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Dept. of Nephrology
Juntendo University

Chairs：Prof. Sydney CW Tang and Chin-Chung Tseng

Ameliorating Complement-mediated Injury in IgA Nephropathy

改善IgA腎病變中補體介導的損傷

Hitoshi Suzuki

Department of Nephrology,

Juntendo University Urayasu Hospital, Japan

COI Disclosure

I have the following relationships to disclose any COI for this research presentation within the period of 36 months

* **Employment/Leadership position/Advisory role:** Otsuka Pharmaceutical, Vera therapeutics, Viatris
* **Stock ownership or options: none**
* **Patent royalties/licensing fees: none**
* **Honoraria:** Novartis, Alexion Pharma, Chugai, Viatris
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* **Subsidies or Donations: none**
* **Endowed departments by commercial entities: none**
* **Travel fees, gifts, and others: none**

Multi-Hit model of pathogenesis of IgA nephropathy

Hit1

Increased circulating galactose-deficient IgA1

Hit2

Production of unique anti-glycan antibodies

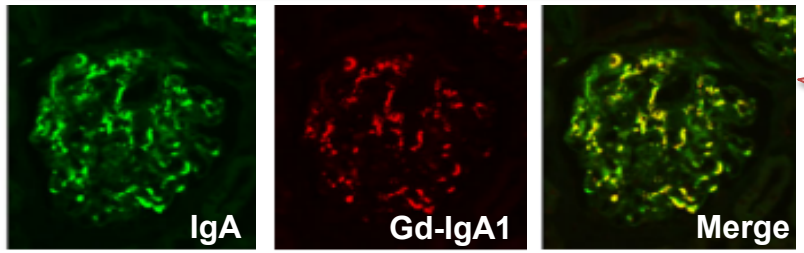
(IgG, IgA)

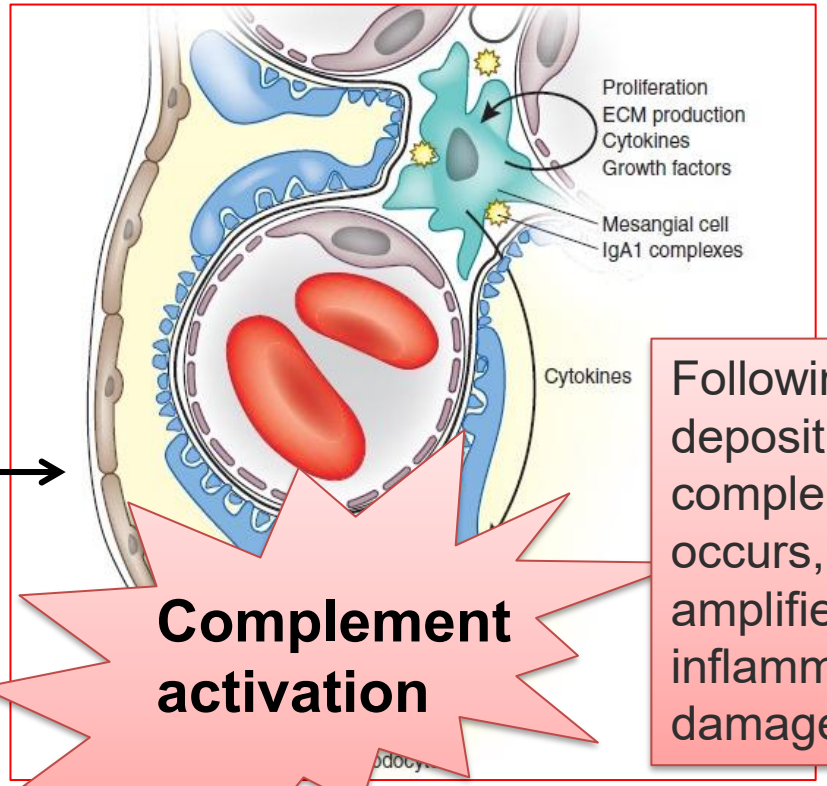
Hit3

Formation of pathogenic IgA1-containing circulation immune complexes

Hit4

Mesangial deposition and activation of mesangial cells resulting in glomerular injury



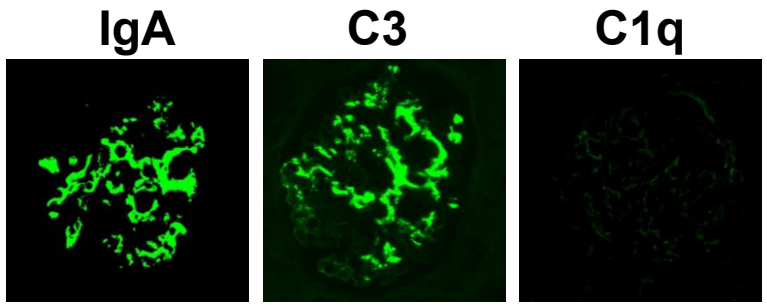


Complement activation

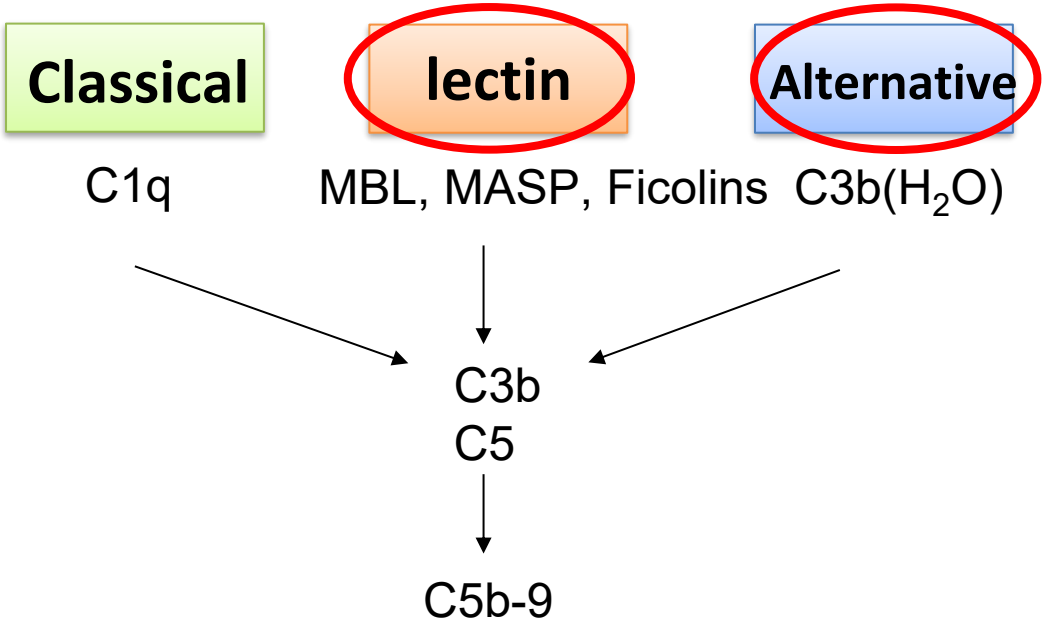
Following the mesangial deposition of IgA-ICs, complement activation occurs, which drives and amplifies glomerular inflammation and damage

Suzuki H, et al: J Am Soc Nephrol, 2011

Glomerular co-deposition of C3 with IgA is detected in >90% of kidney biopsies in IgAN

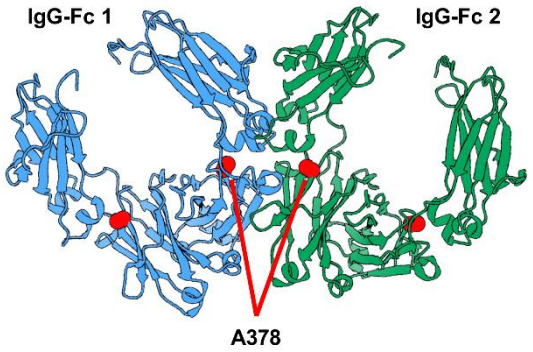


Complement activation

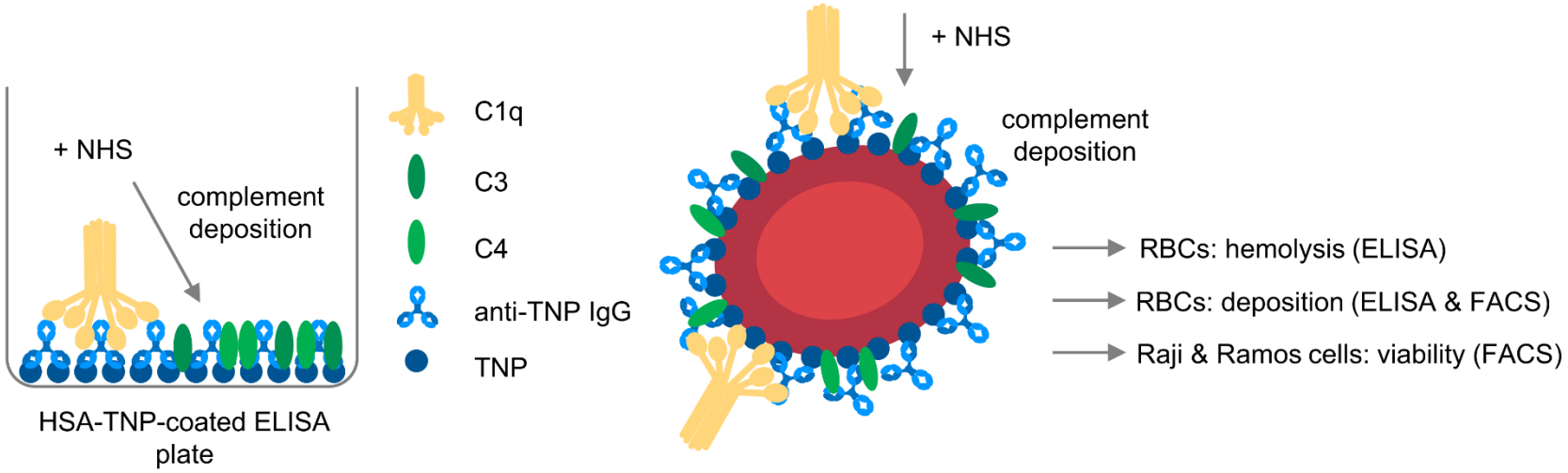


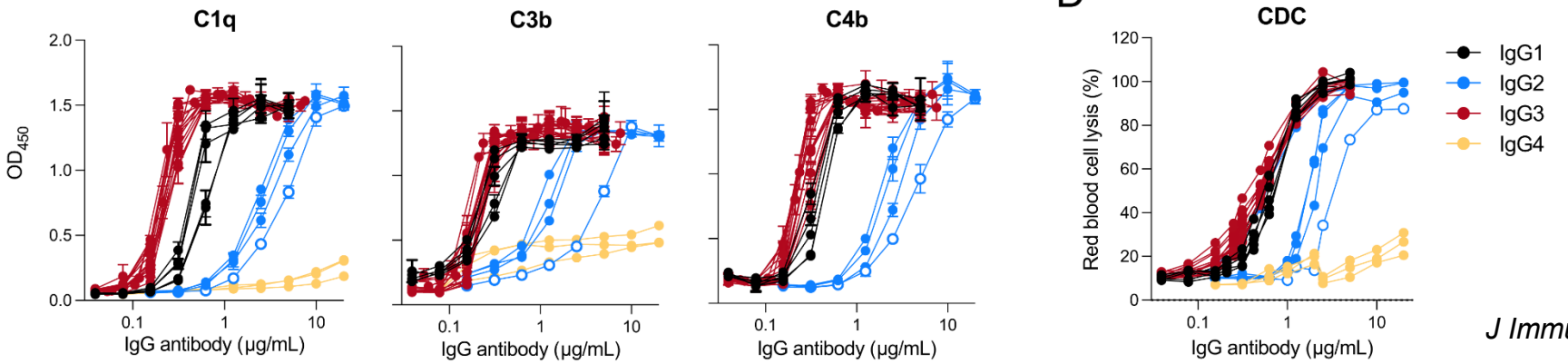
- ✓ What is the extent of the role of complement? Truly only inflammation or more fundamental role in pathogenesis?
- ✓ Ongoing active injury vs. resolving injury?
- ✓ Should we use complement assays/histological staining to guide therapy?
- ✓ Limitations of current complement measurements available to clinicians.

How is the complement system activated?

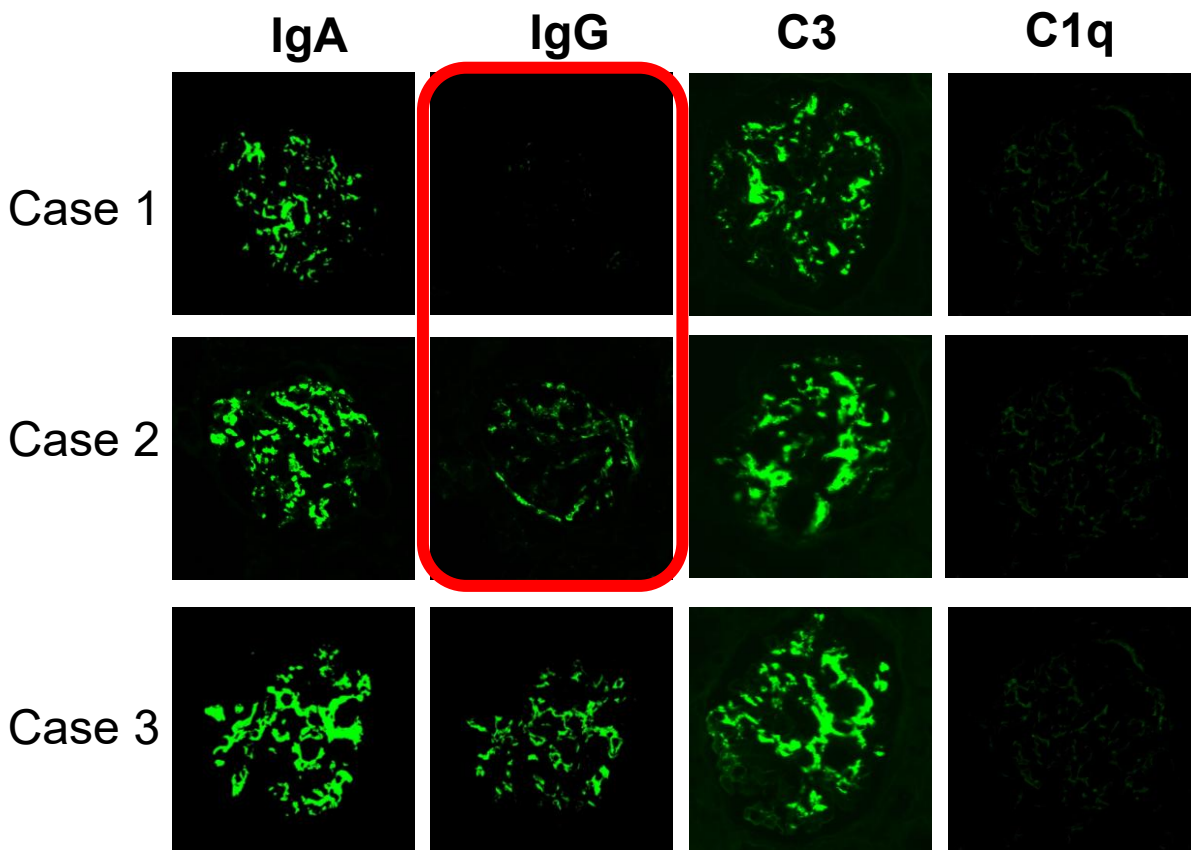


IgG have pro- and anti-inflammatory activities, depending on the engagement of Fcγ receptors and the activation of the complement system, depends on the IgG subclass, glycosylation, and antigen density





