Overview of complement-mediated kidney diseases – aHUS and C3G

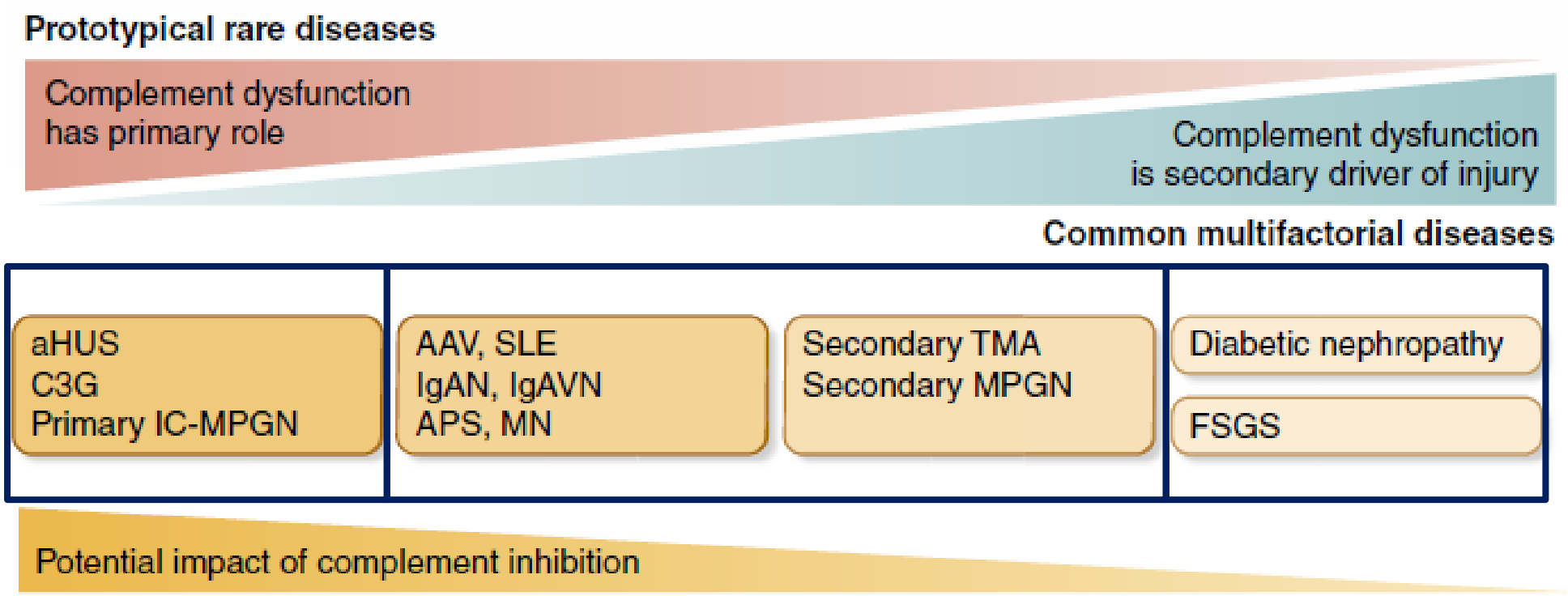
Christoph Licht
Division of Nephrology and RI Cell Biology Program
The Hospital for Sick Children
Toronto, ON
6.12.2025

Disclosures

- **Scientific advisor / speaker**
  - Alexion, AstraZeneca Rare Disease
  - Apellis Pharmaceuticals, Inc. / Sobi
  - Novartis
  - Oak Bay Biosciences
  - Pfizer Inc.
  - Rocket Pharmaceuticals
  - Samsung Bioepis Co, Ltd.

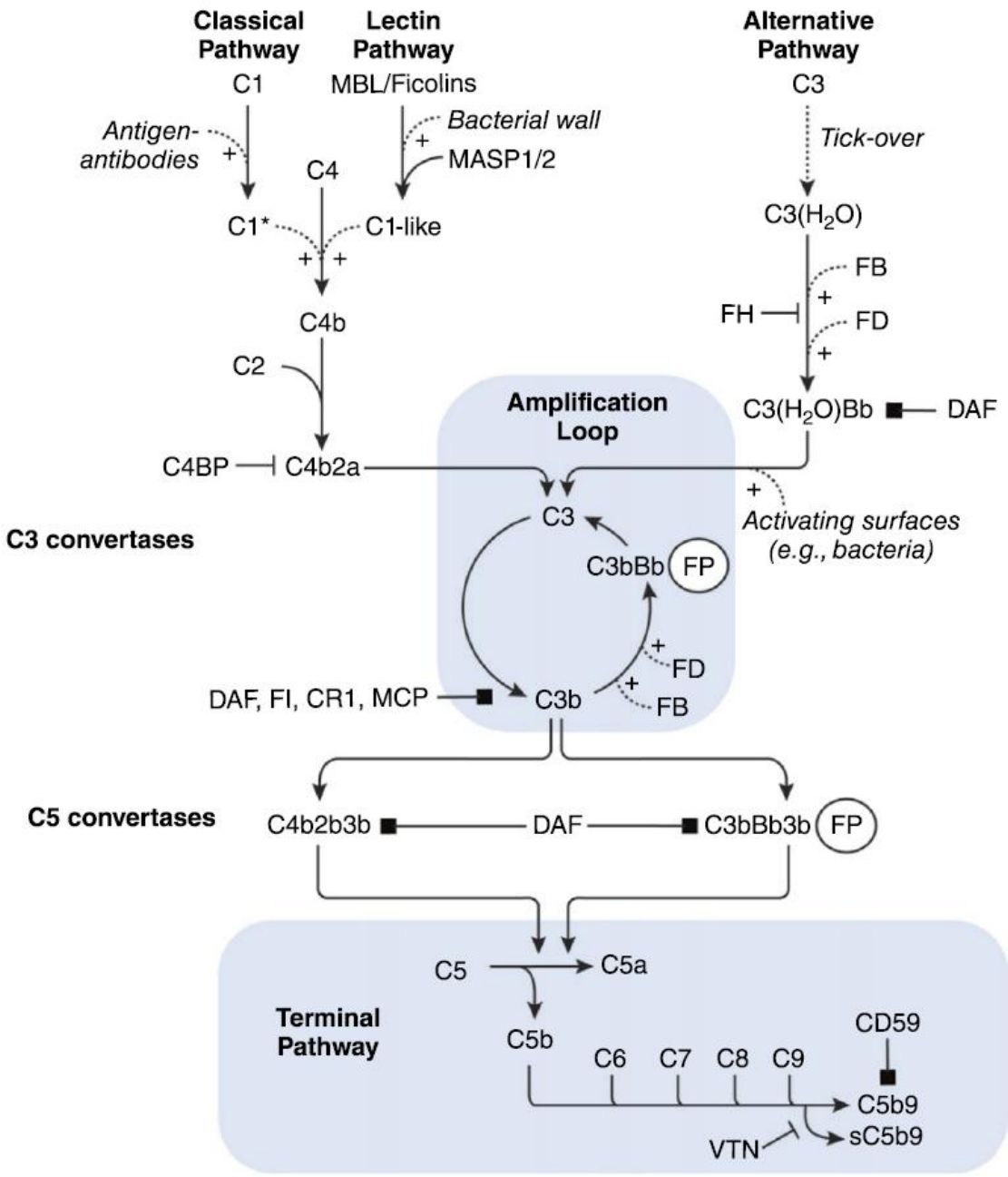
- **DSMB member**
  - Argenx – Axio Research
  - Early Protect Alport / Double Protect Alport / EMPA Alport
  - OPKO Health, Inc.

The role of complement in various kidney diseases



Vivarelli et al, Kidney Int 2024

Complement dysregulation is disease-specific, which allows for targeted treatment



C3G

aHUS

- pMN	CP (all?)
- IgAN	LP (all?)
- SLE	CP (all?)
- AAV	C5aR

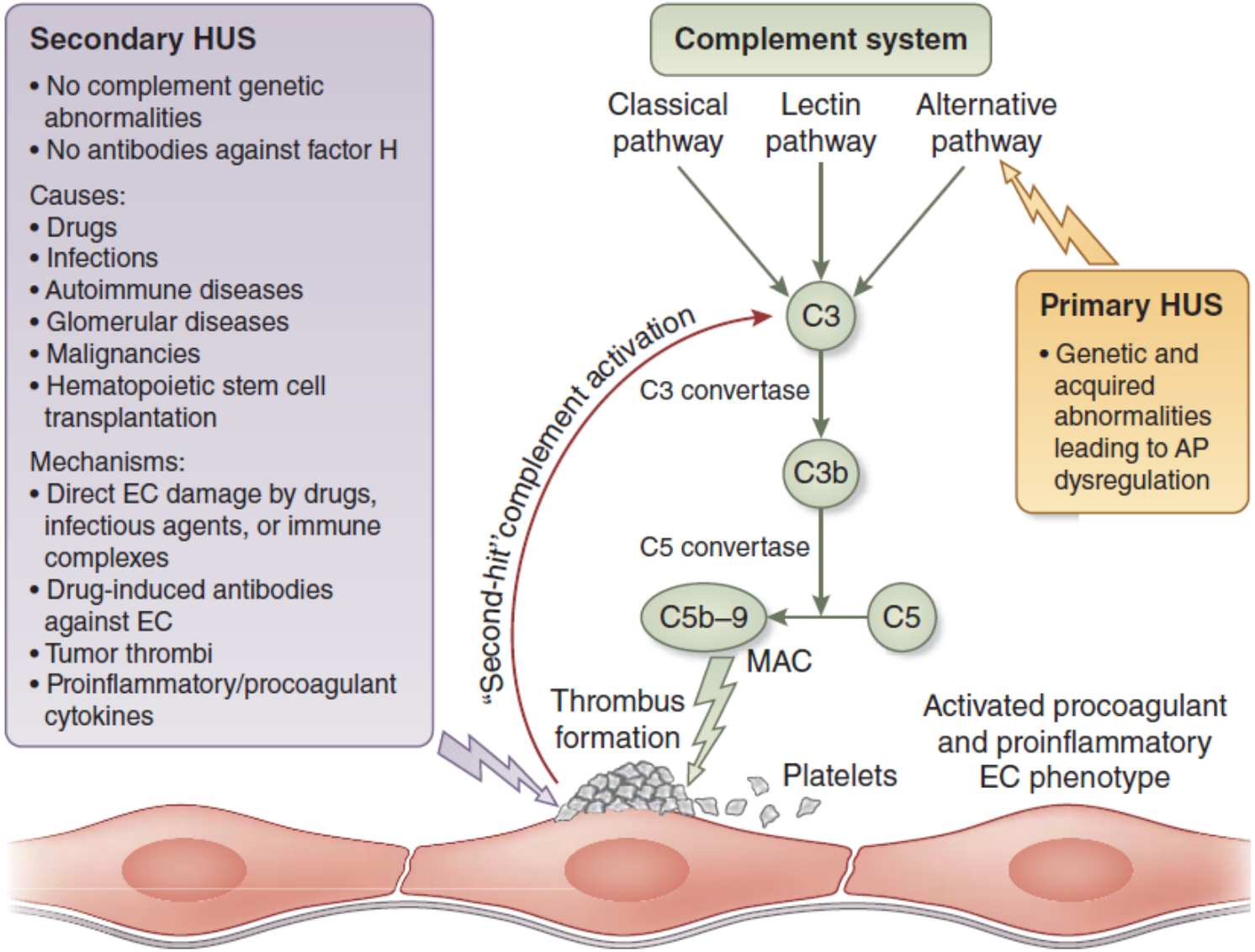
Modified from Lemaire et al, Clin J Am Soc Nephrol 2021

Objectives

New insights into the pathogenesis of two *primary* complementopathies:

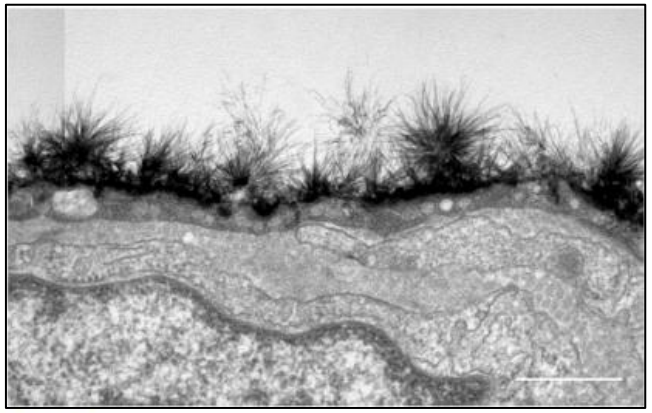
- aHUS — A potential role for the endothelial glycocalyx in aHUS pathogenesis.
- IC-MPGN / C3G — Cluster analysis to predict patient outcomes: A potential role for neutrophils and NETs in C3G pathogenesis.

