european society for paediatric nephrology
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ESPN RESEARCH CONFERENCE

FLORENCE 2026
12-14 MARCH

Complement-mediated kidney diseases in the era of complement inhibitors: future perspectives

Complement in FSGS

Andrea Angeletti MD, PhD

INFANTES · SUMMIS · CARITATIS · ET · SCIENTIAE · BENEFICIIS · SUNT
GASLINI

Disclosures

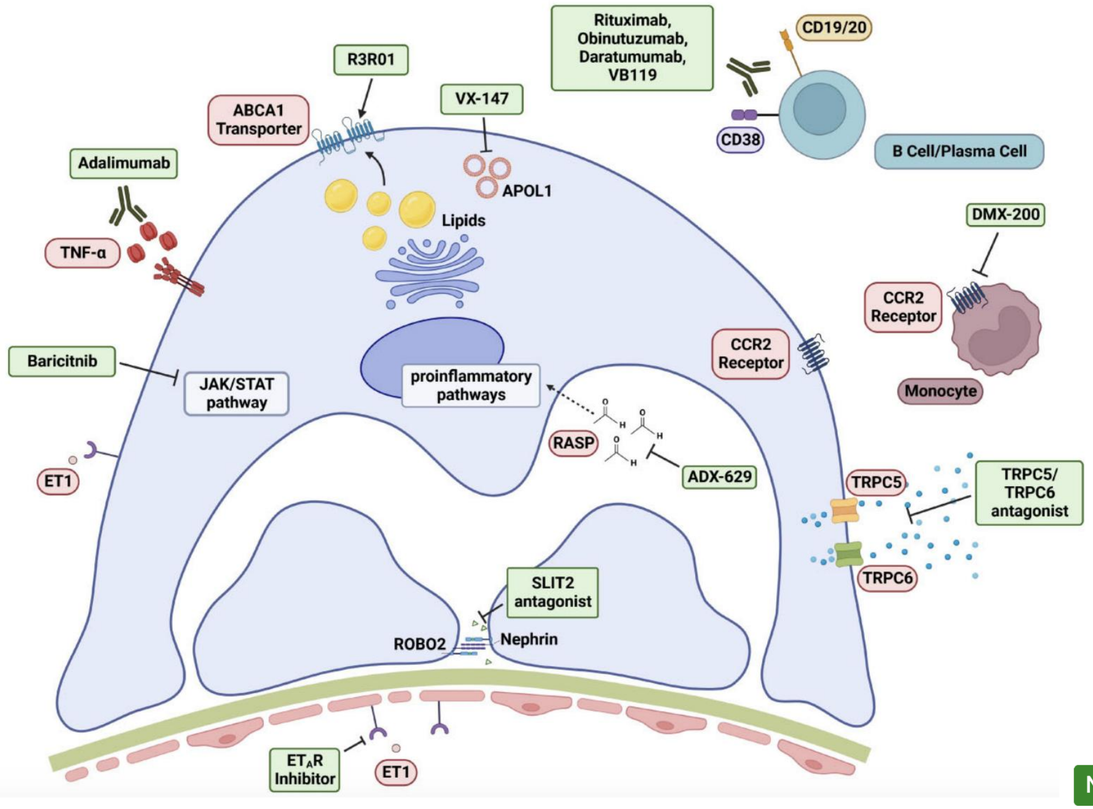
PI/Investigator in Clinical Trials for Roche, Bayer, Angelini, Alexion, Novartis

Consultant for SOBI

Supported for Conferences: Roche, Alexion, Samsung, Otsuka, Bayer, Angelini

Associate Editor: Kidney and Blood Pressure Research, Frontiers in Medicine

A Renaissance in Nephrology:
Potential Drug Targets and Emerging Therapies for Podocytopathies



Nephrol Dial Transplant

Not yet recruiting

A Sequential Phase 2/3 Study of APL2 in Patients With Focal Segmental Glomerulosclerosis

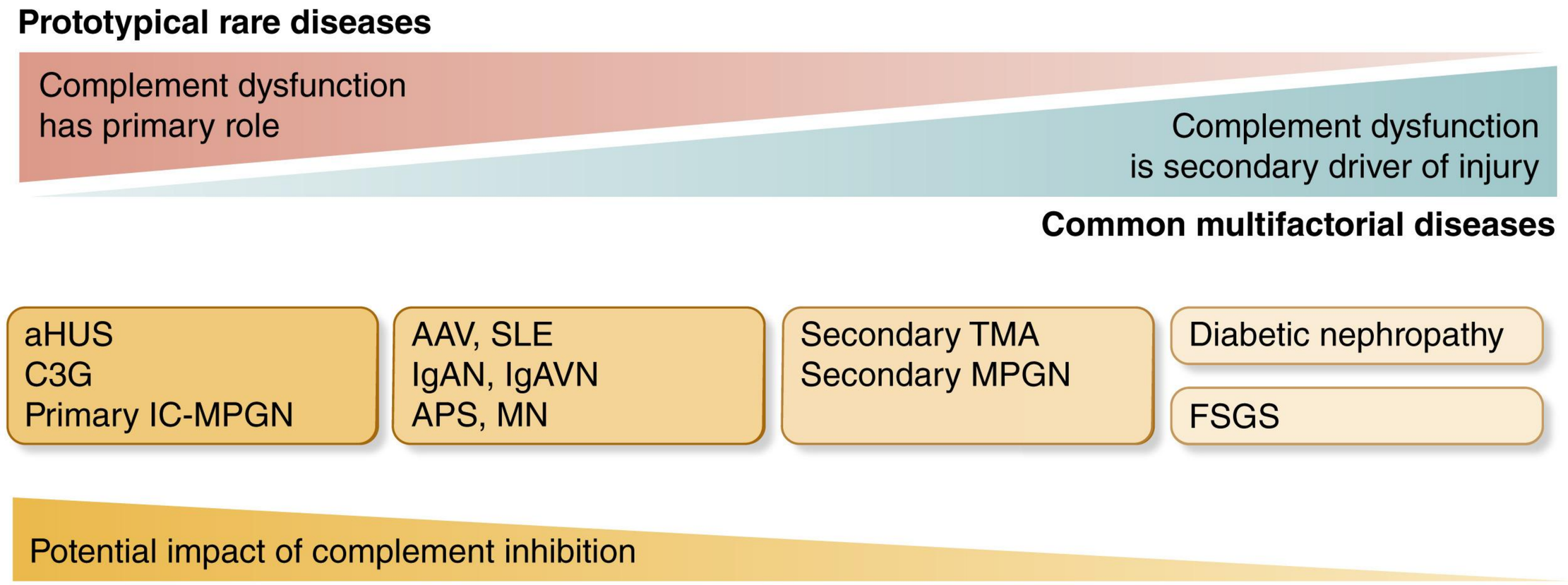
ClinicalTrials.gov ID NCT07213960

Sponsor Apellis Pharmaceuticals, Inc.

Information provided by Apellis Pharmaceuticals, Inc. (Responsible Party)

Last Update Posted 2025-10-09

Complement Targeting Therapies?



Vivarelli, Kidney International, 2024

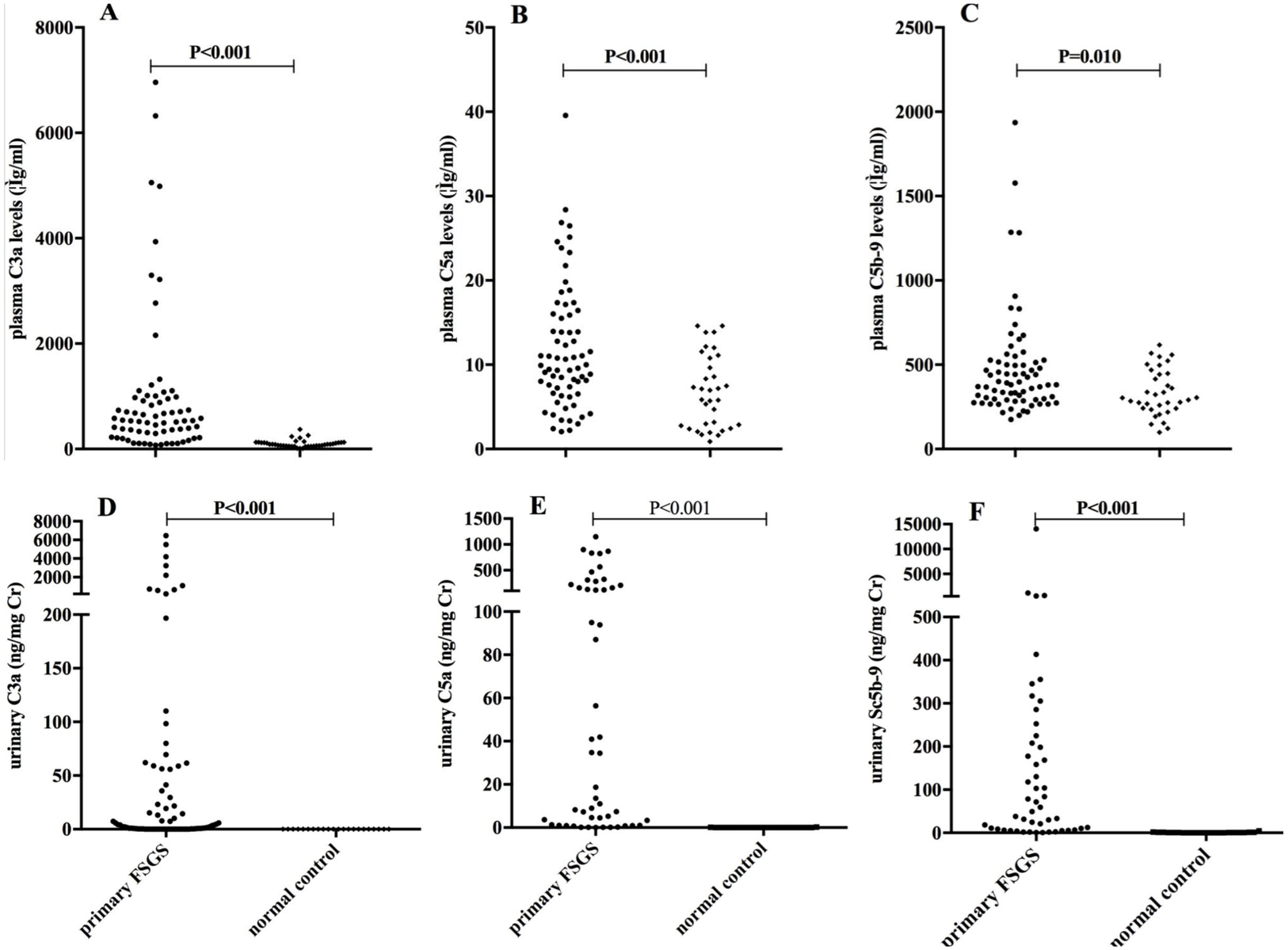
Outline

Is complement activated in FSGS?

Which pathway?

Can complement activation predict disease severity and outcome?

Possible mechanisms



Evidence for the systemic activation of complement in FSGS

Ju et al., *Genome Res* 2013

Huang et al., *Plos One* 2020

Podocytopathies

Giotto - Maestà di Ognissanti
1310 - Galleria degli Uffizi, Florence

Review > Pediatr Nephrol. 2023 Mar;38(3):877-919. doi: 10.1007/s00467-022-05739-3. Epub 2022 Oct 21.

IPNA clinical practice recommendations for the diagnosis and management of children with steroid-sensitive nephrotic syndrome

Review > Pediatr Nephrol. 2020 Aug;35(8):1529-1561. doi: 10.1007/s00467-020-04519-1. Epub 2020 May 7.

IPNA clinical practice recommendations for the diagnosis and management of children with steroid-resistant nephrotic syndrome

IPNA
International Pediatric Nephrology Association

Chapter 4: Nephrotic syndrome in children

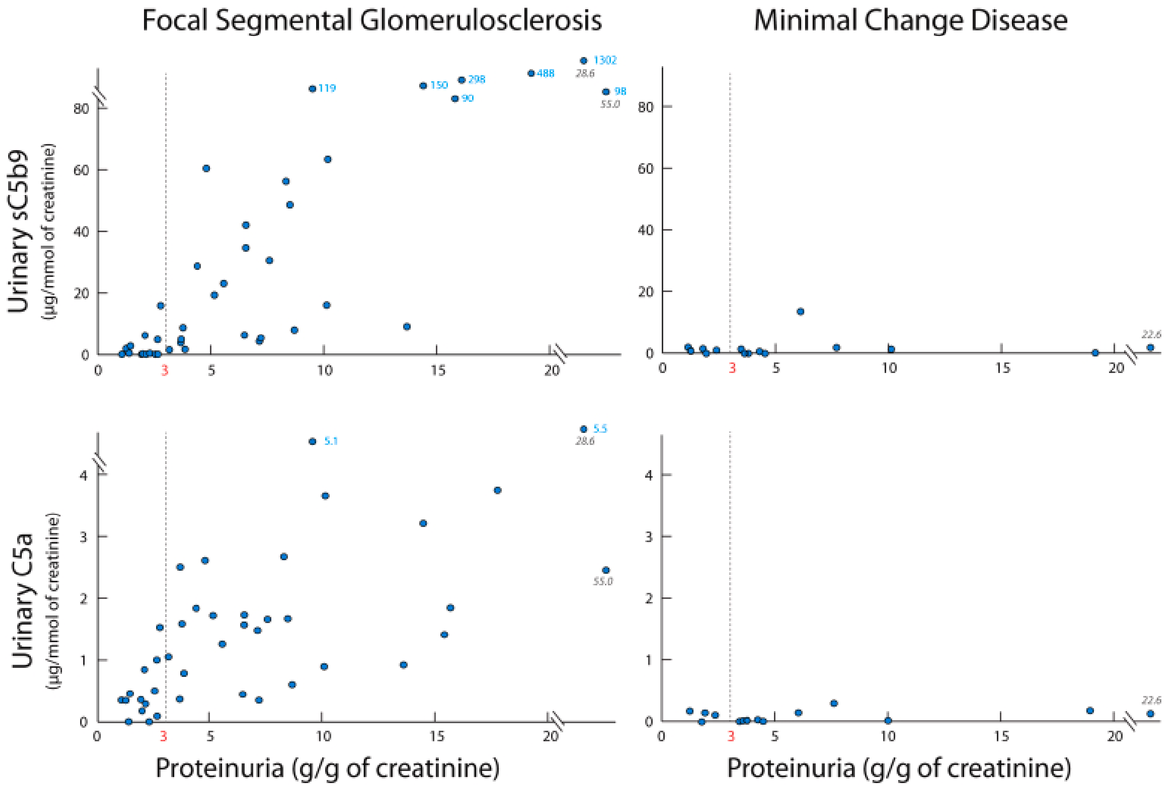
Chapter 5: Minimal change disease (MCD) in adults

Chapter 6: Focal segmental glomerulosclerosis (FSGS) in adults

KIDNEY DISEASE · IMPROVING GLOBAL OUTCOMES · KDIGO

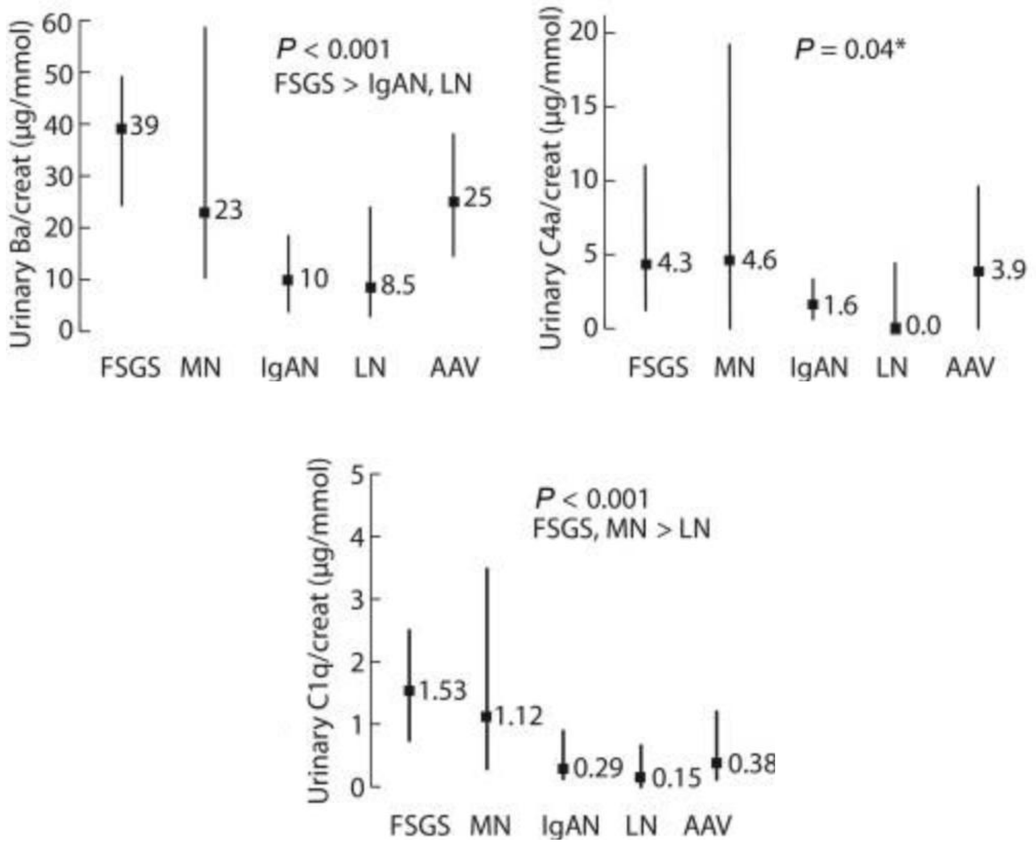
Classification and treatments are still based on steroid responsiveness