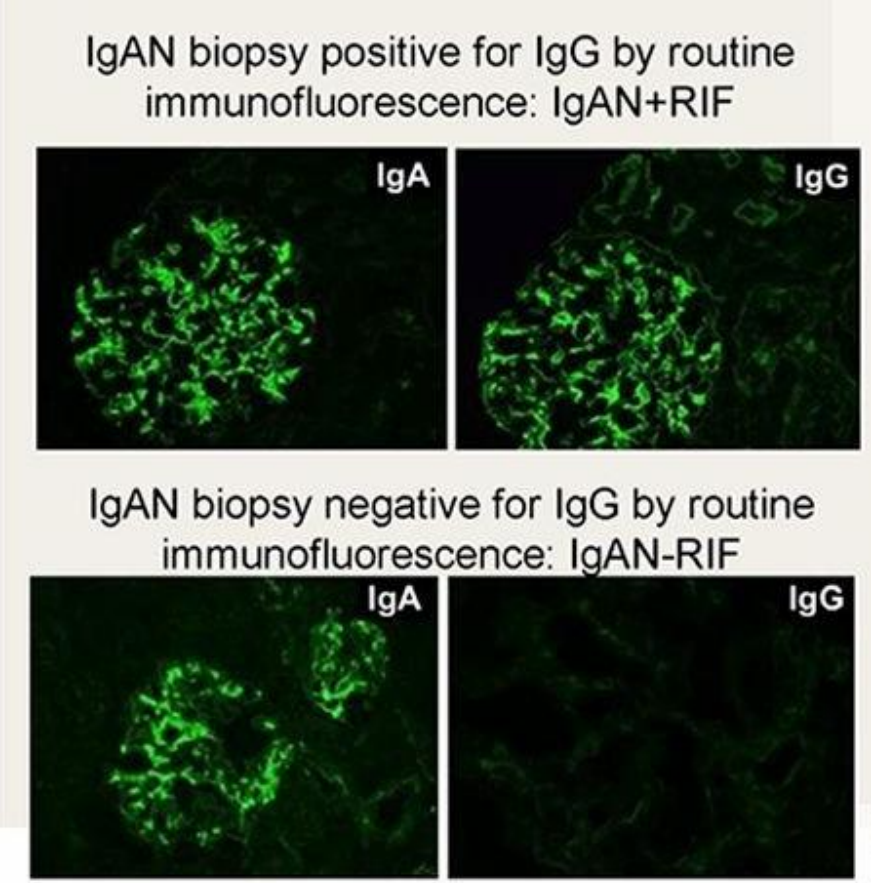
J Immunol 11:1725-1735, 2023

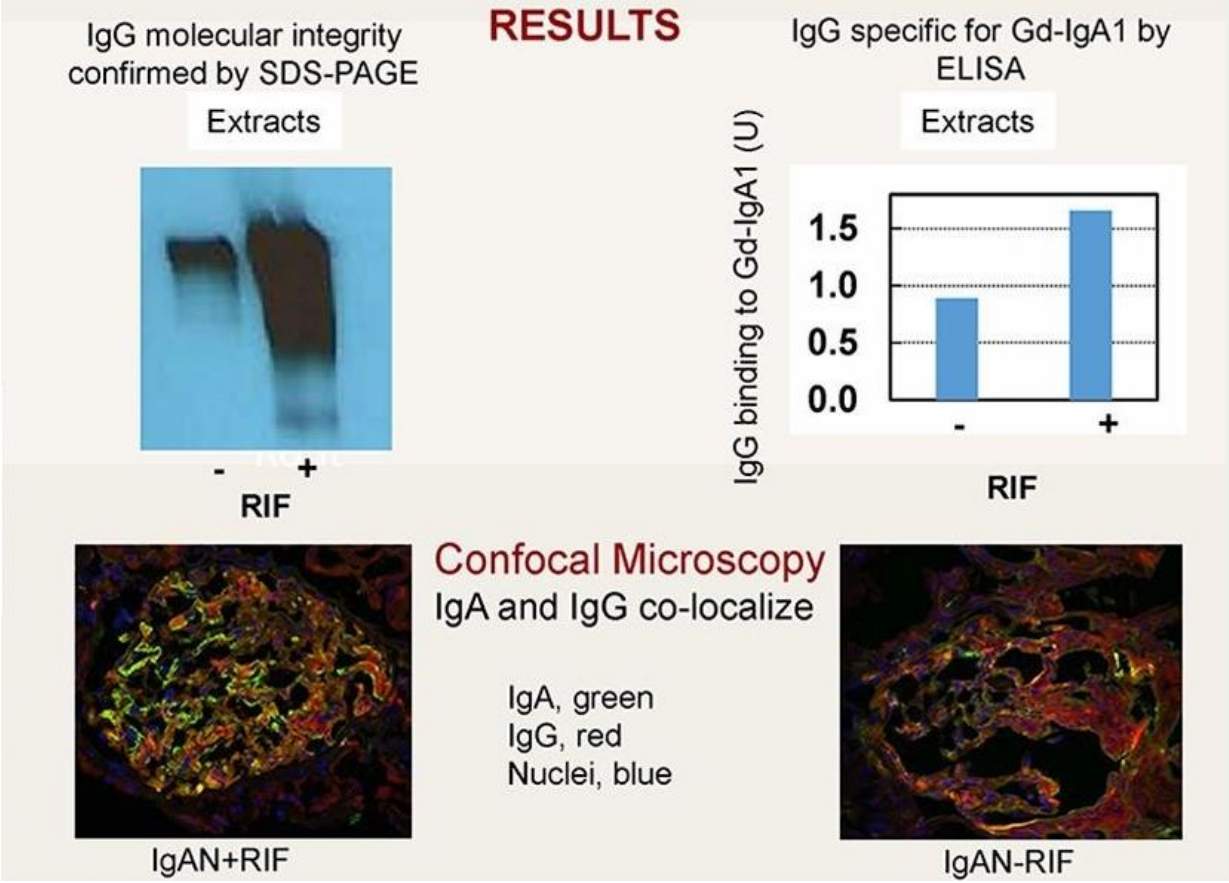


IgAN was described by Berger, in 1968, based on "intercapillary deposits of IgA-IgG".

However, not all of the patients show glomerular IgG deposition by regular clinical immunofluorescent analysis.

Routine immunofluorescence (RIF) microscopy fails to detect IgG in many kidney biopsies from patients with IgAN



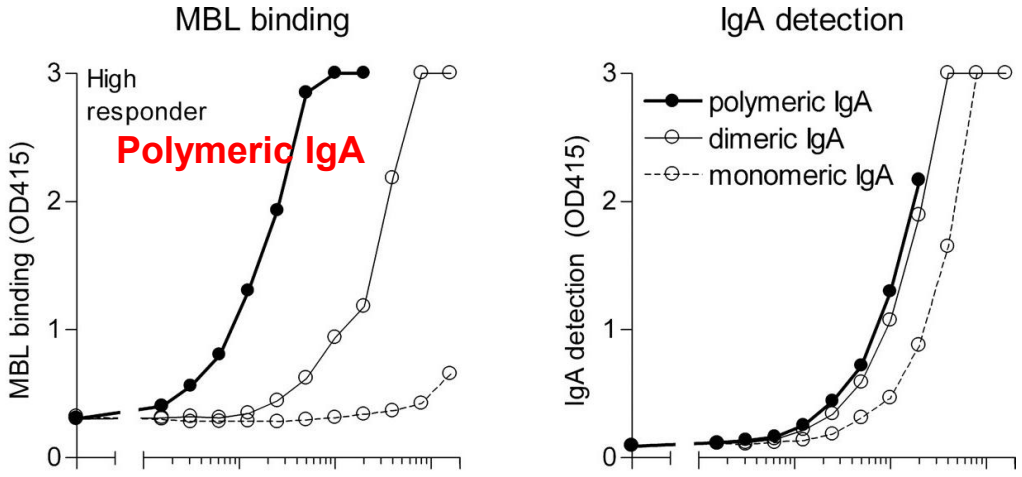


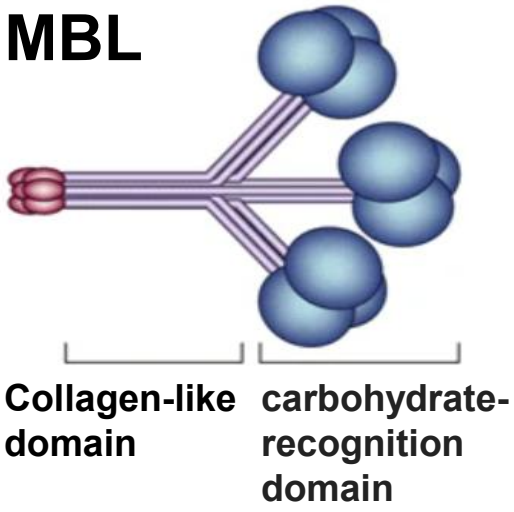
A nanobody specific for the CH3 domain of its Fc portion detects IgG in all patients with IgAN

Rizk DV, et al. J Am Soc Nephrol 30, 2017–2026, 2019

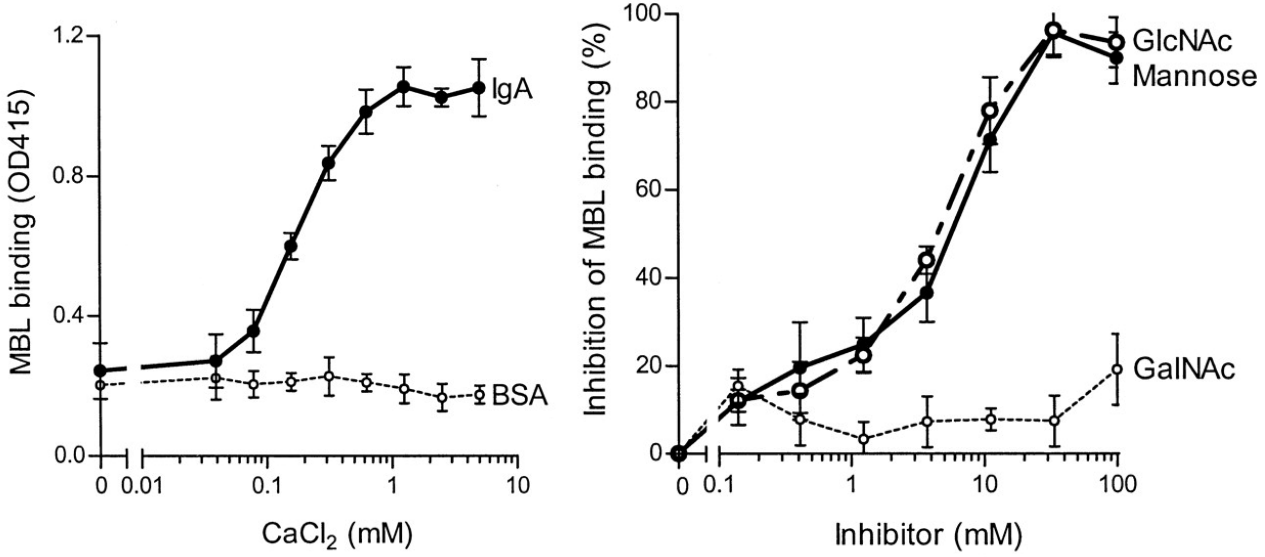
Does IgA have complement activity?

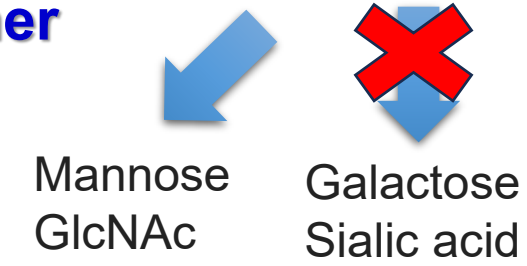
Polymeric IgA binds via the carbohydrate recognition domain of MBL





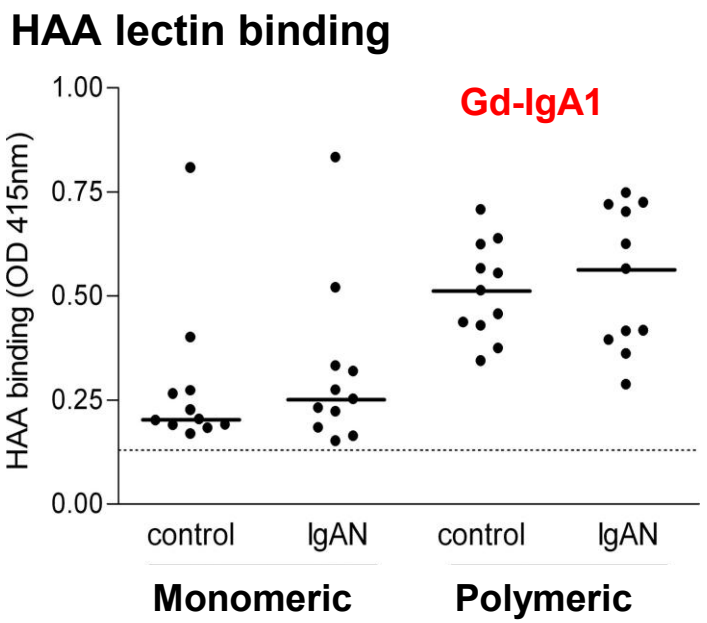
MBL binds to mannose and GlcNAc in a Ca-dependent manner

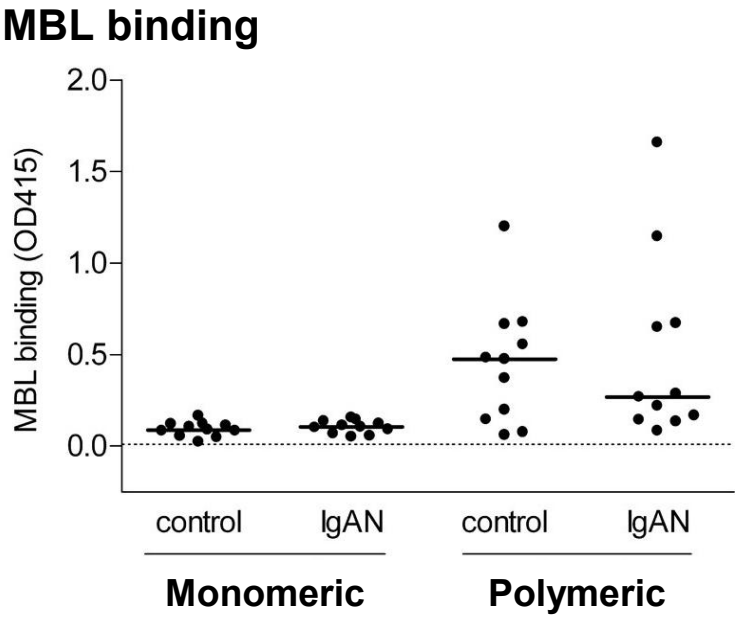


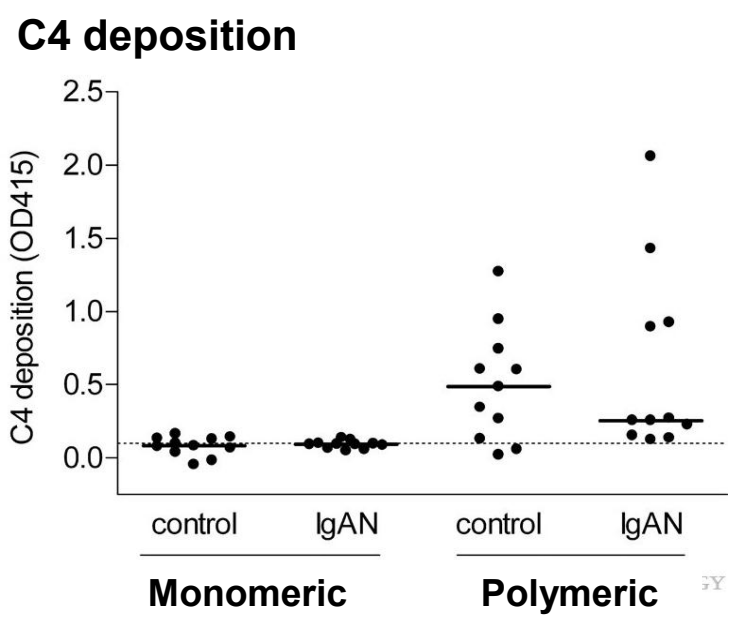


Fujita T. Nat Rev Immunol, 2002
Roos A. J Immunol 167: 2861, 2001
Roos A. JASN 17: 1724-1734, 2006

Complement activity of IgA : polymeric >> monomeric







Oortwijn B, JASN 17: 3529, 2017

Does IgA activate the alternative pathway?

European Journal of Immunology
Basic·Clinical·Translational

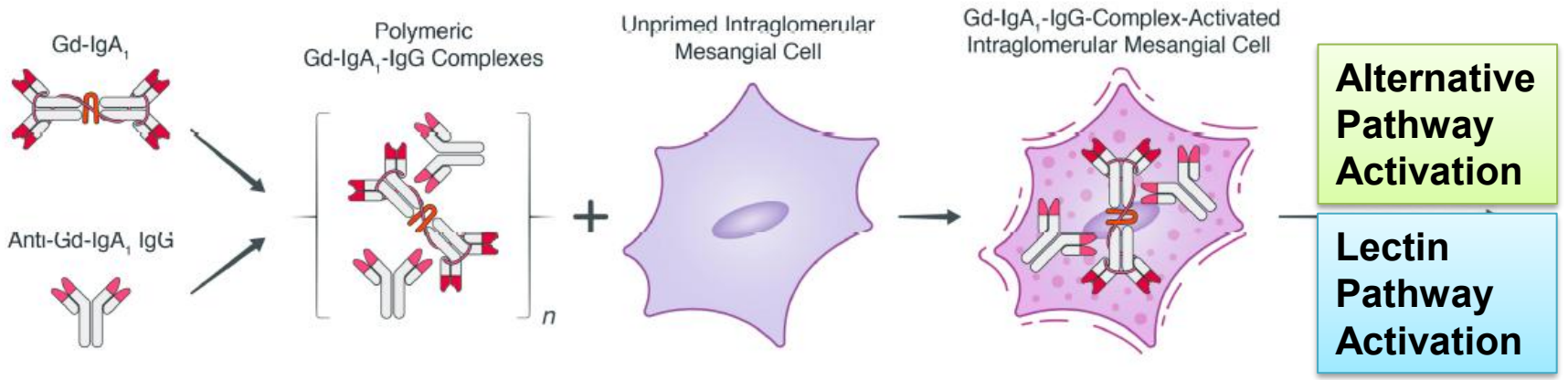
Eur J Immunol 17: 321, 1987

Article

Activation of the alternative pathway of complement by human serum IgA

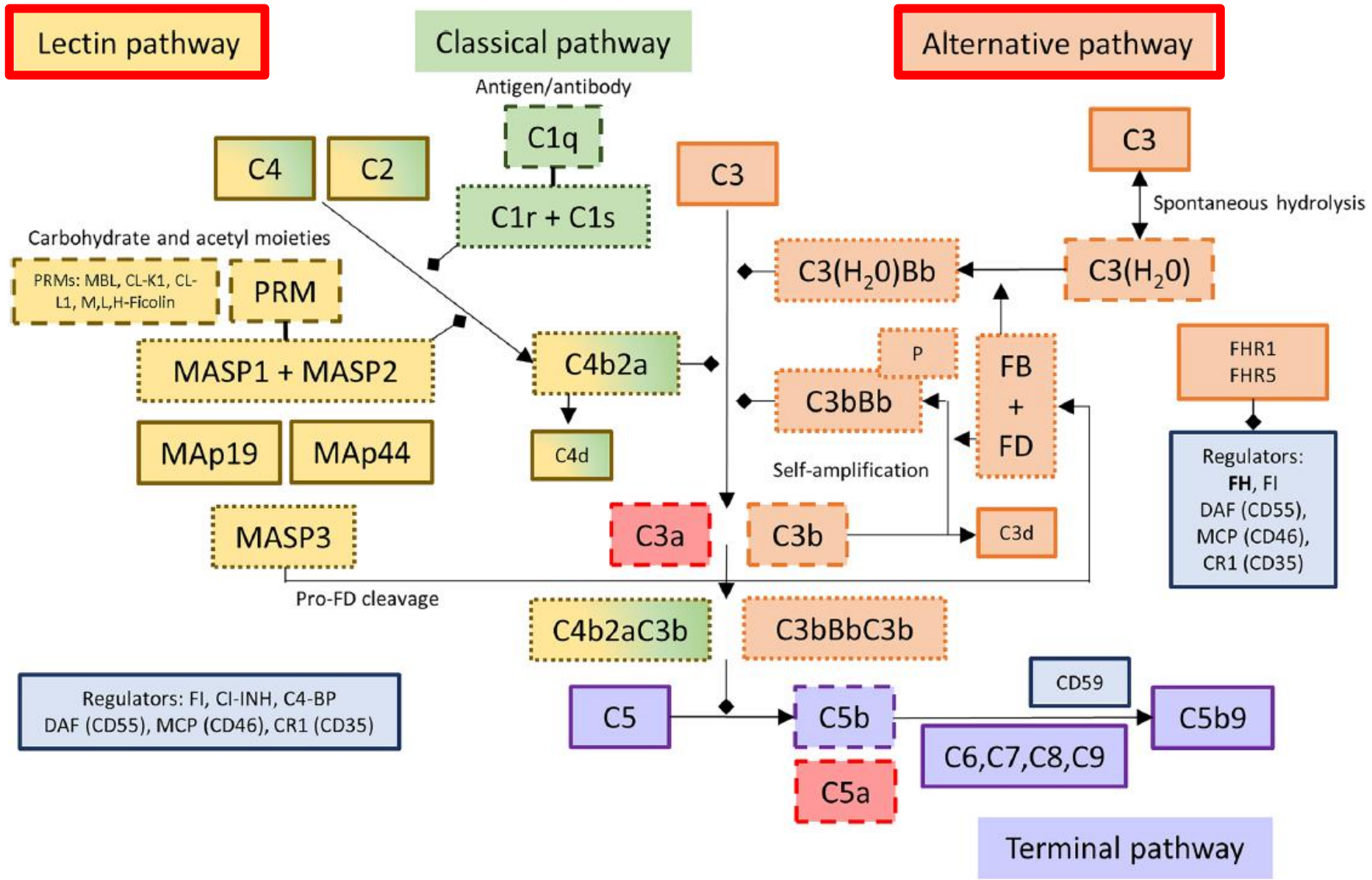
Pieter S. Hiemstra, Arko Gorter, Marly E. Stuurman, Leendert A. Van Es, Mohamed R. Daha

Polymeric IgA is capable of activating the **alternative pathway** of complement.