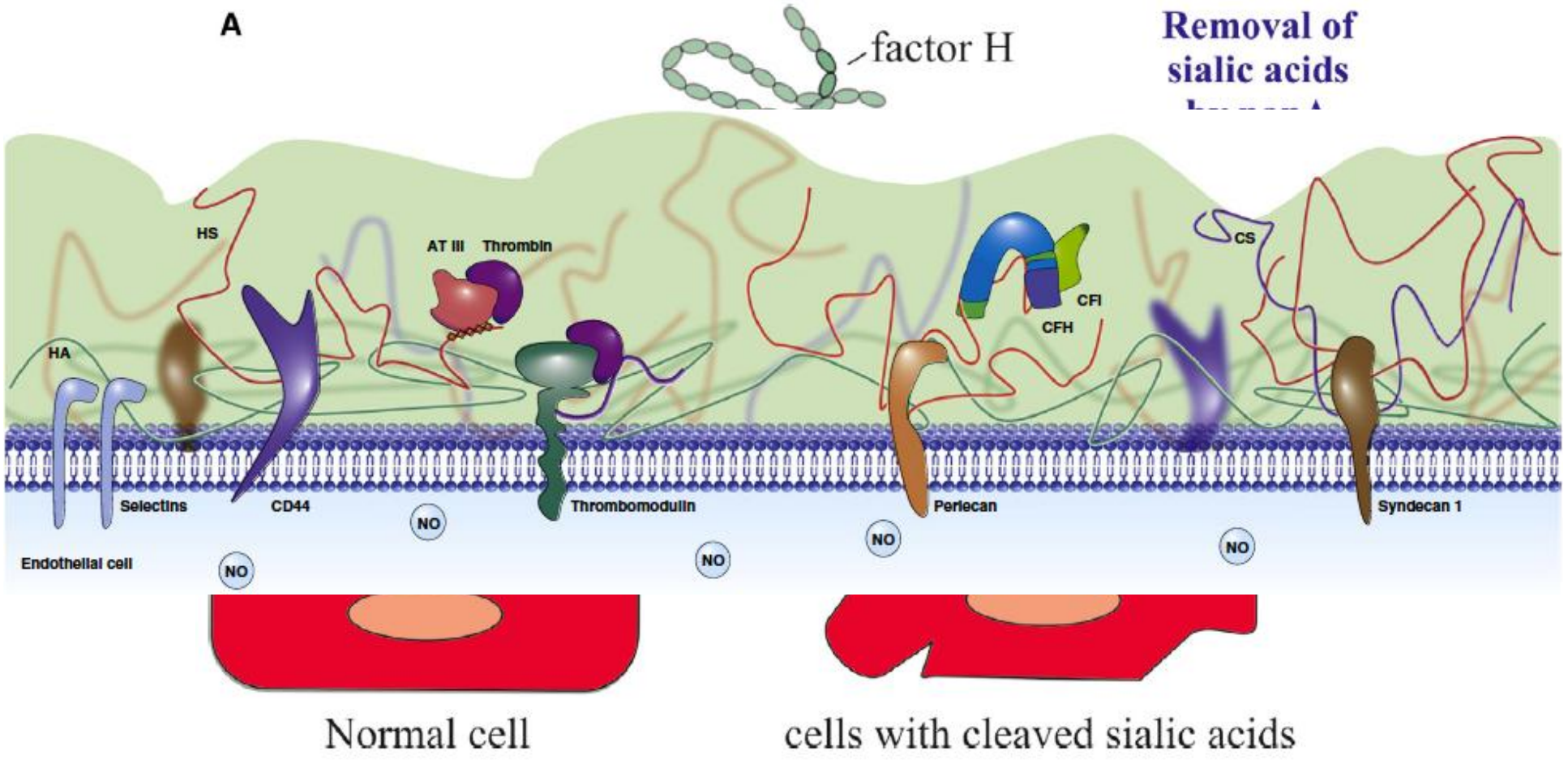
The role of complement in the pathogenesis of aHUS (TMA)



Praga and Rodriguez de Cordoba, Kidney Int 2019

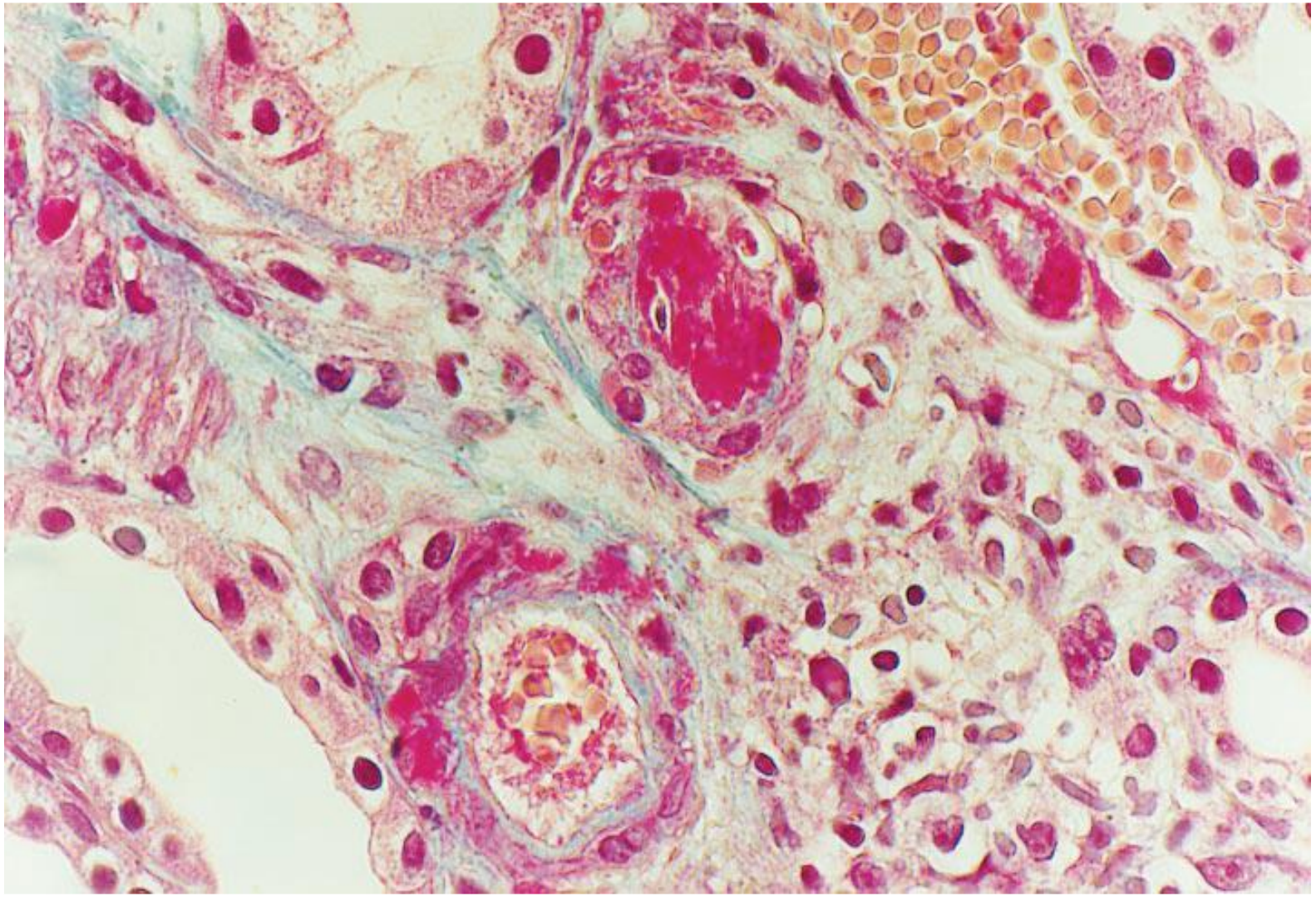
Complement dysregulation due to endothelial glycocalyx injury





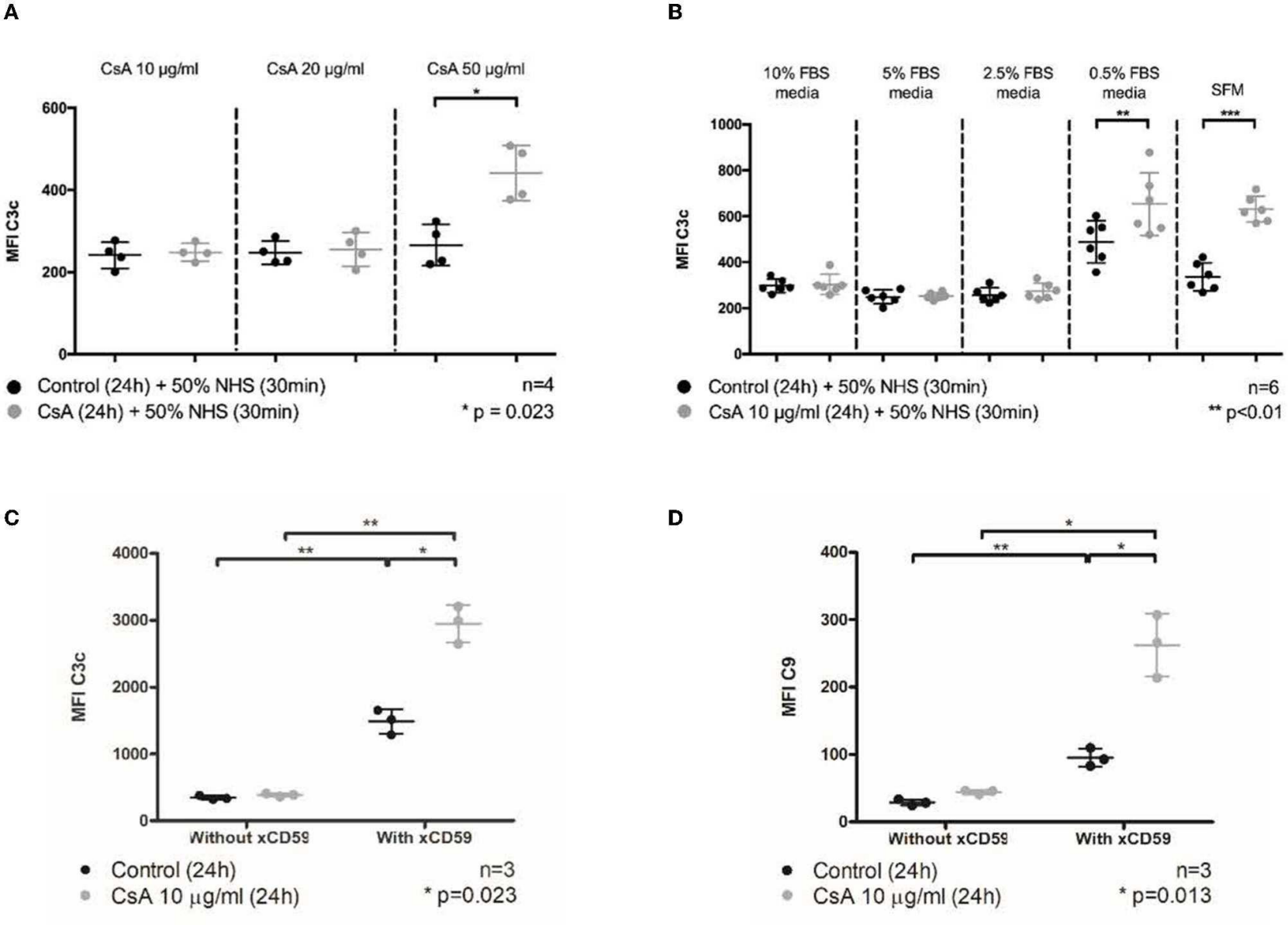
Syed et al, Front Cell Dev Biol 2019; Syed et al, FEBS Letters 2020