Urinary sC5b9 and C5a creatinine ratios compared to proteinuria in FSGS and MCD



Cambier et al. Kidney Int Rep. 2023

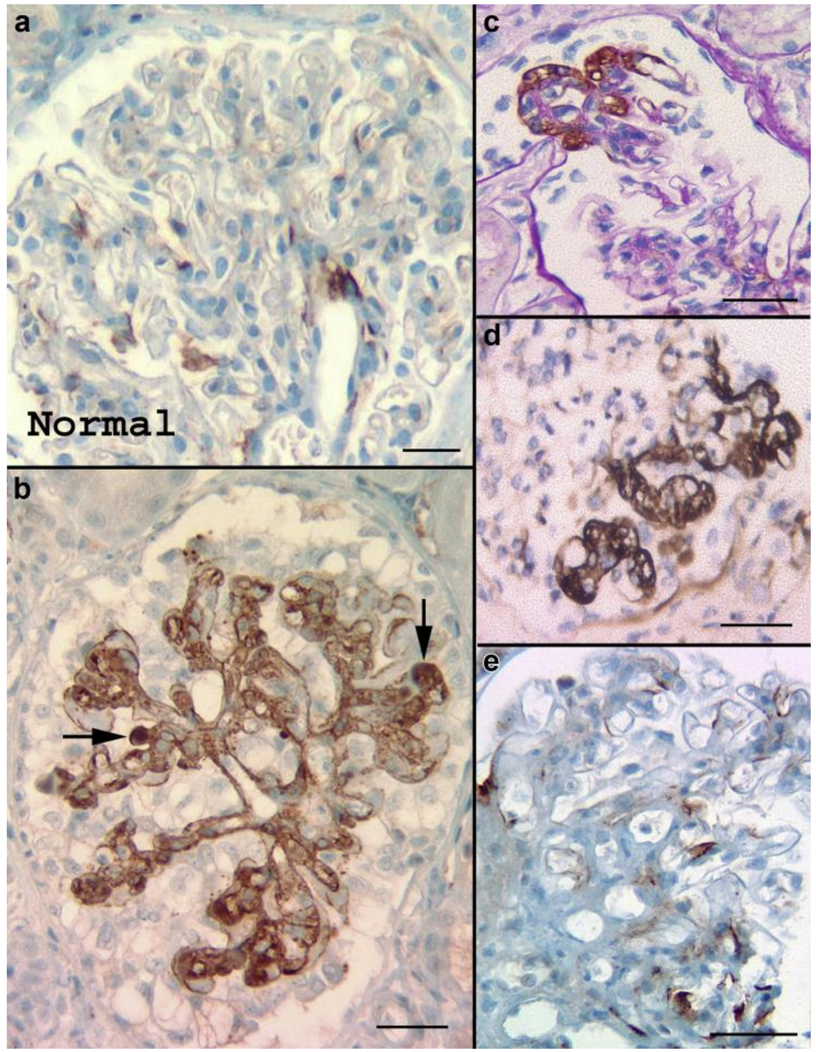
AP Activation

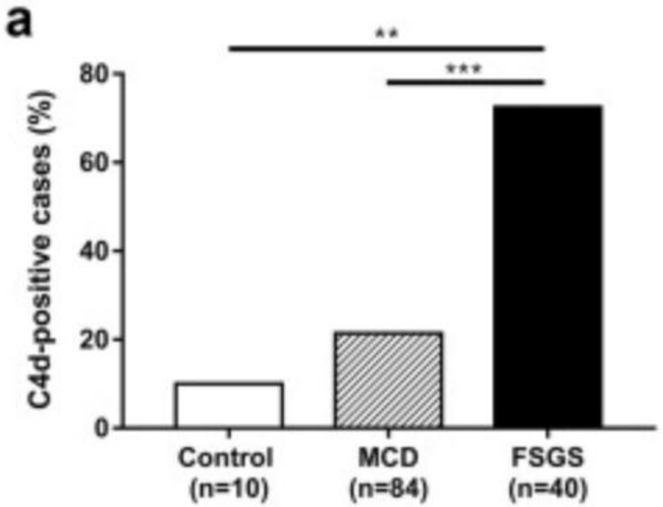


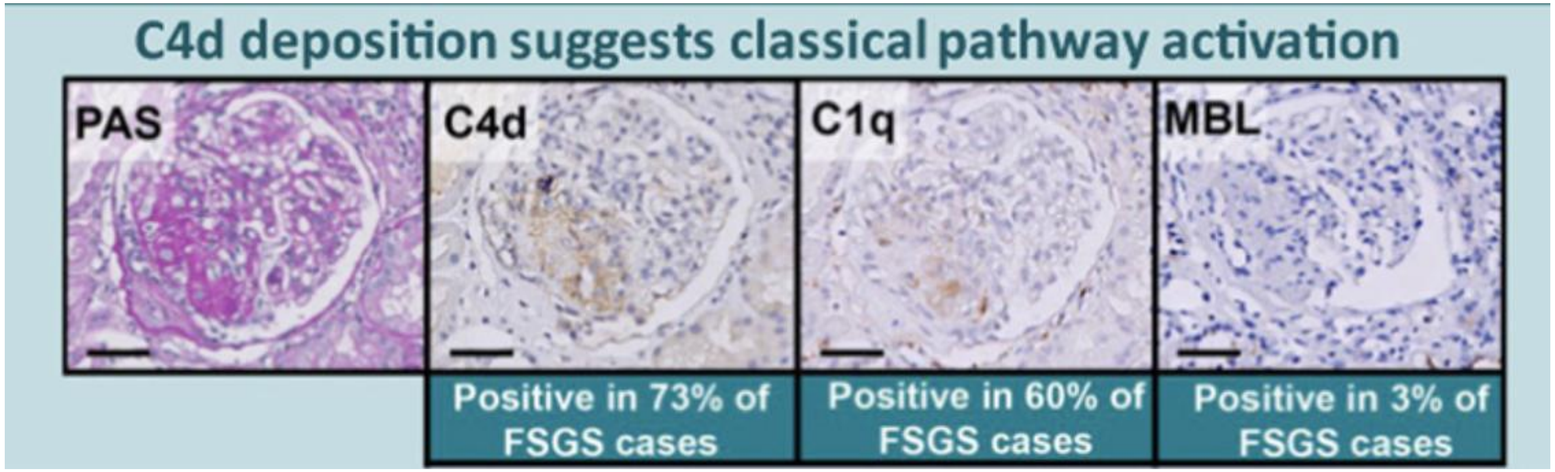
Genest et al. Kidney Int Rep. 2022

Khalili, Kidney Int Rep. 2020

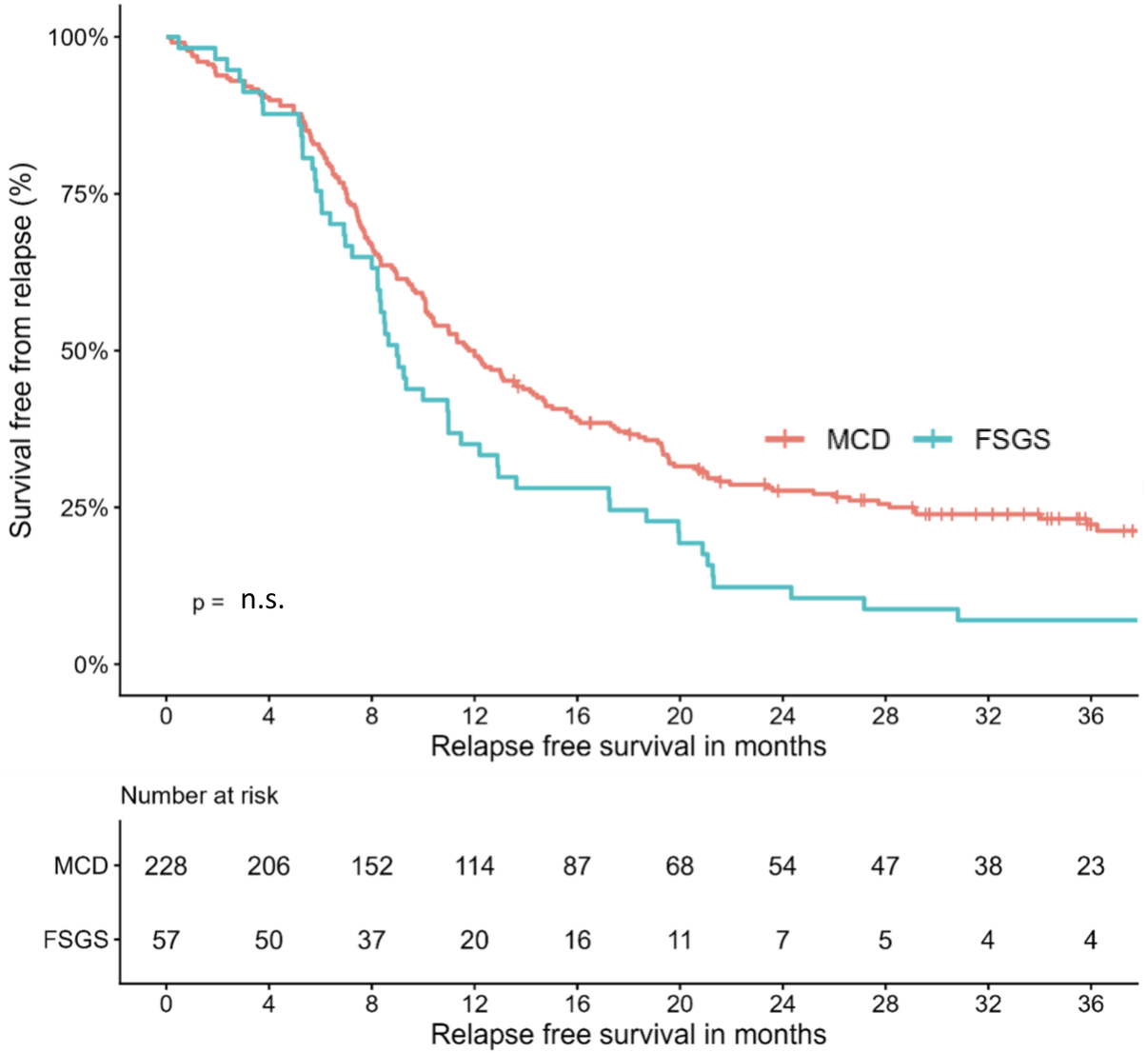
C4d







van de Lest, Kidney Int. 2019
Drachenberg, Kidney Int Rep. 2019
Abedi, Ann Diagn Pathol. 2024
Valencia, Nefrologia 2024

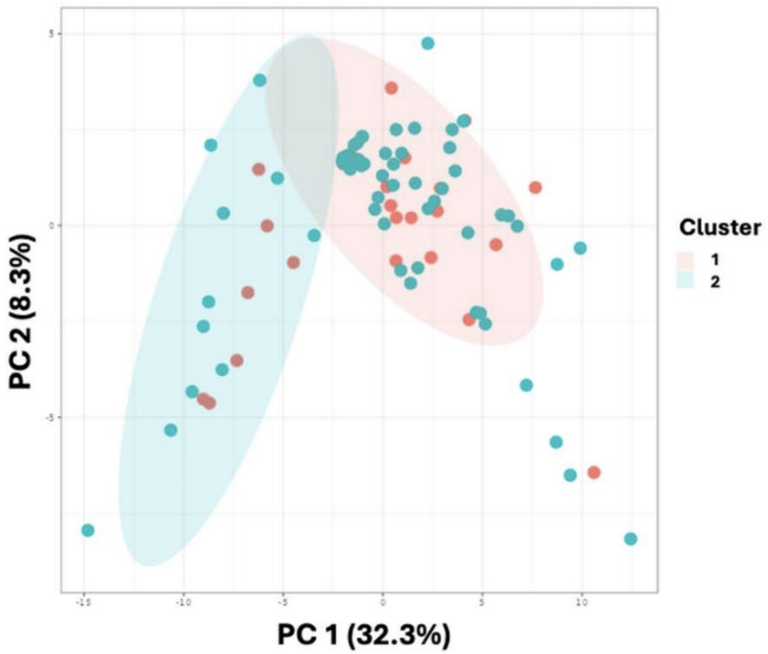


Histology did not correlate with disease severity or clinical course after rituximab

Unpublished

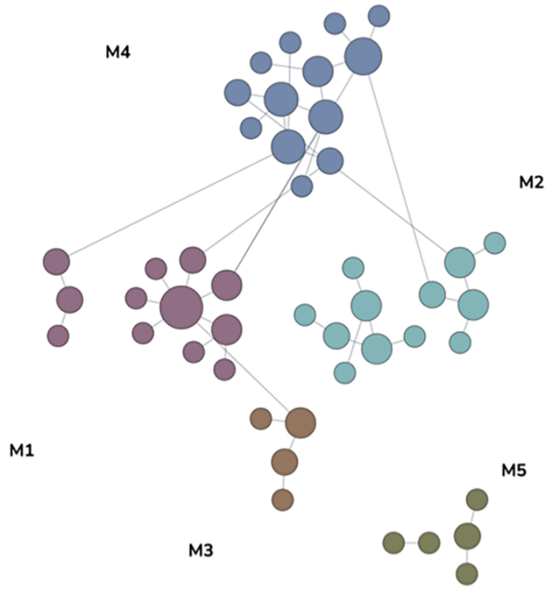
Can complement activation predict disease severity and outcome?

Defining subgroups of pediatric nephrotic patients with urine proteomics - CureGN Consortium



Median (IQR) or N (%)	Cluster 1 (N = 71)	Cluster 2 (N = 17)
Age	10 (7, 15)	12 (6, 14)
Months between enrollment and cluster assignment	0 (0, 6.5)	0 (0, 10.5)
eGFR	98 (69, 126)	105 (57, 141)
UPCR	4.8 (3.1, 10.0)	5.8 (3.6, 10.4)
Hypertension status*		
Normal	22 (32%)	8 (47%)
Elevated BP	12 (15%)	2 (12%)
Stage 1	24 (35%)	7 (41%)
Stage 2	10 (15%)	0 (0%)
Medication use		
Steroids	34 (48%)	9 (53%)
CNI	35 (49%)	8 (47%)
MMF	11 (15%)	3 (18%)
Anti-B cell	5 (7%)	2 (12%)
Any Immunosuppressant	52 (73%)	12 (71%)
Years of follow up after cluster assignment	6.3 (4.3, 7.5)	6.6 (4.0, 7.4)

Tissue Specific Network analysis mapped on Podocytes

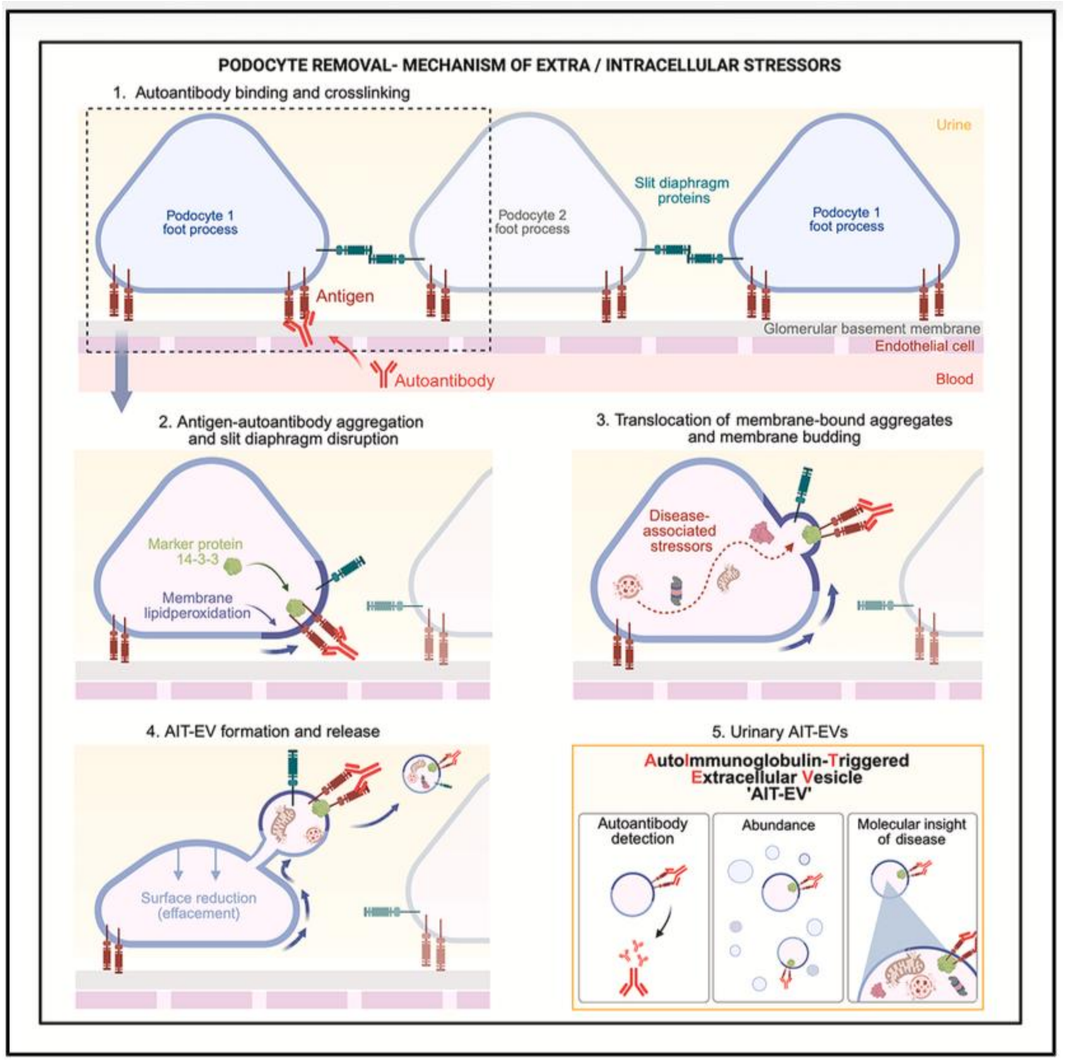


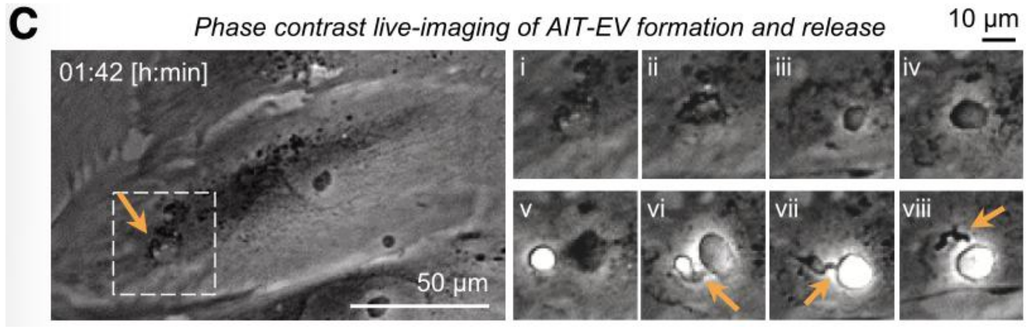
M4		
	positive regulation of vascular endothelial growth factor production	0.00007478
	regulation of vascular endothelial growth factor production	0.00010166
	vascular endothelial growth factor production	0.00011148
	complement activation	0.00015949
	protein activation cascade	0.00027520
	cellular oxidant detoxification	0.00114080