Rizk DV. Front Immunol 10, 504, 2019

Complement Pathway

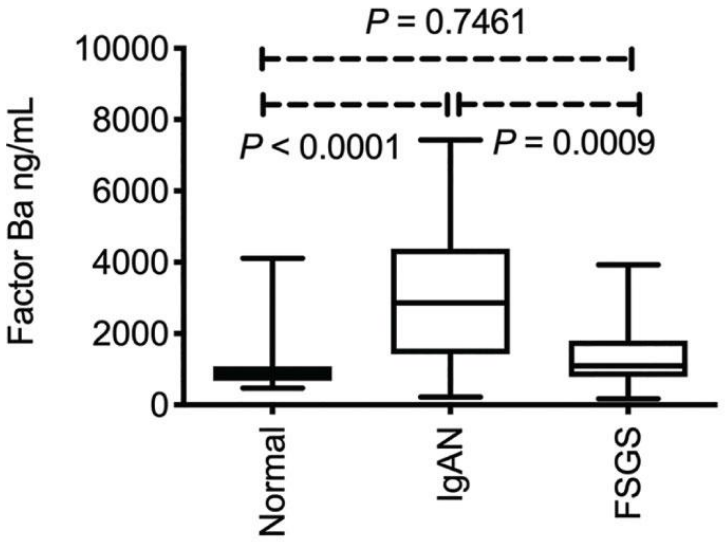


Medjeral-Thomas NR. Semin Immunopathol 43: 679, 2021

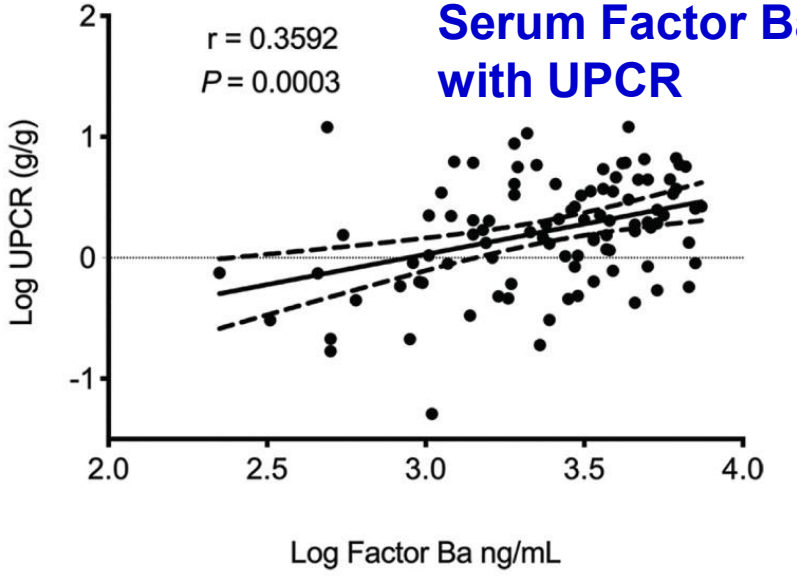
Involvement of Alternative Pathway

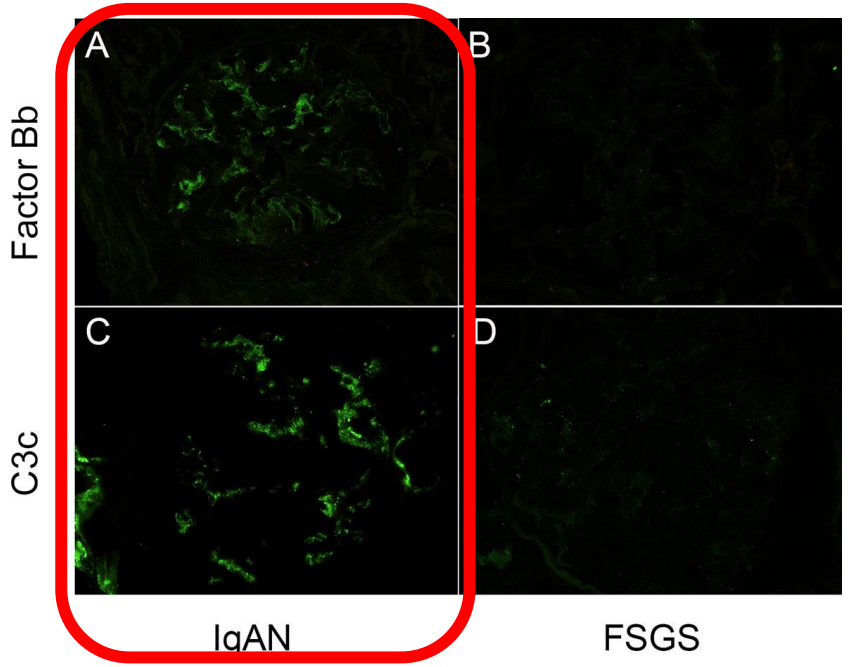
Factor B: key mediator of alternative pathway

Serum Factor Ba

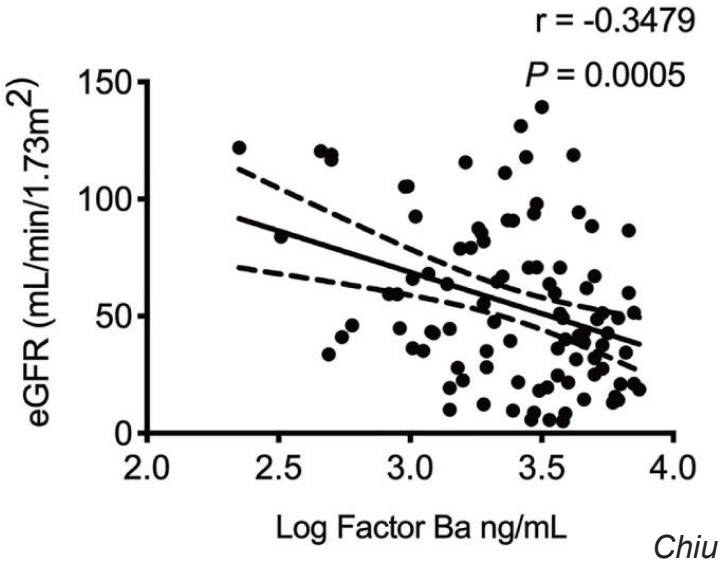


Serum Factor Ba associate with UPCR





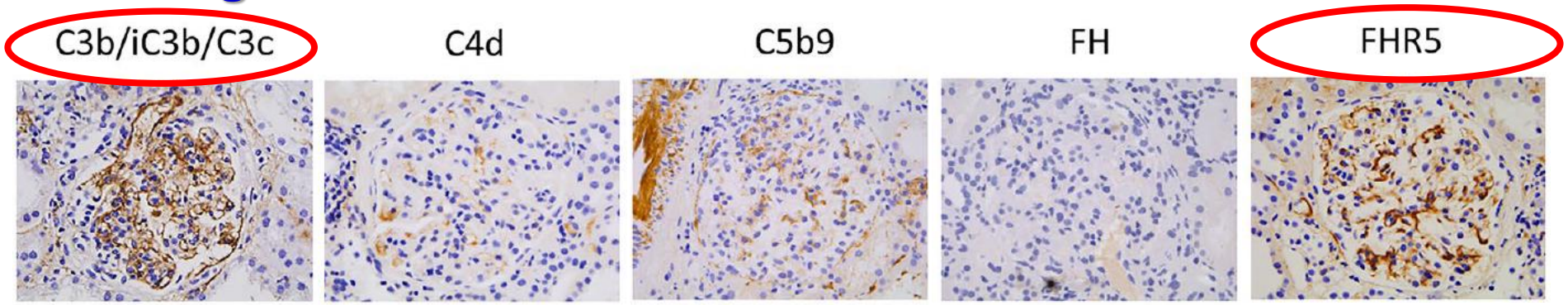
Serum Factor Ba inversely correlated with eGFR



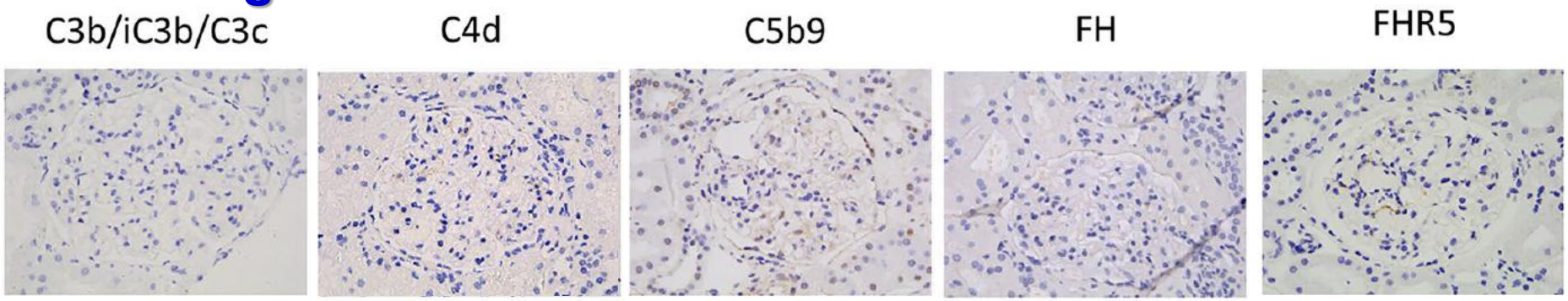
Chiu YL. Front Immunol 10: 12: 638309, 2021

Alternative Pathway

Active IgAN



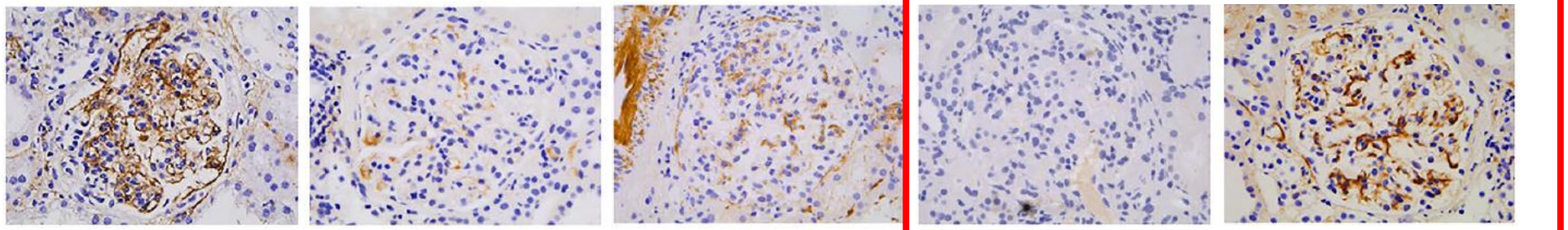
Inactive IgAN



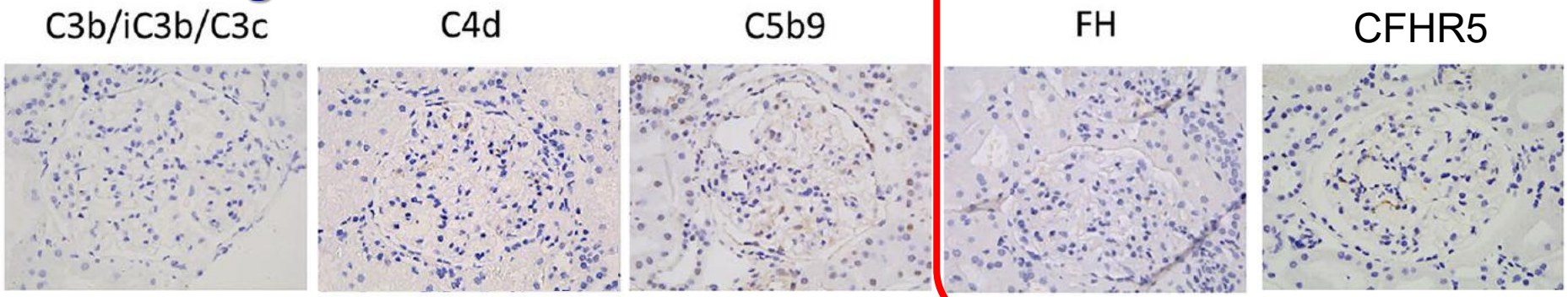
Medjeral-Thomas NR. Semin Immunopathol 43: 679, 2021