Cyclosporine A (CsA) induces TMA



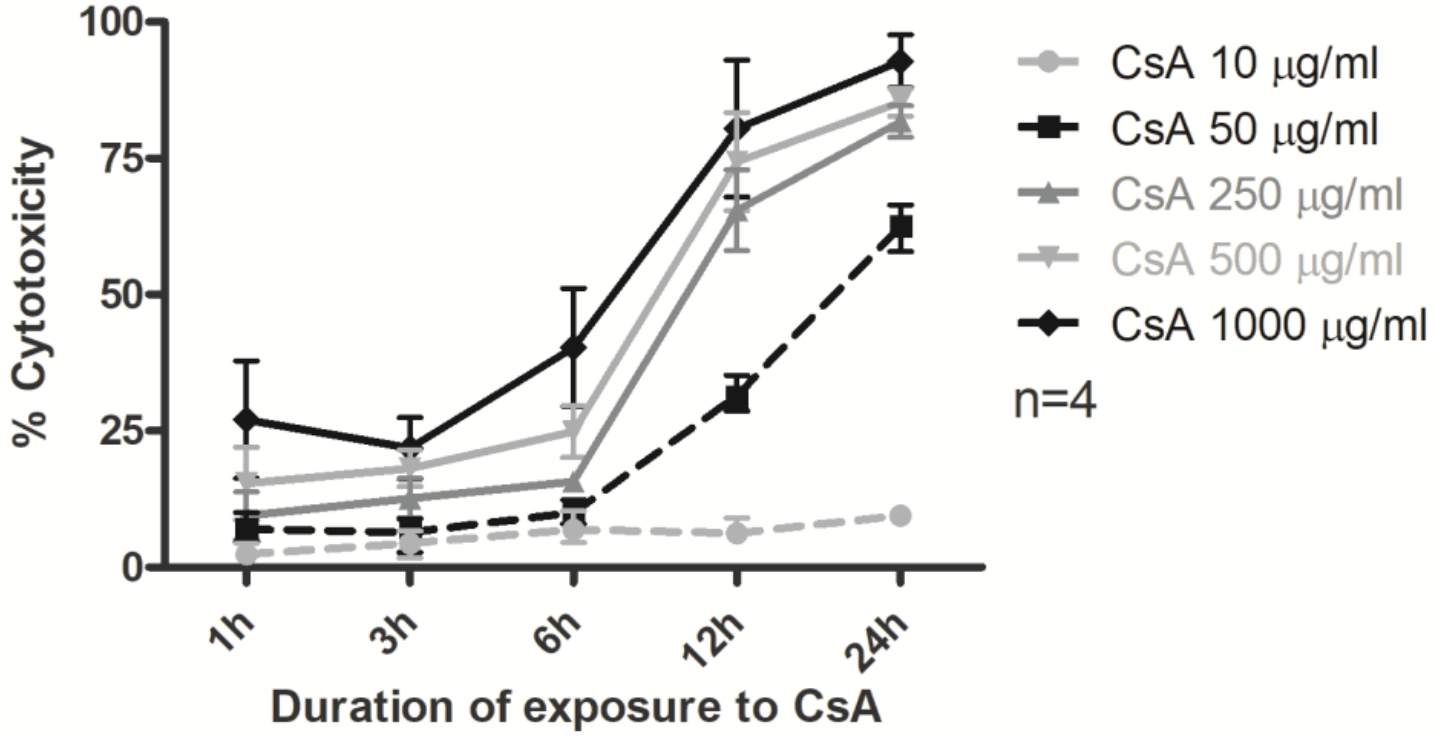
Zarifian et al, Kidney Int 1999

CsA causes complement activation on ECs



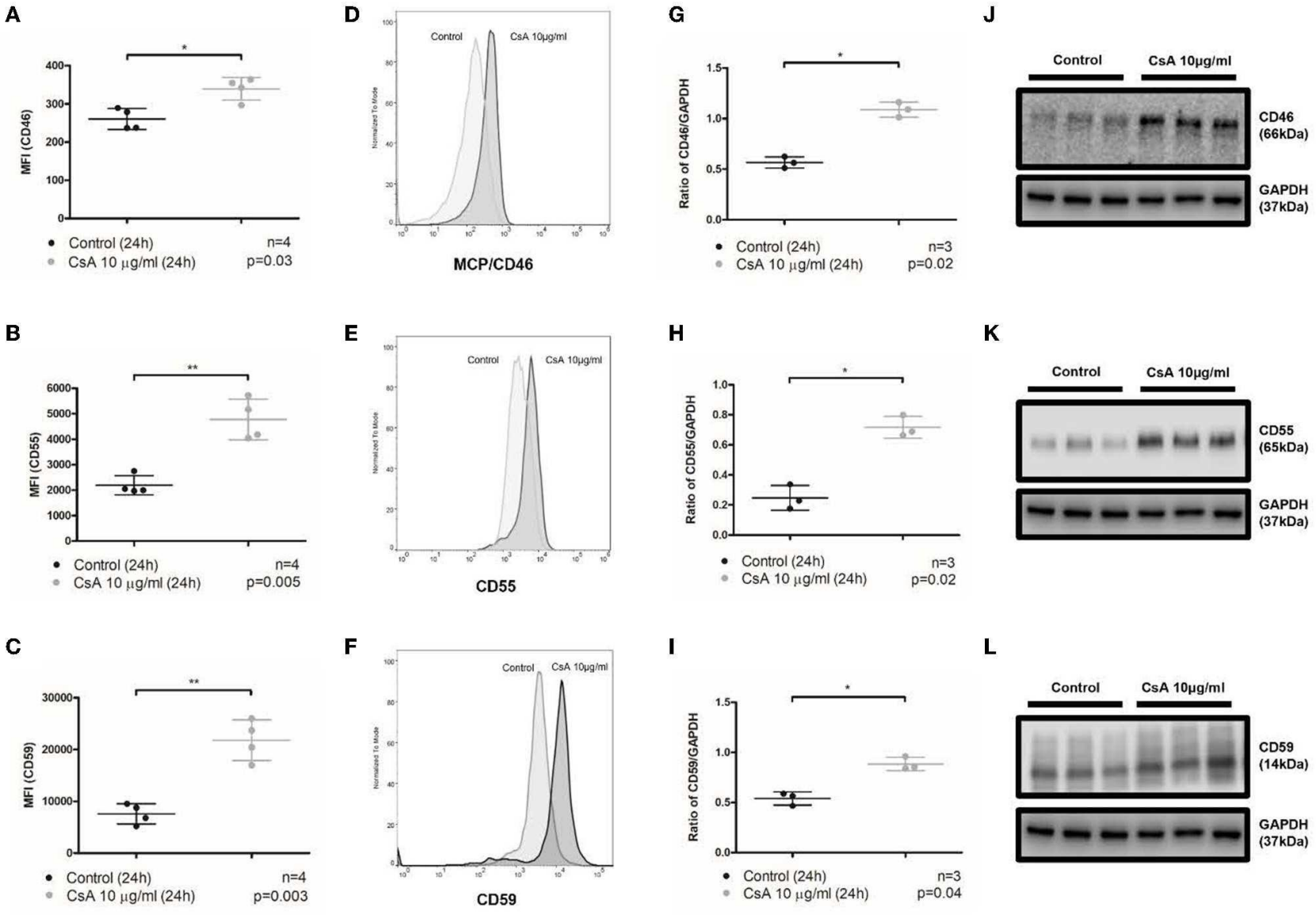
Teoh et al, Front Med 2023

CsA causes dose- and time-dependent cytotoxicity



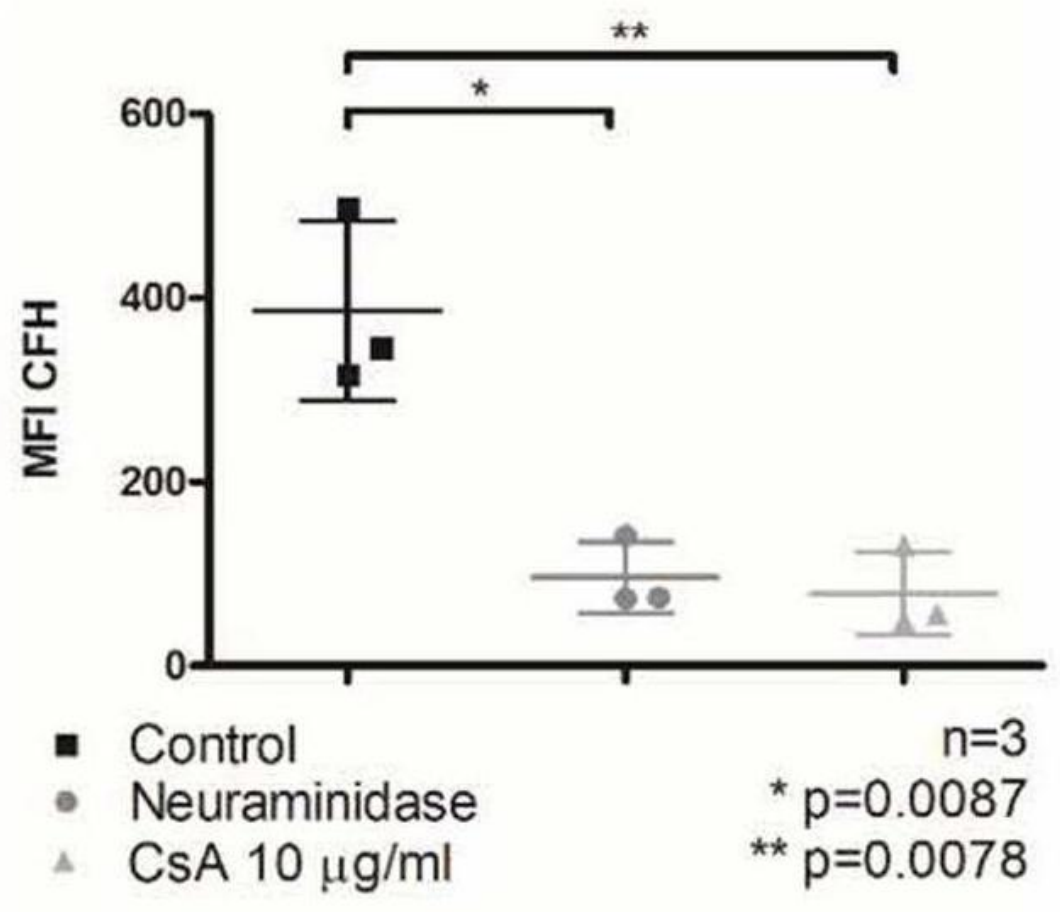
Teoh et al, Front Med 2023

CsA induces upregulation of membrane-bound complement regulators



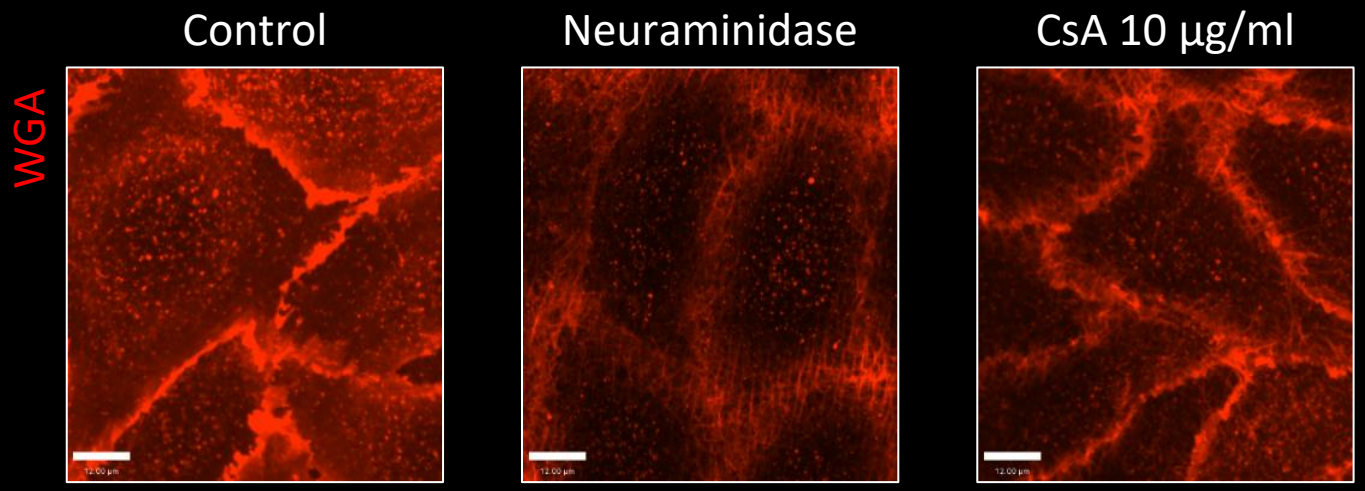
Teoh et al, Front Med 2023

CsA reduces availability of Factor H at the EC surface

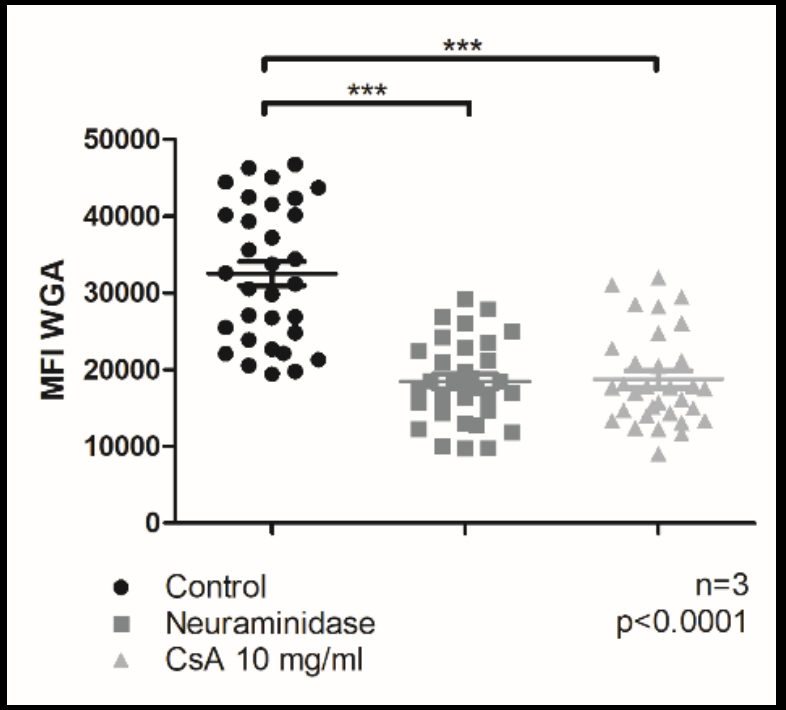


Teoh et al, Front Med 2023

CsA diminishes endothelial glycocalyx



WGA = Wheat Germ Agglutinin

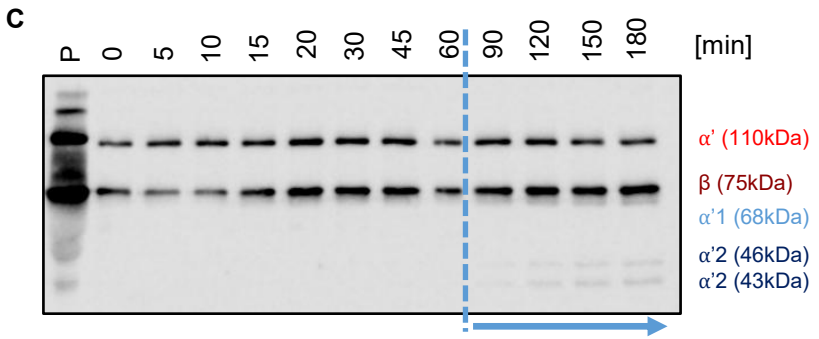


Teoh et al, Front Med 2023

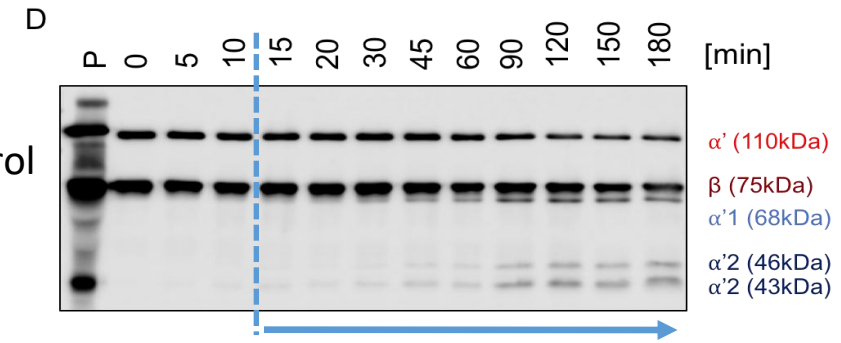
Reduced FH EC surface binding results in reduced FH cofactor activity

Cofactor assay: C3b + FI $\xrightarrow{\text{Factor H}}$ iC3b (α'1 + 2xα'2)

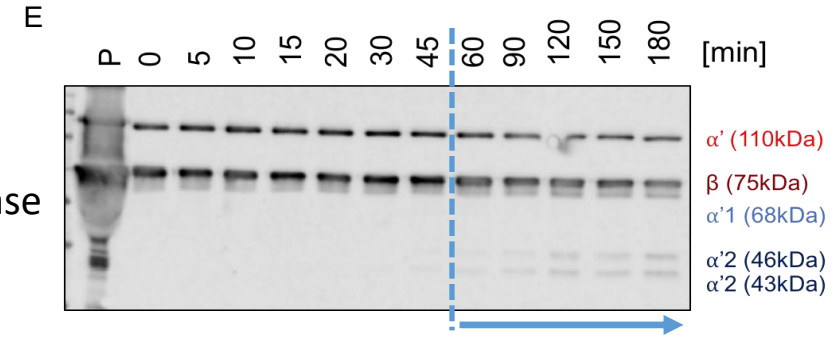
Endogenous (w/o CFH)



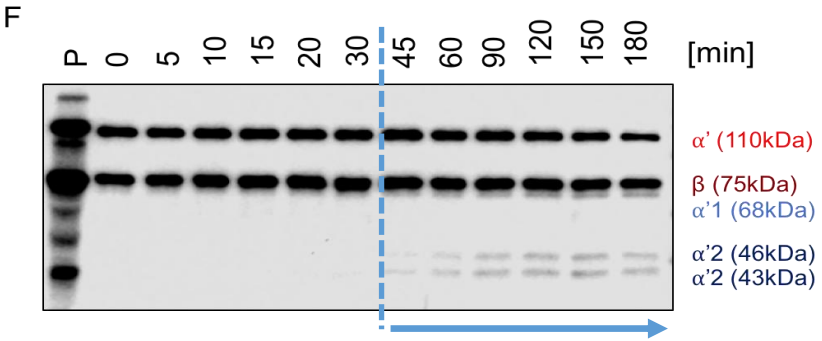
Positive control (w/ CFH)