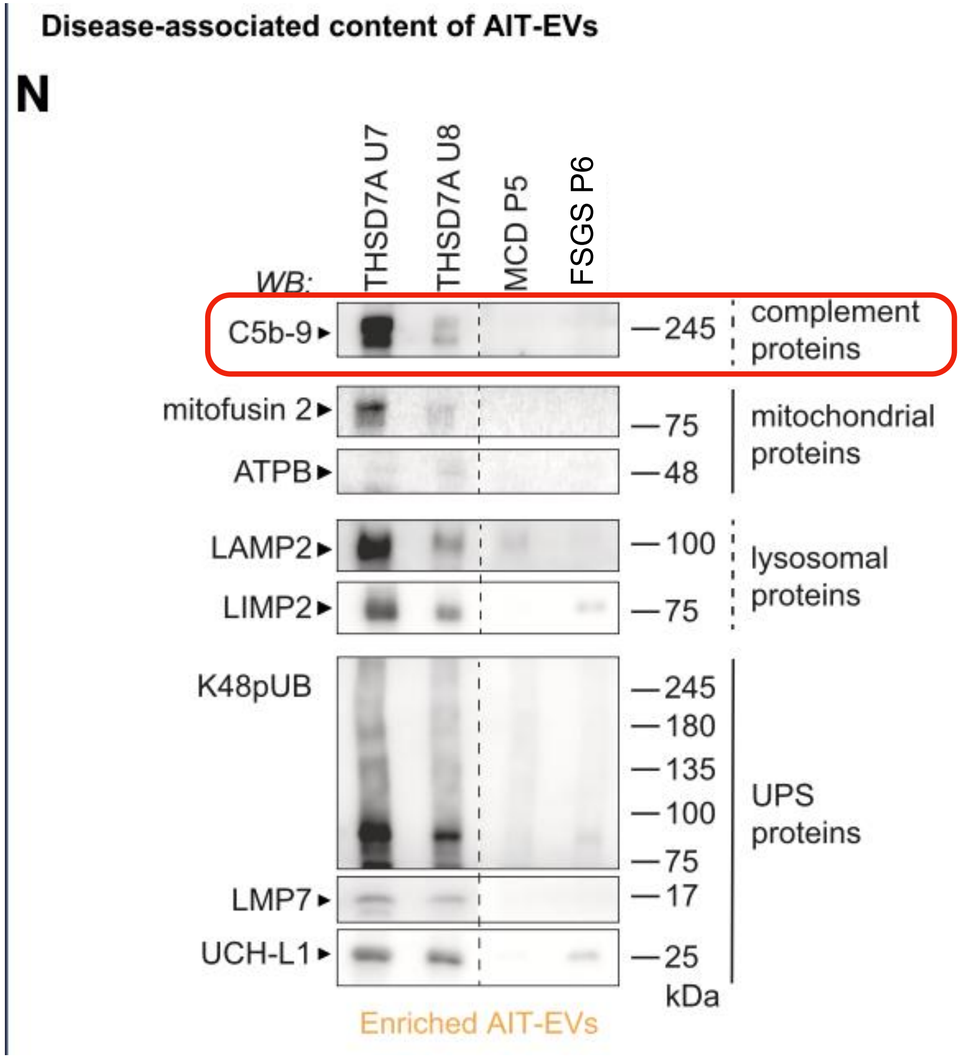
Complement profiling stratified patients into two FSGS clusters with similar clinical characteristics and outcomes.

Suggesting a distinct pathological pathway despite similar clinical phenotypes?

Cummins et al. Sci Rep. 2025







Compared with non-MN, MN-patient AIT-EVs contained abundant disease-associated proteins, including complement (e.g., C1q and C5b-9)

Lahme, 2026, Cell

Is complement activated in FSGS? Yes

Tissue deposits and urinary/plasma activation fragments support complement involvement

Which pathway? Uncertain

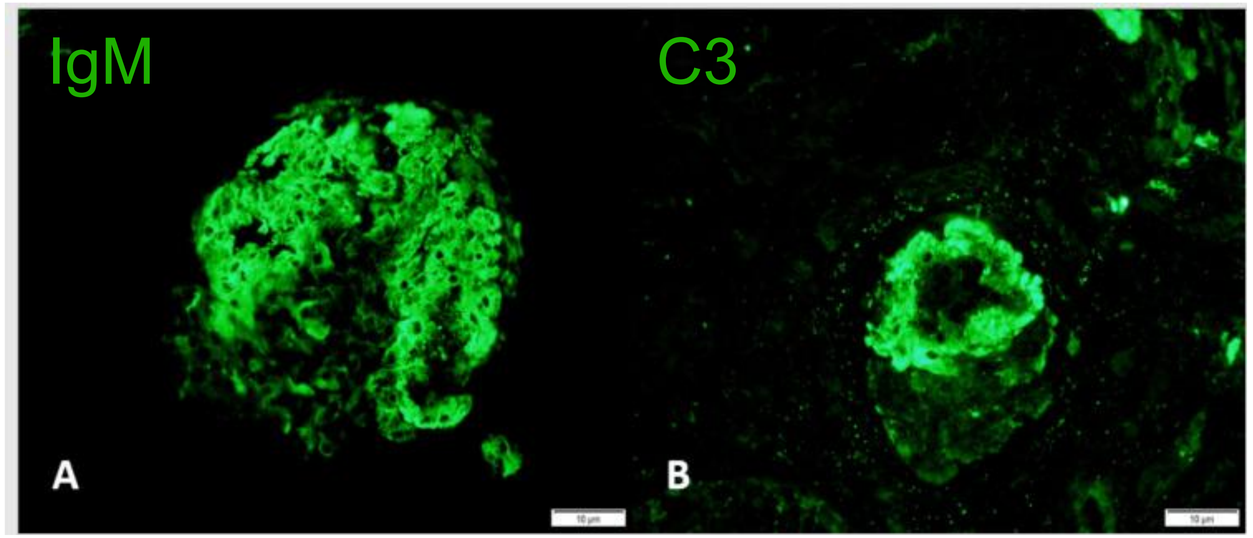
Alternative pathway is most often implicated, but classical/lectin activation may also contribute

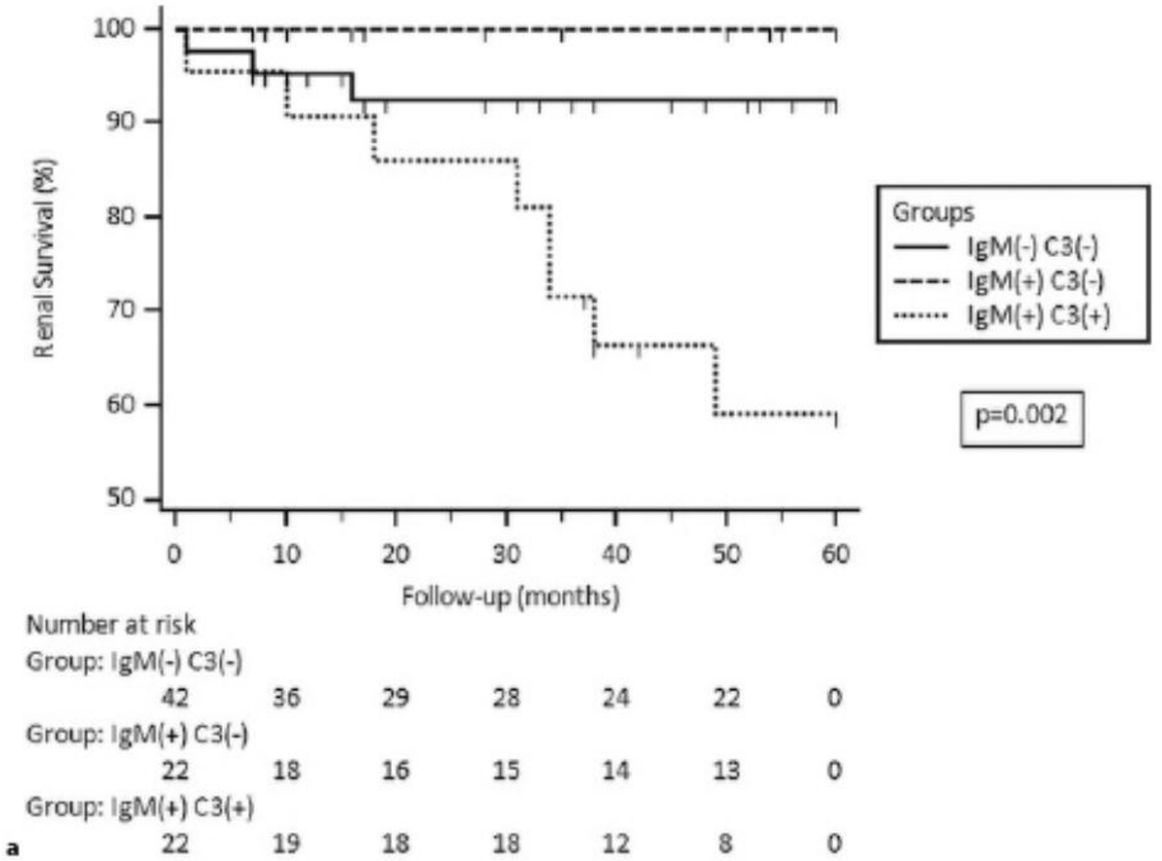
Can complement activation predict disease severity and outcome? Not clearly predictive

Some studies show prognostic associations, but evidence remains heterogeneous and not ready for routine use

Vivarelli, 2024 KI

Complement may define biological subgroups rather than clinical severity





IgM and C3 deposition are associated with worsening renal function in most reports

