk Stratification Given Variable Penetrance
- Better Understanding of the Second Hit Mechanisms
- Better division of the APOL1 mediated renal diseases
- More trials in pediatric patients

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