Neuraminidase

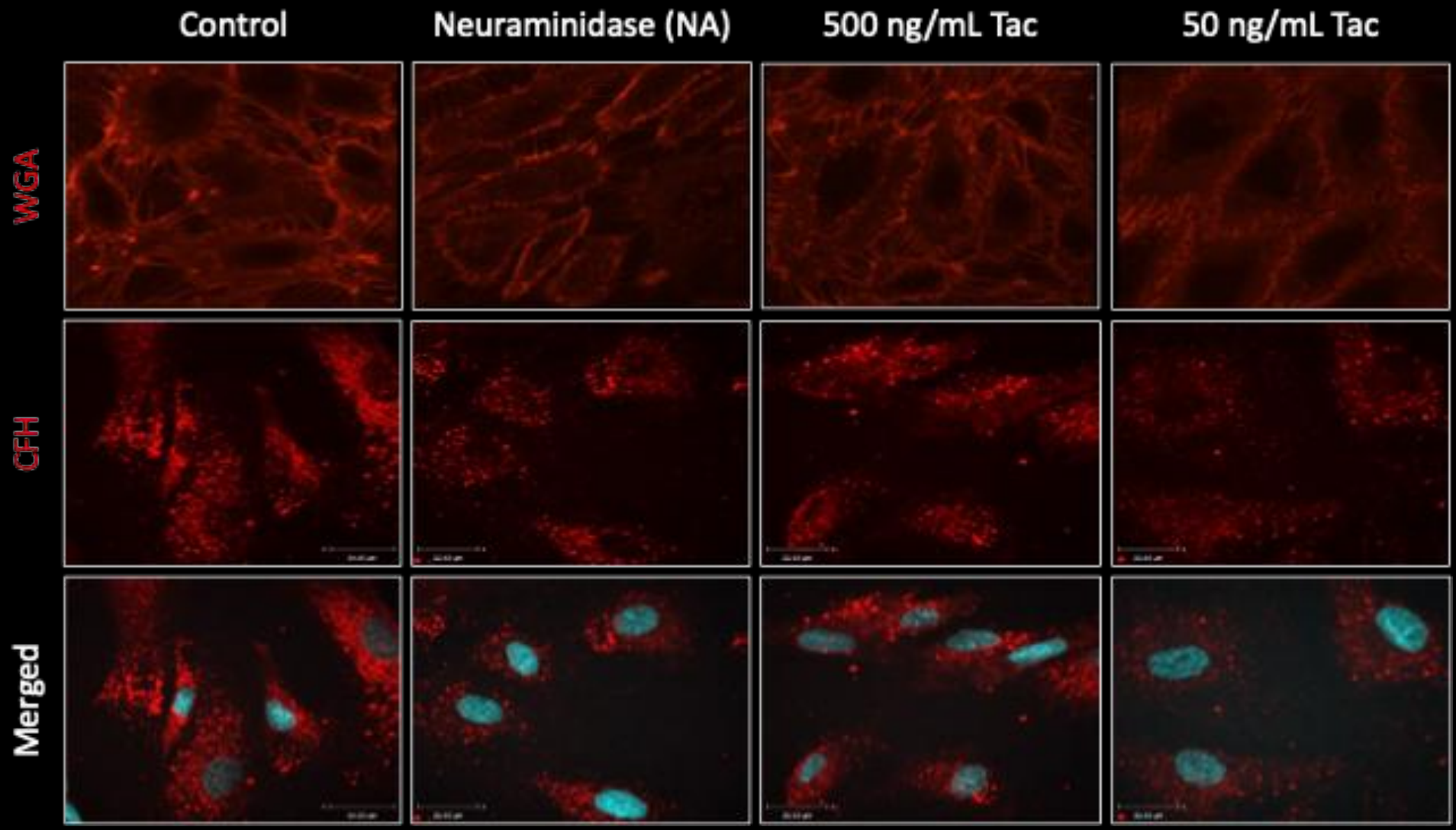


CsA 10



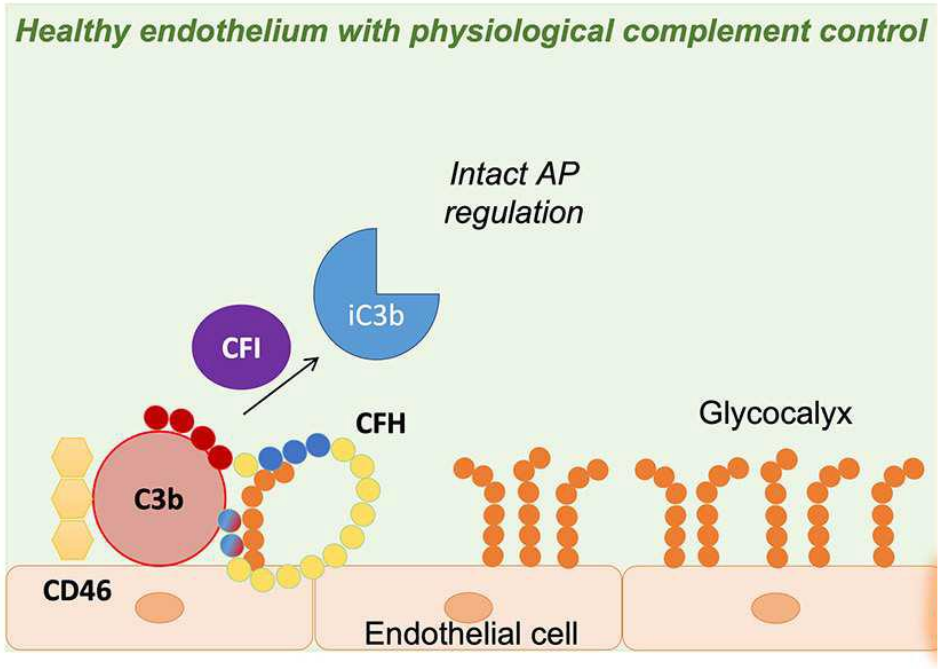
Modified from Teoh et al, Front Med 2023

Tacrolimus diminishes endothelial glycocalyx and reduces Factor H binding



Mahmud / Zekri et al – unpublished data

Endothelial glycocalyx and TMA – *concept*



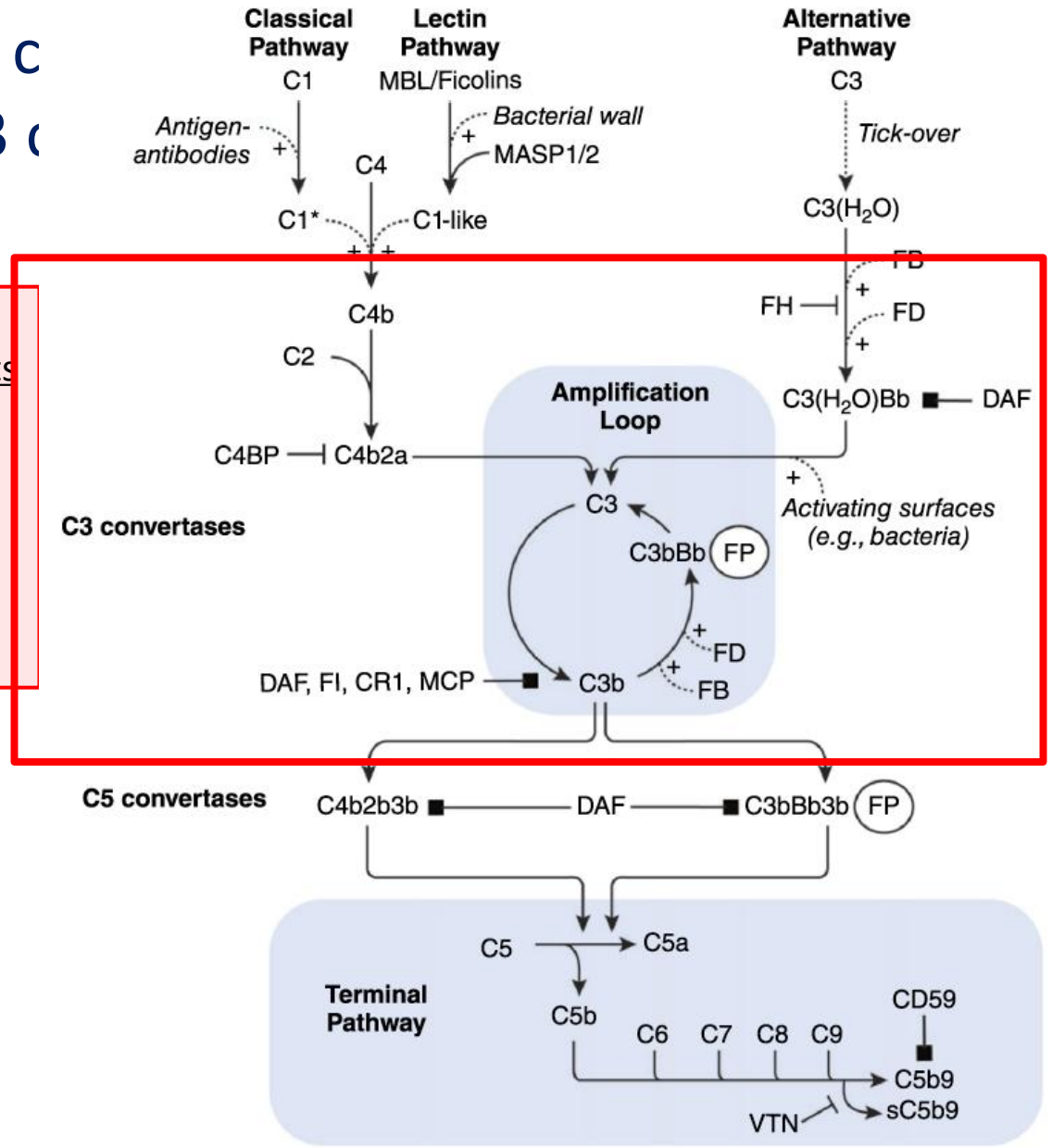
Teoh et al, Front Med 2023

C3G is c … thway
C3 c … se

Autoantibodies

<u>C3bBb components</u>
- C3NeF etc.
- FB
- C3b

<u>C3bBb regulators</u>
- FH



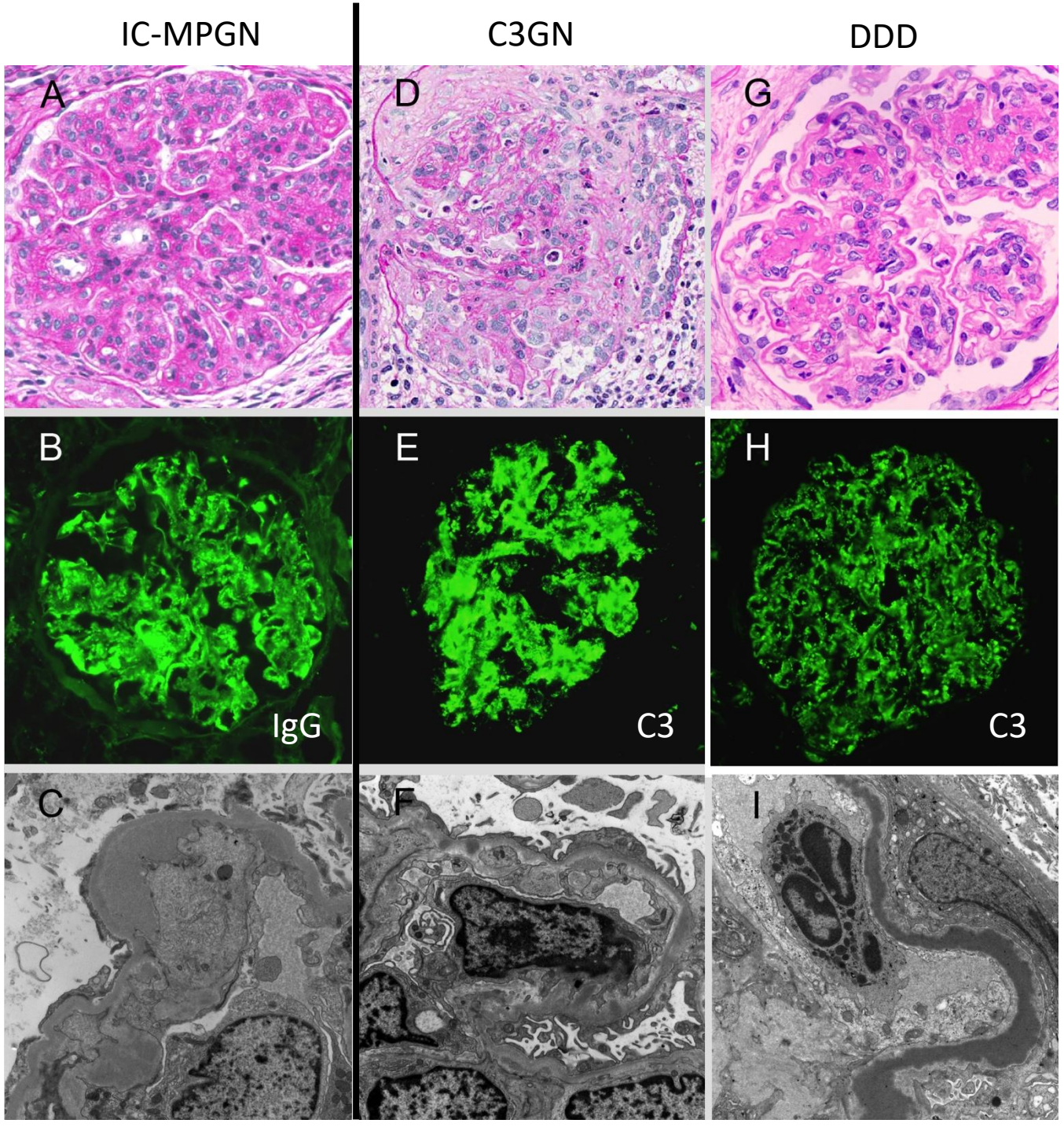
utations

<u>bBb components</u>
3
B

<u>bBb regulators</u>
H
I
MCP/CD46
THBD/CD141

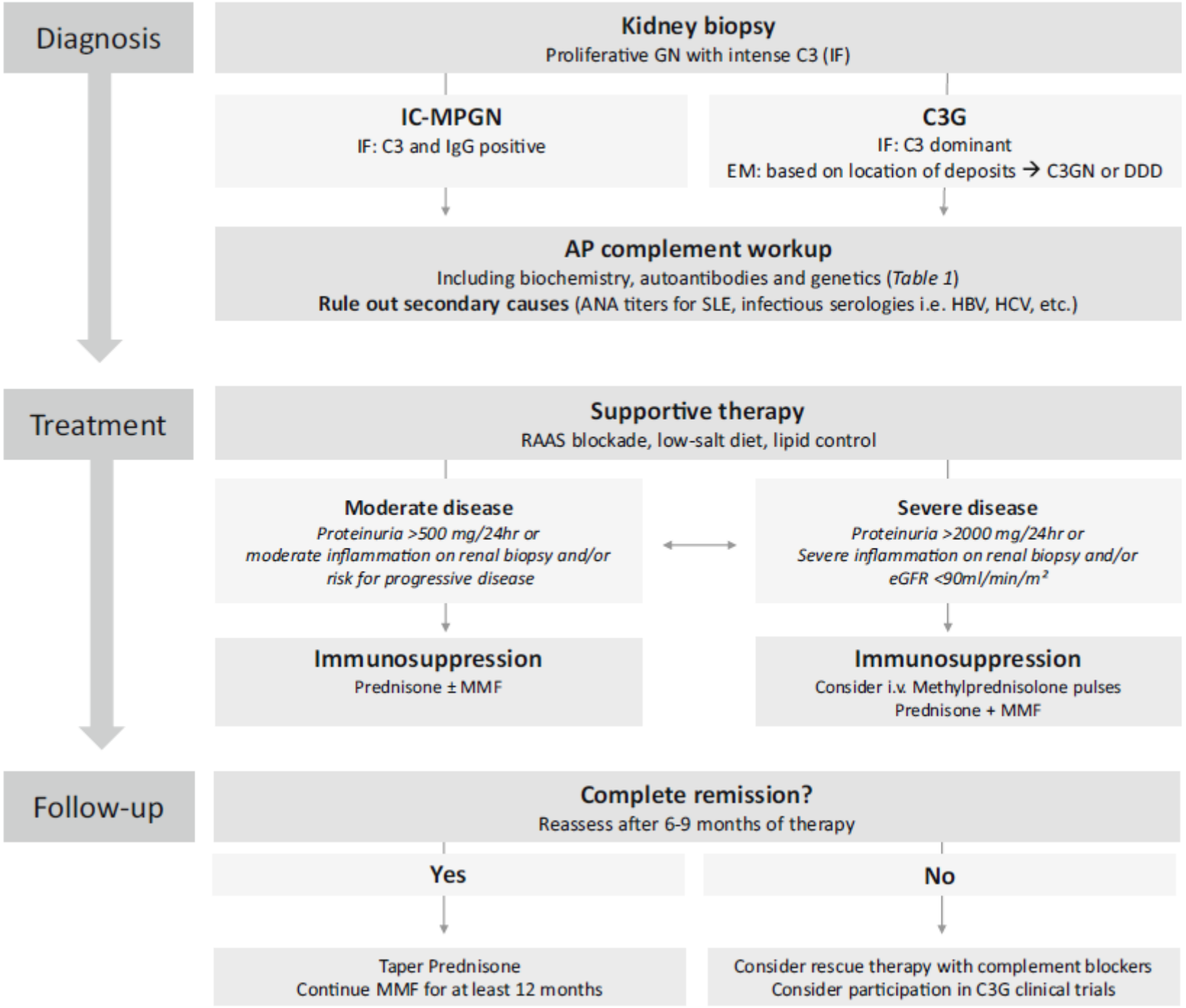
Lemaire et al, Clin J Am Soc Nephrol 2021