Aparecida Ferreira, 2024, Ann Diagn Pathol

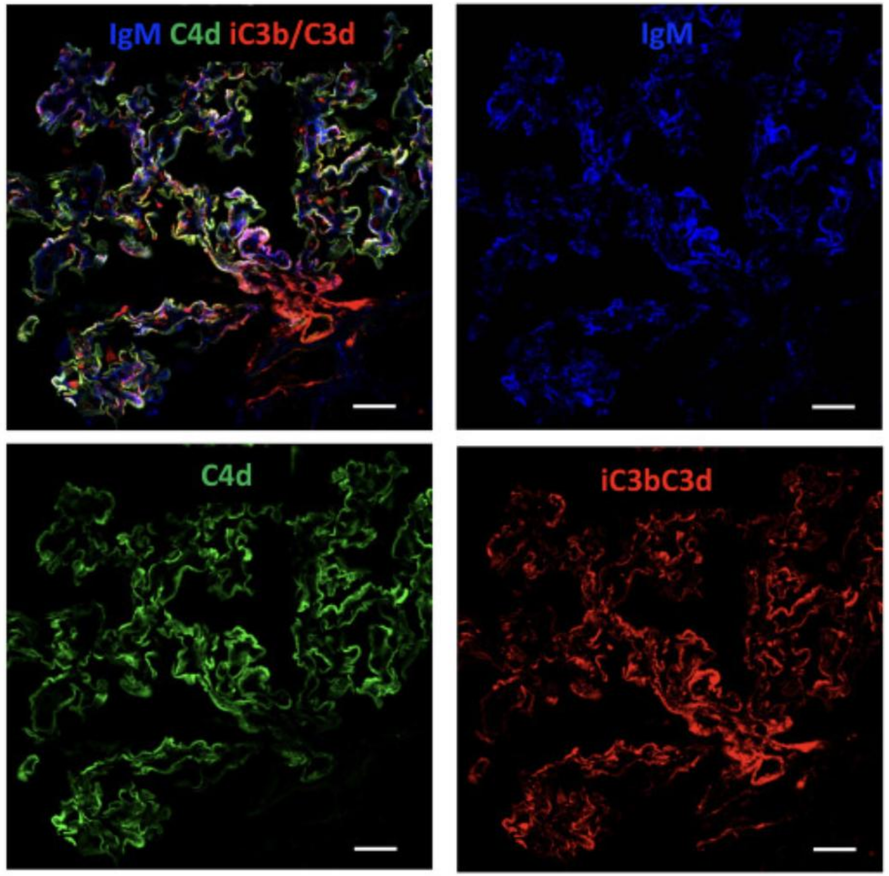
Peng, 2023, Front Ped

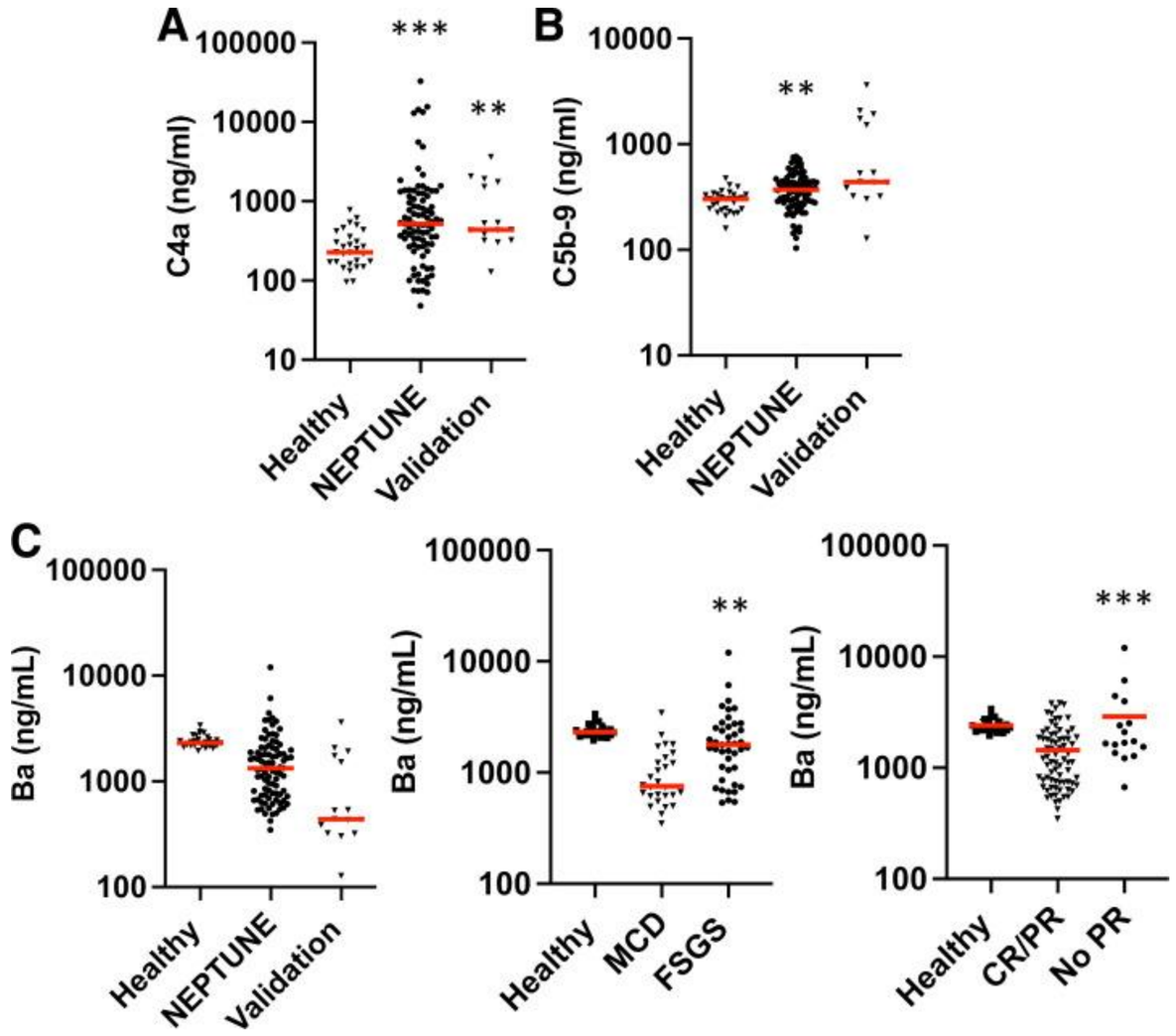
Amer, 2023, Cureus

Mirioglu, 2019, Kidney Blood Press Res

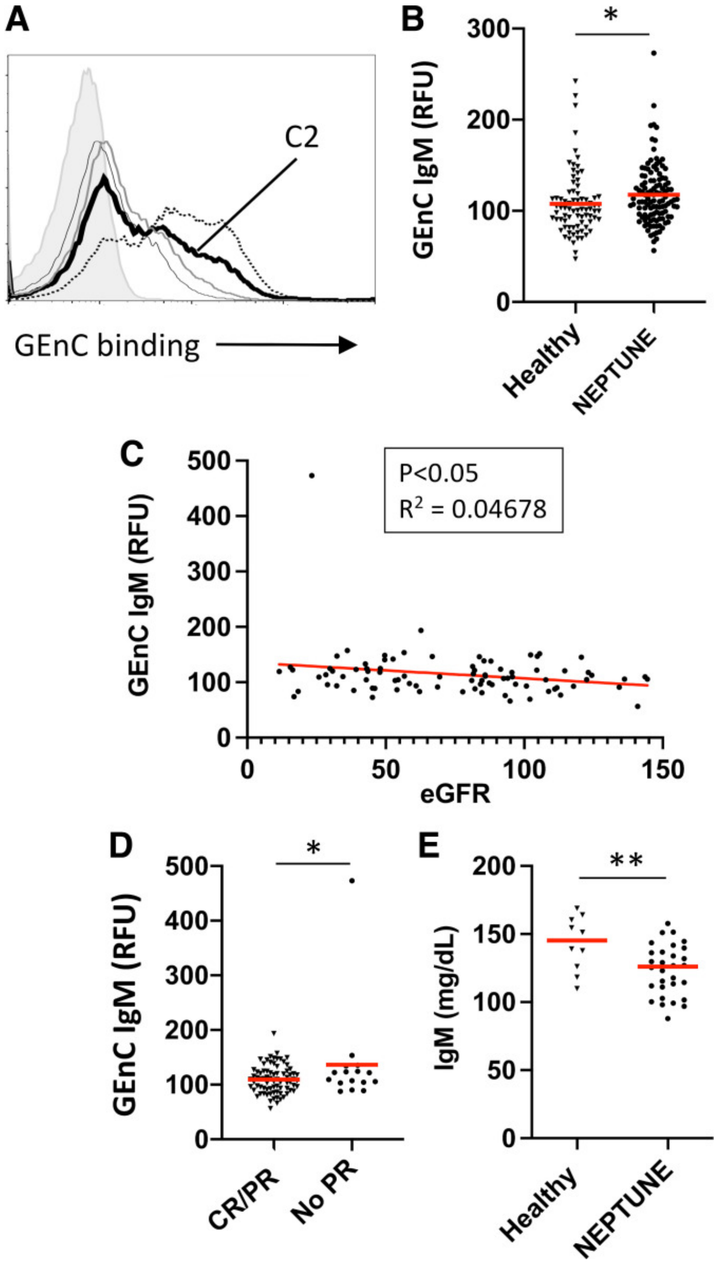
Zhang, 2016, cJASN

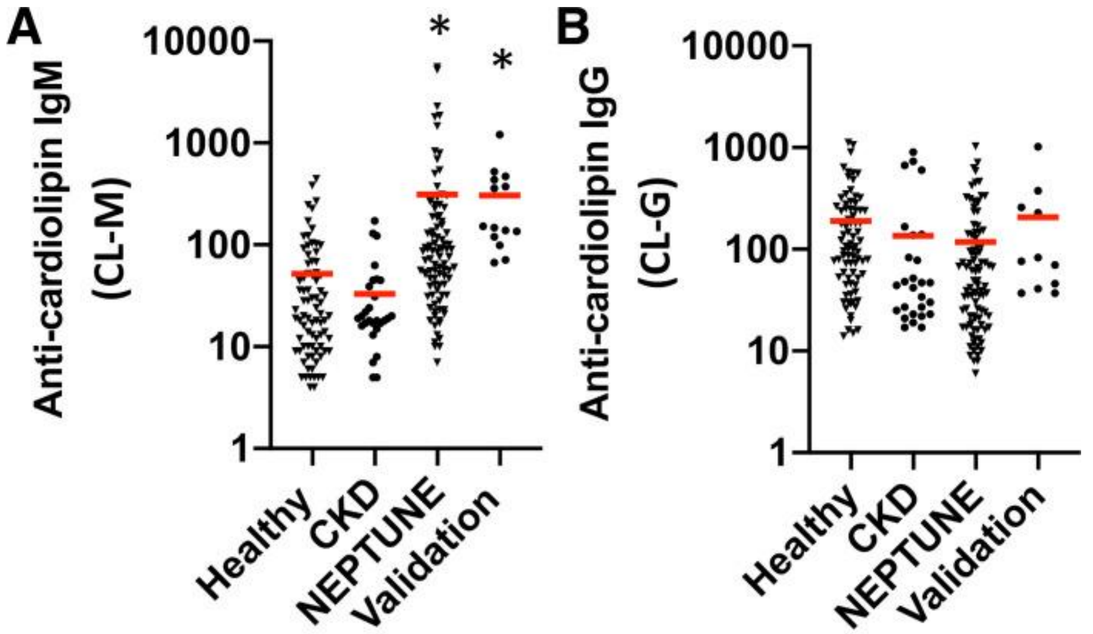
IgM can bind to glomerular epitopes and activate the classical pathway

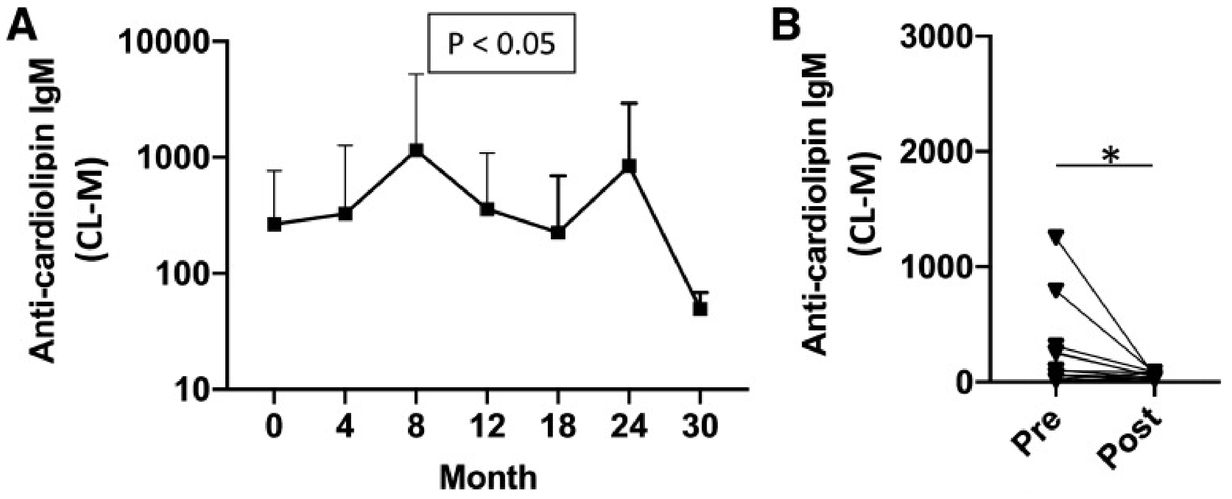




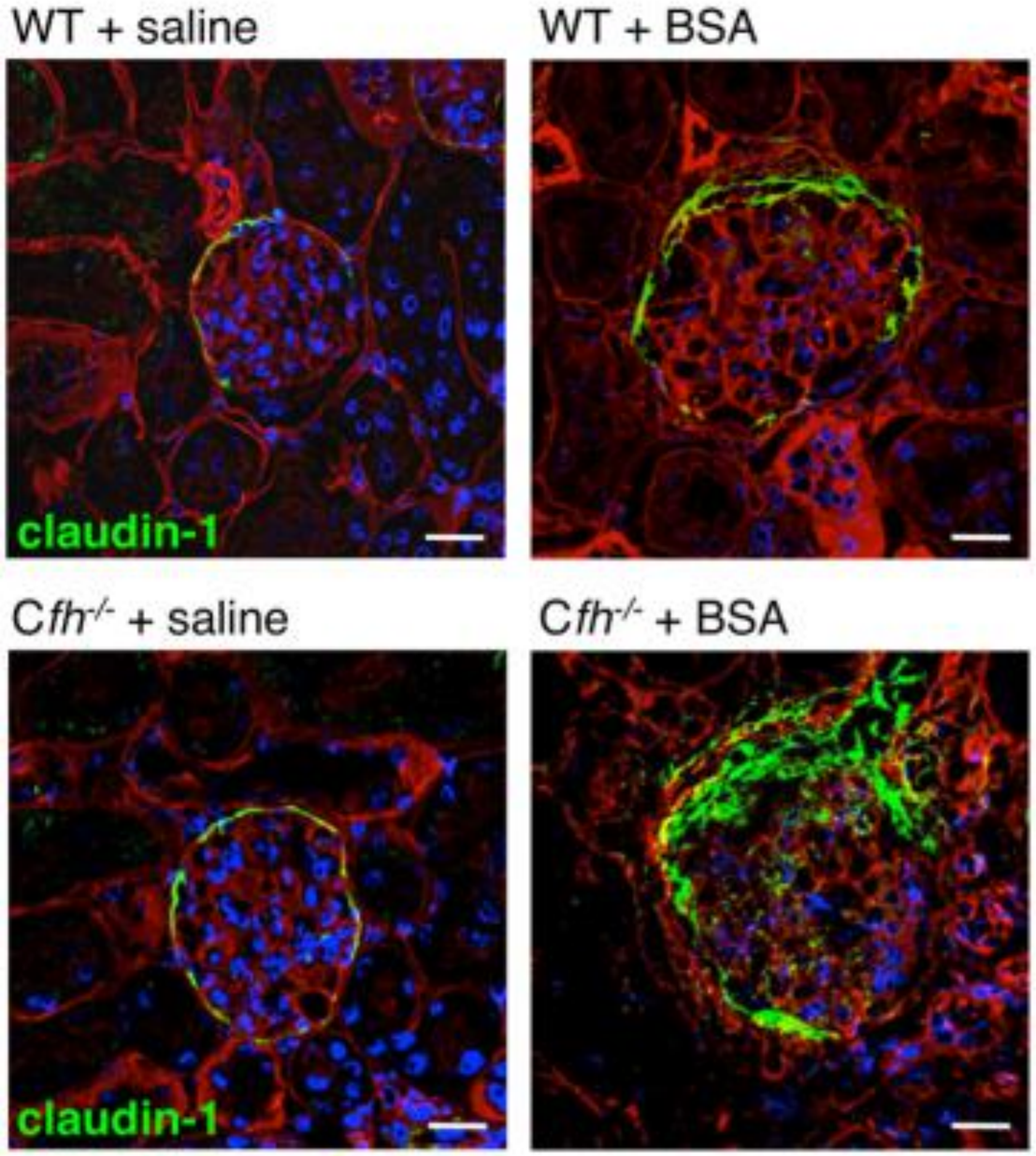
Trachtman, 2021, Am J Physiol Renal Physiol





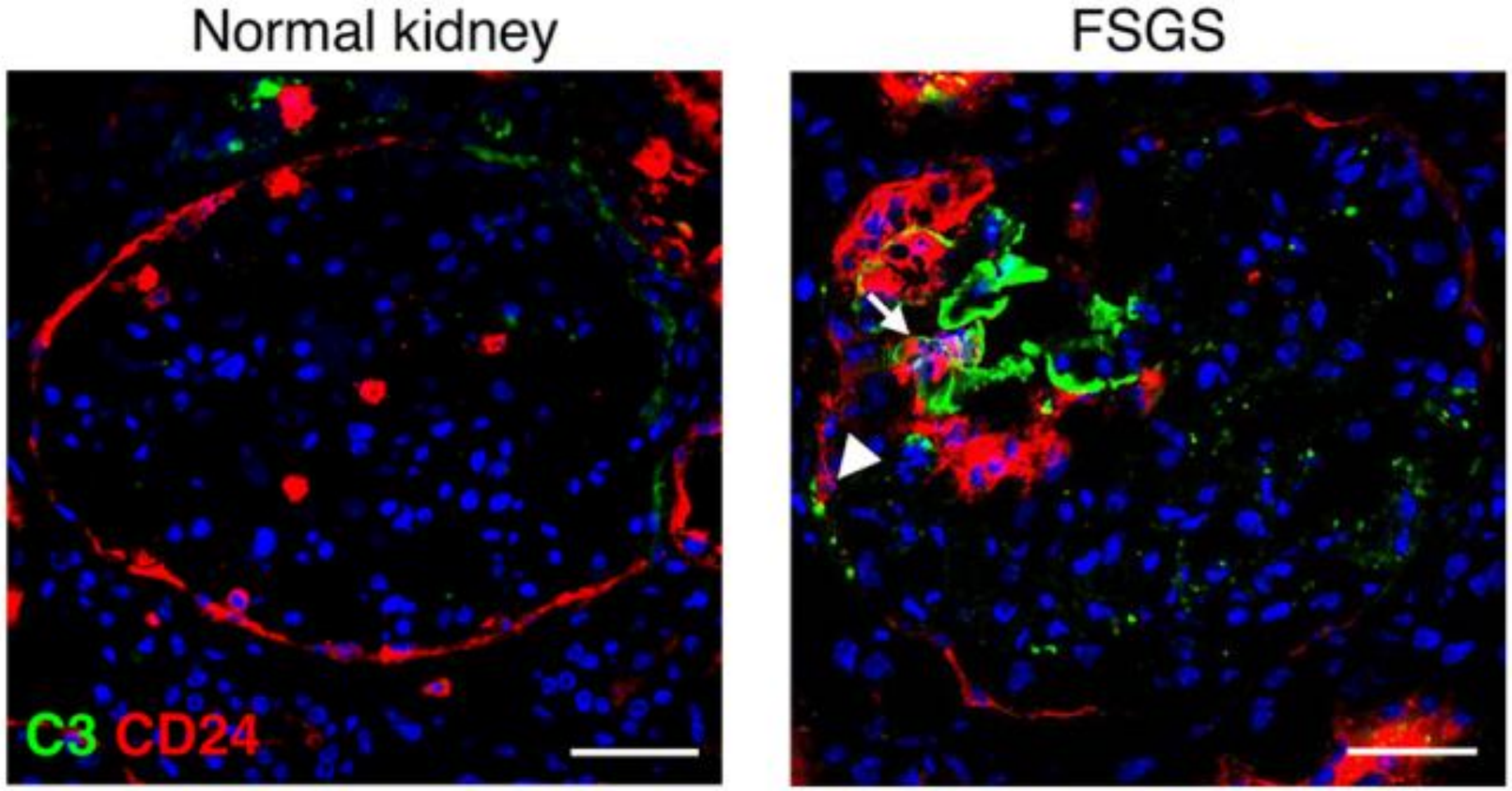


Trachtman, 2021, Am J Physiol Renal Physiol



Complement activation induces PEC dysregulation and proliferation in response to protein-overload

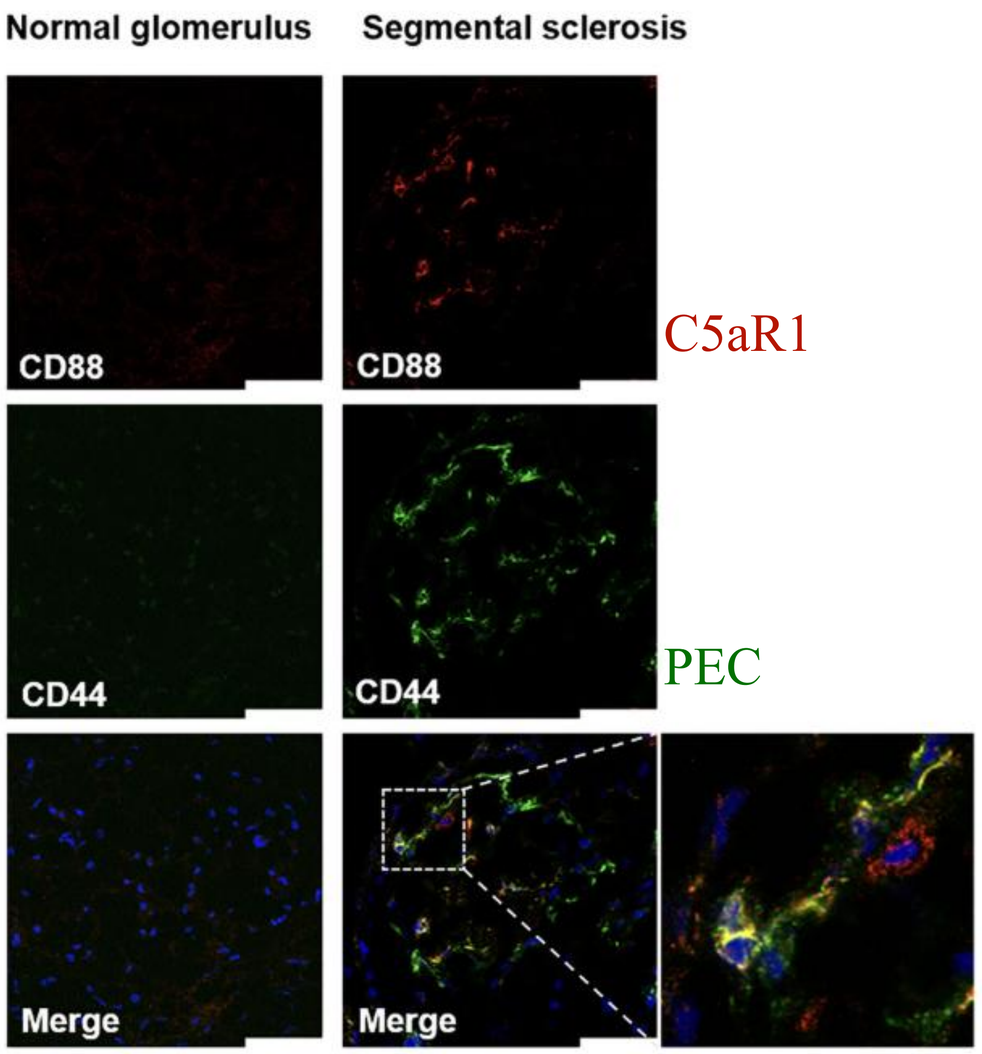
Morigi, Sci Rep. 2016

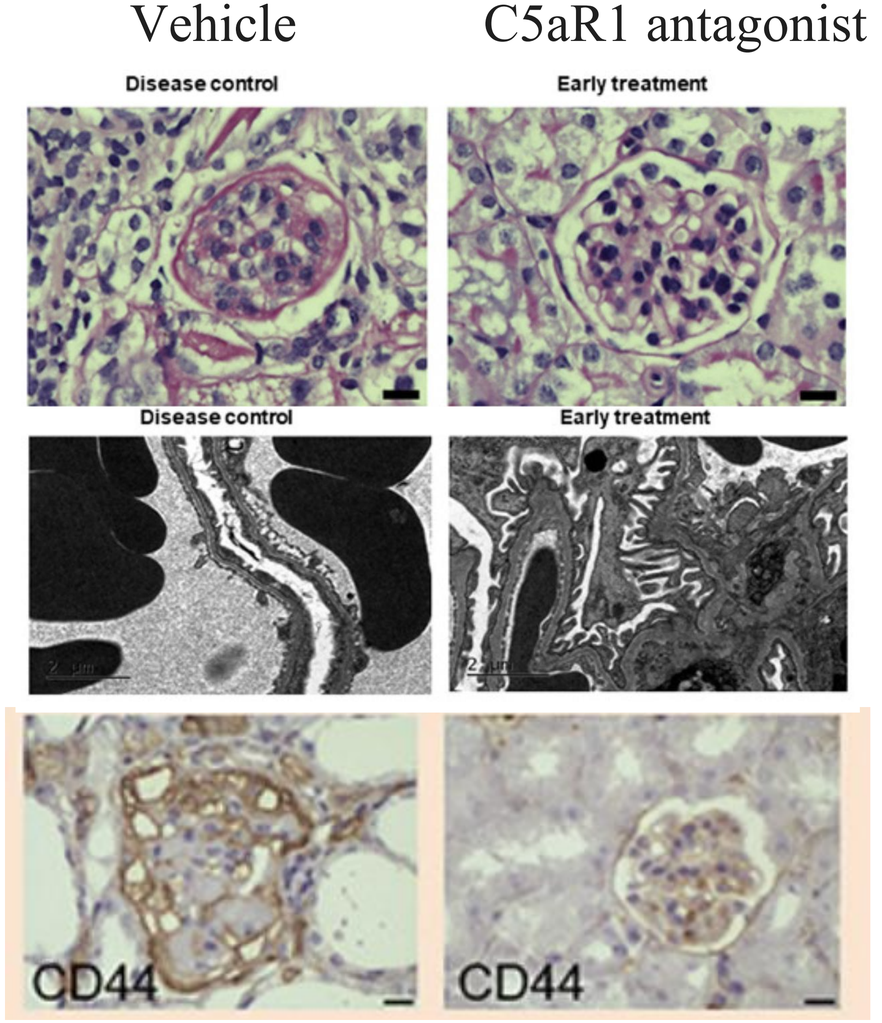


In proteinuric patients, glomerular C3 deposits were associated with the presence of exuberant accumulation of activated PECs (CD24)