Alternative Pathway

Active IgAN

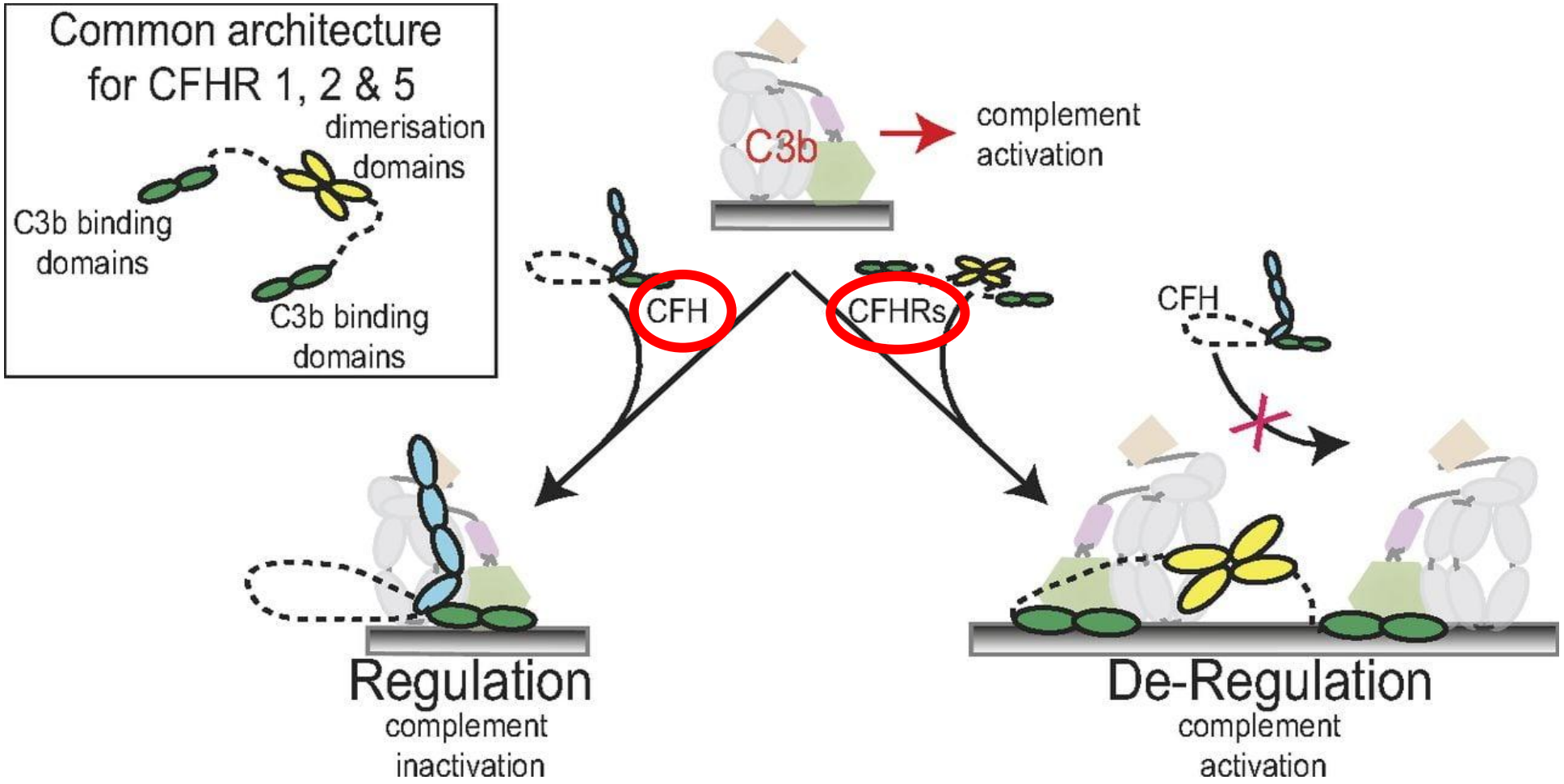


Inactive IgAN



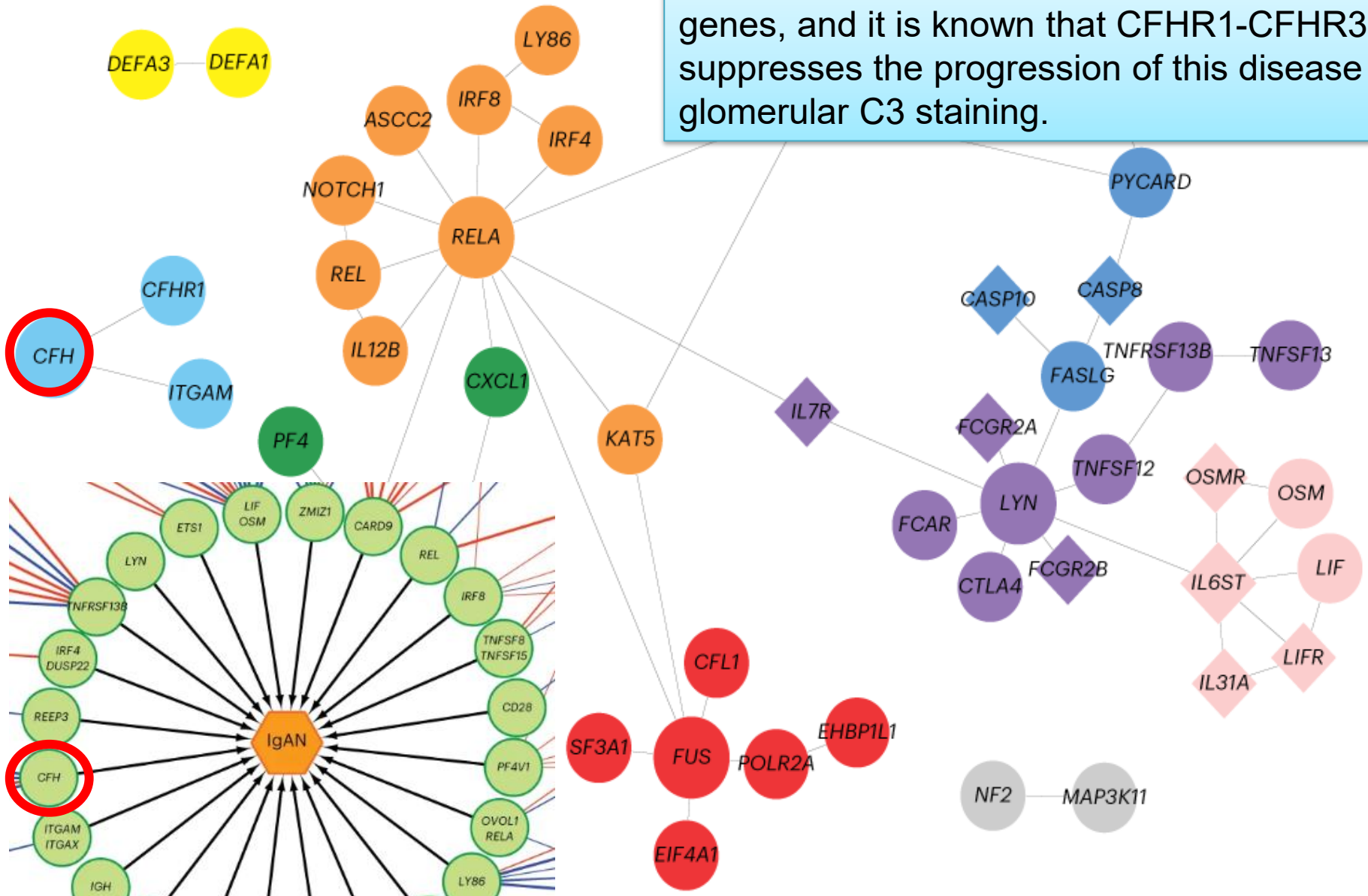
Medjeral-Thomas NR. Semin Immunopathol 43: 679, 2021

- **Inactivation of the complement system by Factor H**
- **CFHR competes with Factor H to activate complement**



PNAS 110: 4685, 2013

GWAS studies have identified CFHR1/3 as candidate genes, and it is known that CFHR1-CFHR3 deficiency suppresses the progression of this disease and reduces glomerular C3 staining.



Kiryluk K. Nat Genet 55: 1091, 2023

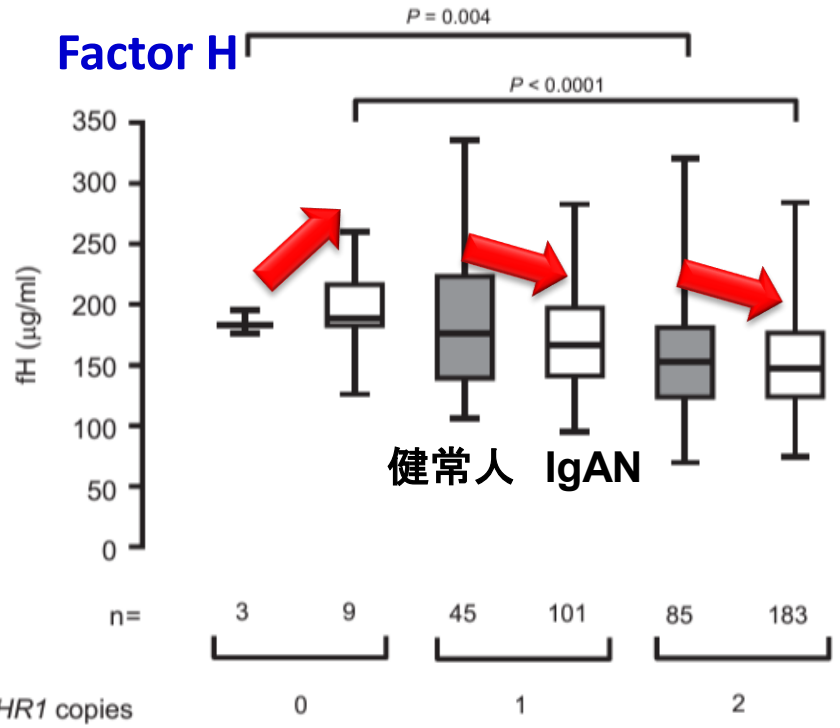
clinical investigation www.kidney-international.org

Circulating complement factor H–related proteins 1 and 5 correlate with disease activity in IgA nephropathy

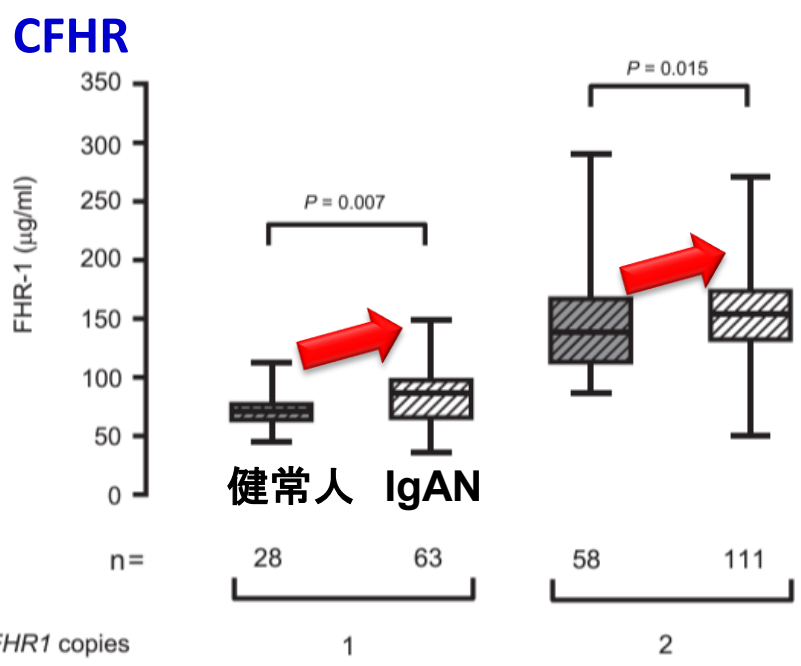
Nicholas R. Medjeral-Thomas[1,6], Hannah J. Lomax-Browne[1,6], Hannah Beckwith[1], Michelle Willicombe[2], Adam G. McLean[2], Paul Brookes[3], Charles D. Pusey[4], Mario Falchi[5], H. Terence Cook[1] and Matthew C. Pickering[1]