The current consensus classification – from morphology to pathogenesis



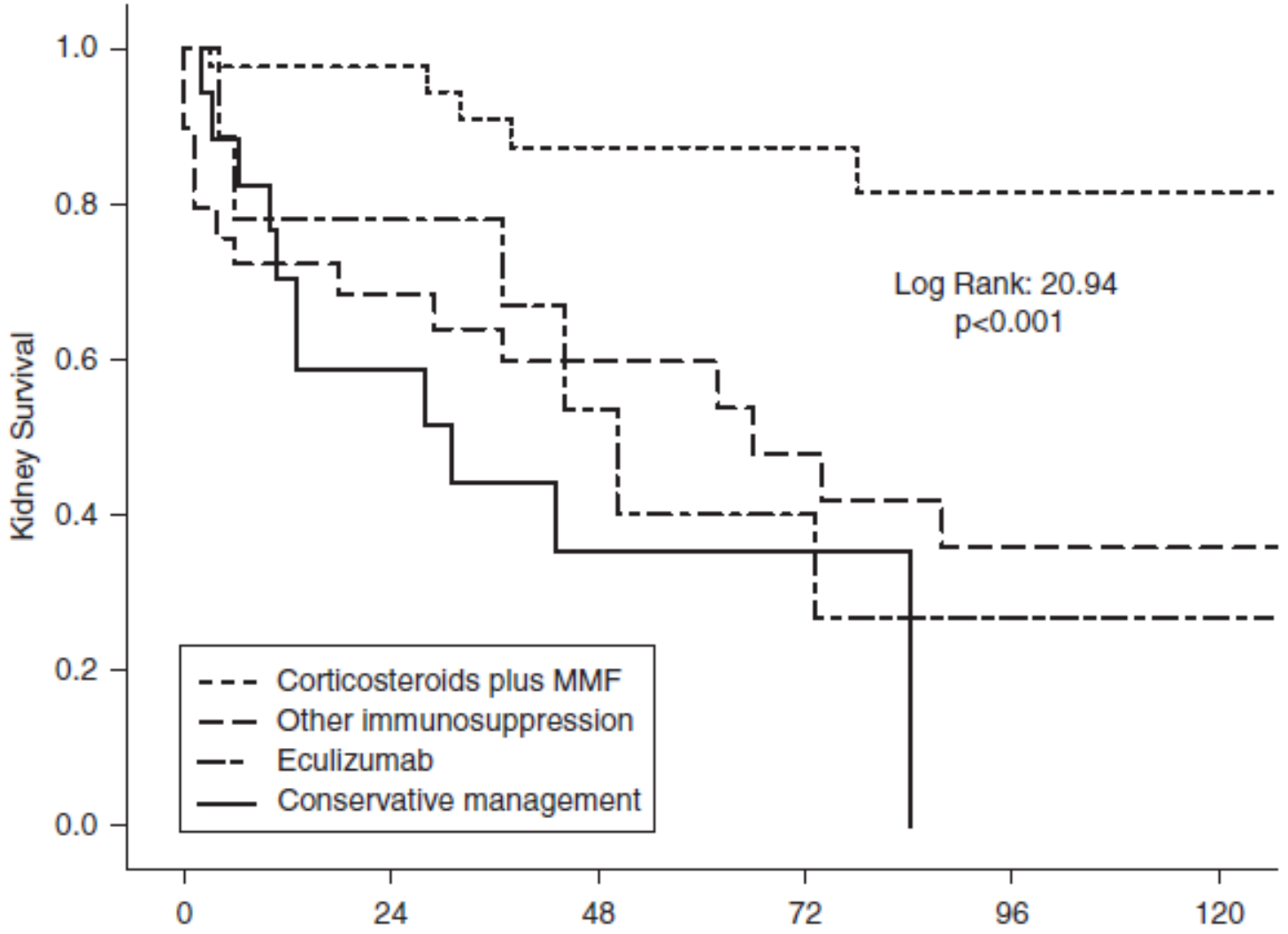
Riedl et al,
Pediatr Nephrol 2017

Current treatment recommendations for MPGN/C3G



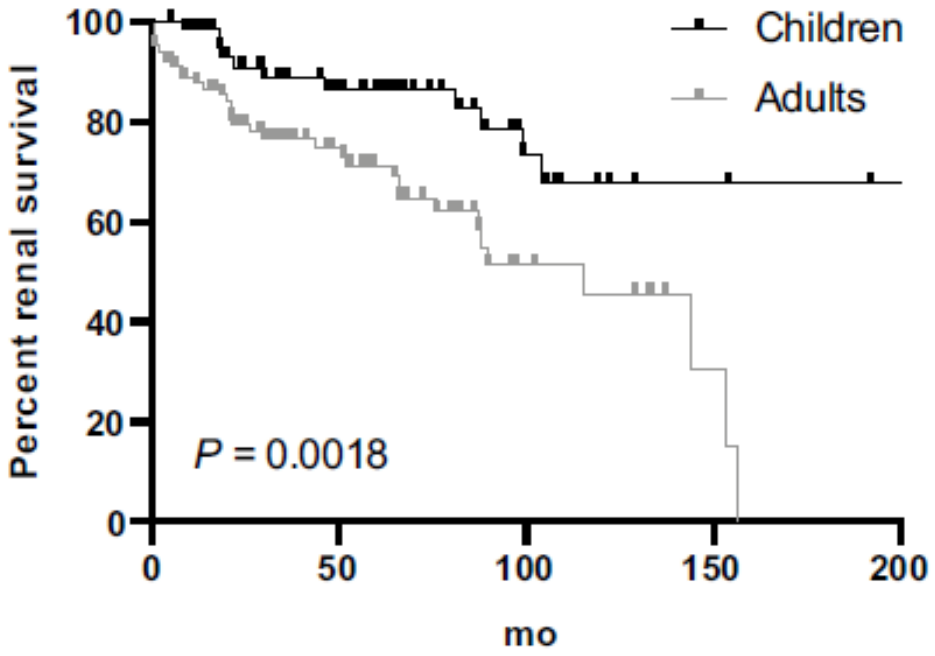
Vivarelli et al,
Pediatr Nephrol 2022 &
Kidney Int 2024 (KDIGO)

Outcome of C3G and IC-MPGN patients - *Treatment*

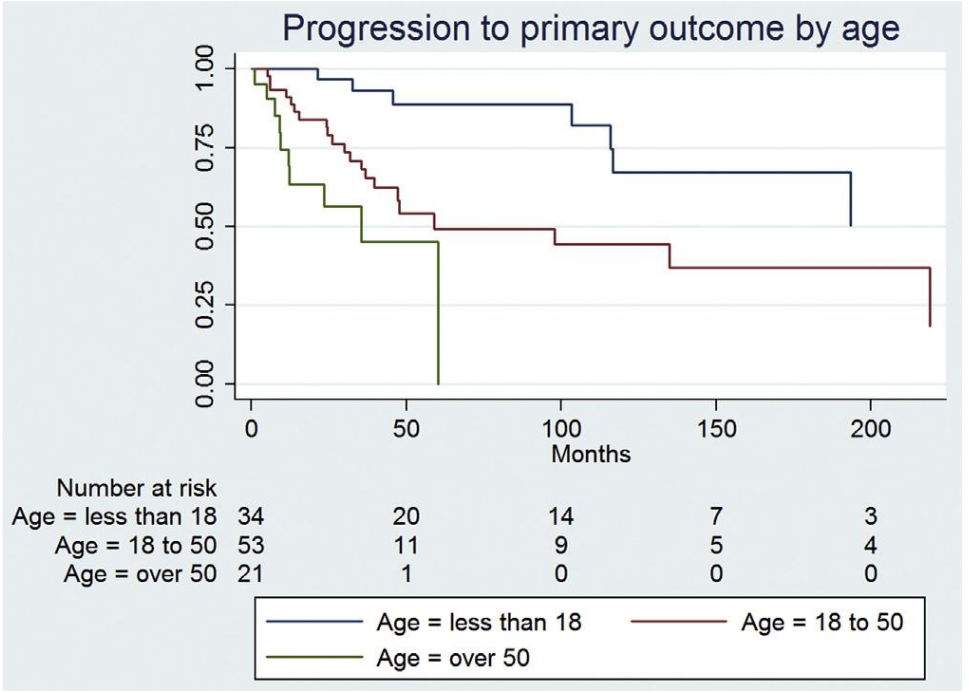


Caravaca-Fontan et al, Clin J Am Soc Nephrol 2020

Comparison of pediatric and adult onset C3G patients
Long-term outcome



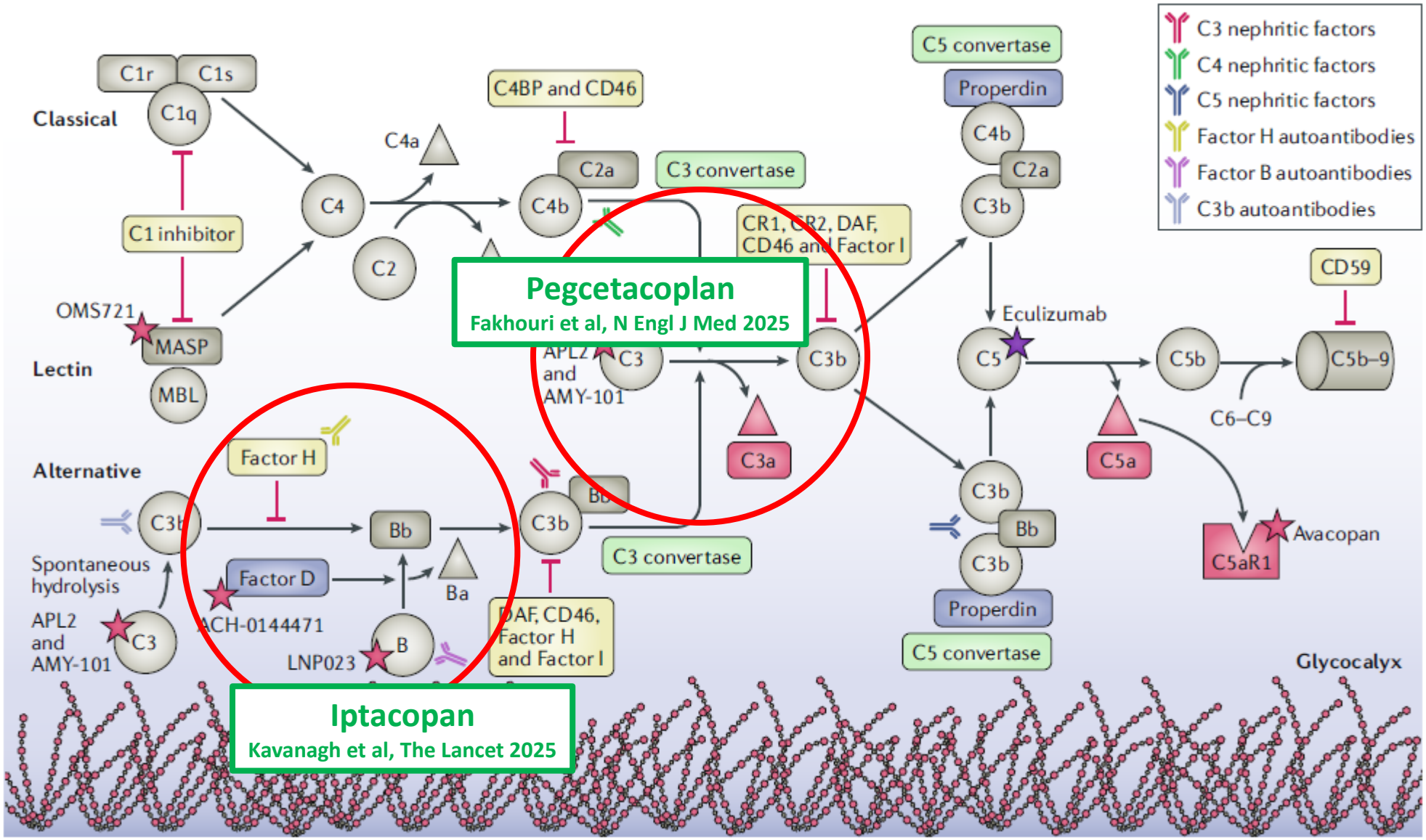
N=64 children, 101 adults
Retrospective - France



N=34 children, 74 adults
Retrospective - USA
(~20% DDD)

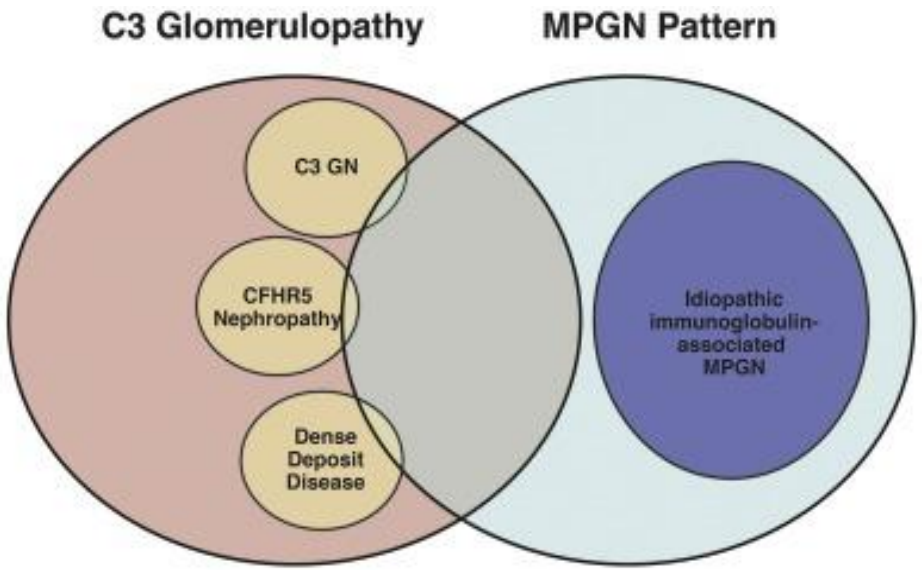
Chauvet et al, Kidney Int 2022; Bomback et al, Kidney Int 2018