Morigi, Sci Rep. 2016

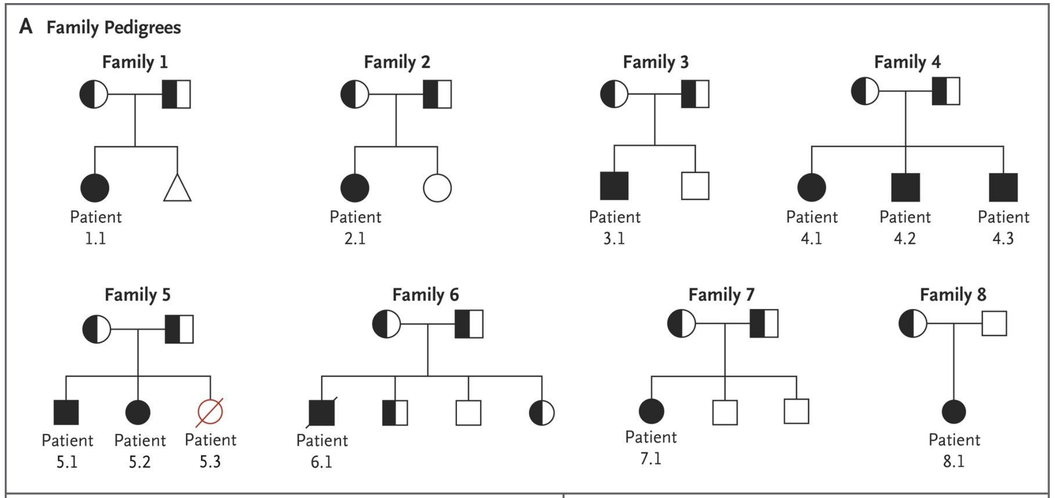
C5a receptor may mediate glomerular damage in FSGS activating PEC

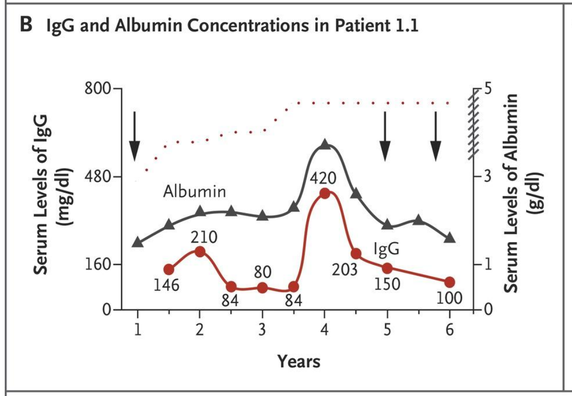


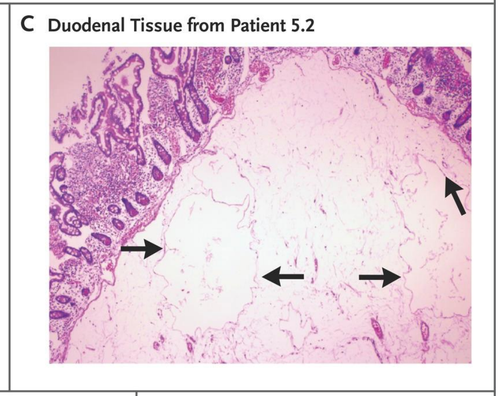


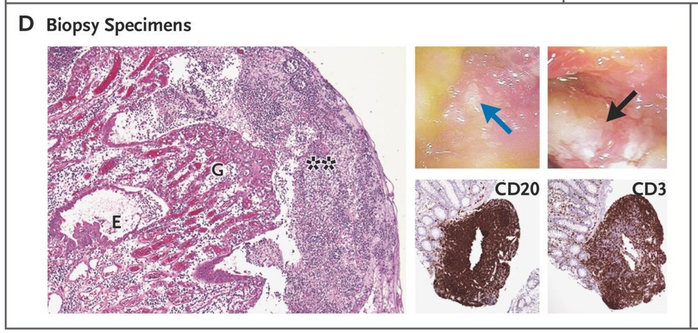
Gong et al. Clin Immun. 2025

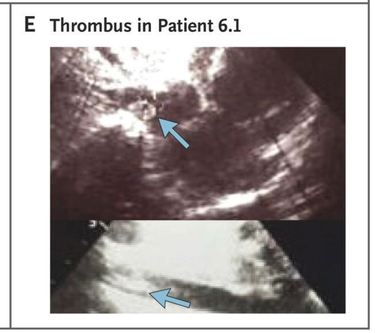
CD55 Deficiency, Early-Onset Protein-Losing Enteropathy, and Thrombosis









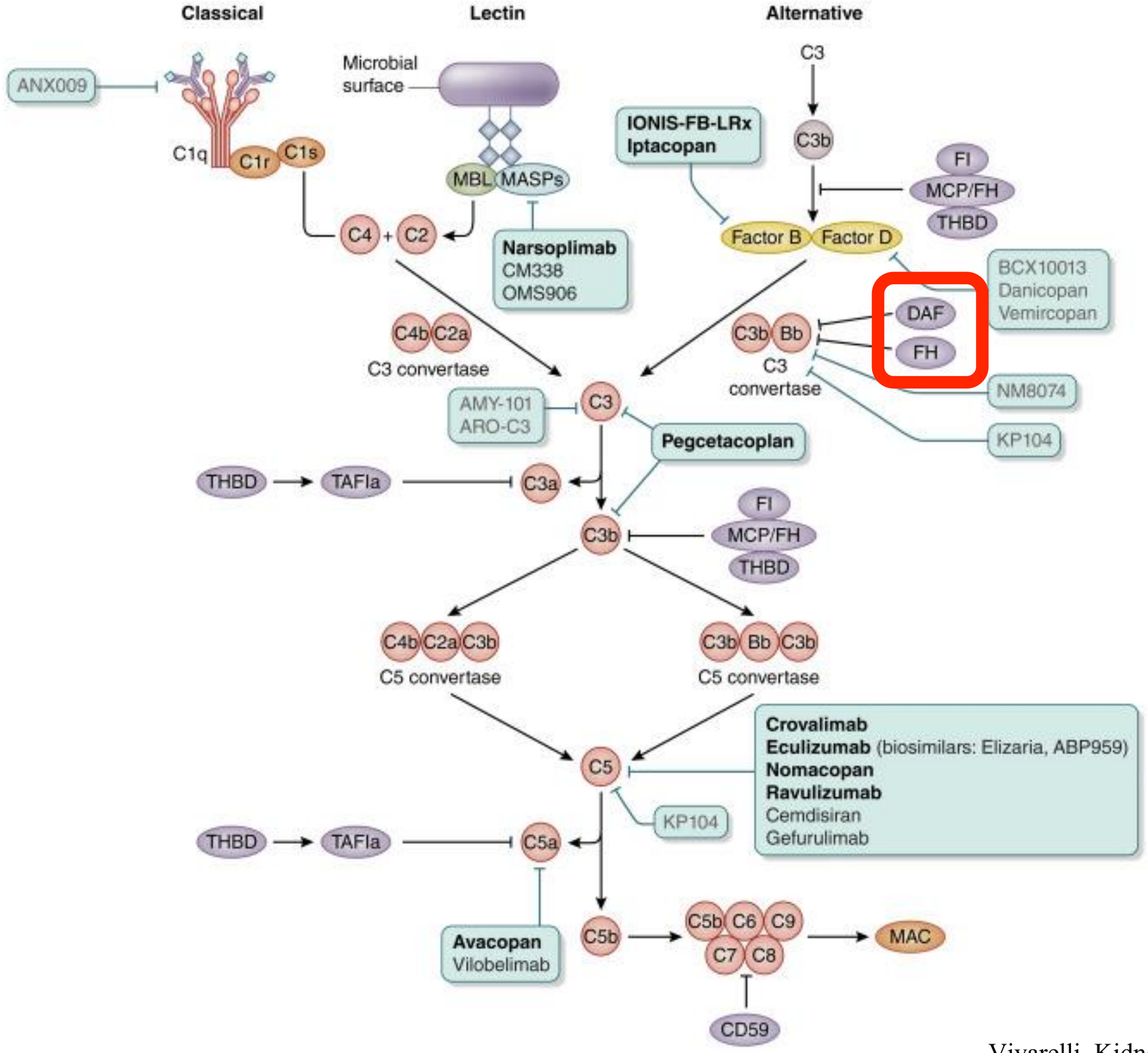


Ozen et al.
N Engl J Med 2017

Patients had also proteinuria

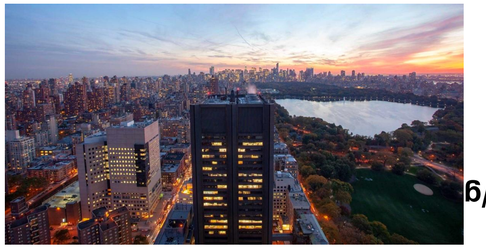
Angeletti et al.
N Engl J Med 2017

Piero del Pollaiolo - Justice
1470 - Galleria degli Uffizi,
Florence



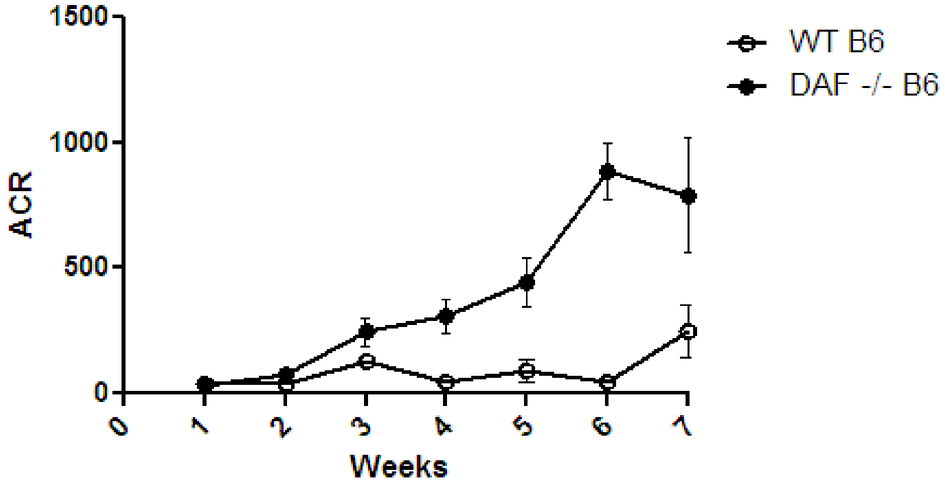
Vivarelli, Kidney International, 2024

Mount Sinai Hospital

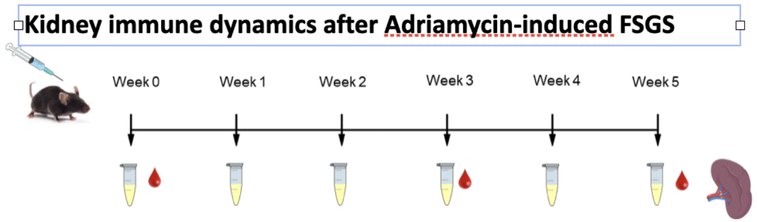


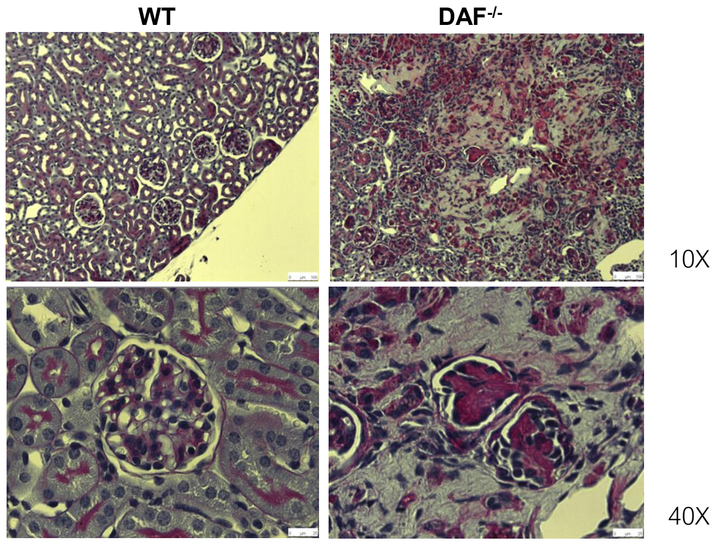
6/6w)

Paolo Cravedi



(n=12)
(n=24)



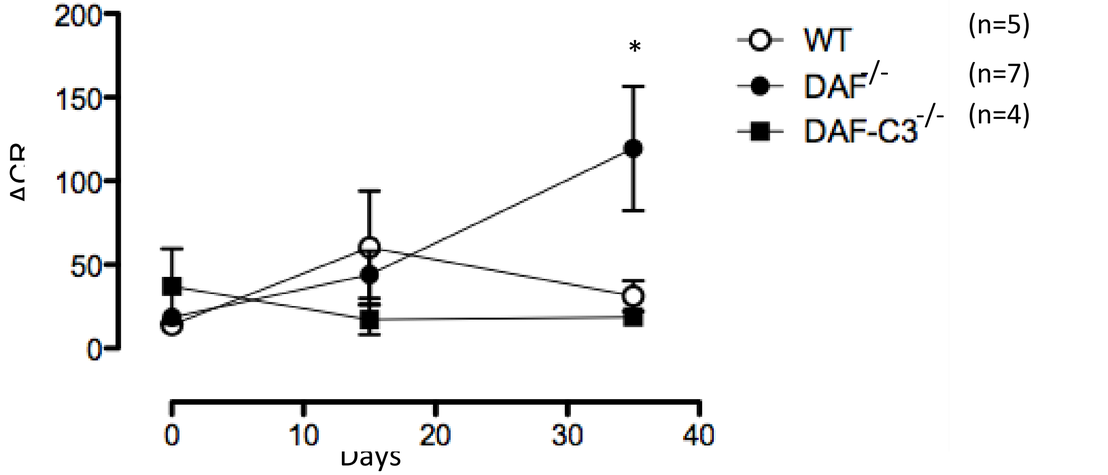


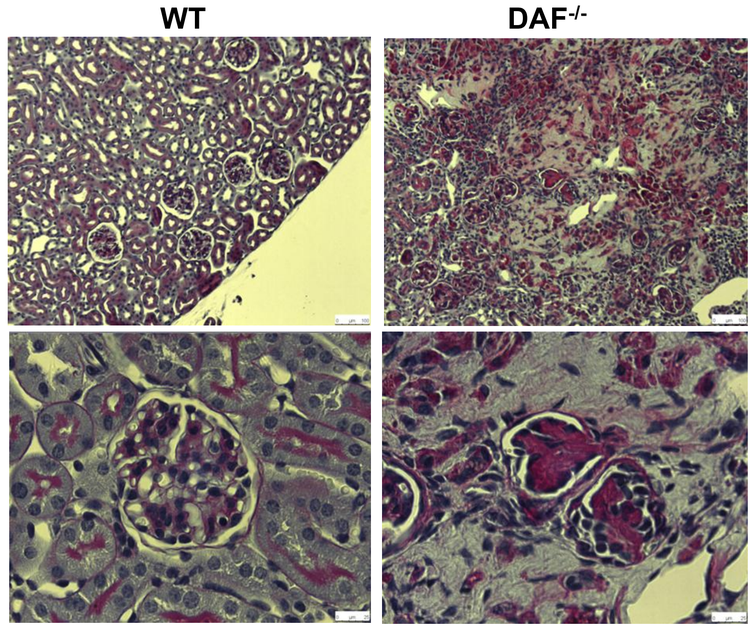
10X

40X

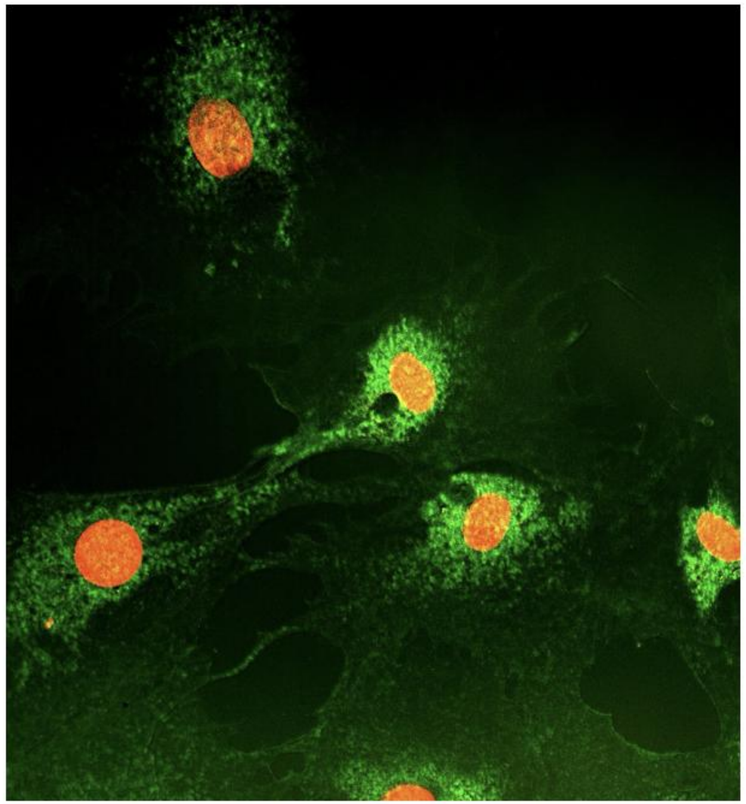
Albuminuria and renal injury significantly increased in DAF$^{-/-}$ mice in response to adriamycin in B6 mice

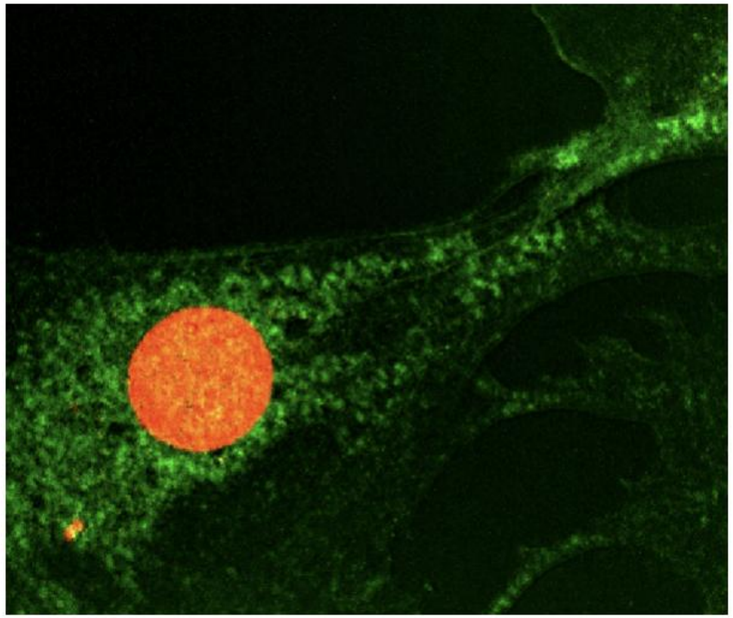
Angeletti, J Exp Med.