Kideny Int 92: 942, 2017

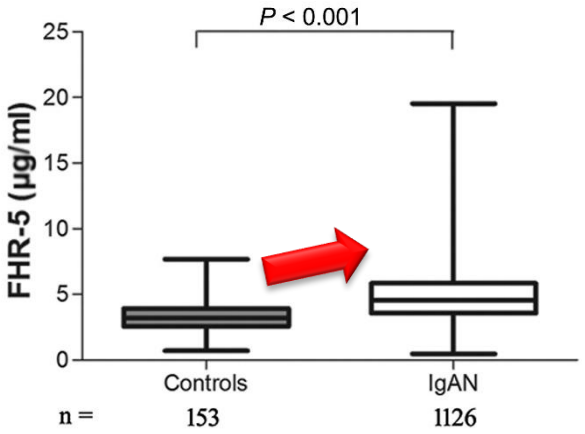
CFHR suppresses Factor H

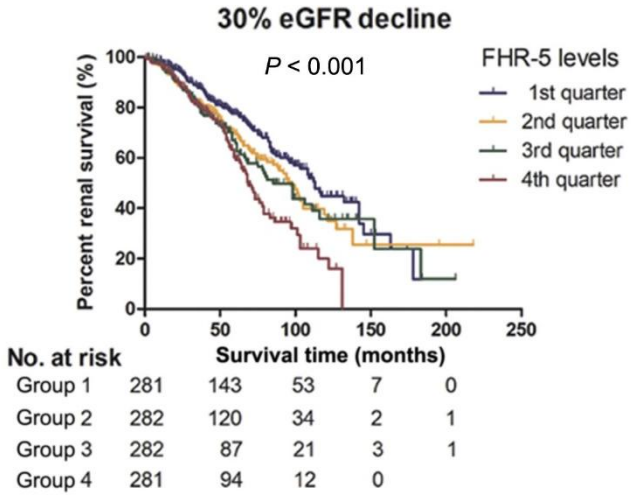


CFHR increase in active IgAN

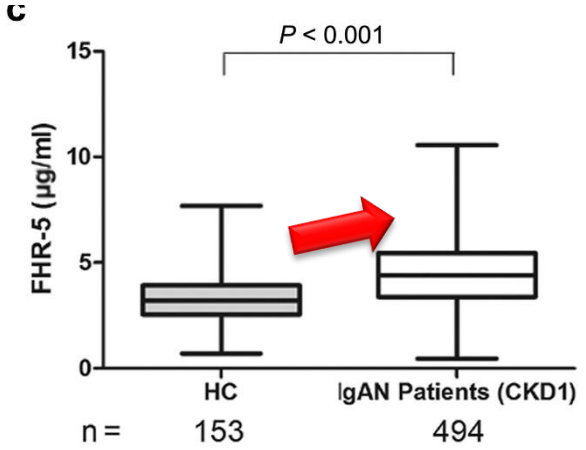


Serum CFHR5 levels are elevated in IgAN and correlate with renal prognosis

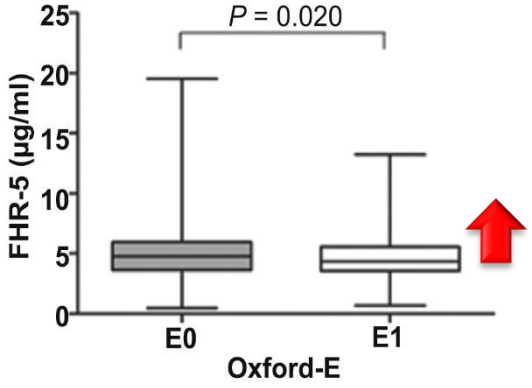


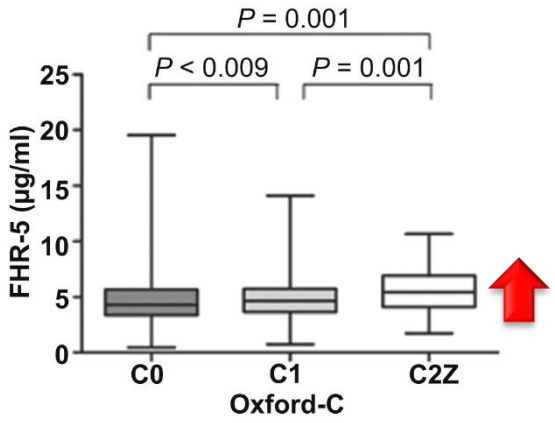


CFHR5 levels increase from disease stages where renal function is preserved



FHR5 levels correlate with acute (active) lesions

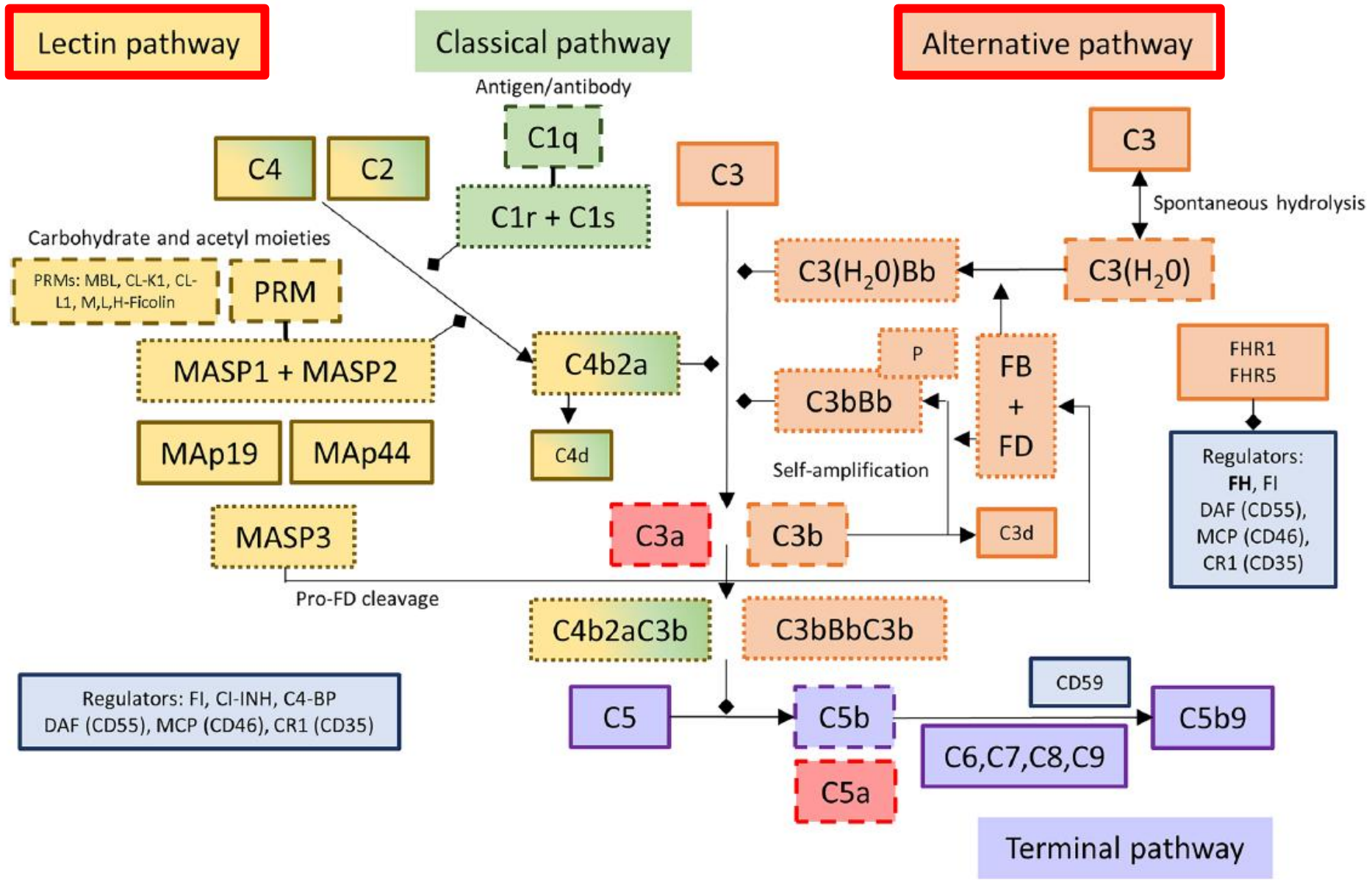




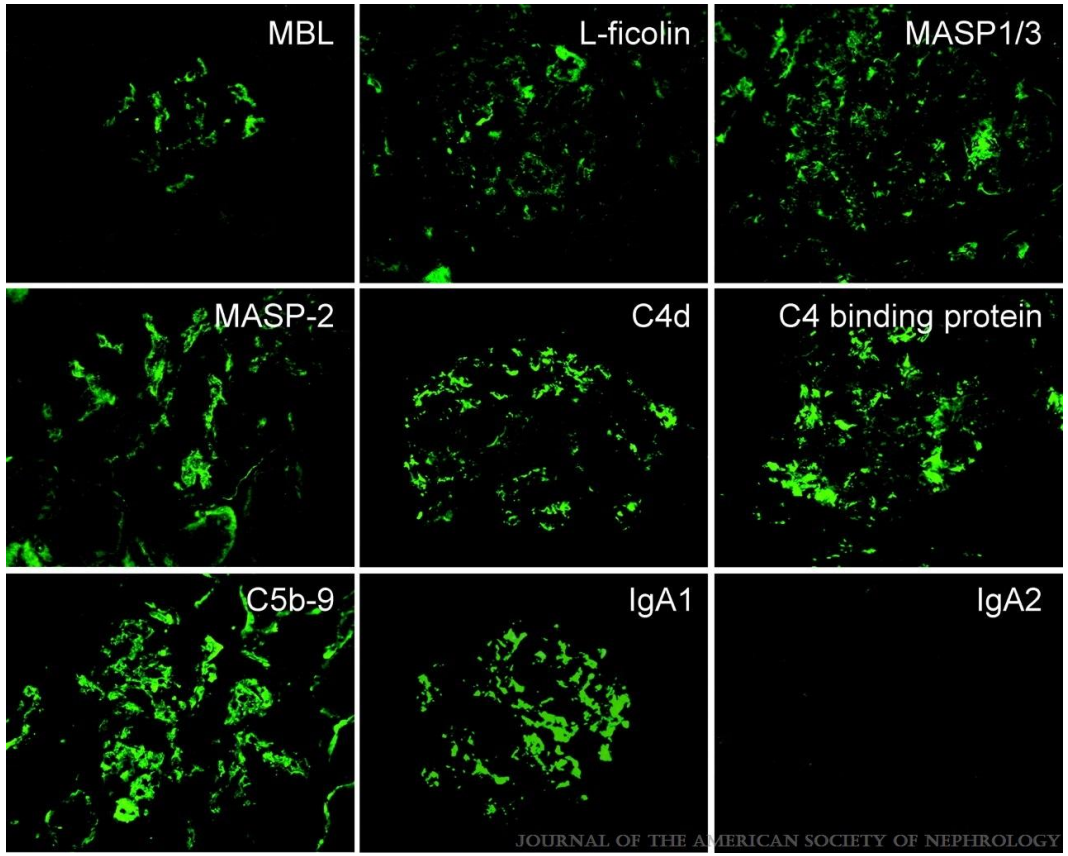
Kidney Int 94: 150, 2018

Involvement of Lectin Pathway

Complement Pathway

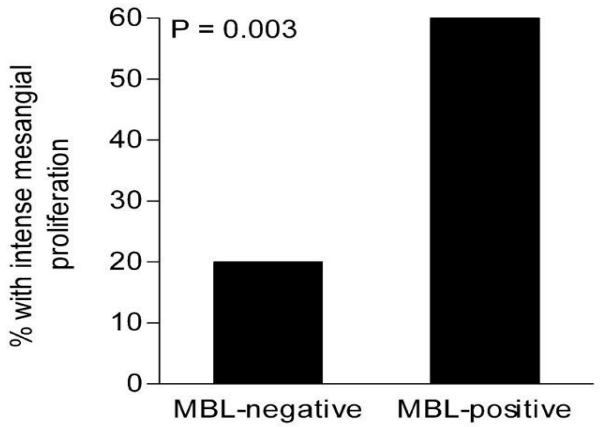


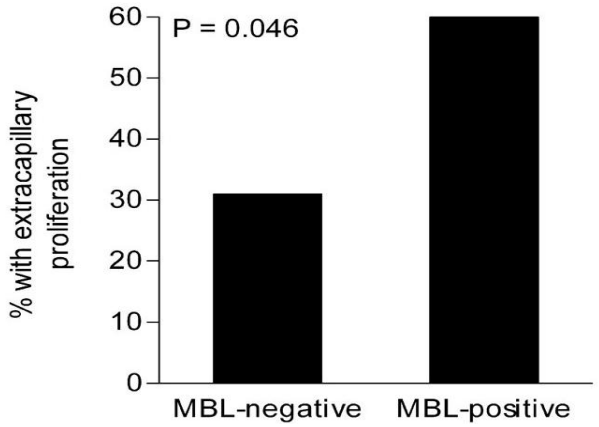
Medjeral-Thomas NR. Semin Immunopathol 43: 679, 2021

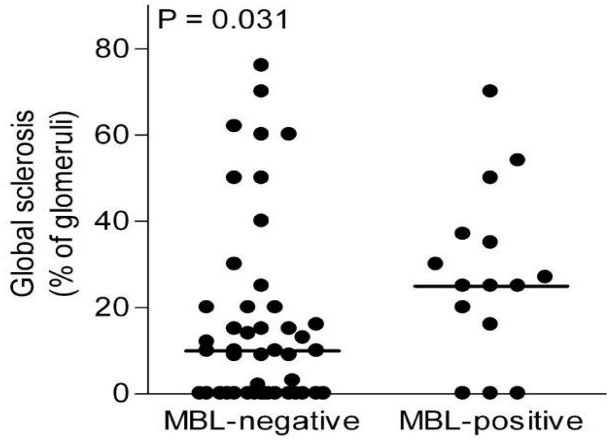


Active lectin pathway (25%)

Association with;
-- M lesion,
-- E lesion,
-- global sclerosis







Roos A. JASN 17: 1724-1734, 2006

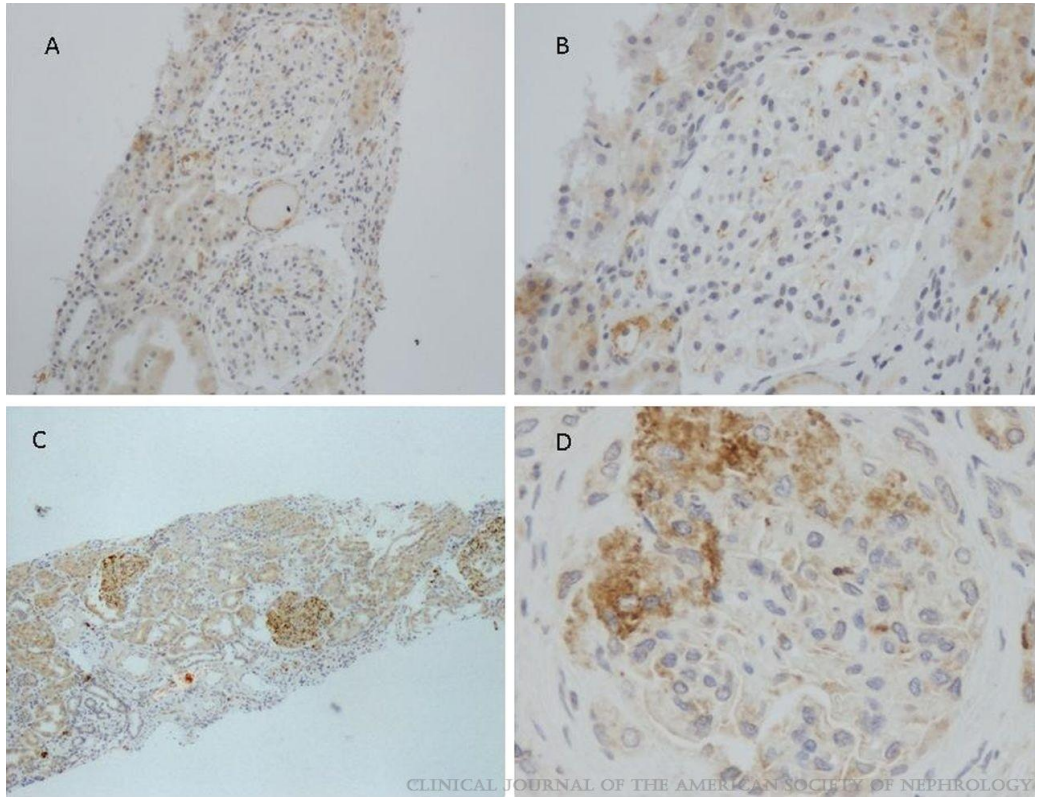
Glomerular C4d positivity rate: 19-56%

Study, y	Nam et al[21] (2020)	Sato et al[10] (2019)	Segarra et al[9] (2018)	Fabiano et al[16] (2017)	Sahin et al[13] (2014)	Espinosa et al[12] (2014)
Country	Korea	Japan	Spain	Brazil	Turkey	Spain
No. of patients	380	25	190	47	33	283
Age, y (C4d+/C4d−)	37.2/35.8	9.5/13.0	28.0/29.0	10.5/8.8	32.2/36.3	38.6/39.4
Patients C4d+	72 (18.9%)	14 (56.0%)	38 (20.0%)	10 (21.3%)	11 (33.3%)	109 (38.5%)
Definition of C4d positivity	>25% G	>50% G	>1 G	>50% G	>75% G	>25% G
C4d staining method	IHC	IF	IHC	IHC	IHC	IHC
Male sex (C4d+/C4d−)	48.6%/41.9%	43.0%/27.0%	63.0%/65.0%	60.0%/62.0%	55.0%/50.0%	74.0%/73.0%
Follow-up, y	7.9	2.0	15.8	5.6/9.5	2.7	6.0
Proteinuria (g/d or g/g) (C4d+/C4d−)	1.6/0.7	2.0/0.8	1.9/1.5	0.9/0.1	4.0/1.3	2.2/1.7
Baseline eGFR, mL/min/1.73 m^2 (C4d+/C4d−)	72.8/88.0	121.0 /125.0	98.0/99.0	127.0/148.5	45.6/68.7	58.9/73.2
Serum creatinine, mg/dL (C4d+/C4d−)	1.4/1.0	NA	1.0/1.0	NA	3.0/1.8	NA
Macroscopic hematuria (C4d+/C4d−)	NA	64.0%/45.0%	42.0%/43.0%	NA	NA	39.0%/49.0%
Hypertension (C4d+/C4d−)	41.7%/47.1%	NA	16.0%/12.0%	10.0%/22.0%	64.0%/36.0%	72.0%/44.0%
M1 (C4d+/C4d−)	39/80	12/9	15/42	3/13	11/6	77/106
E1 (C4d+/C4d−)	11/40	4/1	5/14	1/3	NA	28/34
S1 (C4d+/C4d−)	51/191	9/4	6/16	2/10	10/8	35/22
T (1) (C4d+/C4d−)	19/18	0(7/1)	12/28	1/0	7/3	41/49
T (2) (C4d+/C4d−)	1/3	0	3/14	NA	NA	53/28
C (1) (C4d+/C4d−)	13/34	10/6	NA	NA	NA	NA
C (2) (C4d+/C4d−)	2 /7	NA	NA	NA	NA	NA
RAS blockers (C4d+/C4d−)	63/201	14/10	32/123	7/14	NA	90/135
immunosuppression (C4d+/C4d−)	11/21	11/7	26/47	7/7	58/102	19/6

Jiang Y. Kidney Med 3: 1014–1021, 2021

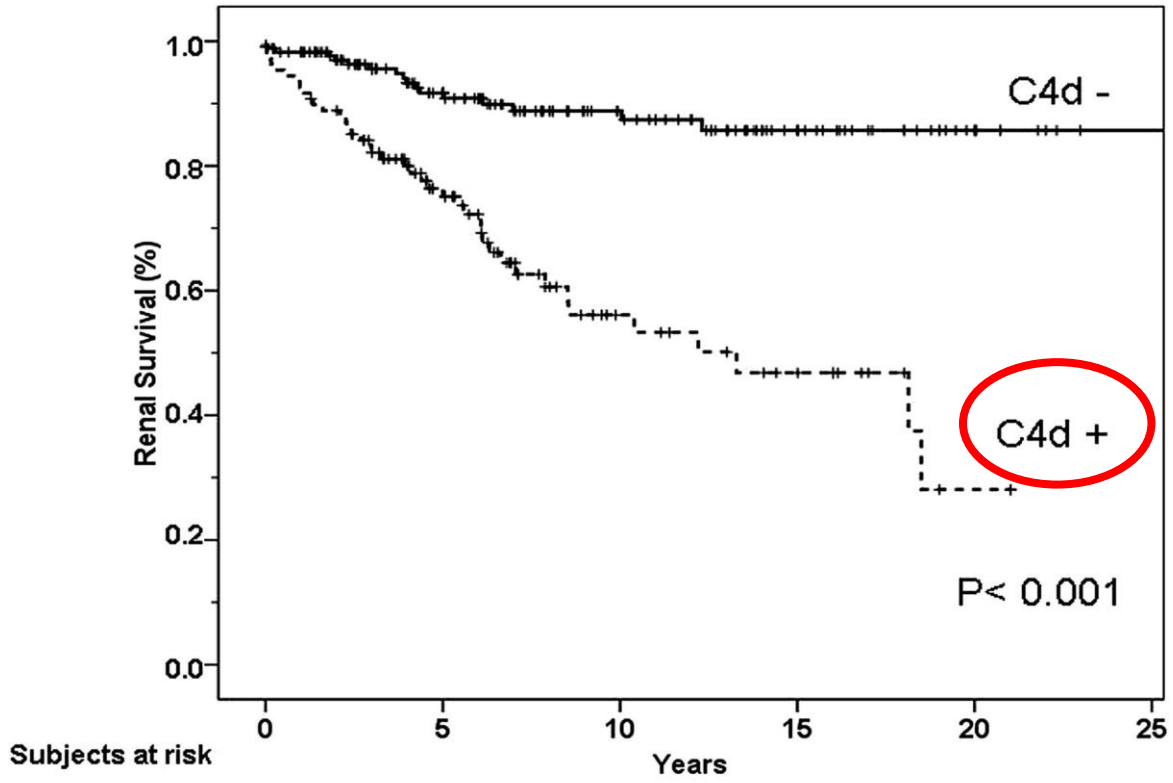
Poor prognosis in C4d positive case

C4d negative



C4d positive in glomerulus

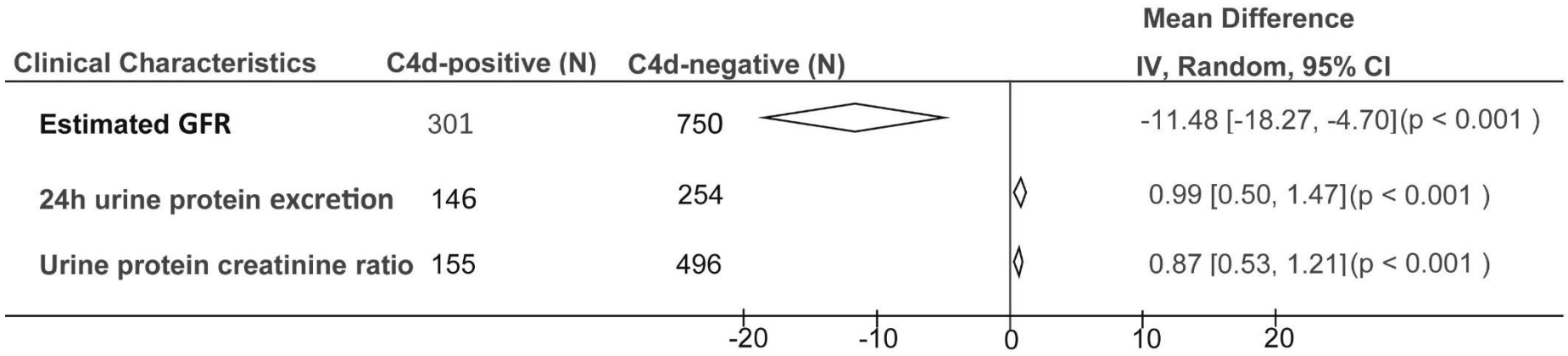
Renal survival

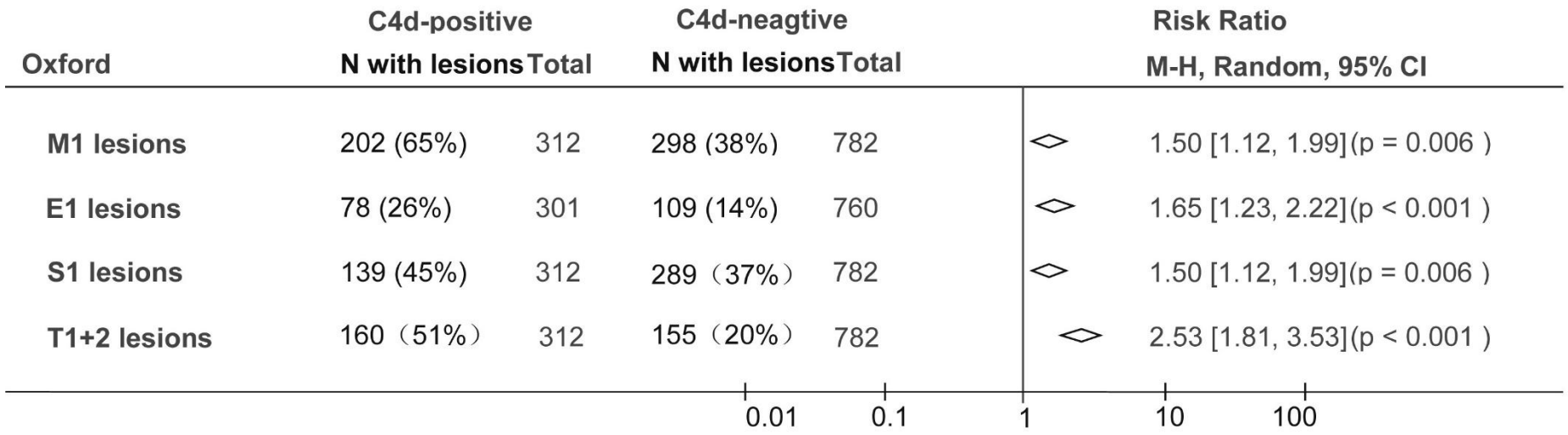


Mario E. CJASN 9: 897-904, 2014

Meta-analysis

Glomerular C4d positivity: Associated with decreased renal function and severe proteinuria