New treatment options for C3G

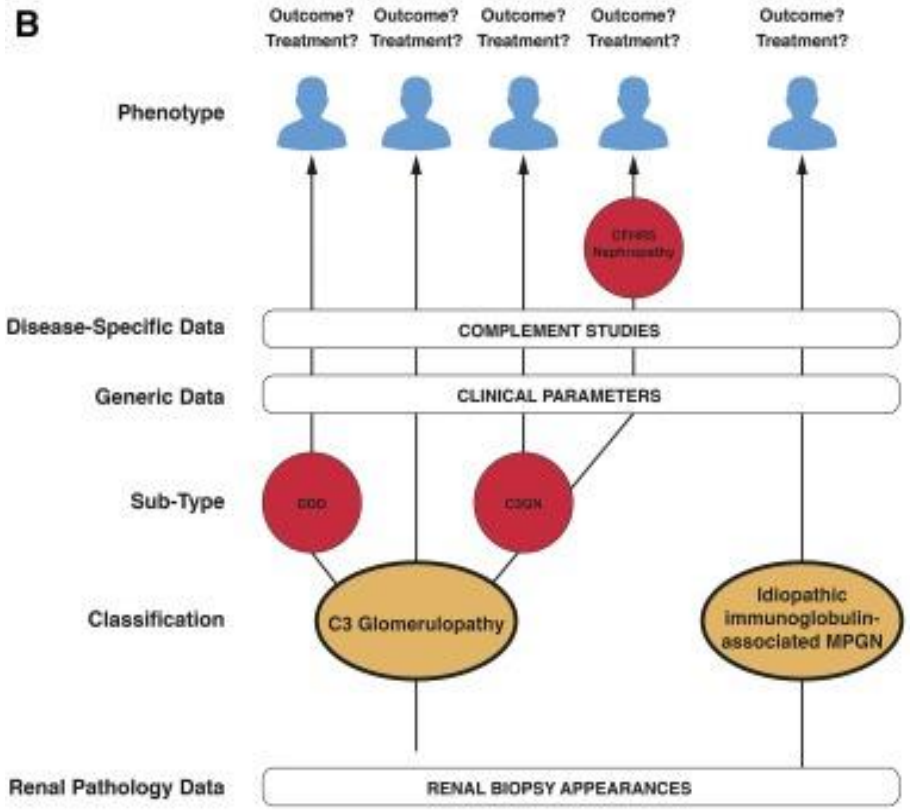


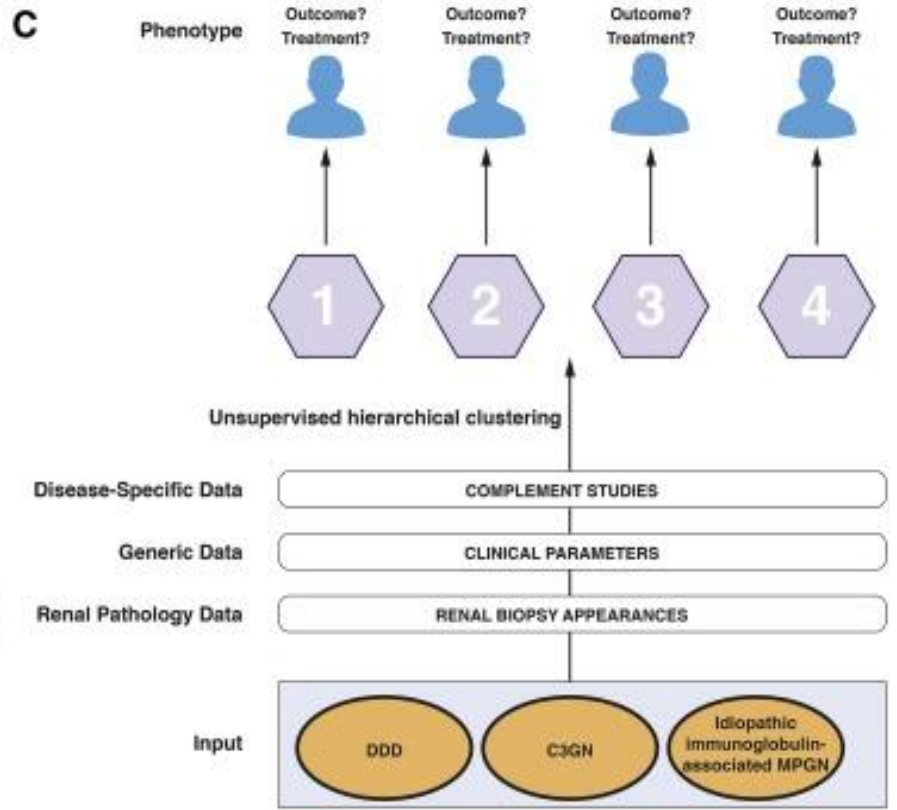
Smith et al, Nat Rev Nephrol 2019

Current consensus clasification



New clusters

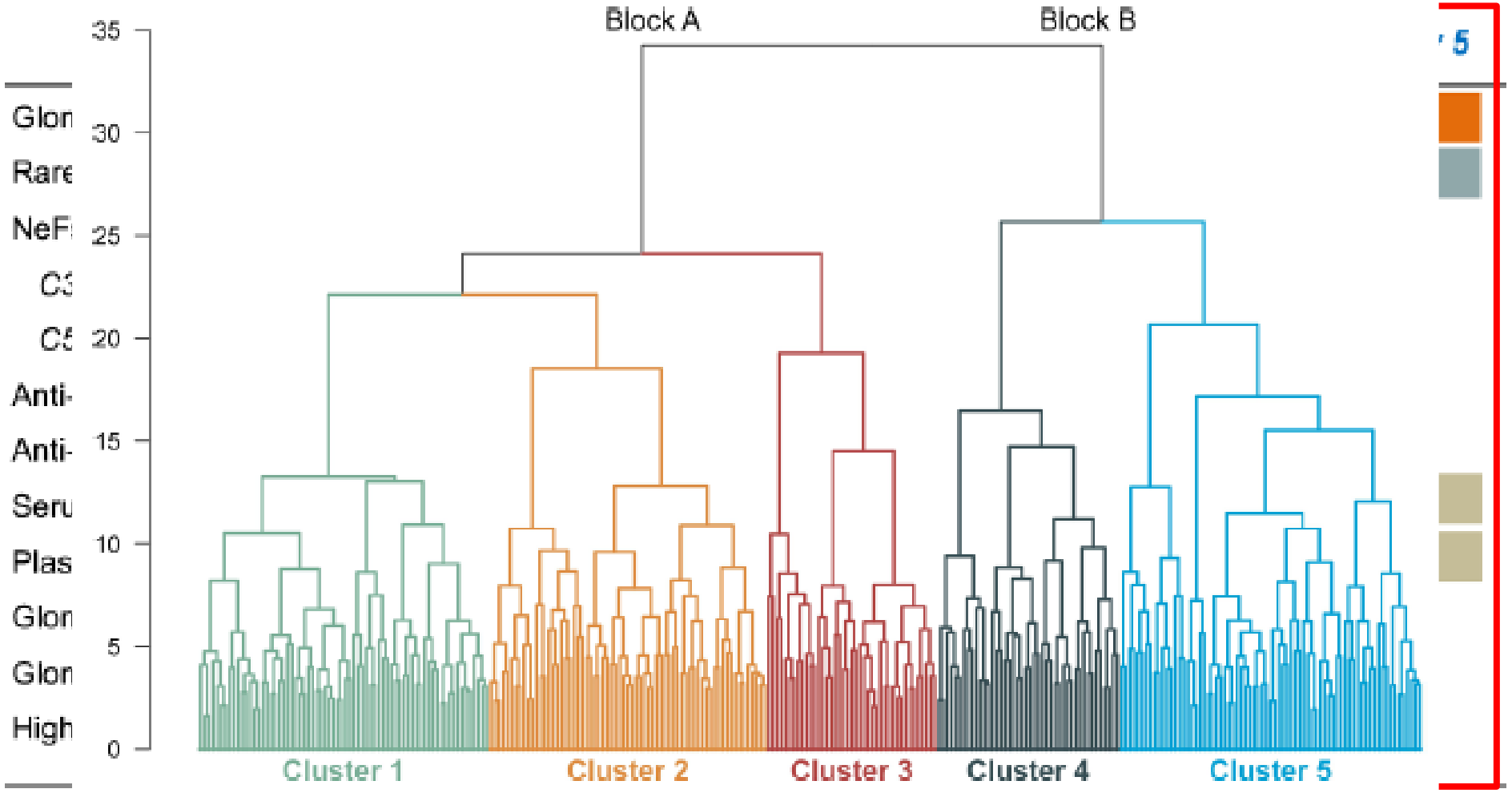




Cook and Pickering,
J Am Soc Nephrol 2017

Clustering of IC-MPGN and C3G patients by clinical and immunologic profile at biopsy

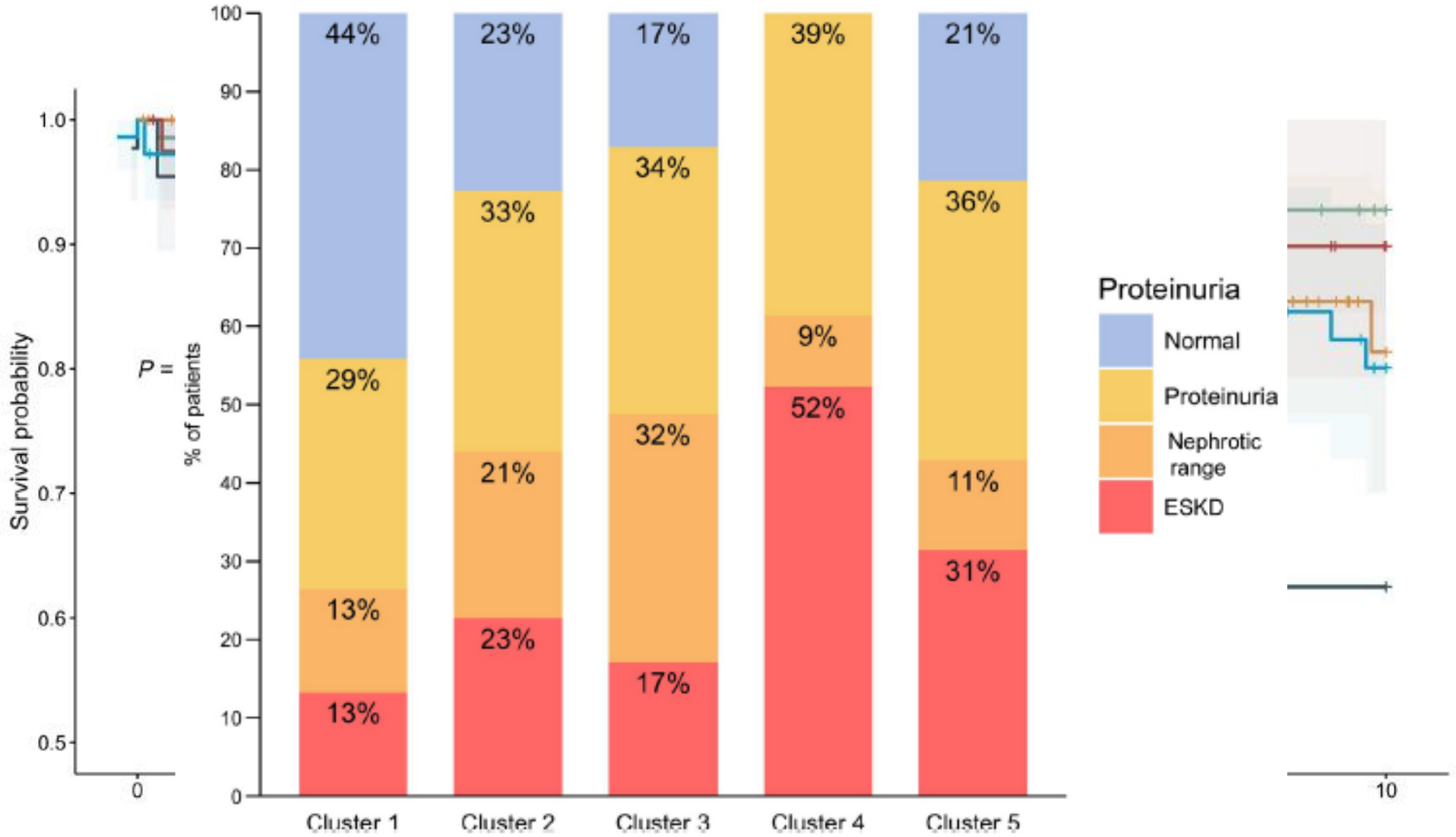
Italian cohort (n=295; 178 children and 117 adults)



Iatropoulos et al, J Am Soc Nephrol 2018; Benigni et al, Kidney Int 2025

Clustering of IC-MPGN and C3G patients by clinical and immunologic profile at biopsy

Italian cohort (n=295; 178 children and 117 adults)



Benigni et al, Kidney Int 2025

Hierarchical clustering uncovered disease patterns and further untangled complexities in immune complex-mediated idiopathic MPGN and C3 glomerulopathy

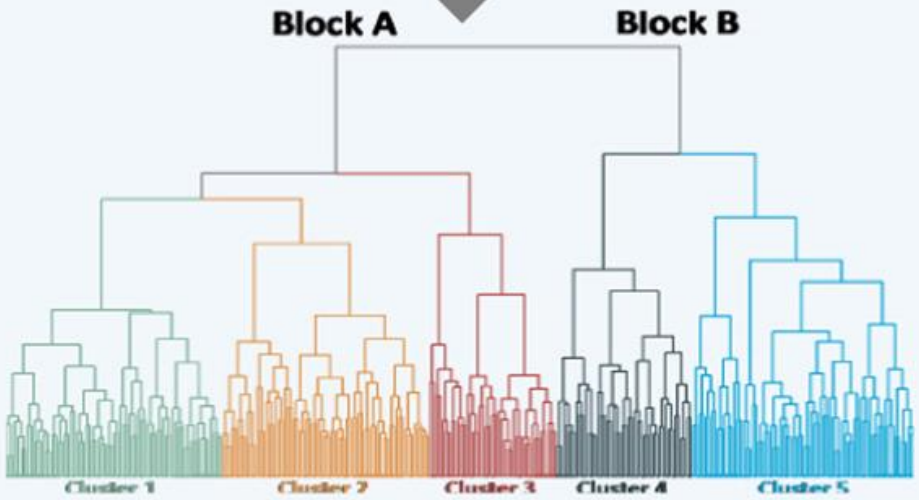
kidney INTERNATIONAL

ISN INTERNATIONAL SOCIETY OF NEPHROLOGY

Study design and cohort

295 C3G/IC-MPGN patients

Histology, genetic, immune and clinical parameters → Hierarchical clustering

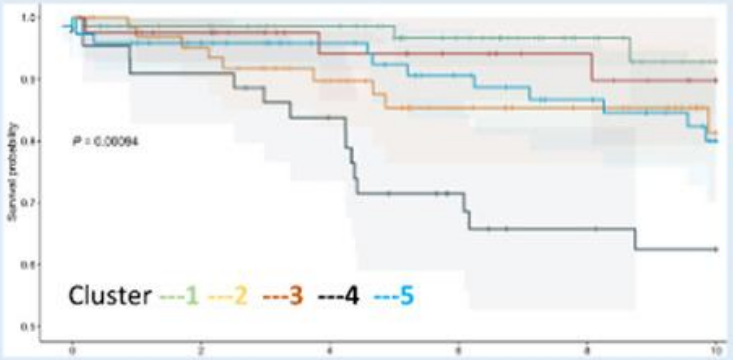


Results (1)