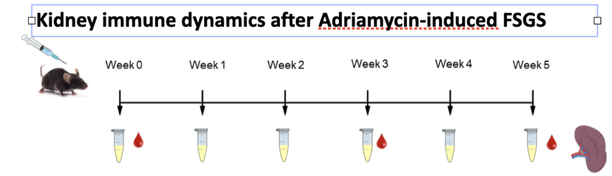


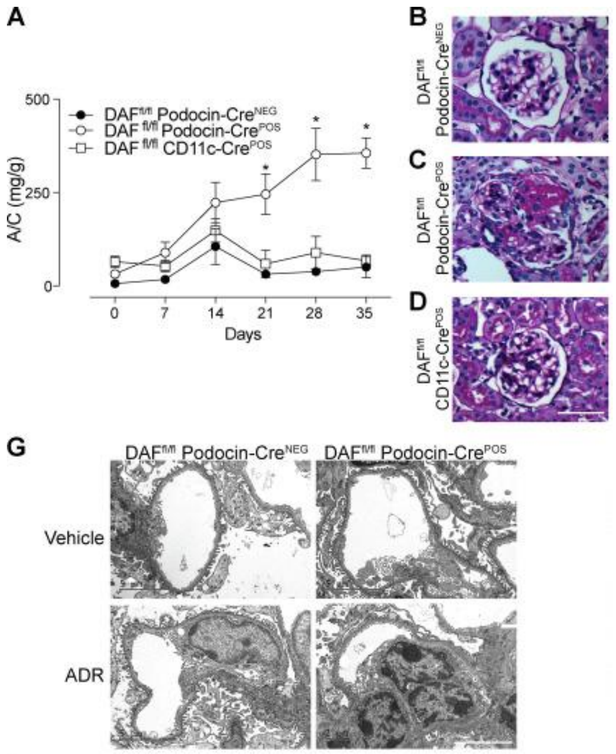
Albuminuria and renal injury significantly increased in DAF$^{-/-}$ mice in response to adriamycin, but not in DAF$^{-/-}$C3$^{-/-}$

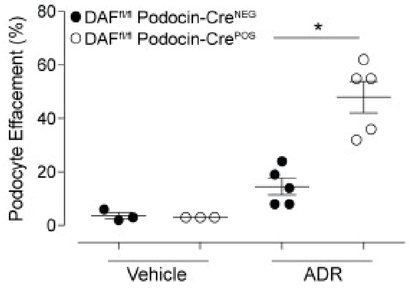




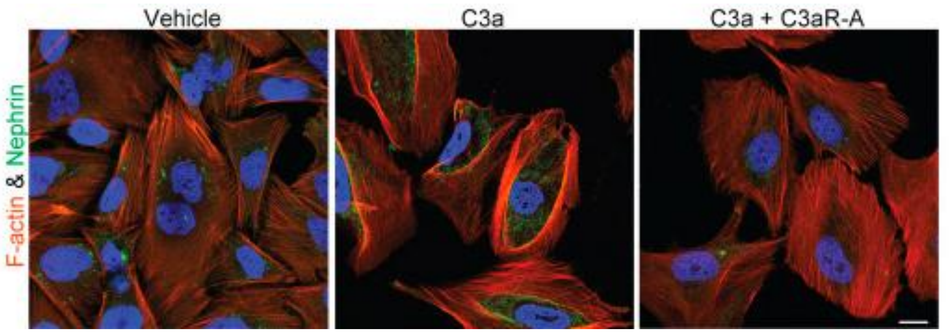
Podocytes express CD55 (DAF)

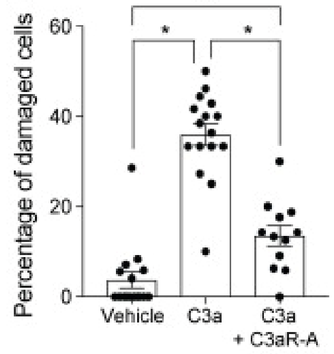




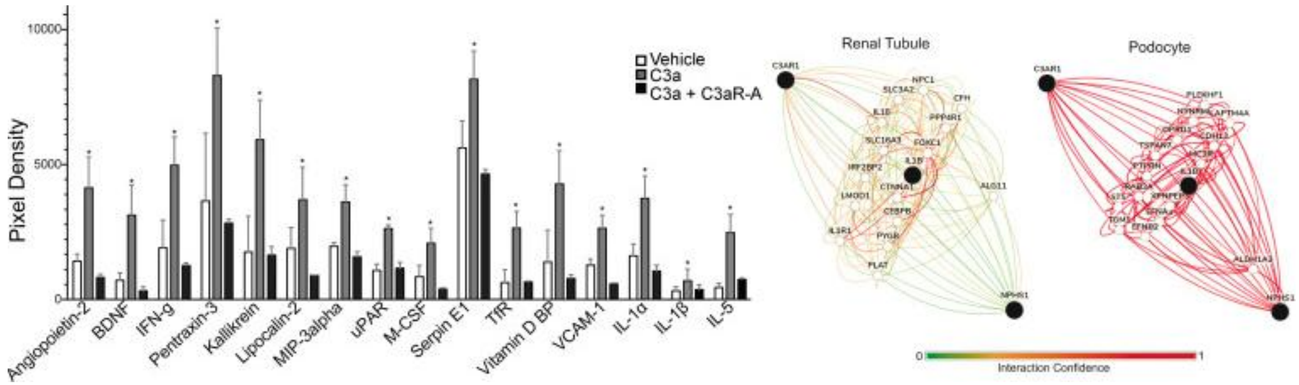


Podocyte-specific removal of DAF from podocytes increases susceptibility to ADR-induced injury through C3a/C3aR signaling.



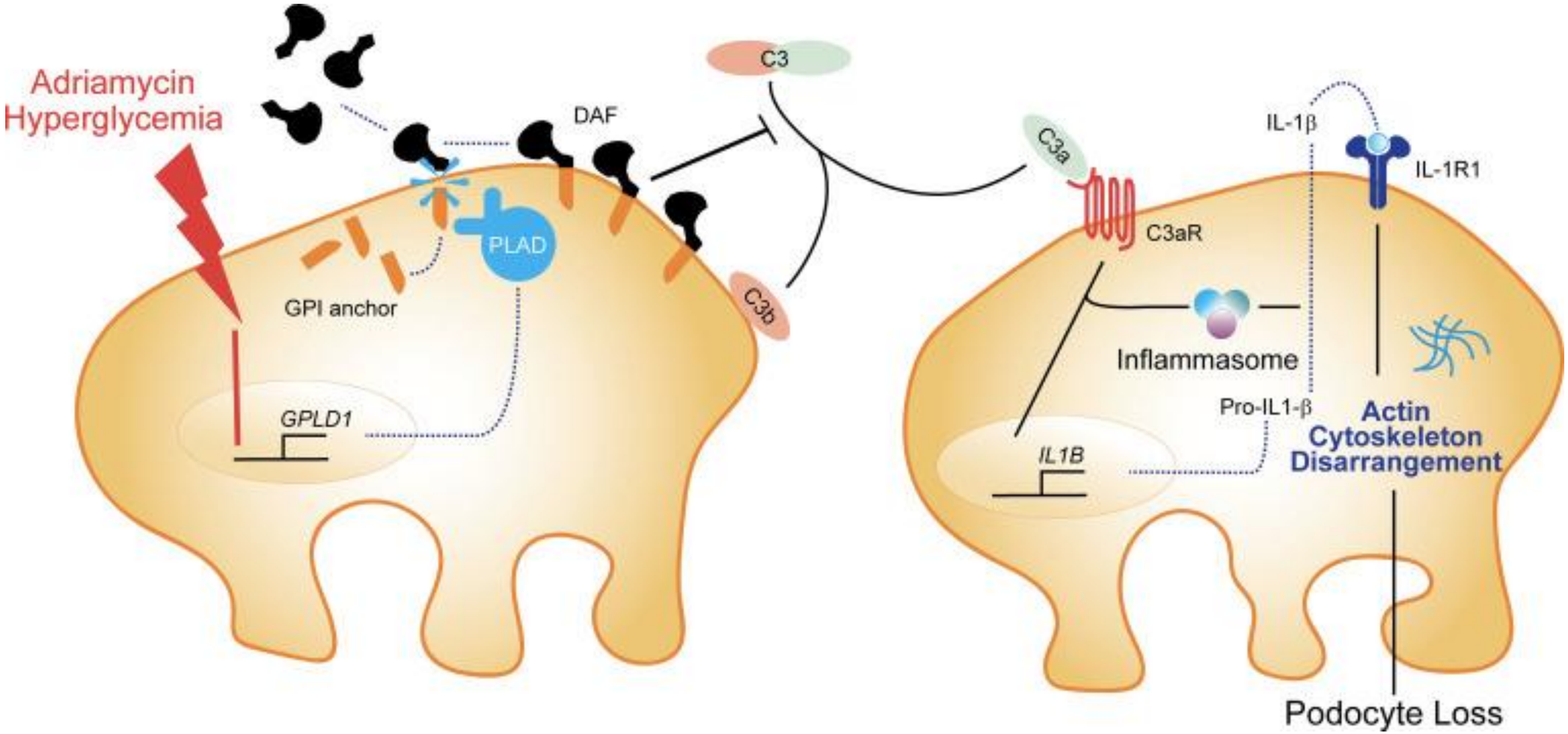


IL-1β mediates complement-induced podocyte injury in vivo

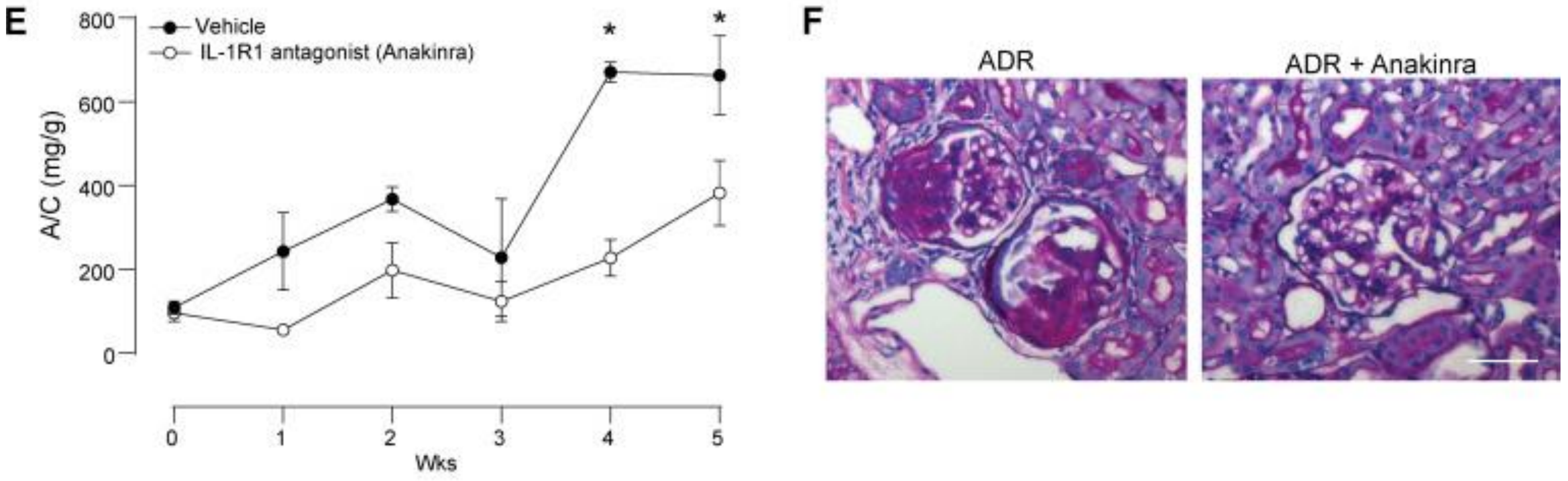


Angeletti, J Exp Med.

The development and progression of glomerulosclerosis involve loss of podocyte DAF, triggering local, complement-dependent, IL-1β-induced podocyte injury potentially identifying new therapeutic targets

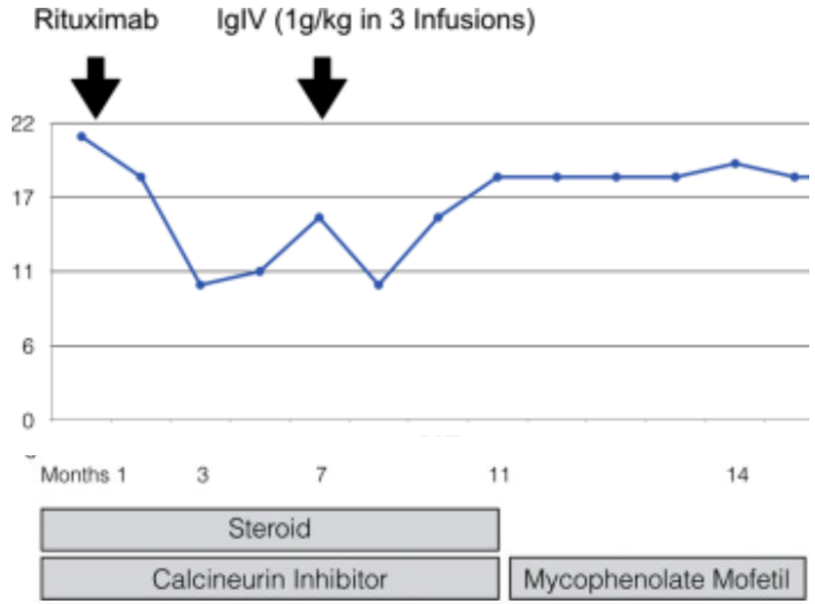


Angeletti, J Exp Med. 2020



IL-1β mediates complement-induced podocyte injury in vivo

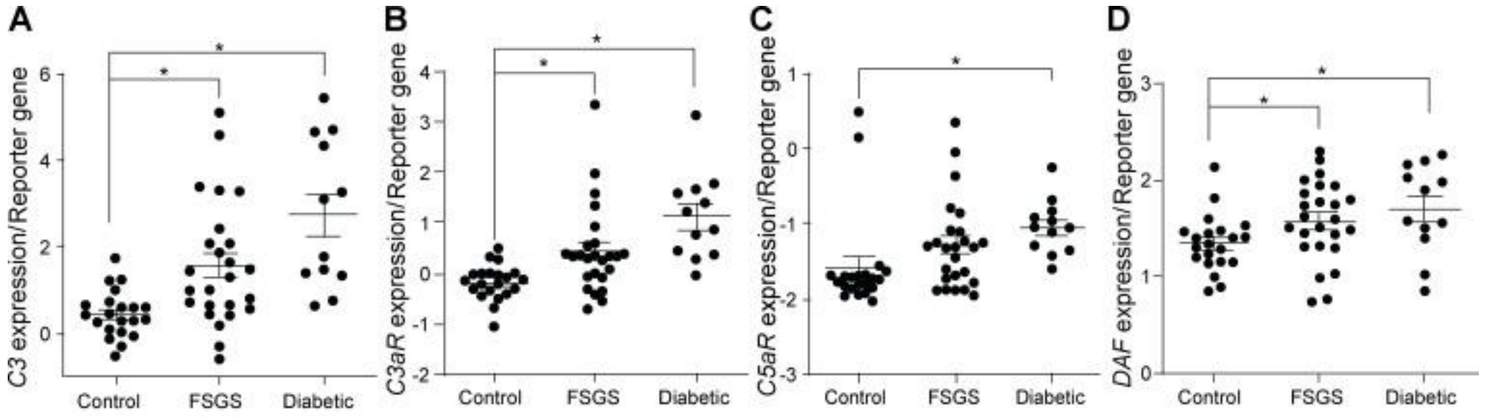
Angeletti, J Exp Med. 2020



24yo, woman, **FSGS**, treated with **Anakinra**

Angeletti, KI Reports 2022

Complement Involvement in Podocytopathies



Increased expression of mRNA for *C3*, *C3aR*, and *C5aR* in samples from patients with FSGS or diabetic kidney disease compared with control individuals

Ju et al., *Genome Res* 2013

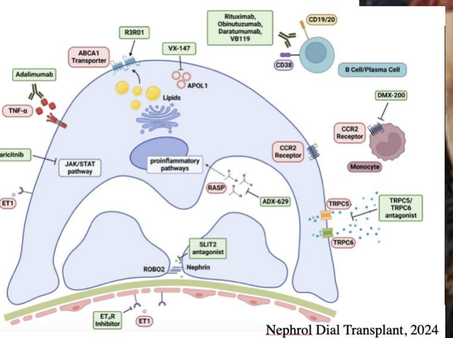
TABLE 1 | Murine models of diabetic nephropathy with documented complement activation.