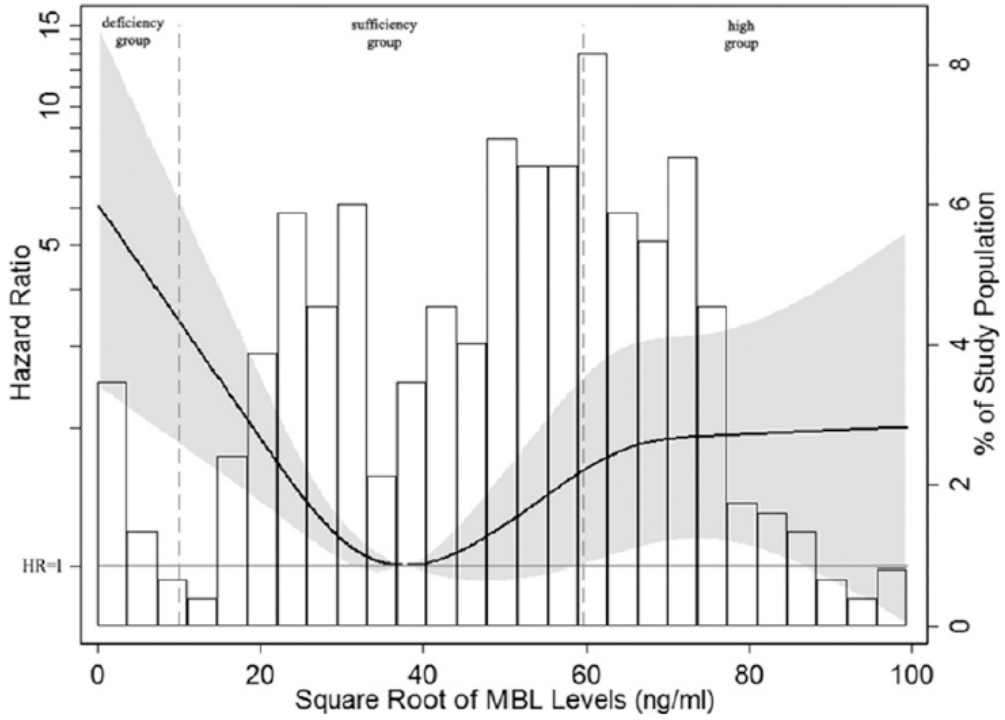
Jiang Y. Kidney Med 3: 1014–1021, 2021

BRIEF COMMUNICATION www.jasn.org JASN 28: 317, 2017

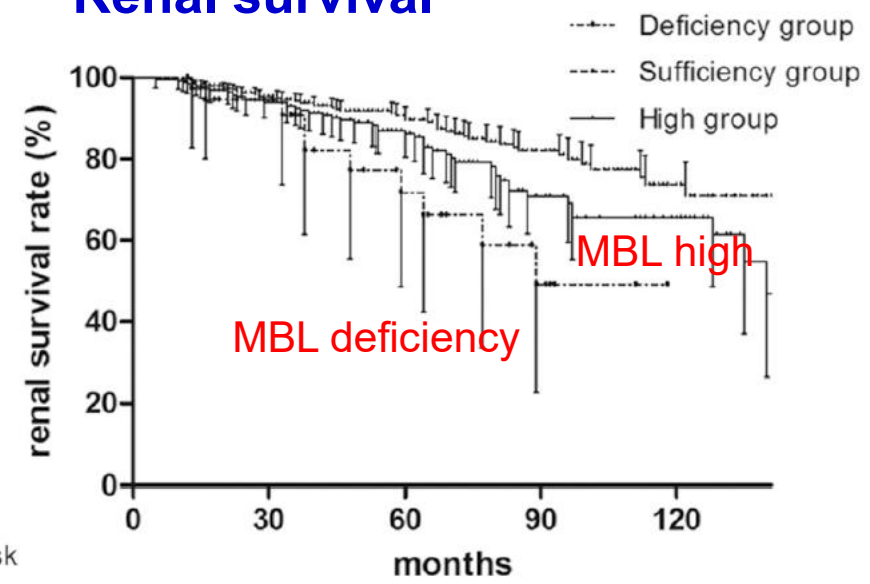
Mannose-Binding Lectin Levels Could Predict Prognosis in IgA Nephropathy

Wei-yi Guo,*†‡§ Li Zhu,*†‡§ Si-jun Meng,*†‡§ Su-fang Shi,*†‡§ Li-jun Liu,*†‡§ Ji-cheng Lv,*†‡§ and Hong Zhang*†‡§

Nonlinear association between MBL levels and adjusted hazard ratios of 50% eGFR decline or ESRD

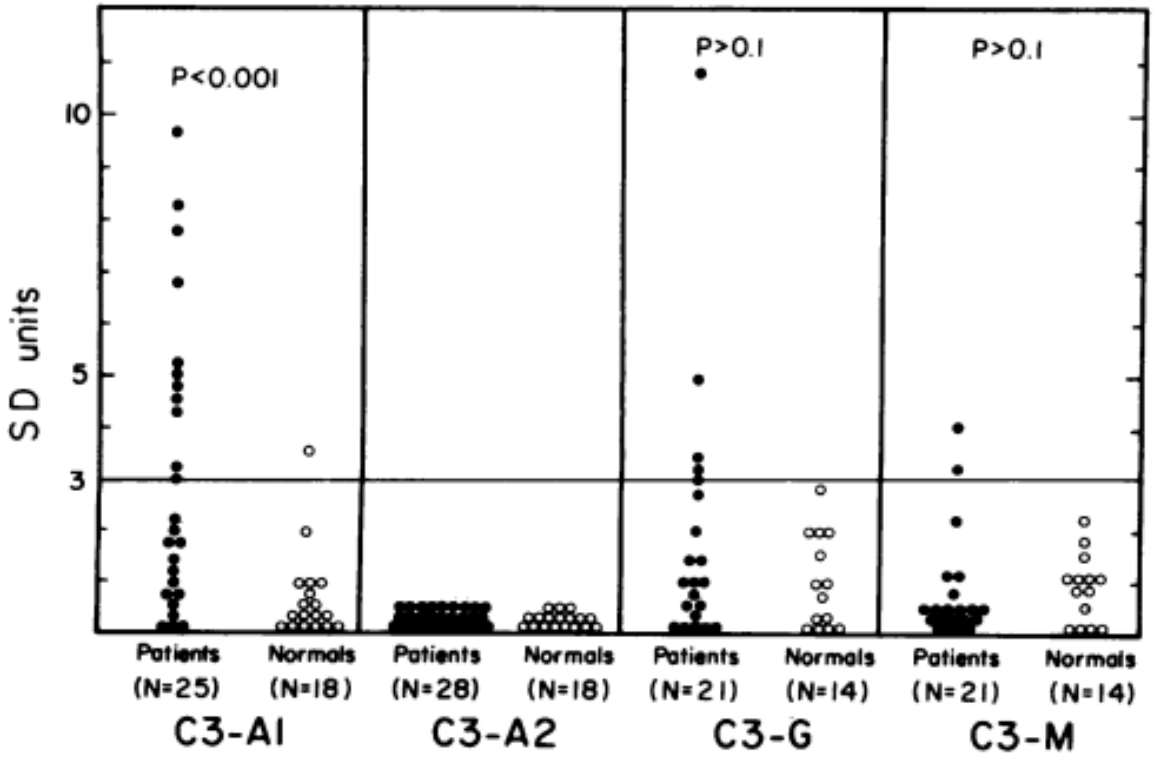


Renal survival



Both MBL deficiency and high levels have poor renal prognosis

C3 is present in IgA1-containing circulating ICs of patients with IgAN



IgG-C3-containing ICs were detected in 24% of the patients and correlated with levels of IgA-C3 containing ICs

IgM-C3-containing ICs were elevated in only 9%

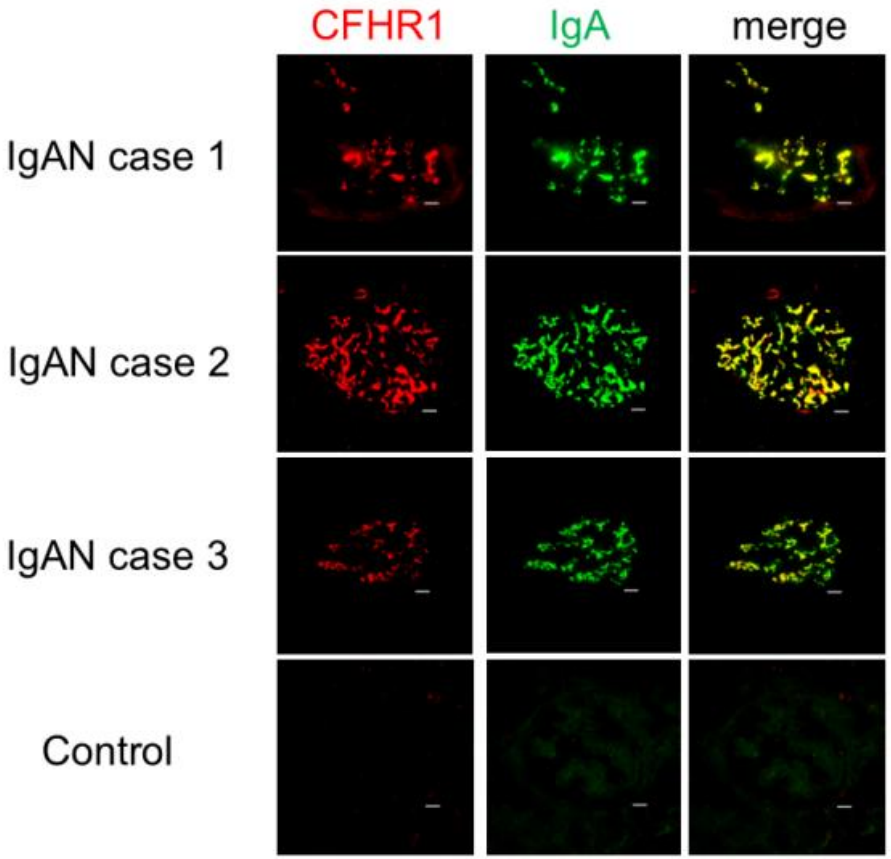
Czerkinsky C, et al. J Clin Invest 77: 1931–8, 1986

Scientific Reports

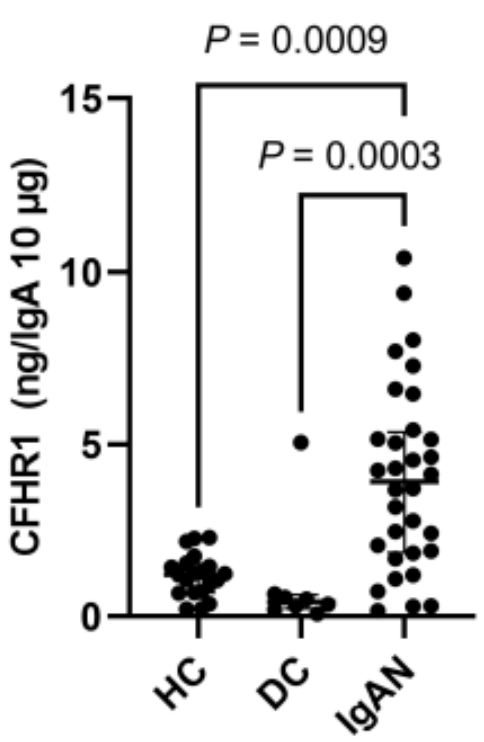
https://doi.org/10.1038/s41598-025-29024-z

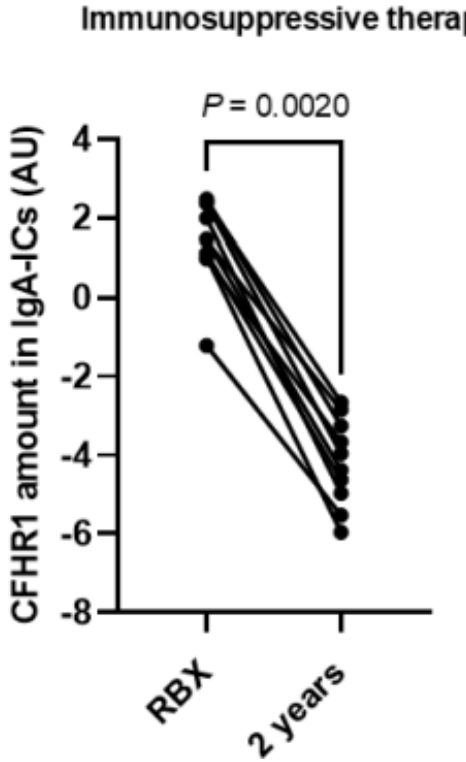
Article in Press

Complement proteins associated with circulatory and glomerular IgA-containing immune complexes in patients with IgA nephropathy



Circulatory IgA-ICs of patients with IgAN have a greater abundance of complement proteins CFHR1





Complement proteome found in glomerular and circulatory IgA-ICs.
It is suggested an association of complement regulatory proteins, such as CFHR1, with pathogenic IgA-ICs.

Tsuji Y. Sci Rep, 2025

Several techniques can be used to interrogate complement in affected patients with IgAN

Genetic

- Variants in *CFH* and *CFHR* genes associate with disease

Tissue staining

- C3c detected in nearly all active IgAN biopsies
- FHR5 detected in glomeruli

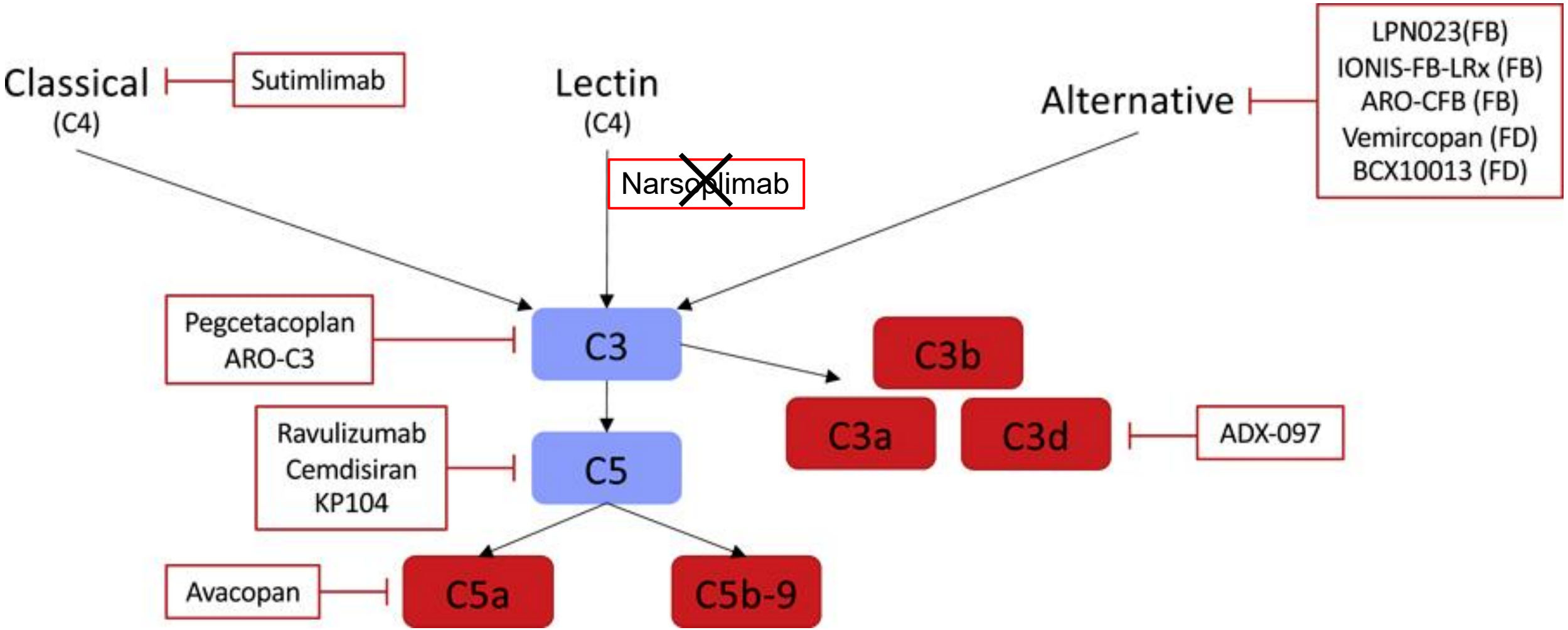
Complement biomarkers

- Increased levels of plasma and urine complement activation fragments
- Presence of alternative pathway activation fragments
- Elevated plasma Ba levels
- Elevated circulating levels of FHR1 and FHR5

Drugs

- **Several positive clinical trials of complement inhibitory drugs have been reported**
- **A complement inhibitor, iptacopan, was recently approved for use in IgAN patients**

Complement inhibitory drugs and their targets



Kalyanaraman KJ. Glomerular Dis 5: 48-59, 2024

Results of a randomized double-blind placebo-controlled Phase 2 study propose iptacopan as an alternative complement pathway inhibitor for IgA nephropathy