The clusters differ for complement abnormalities

		Cluster 1	Cluster 2	Cluster 3	Cluster 4	Cluster 5
Glomerular C3	score	2.8	2.9	2.7	2.4	2.4
Rare genetic abnormalities	%	7	21	10	9	26
NeFs	%	33	64	90	36	6
C3NeF	*fraction*	0.17	0.22	0.72	0.3	0
C5NeF	*fraction*	0.83	0.78	0.28	0.7	1
Anti-CFB	%	23	20	3.3	4.8	11
Anti-CFH	%	4.8	3.1	11.8	4.8	1.6
Serum C3	mg/dl	↓↓	↓↓	↓↓	N	N
Plasma sC5b-9	ng/ml	↑↑	↑↑	N↑	N	N
Glomerular IgG	score	0.5	1.5	0.5	0.7	0.8
Glomerular C1q	score	0.2	1.3	0.3	0.7	0.4
Highly electron dense deps	%	6	2	71	11	3

Patients in cluster 4 have poor renal outcomes

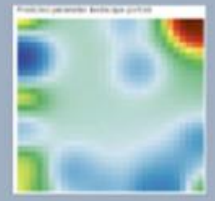


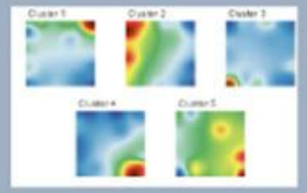
Results (2)

An interface to assign new patients to a cluster with a limited set of data available at diagnosis

Profile of new patients

Compare to the profiles of the 5 clusters





Benigni at al, 2025

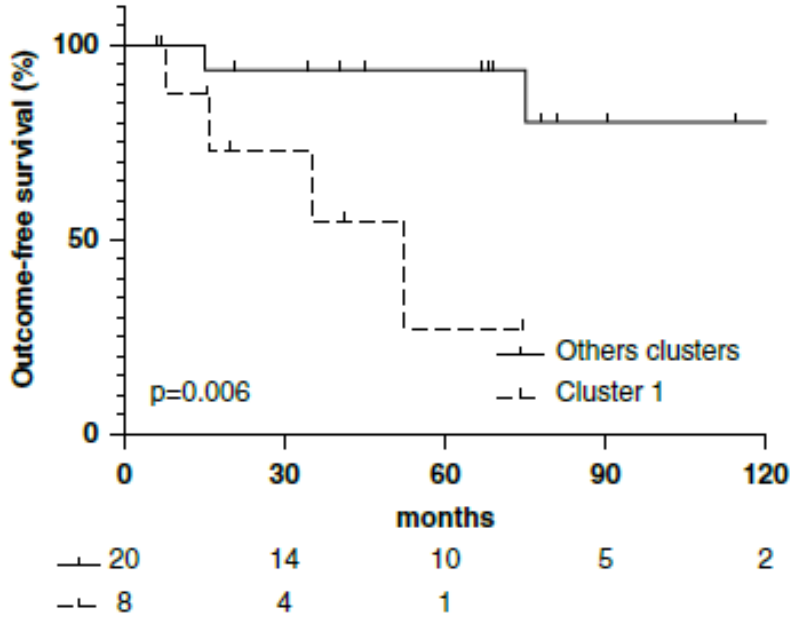
CONCLUSION: *Cluster-based classification allows etiologic diagnosis of C3G/IC-MPGN and has better prognostic value than current approaches.*
The cluster-based web-application is a promising approach for predicting outcomes and aiding future research and treatment strategies.

Clustering of C3G patients by transcriptome profiles at biopsy

French cohort (n=42; 21 children and 21 adults)

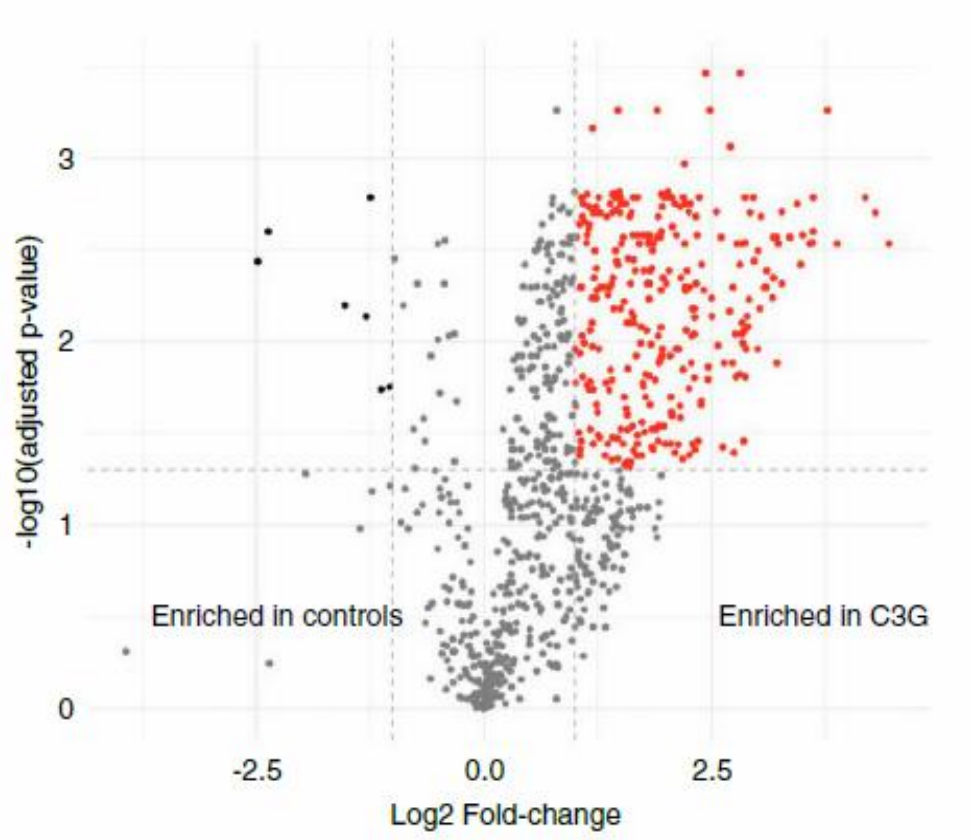
Total N	8	11	6	3
Children, N	2	8	2	2

	Cluster 1	Cluster 2	Cluster 3	Cluster 4
Age	Minority of children	Majority of children	Minority of children	Majority of children
eGFR	CKD3a	CKD3b	CKD 2	CKD 1
Proteinuria	Nephrotic range	Nephrotic range	Glomerular	Glomerular
Median Histological activity score	Intermediate	High	High	Intermediate
Median Histological chronicity score	High	Low	Intermediate	Low
Glomerular C5b-9 deposits	High dominant	Low/intermediate	Low/intermediate	Low
T cells	High	High	High	Low
Myeloid cells	High	High	Low	Low
Neutrophils	Low	High	High	Low
Fibroblasts	High	High	Low	Low



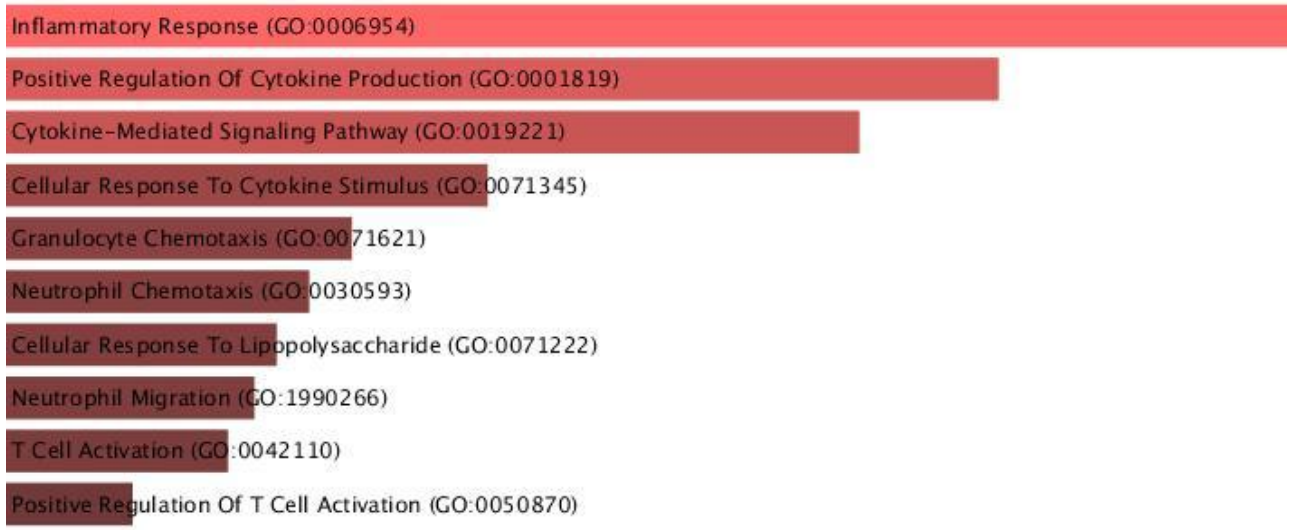
Chauvet et al, Kidney Int 2022; Meuleman et al, J Am Soc Nephrol 2024

Terminal pathway activation in C3G patients is associated with glomerular immune response and determines outcome