Model	Induction	Diabetes type	Model description		Signs of complement activation
Streptozotocin (STZ)	Drug	1	Induction of hyperglycemia through STZ injury to the beta cells of the pancreas	(33)	C3aR and C5aR of glomerular endothelial cells
				(41)	C3 deposition in mesangium reversed in transplant
				(25)	DAF reduction in podocytes
				(42–44)	Lectin pathway involvement (MBL)
NOD	Genetic	1	Autoimmune destruction of beta cells	(45)	C3 deposition in glomeruli
OVE26	Genetic	1	Transgene that increases calmodulin expression in the beta cells of the pancreas	(46)	C3 gene expression in tubules
ob/ob	Genetic	2	Mutation in leptin that causes obesity induced hyperglycemia	(24)	C3/C3aR signaling in podocytes
db/db	Genetic	2	Mutation in the leptin receptor that causes obesity-induced hyperglycemia	(34)	C5a deposition in tubules
KK-Ay	Genetic	2	Mutation in nonagouti (A^y) that casues obesity-induced hyperglycemia	(47)	C3 deposition in glomeruli and glomerular capillaries

Front Med (Lausanne). 2021 Jan 21;7:599236.

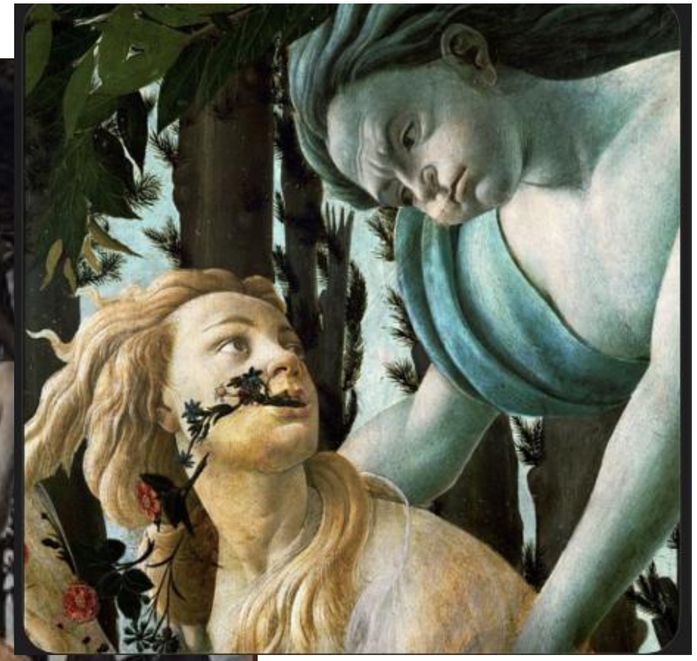
Pre-clinical studies demonstrated that complement inhibition prevents DKD progression

Like Zephyrus, complement may act as a force amplifying podocyte injury.



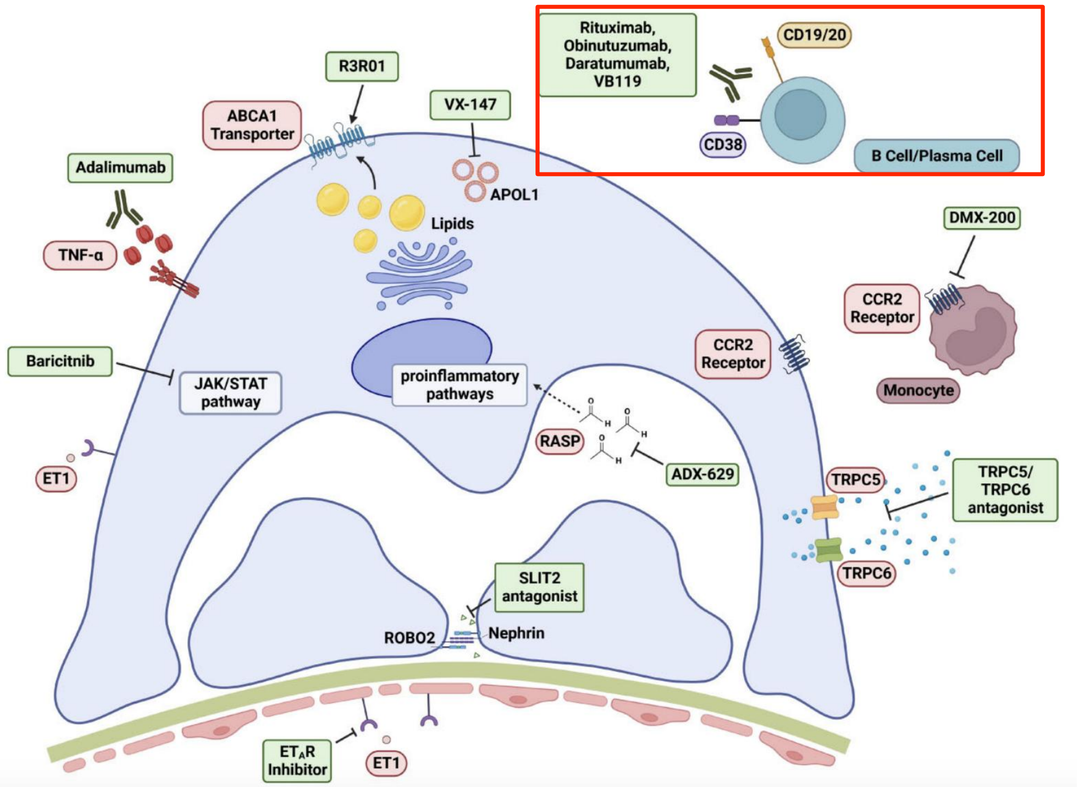
Nephrol Dial Transplant, 2024

Complement Targeting Therapies?

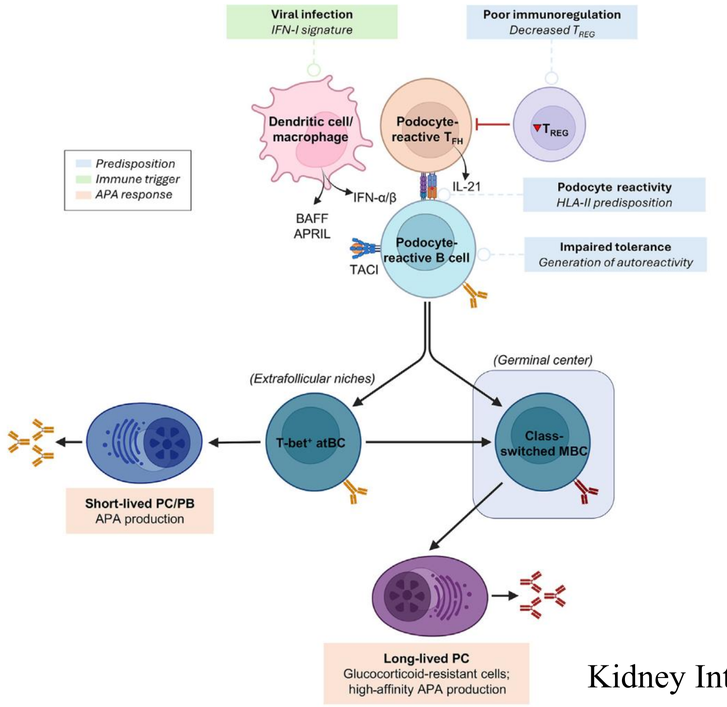


Botticelli - Primavera AD 1480 - Galleria degli Uffizi, Florence

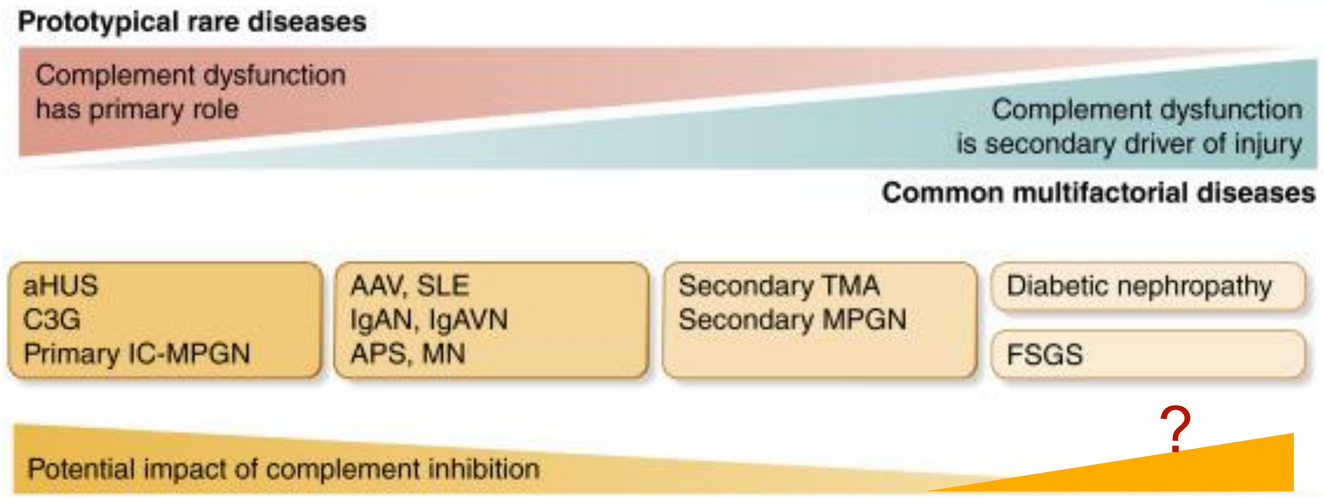
Proposed model for autoimmunity in podocytopathies



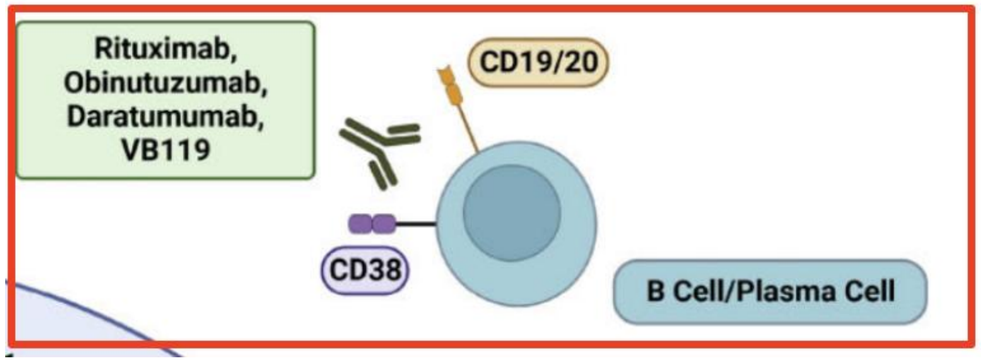
Nephrol Dial Transplant, 2024



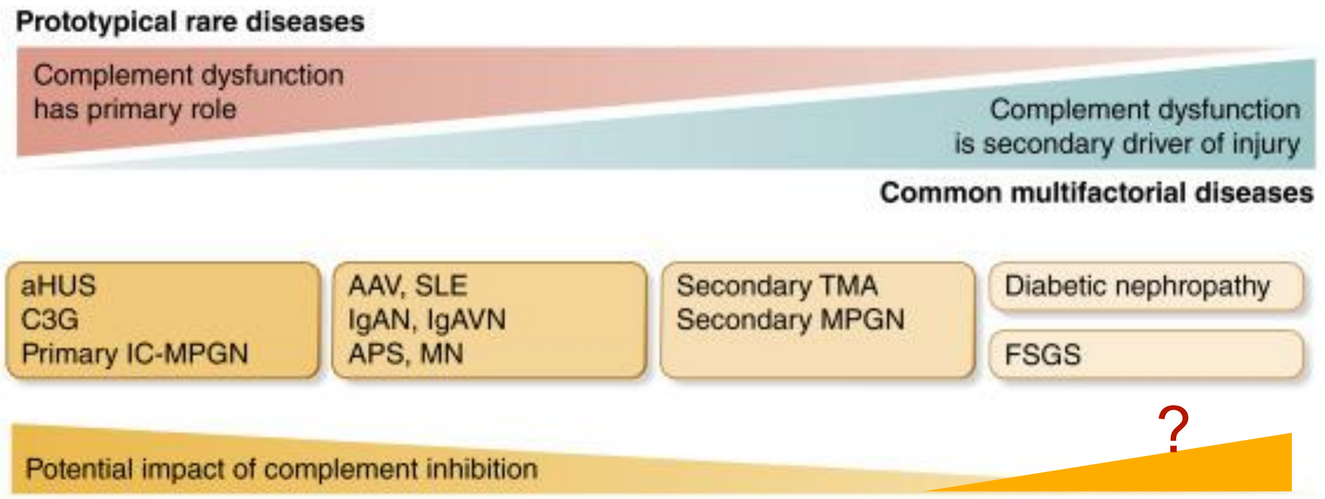
Kidney International 2024



Vivarelli, Kidney International, 2024



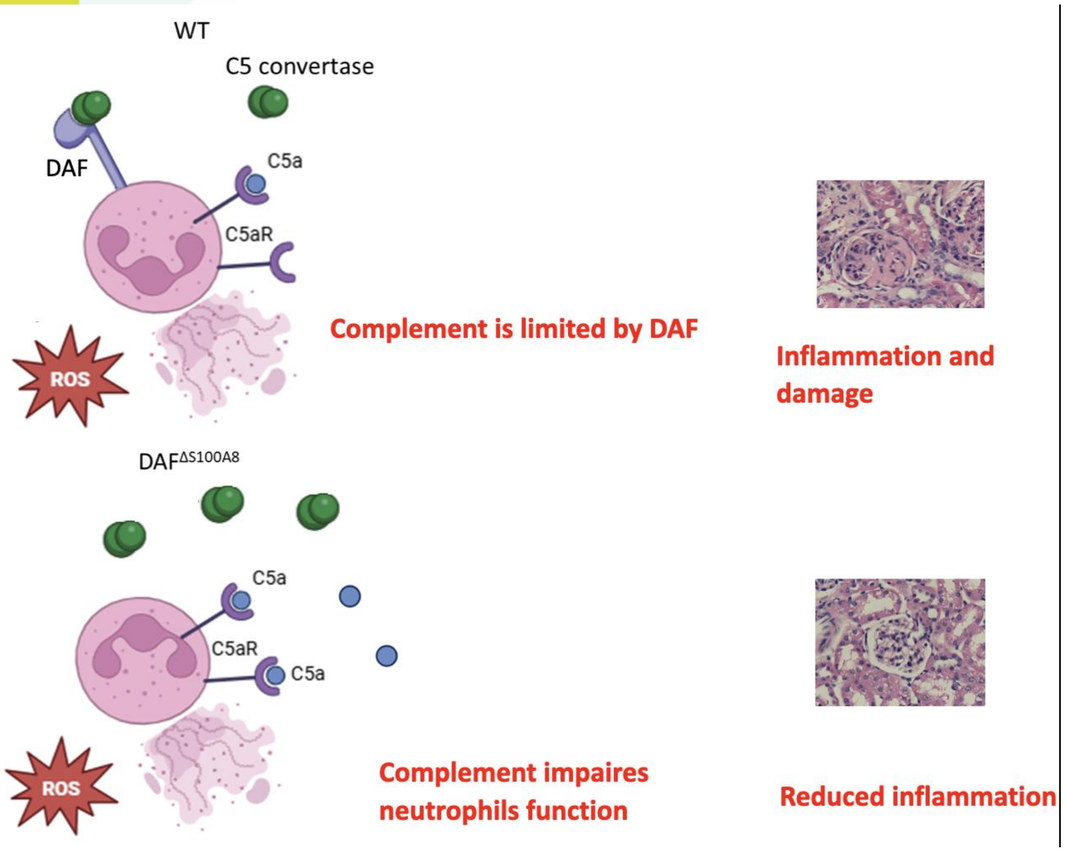
\+ AP targeting therapies



Vivarelli, Kidney International, 2024

18:05 Loss of DAF in neutrophils attenuates proteinuria in a murine model of FSGS

Carolina Bigatti[1], Lorenzo Cocchini[1], Andrea Angeletti[1], Paolo Cravedi[2]
([1]Italy, [2]United States)



Thanks to…

Clinical Crew

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Edoardo La Porta
Francesca Lugani
Gabriele Mortari
Silvio Chiarenza
Antonella Trivelli
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FMRB

Long-term outcomes of rituximab-treated adult patients with podocytopathies

JASN
Journal of the American Society of Nephrology
Clinical Research

Methods and Cohort

Retrospective study at 30 nephrology departments from 15 countries

Adult patients with primary podocytopathies treated with rituximab as part of a remission Induction agent

Primary outcome: relapse-free survival at 36 months

183 adult patients with difficult to treat nephrotic syndrome

64 FSGS

119 MCD

68% steroid dependent/ frequently relapsing

22% steroid resistant

85% previously treated with 2 or more immunosuppressants

Induction

82% complete or partial remission at 6 months

55% initial responders achieved long-term relapse free survival at 3 years

Annual relapse rate reduced from 1.0 before to 0.17 relapses per year after rituximab

Maintenance

Associated with a better relapse-free survival, irrespective of dosing regimen (HR 2.05, 95% CI: 1.07-3.91)

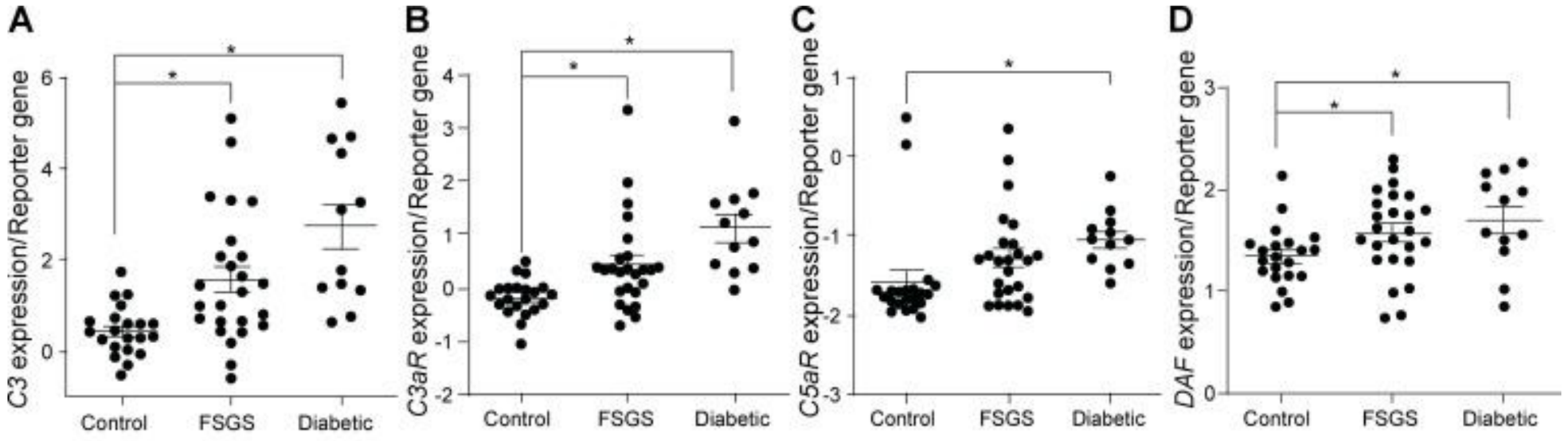
Associated with a higher rate of withdrawal of other immunosuppressants