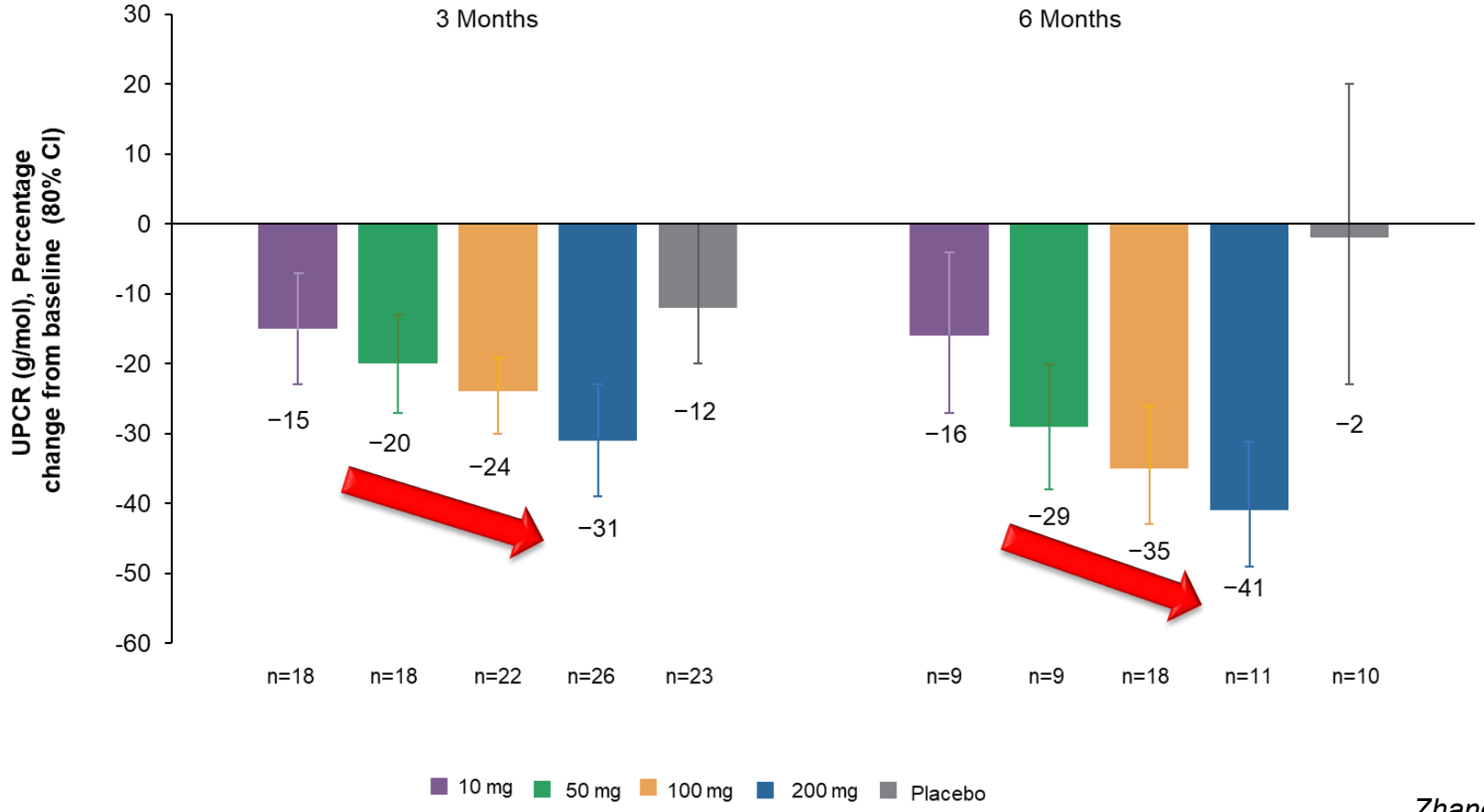
iptacopan: a factor B inhibitor

see commentary on page 28

OPEN

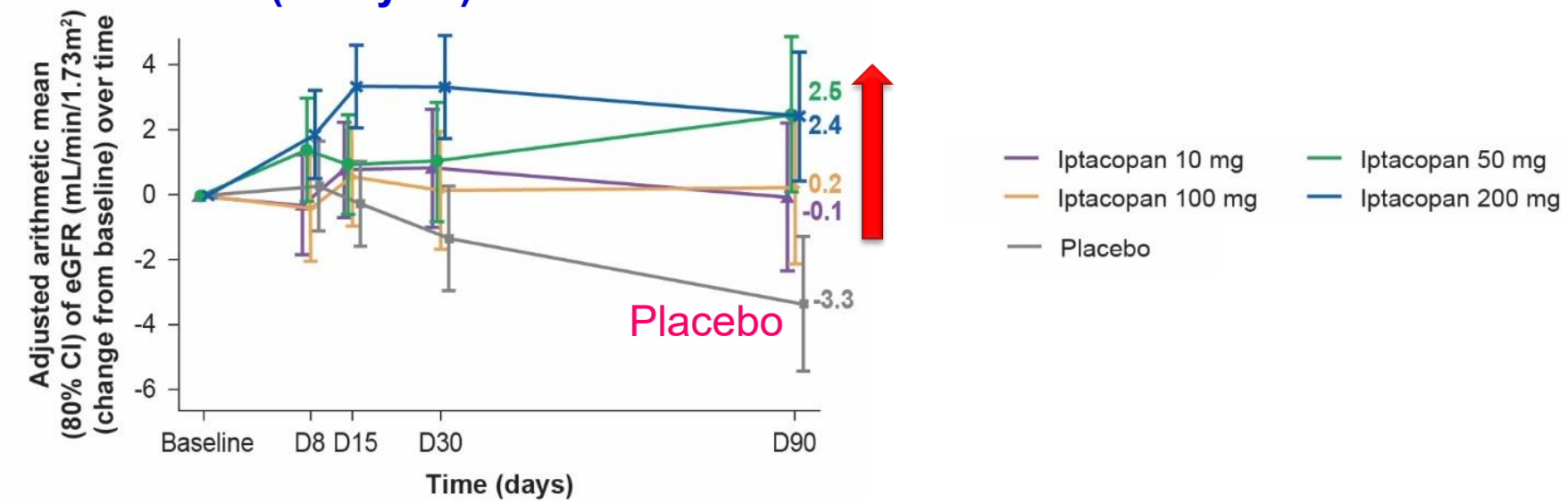
Hong Zhang[1], Dana V. Rizk[2], Vlado Perkovic[3], Bart Maes[4], Naoki Kashihara[5], Brad Rovin[6], Hernán Trimarchi[7], Ben Sprangers[8,9], Matthias Meier[10], Dmitrij Kollins[10], Olympia Papachristofi[10], Julie Milojevic[11], Guido Junge[11], Prasanna Kumar Nidamarthy[12], Alan Charney[13] and Jonathan Barratt[14,15]

eGFR > 30 mL/min/1.73 m^2
UPCR > 0.75 g/24 hours

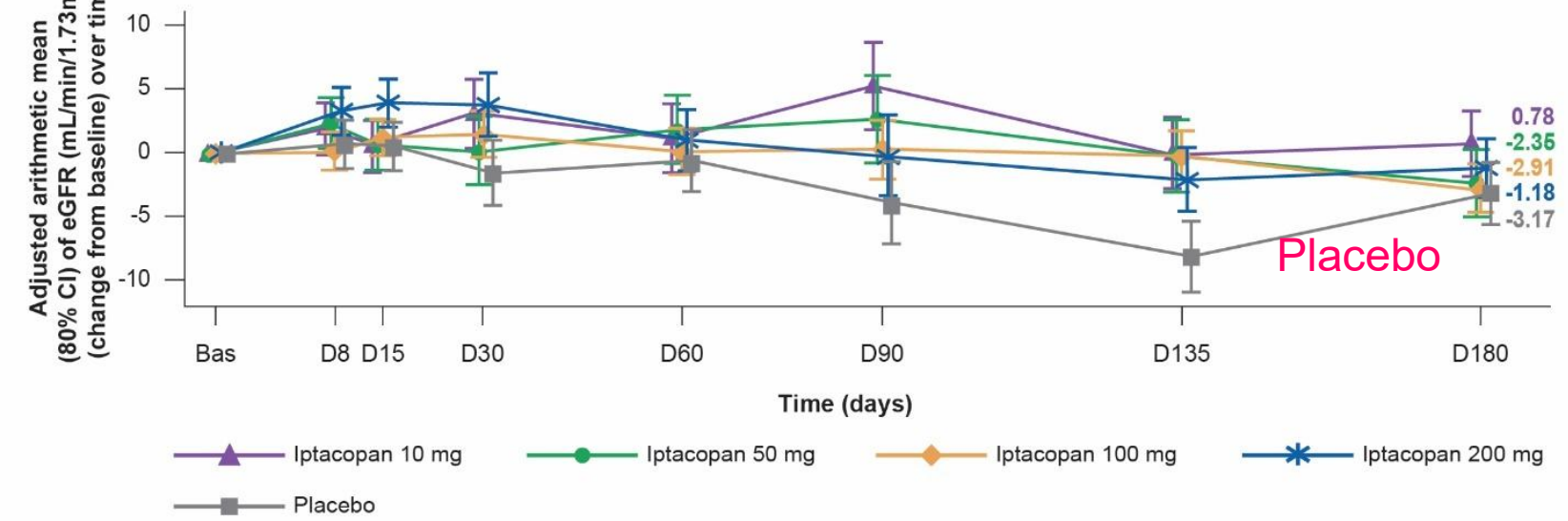


Zhang H. Kidney Int, 105: 189, 2024

eGFR (～day 90)



eGFR (～day 180)



Zhang H. Kidney Int, 105: 189, 2024

The NEW ENGLAND JOURNAL of MEDICINE

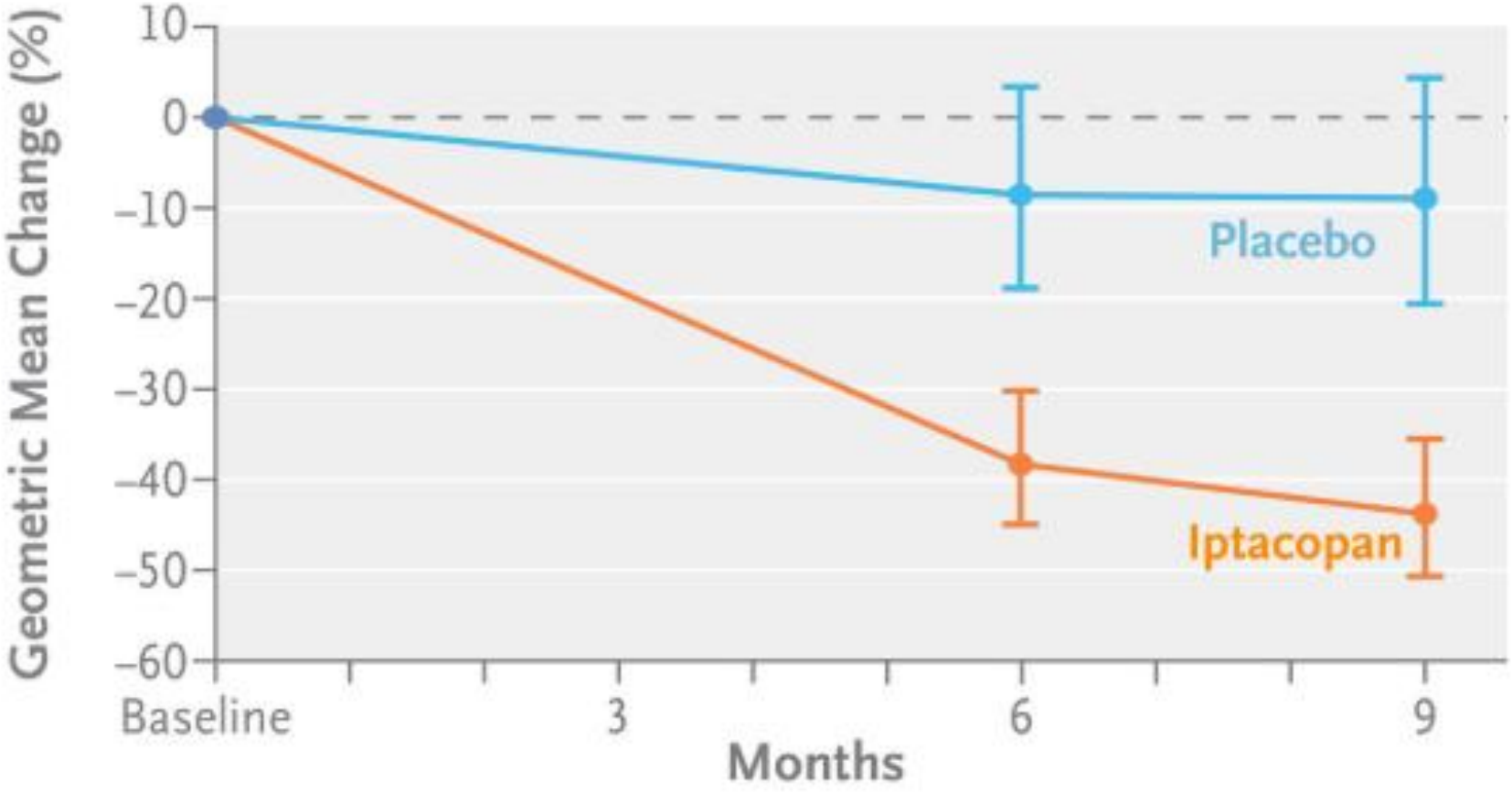
Iptacopan in IgA Nephropathy

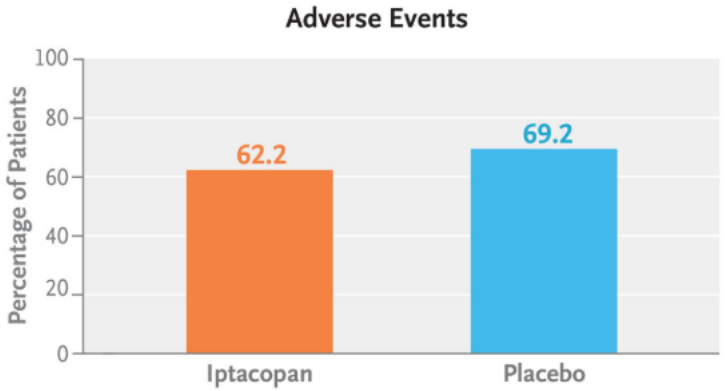
A Research Summary based on Perkovic V et al. | 10.1056/NEJMoa2410316 | Published on October 25, 2024

Iptacopan = specifically binds to factor B and inhibits the alternative pathway

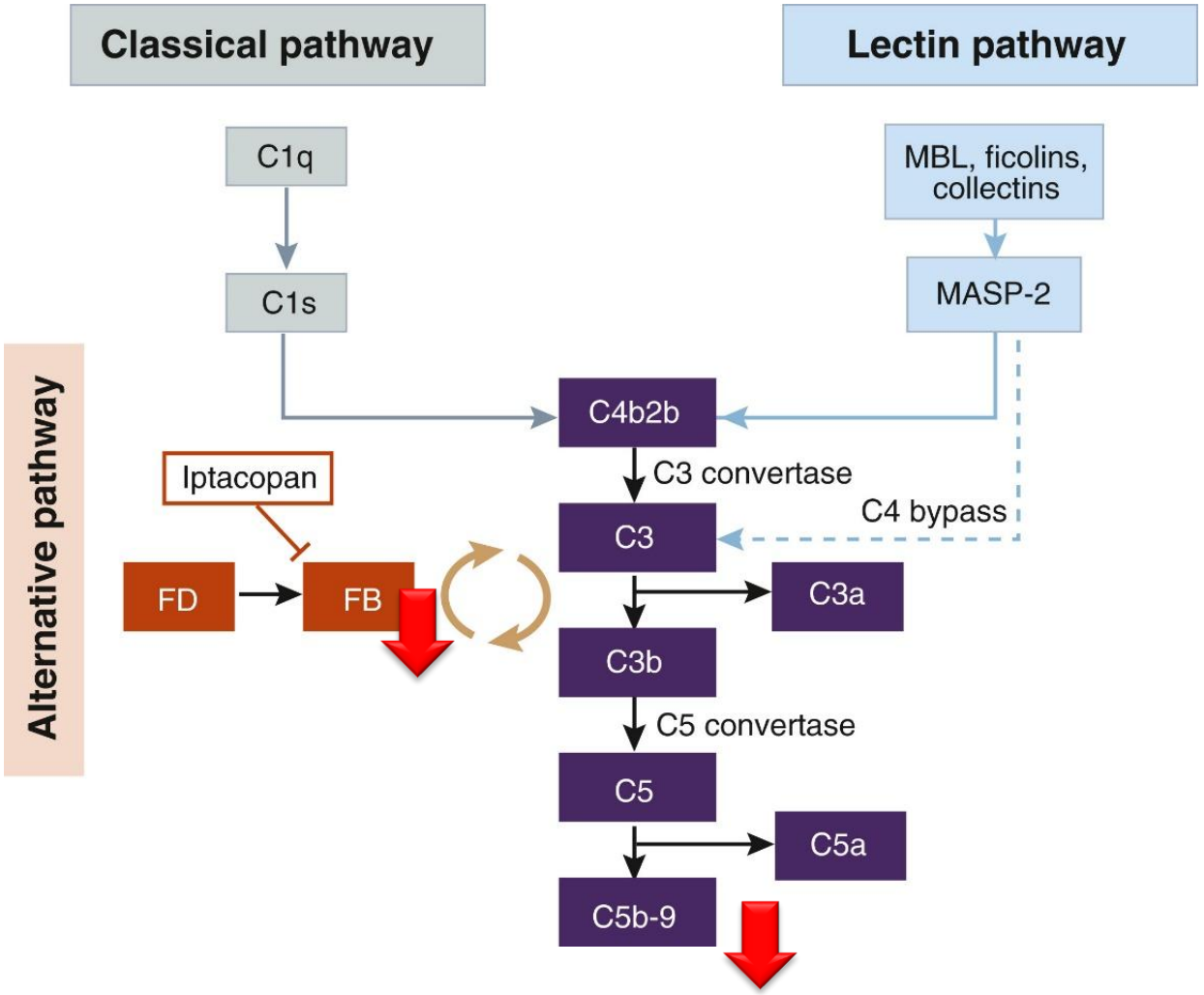
Change in 24-Hour Urinary Protein-to-Creatinine Ratio