Genes enriched in C3G patients

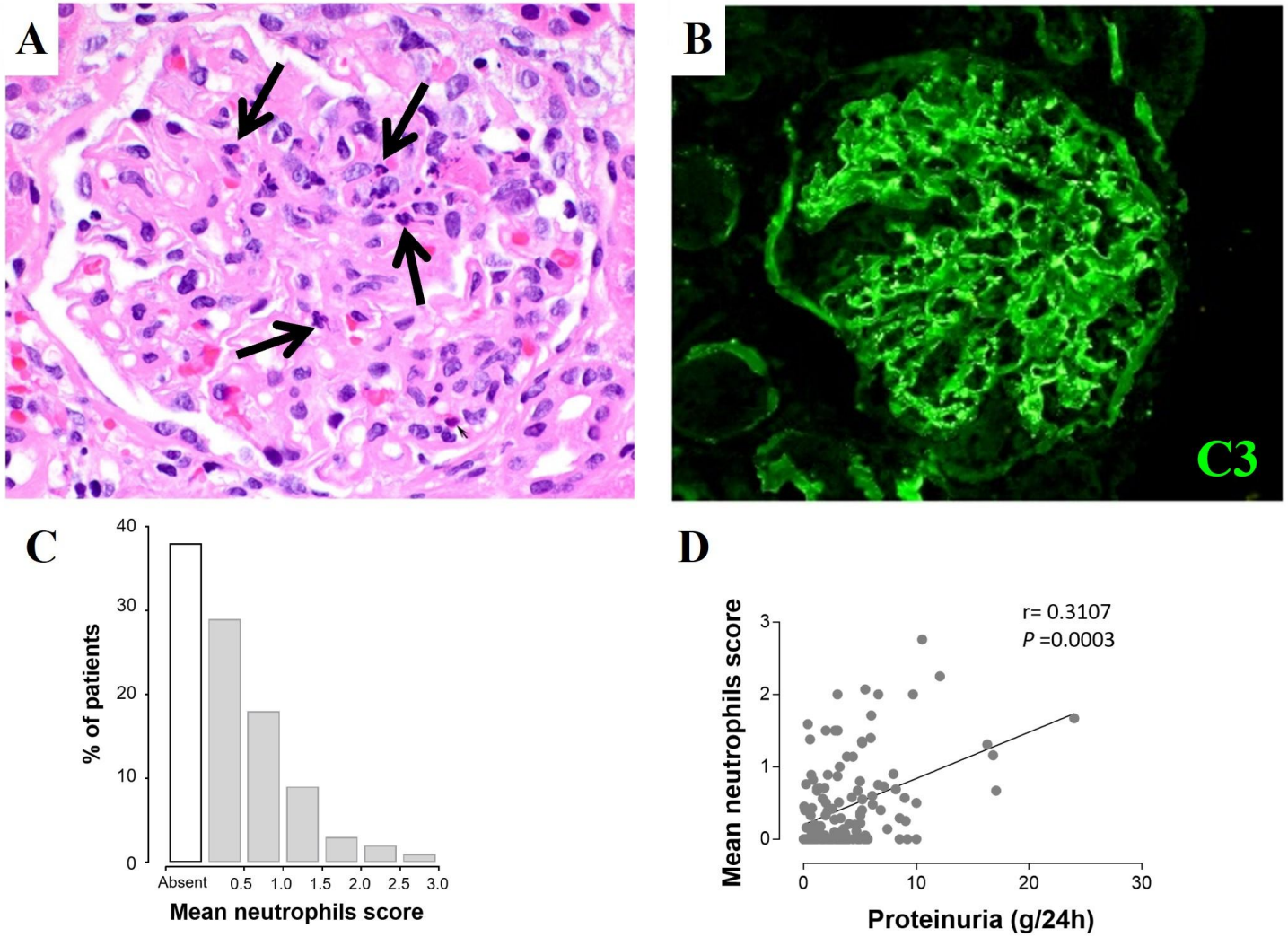
GO Biological Processes



https://maayanlab.cloud/Enrichr/

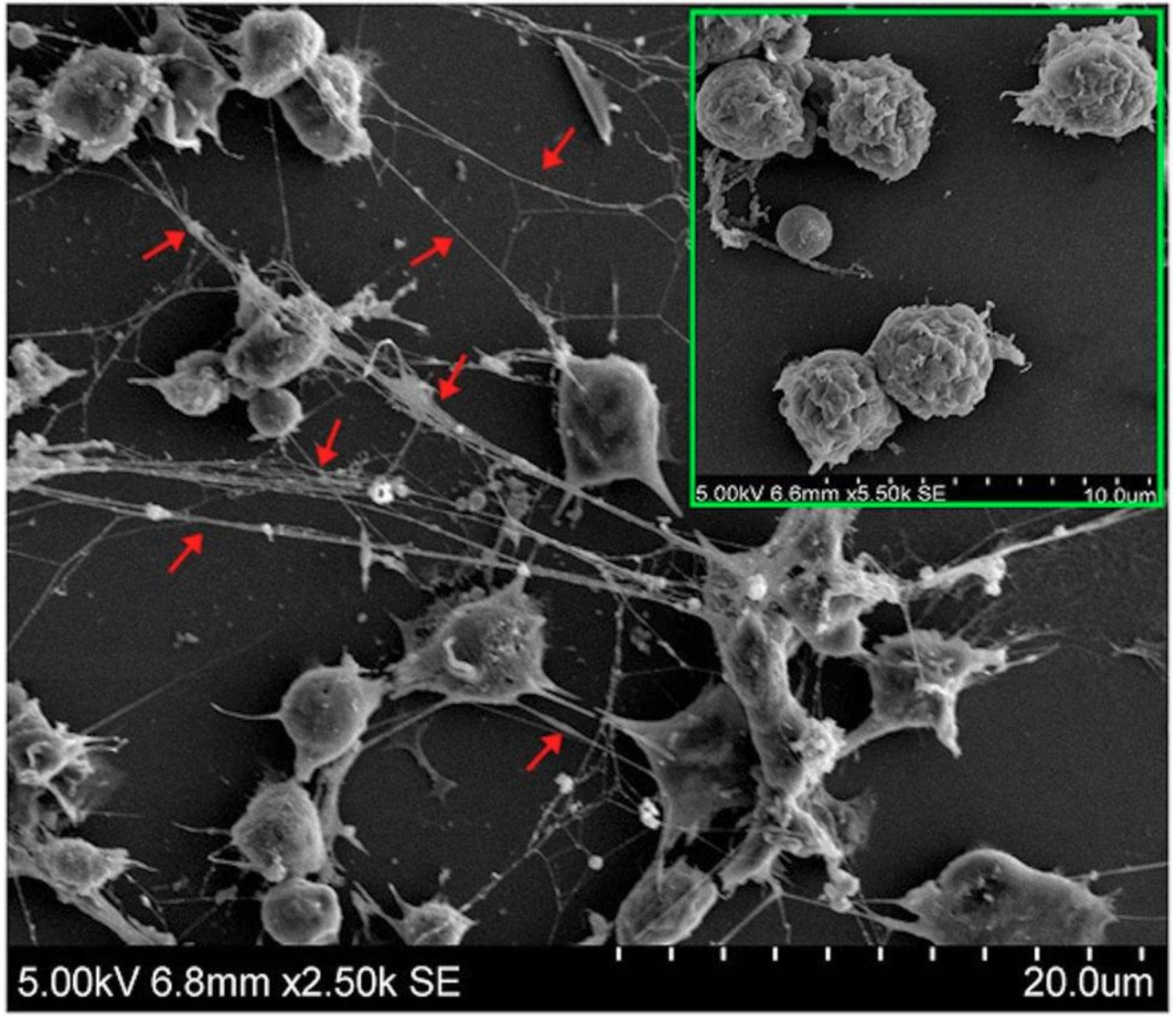
Meuleman et al, J Am Soc Nephrol 2024

Glomerular neutrophil infiltration is found in C3G patients and correlates with proteinuria



C3G patient data courtesy of Terrence Cook, Imperial College, London, UK

Neutrophil extracellular traps (NETs)



DNA +
- Myeloperoxidase (MPO)
- Neutrophil elastase (NE)
- Histone proteins

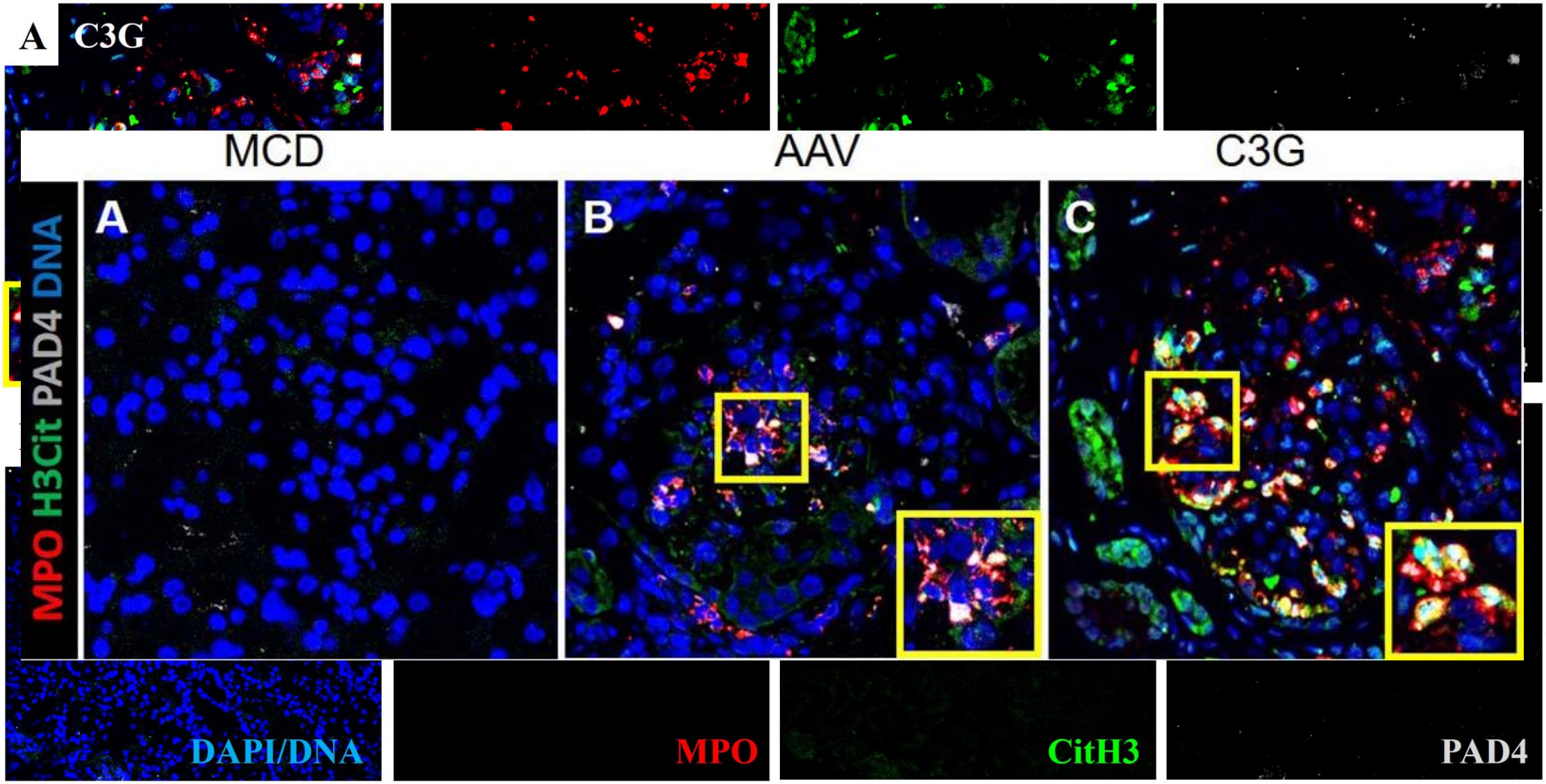
Anti-microbial mechanism

Potential cause of glomerular injury

Jariwala and Laxer, Current Rheumatology Reports 2021

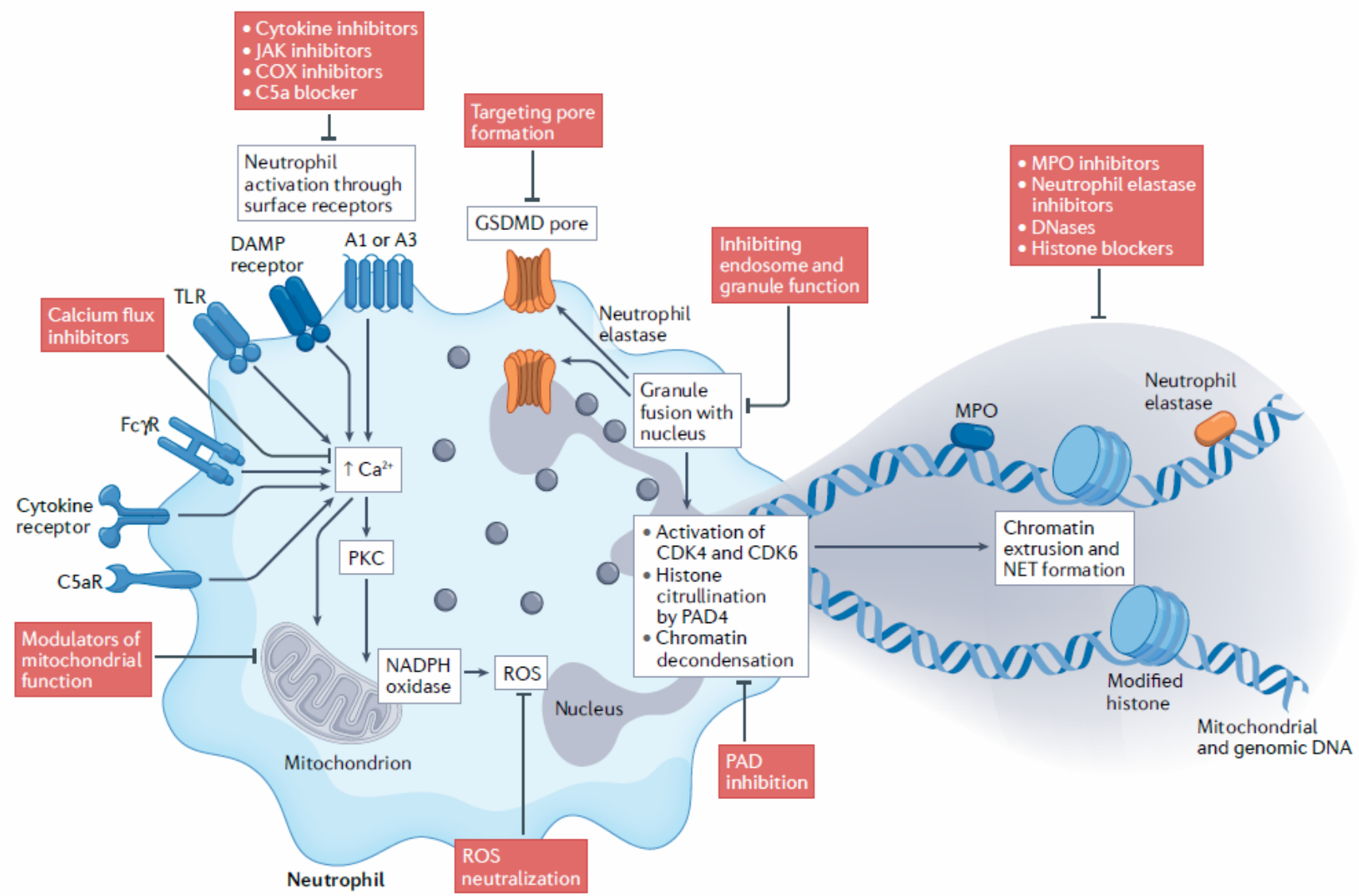
Brinkmann et al, Science 2004

NETs are found in the glomeruli of C3G patients



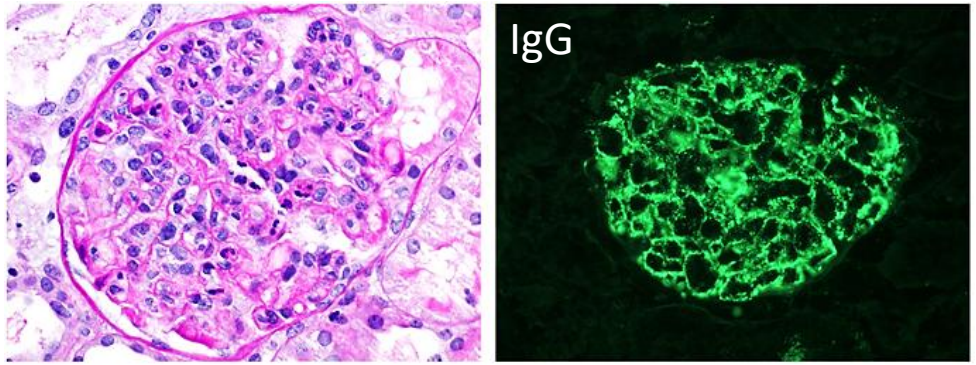
Kim O'Sullivan, Monash University, Melbourne, Australia – unpublished data

NETs might be a novel treatment target in C3G?

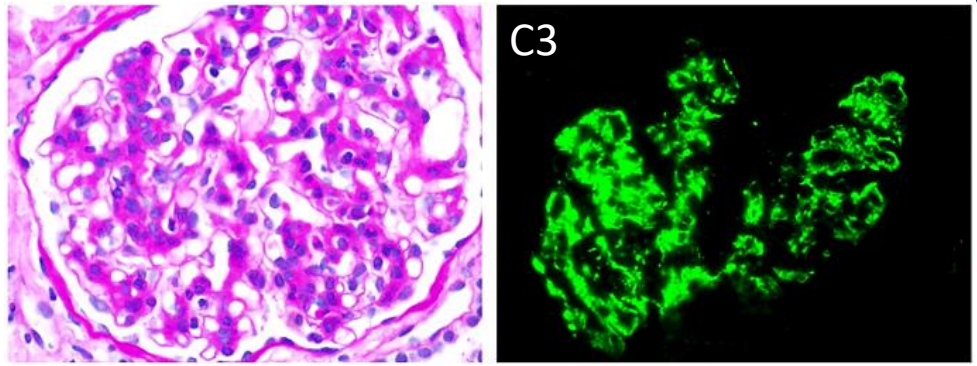


Wigerblad et al, Nat Rev Immunol 2023

Proposed concept



IC-MPGN



C3G

Disease state	**Therapeutic strategy**
Predominant inflammation	Anti-inflammatory / IS
Neutrophils / NETs	**Steroids / MMF** **? Anti-NETosis therapy**
Predominant complement dysregulation	Complement blockade
Complement deposition	**AP C3 convertase blocker**

Repeat pattern during disease flare up

Take home messages

- The pathogenesis of complement-mediated kidney diseases includes *canonical* and *non-canonical* pathways / mechanisms.
- Disturbance of cellular / tissue integrity (e.g., eGC; NETs) causes “complementopathies”.
- Future *diagnostic* strategies should include mechanisms affecting complement homeostasis.
- Future *therapeutic* strategies should consider the combination of complement-targeting and non-complement targeting concepts.

Licht Lab 2024 / 2025

THANK YOU

SAVE THE DATE!

TORONTO COMPLEMENT CONFERENCE SEPT 24-26, 2026

Friday, September 15 to Saturday, September 26, 2026
In-person and hybrid registration available – *opening Spring 2026*
Toronto, Ontario

Introducing…

TCC Academy!

An exclusive webinar series for complement-curious scientists and clinicians

First Webinar: Wednesday, December 17, 2025 | 12:00 – 1:30 p.m. (ET)

Scan for more info and a link to register!

TORONTO COMPLEMENT CONFERENCE