Estimated GFR

Over the 36 months of follow-up, eGFR was stable in initial responders, whereas non-responders experienced a reduction in eGFR reaching -11 mL/min/1.73m^2

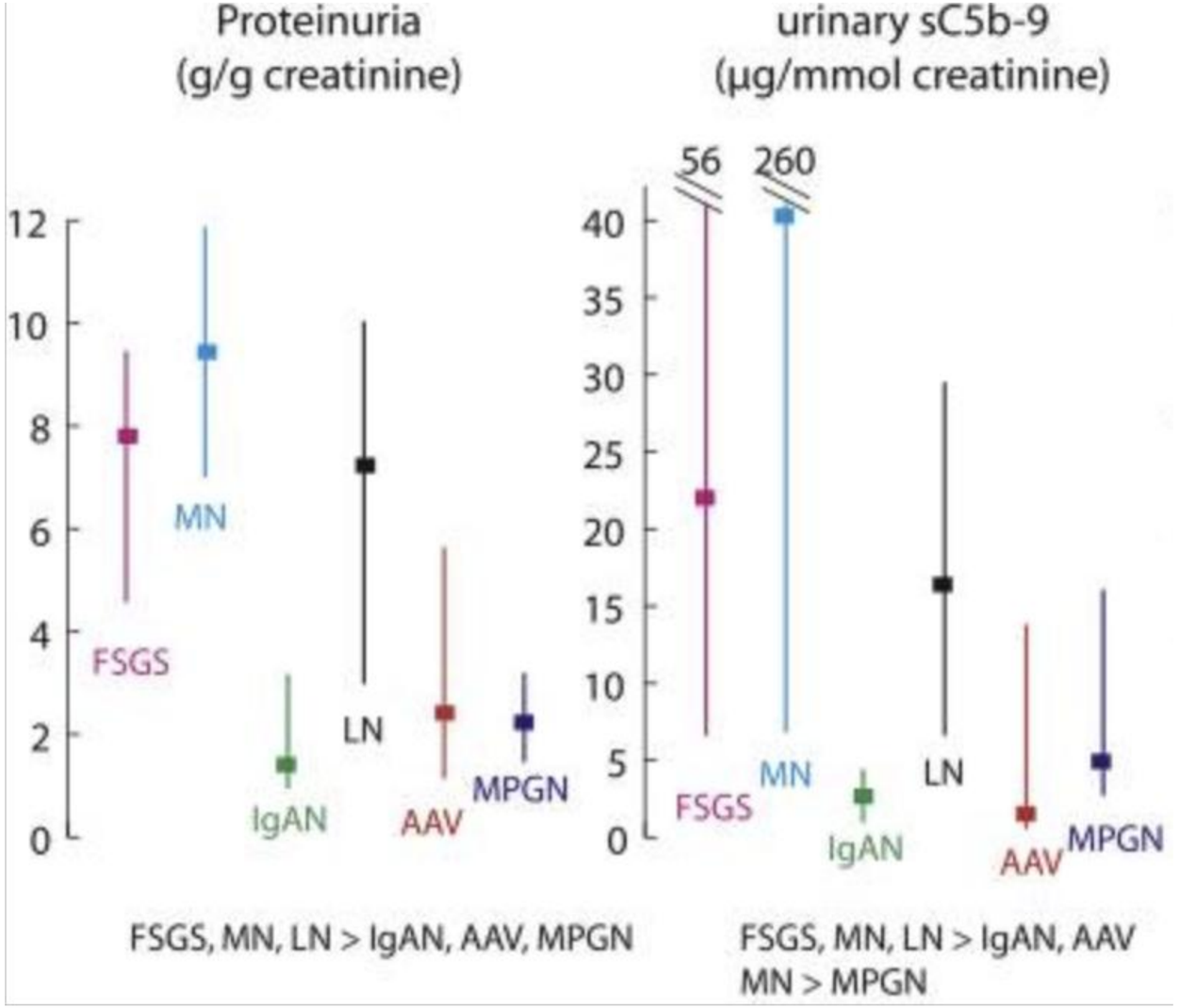
Steroid responsiveness is more useful

Is complement cascade activated in podocytopaties?



Increased expression of mRNA for *C3*, *C3aR*, and *C5aR* in samples from patients with FSGS or diabetic kidney disease compared with control individuals

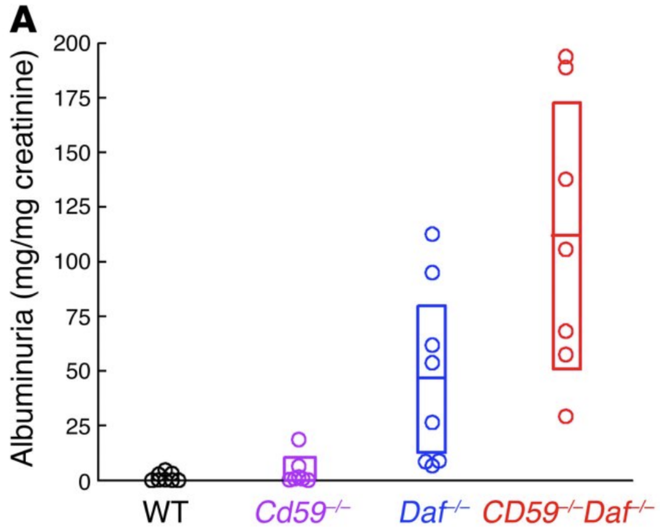
Ju et al., *Genome Res* 2013



Not specific for FSGS

Khalili, Kidney Int Rep. 2020

Mice treated with sheep anti–mouse podocyte antibodies



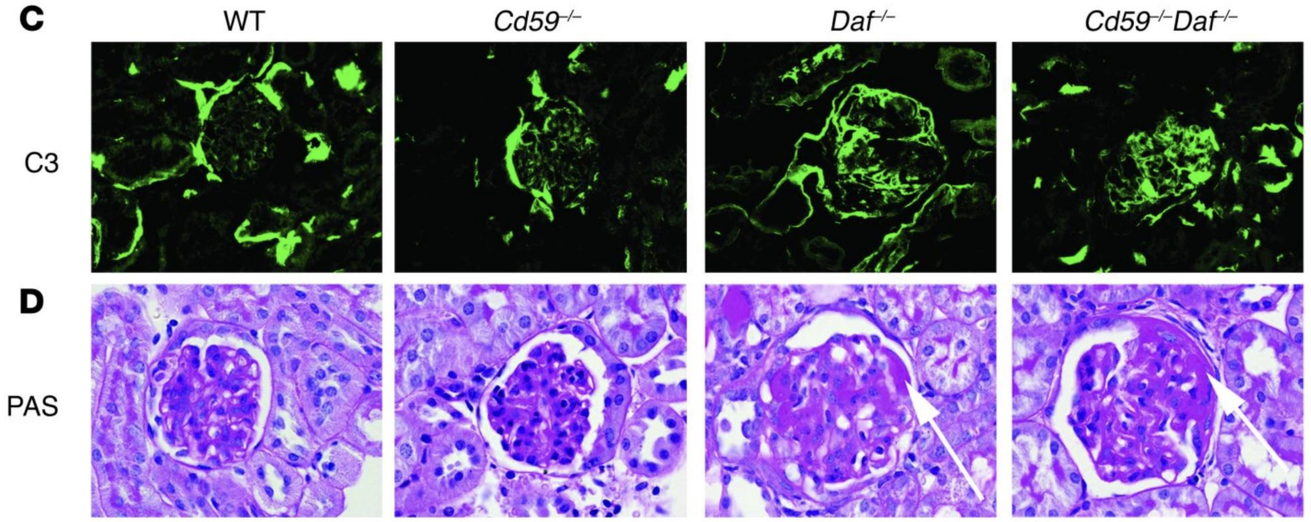
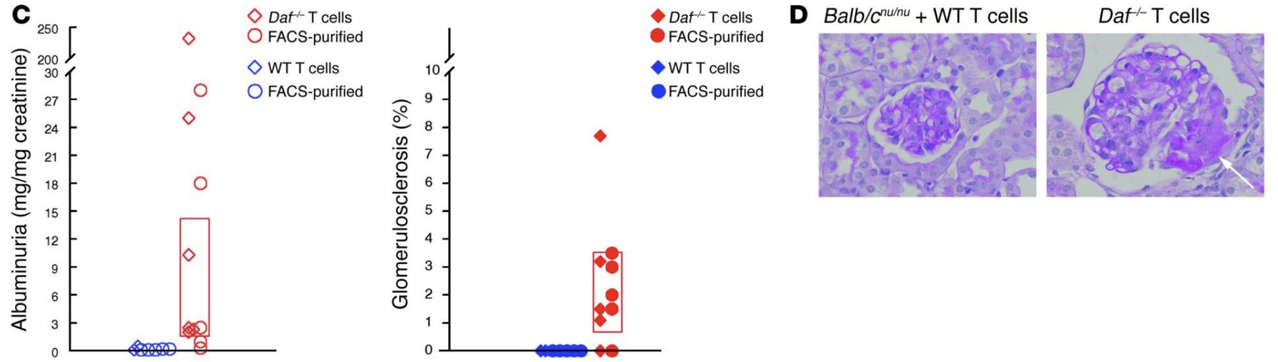


Table 1

Accumulation of monocytic and T lymphocytic cells in kidneys of mice given anti-podo Abs

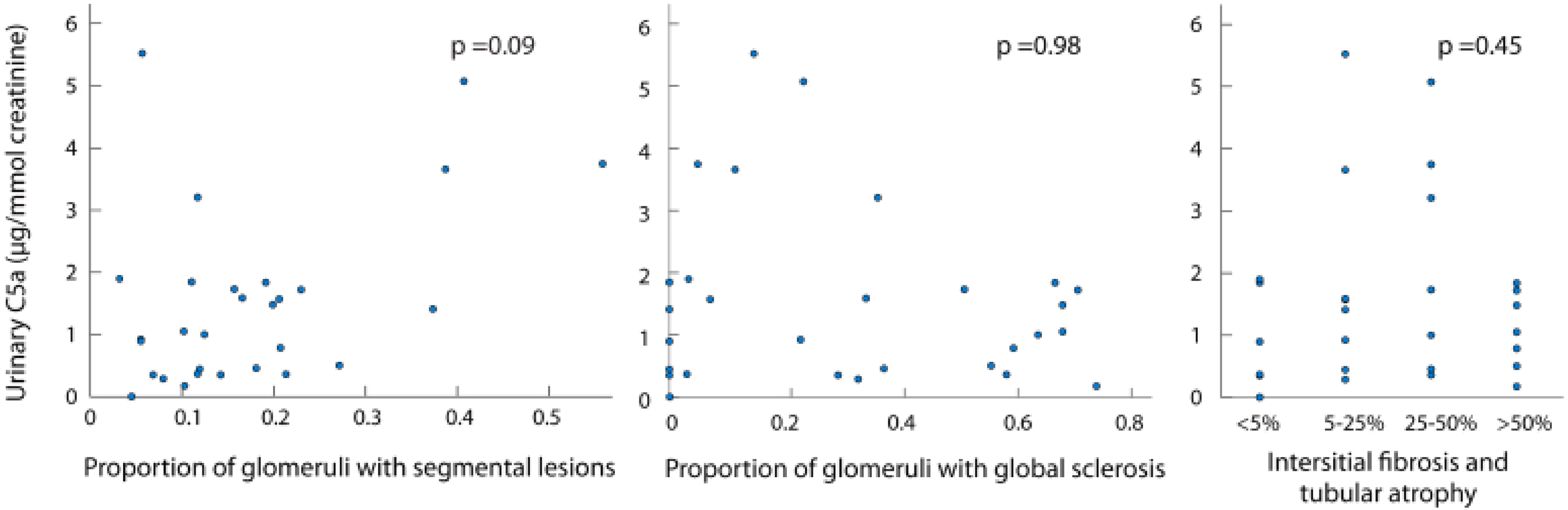
Cell	WT	*Cd59*$^{-/-}$	*Daf*$^{-/-}$	*Cd59*$^{-/-}$*Daf*$^{-/-}$
F4/80^{+A}	35.5 ± 2.8	49.2 ± 8.5	65.0 ± 6.5^{B}	95.3 ± 21.0^{B}
Thy-1.2^{+A}	4.7 ± 0.8	5.3 ± 0.5	15.3 ± 1.7^{B}	31.0 ± 12.5^{B}

Shown are cell numbers per renal cortical hpf. ^{A}The 4 groups had unequal variances ($P \leq 0.002$, 1-way ANOVA). $^{B}P < 0.02$ vs. WT and *CD59*$^{-/-}$ mice (Tukey's pairwise comparisons).



Complement dysregulation in T cells drives FSGS in this model

Bao et al., 2009, JCI



No association between urinary TP and eGFR, or chronic lesions

Cambier et al. Kidney Int Rep. 2023

Is complement activated in FSGS?

Which pathway?

Current studies on complement system inhibition in various renal diseases

Disease	Inhibitor	Pathway	Phase	NCT-Number
Primary membranous nephropathy	Iptacopan	Alternative (factor B)	II	NCT04154787
	Pelecopan	Alternative (factor D)	II	NCT05162066
	Narsoplimab	Lectin (MASP2)	II	NCT02682407
	Pegcetacoplan	Central (C3)	II	NCT03453619
	Gefurulimab	Terminal (C5)	I	NCT05314231
C3G	Iptacopan	Alternative (factor B)	II, III, OLE	NCT03832114, NCT04817618, NCT03955445
	NM8074	Alternative (factor Bb)	Ib	NCT05647811
	Pelecopan	Alternative (factor D)	II	NCT05162066
	Danicopan	Alternative (factor D)	IIa, IIb	NCT03124368, NCT03369236, NCT03459443, NCT03723512
	Narsoplimab	Lectin (MASP2)	II	NCT02682407
	TP10	Inhibition (scR1)	IIa	NCT02302755
	Pegcetacoplan	Central (C3)	II, III, OLE	NCT04572854, NCT03453619, NCT05067127, NCT05809531
	ARO-C3	Central (C3)	I/II	NCT05083364
	AMY-101	Central (C3)	I	NCT03316521
	KP104	Inhibition (CFH/C5)	II	NCT05517980
	Avacopan	Inflammation (C5aR)	II	NCT03301467
IC-MPGN	Iptacopan	Alternative (factor B)	III	NCT05755386
	Danicopan	Alternative (factor D)	IIa, IIb	NCT03124368, NCT03459443, NCT03723512, NCT03369236
	Pegcetacoplan	Central (C3)	II, III, OLE	NCT04572854, NCT05067127, NCT05809531
Lupus Nephritis	Iptacopan	Alternative (factor B)	II	NCT05268289
	Vemircopan	Alternative (factor D)	II	NCT05097989
	Narsoplimab	Lectin (MASP2)	II	NCT02682407
	ANX009	Classical (C1q)	I	NCT05780515
	Pegcetacoplan	Central (C3)	II	NCT03453619
	Gefurulimab	Terminal (C5)	I	NCT05314231
	Ravulizumab	Terminal (C5)	II	NCT04564339

Nell, 2024 Biomedicines

Kant, 2022 Am J Kidney Dis

Not yet recruiting

A Sequential Phase 2/3 Study of APL2 in Patients With Focal Segmental Glomerulosclerosis

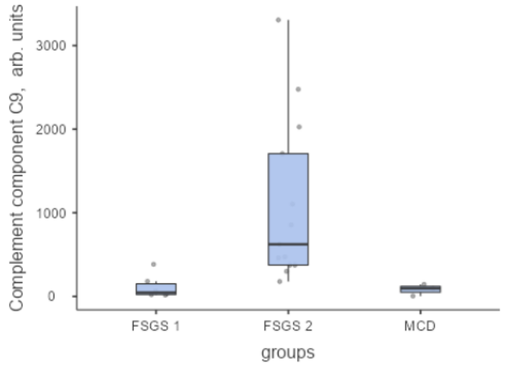
ClinicalTrials.gov ID NCT07213960

Sponsor Apellis Pharmaceuticals, Inc.

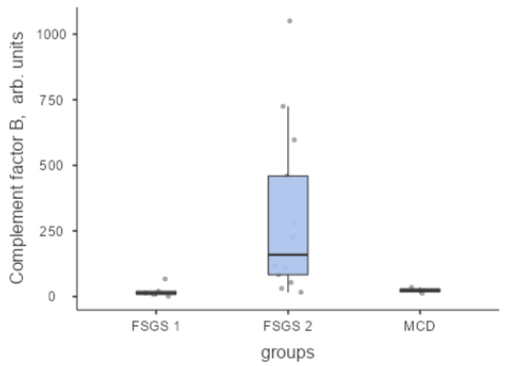
Information provided by Apellis Pharmaceuticals, Inc. (Responsible Party)

Last Update Posted 2025-10-09

Potential Urine Proteomic Biomarkers for FSGS and MCD



(d)



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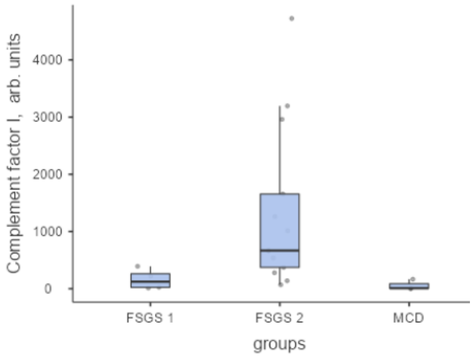

(f)

Increased urinary levels of complement components C4b and factors B and I were associated with more severe FSGS

Chebotareva et al., Int. J. Mol. Sci. 2022