Difference, 38.3% (95% CI, 26.0–48.6); P<0.001

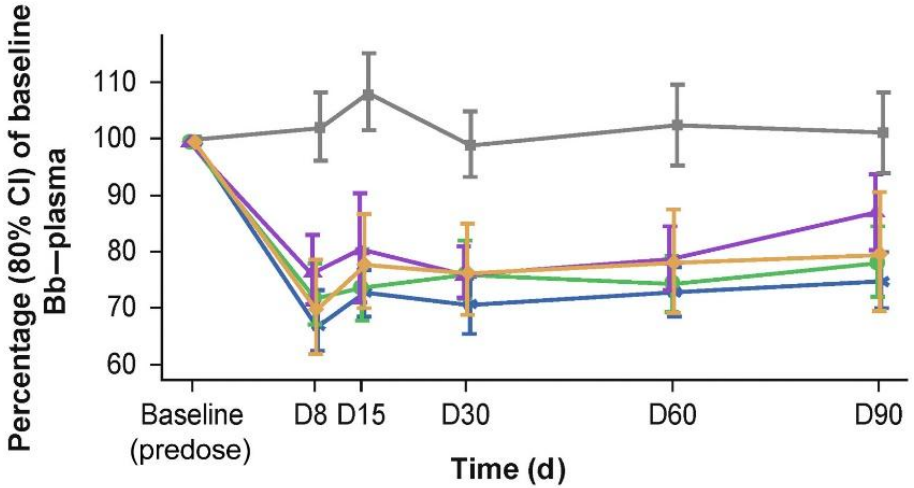




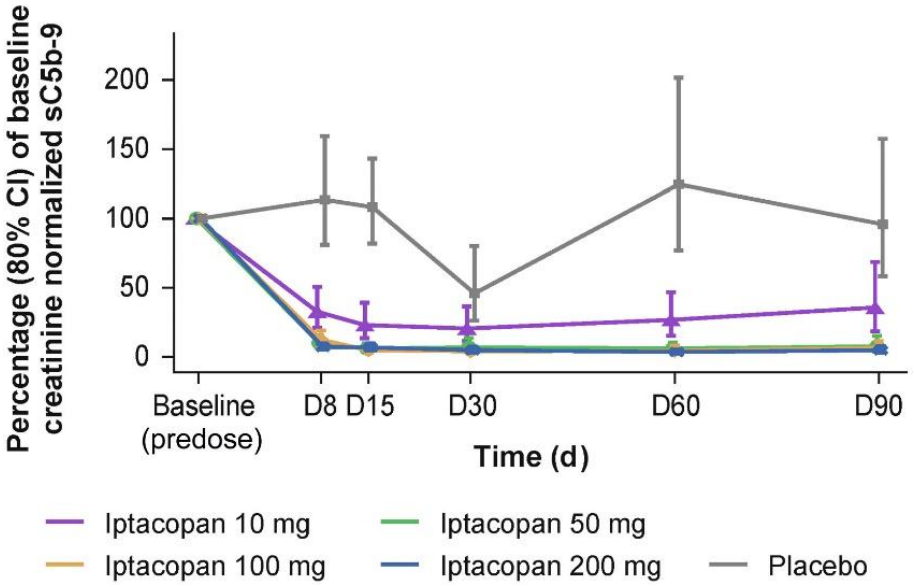
N Engl J Med 392: 531-543, 2025



Plasma Factor B



Urinary C5b-9



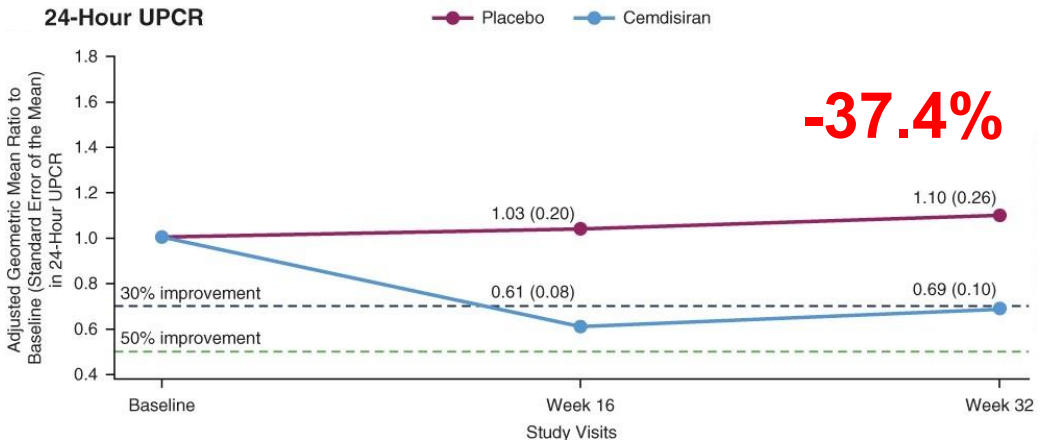
Floege J. Kidney Int, 105: 28, 2024

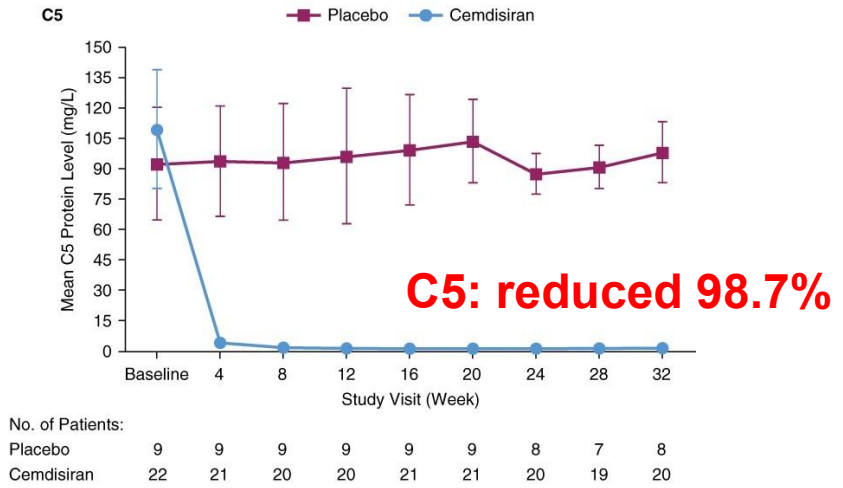
Phase 2 Trial of Cemdisiran in Adult Patients with IgA Nephropathy: A Randomized Controlled Trial

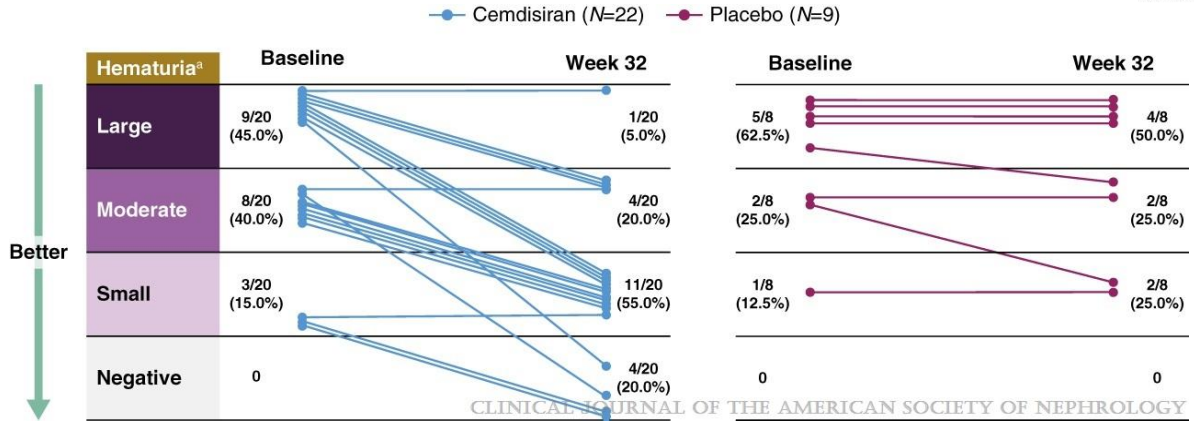
CJASN 19: 452, 2024

Barratt, Jonathan[1]; Liew, Adrian[2]; Yeo, See Cheng[3]; Fernström, Anders[4]; Barbour, Sean J.[5]; Sperati, C. John[6]; Villanueva, Russell[7]; Wu, Ming-Ju[8]; Wang, Dazhe[9]; Borodovsky, Anna[9]; Badri, Prajakta[9]; Yureneva, Elena[9]; Bhan, Ishir[9]; Cattran, Daniel[10]; on behalf of the Cemdisiran Phase 2 Study Investigators and Collaborators

Cemdisiran (siRNA): RNA interference therapeutic that suppresses hepatic production of complement component 5 (C5)







Hematuria also improved in 77% patients with IgAN at 32W.

ORIGINAL ARTICLE

C5a receptor inhibitor avacopan in immunoglobulin A nephropathy—an open-label pilot study

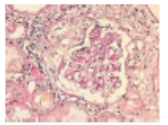
Annette Bruchfeld[1,2], Hasan Magin[2], Patrick Nachman[3], Samir Parikh[4], Richard Lafayette[5], Antonia Potarca[6], Shichang Miao[6] and Pirow Bekker[6]

Open-label pilot trial

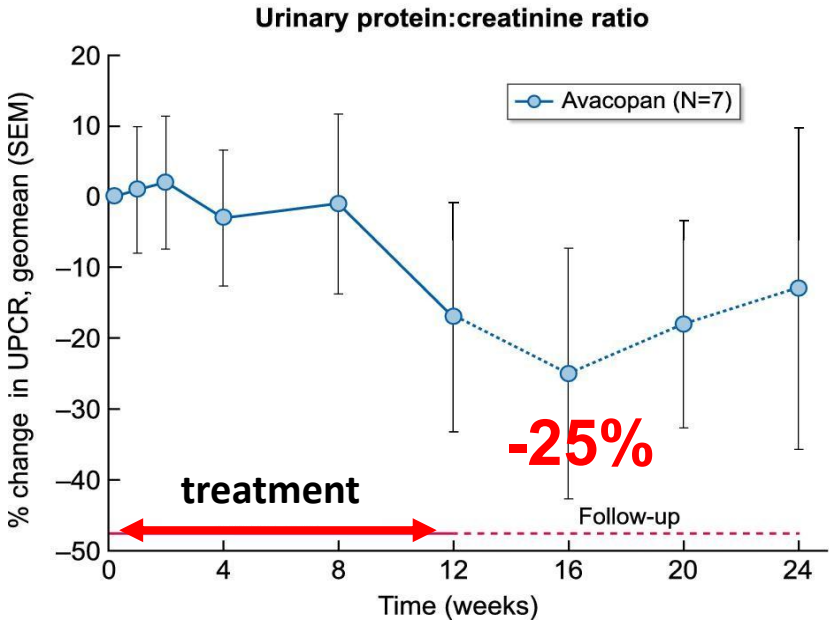
- ✓ UPCR > 1g/g
- ✓ eGFR > 60 mL/min/1.73 m²

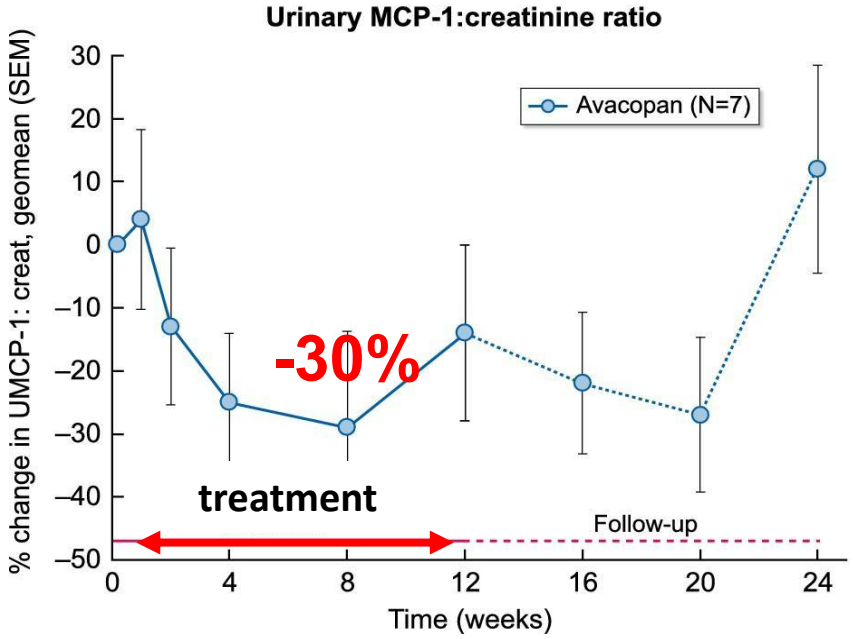
OR

- ✓ eGFR > 45 mL/min/1.73 m² (if eGFR has not declined > 10 mL/min/1.73 m² in 24w)



Avacopan: C5a receptor selective inhibitor





CKJ 15: 922, 2022

Ravulizumab in IgA nephropathy

JASN®
Journal of the American Society of Nephrology
Clinical Research

SANCTUARY
Clinical Trial for Lupus Nephritis or IgA Nephropathy
(NCT04564339)

- Randomized
- Double-blind
- Placebo controlled
- Adults with biopsy-proven IgA nephropathy

- Proteinuria ≥1 g/day (Mean of two 24-hour urine collections)
- eGFR ≥ 30 mL/min/1.73 m²
- On stable and optimized RAS blockade

	% Change in proteinuria from baseline (at week 26)	Annualized eGFR slope (mL/min/1.73 m²)	
	PRIMARY END POINT		
Ravulizumab n=43	**-41.9** (95% CI -50.2%, -32.0%)	**-1.35** (through week 26)	**-2.34** (through week 50)
Placebo n=23	**-16.8** (95% CI -31.8%, +1.6%)	**-6.74** (through week 26)	**-4.09** (through week 50)
	30.1 Treatment effect *p=0.0053*	Placebo to week 26, crossover to ravulizumab week 26-50	

Ravulizumab treatment was well tolerated, with an adverse event profile similar to placebo, with no study withdrawals due to adverse events

Conclusions: An early and sustained reduction in proteinuria and stabilization of eGFR was observed with ravulizumab versus placebo.

Richard Lafayette, James Tumlin, Roberta Fenoglio, et al. ***Efficacy and Safety of Ravulizumab in IgA Nephropathy: A Phase 2 Randomized Double-Blind Placebo-Controlled Trial***. JASN doi: 10.1681/ASN.0000000534.

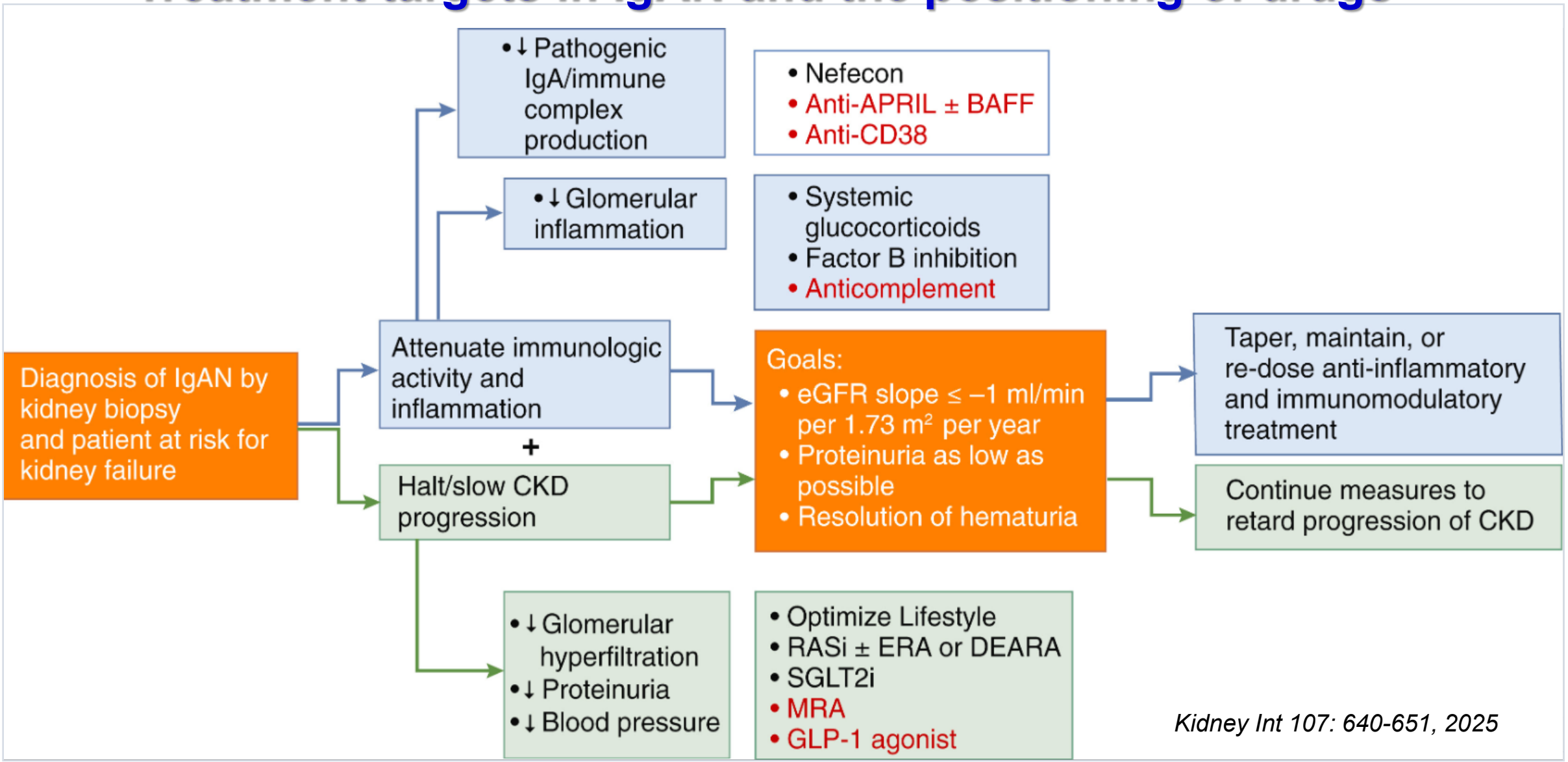
Visual Abstract by Edgar Lerma, MD, FASN

Phase 3 clinical trials open in 2025 evaluating new treatments for IgAN

Drug targets	Drug	Target	Clinical trial
Drugs targeting the production of pathogenic forms of IgAN	Iptacopan (LNP023)	Complement alternative pathway factor B	APPLAUSE-IgAN NCT04578834
	Sefaxersen (RO7434656)	Complement alternative pathway factor B	IMAGINATION NCT05797610
	Ravulizumab	Complement terminal pathway C5	I CAN NCT06291376

Kidney Int 108: S1-S71, 2025

Treatment targets in IgAN and the positioning of drugs



Kidney Int 107: 640-651, 2025

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Acknowledgment

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非常感谢您的聆听

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