Development of Complement Inhibitors

Joshua M. Thurman, MD

DISCLOSURES

Consultant for Q32 Bio, Inc., a company developing complement inhibitors.

Stock and royalty income from Q32 Bio, Inc.

Stock in Compsit3, Inc., a company developing complement imaging.

Outline: Complement inhibitory drugs

- The clinical impact
- History of development
- Molecular types and specific targets
- Established and potential indications
- Future perspectives
  - Challenges

Complement inhibitors for kidney disease – the long wait

EDITORIALS

J Am Soc Nephrol 14: 815–818, 2003

Complement Inhibitors And Glomerulonephritis: Are We There Yet?

WILLIAM G. COUSER
Editor-In-Chief, Journal Of The American Society Of Nephrology

Kidney International, Vol. 67 (2005), pp. 1692–1703

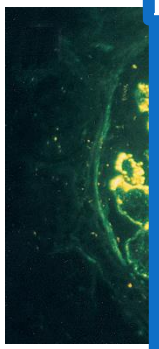
PERSPECTIVES IN BASIC SCIENCE

Treatment of glomerulonephritis: Will we ever have options other than steroids and cytotoxics?

BASIT JAVAID and RICHARD J. QUIGG

Section of Nephrology, The University of Chicago, Chicago, Illinois

Ab →



r Injury

Cells

angial cells

a

Couser WG. NDT 1998;13 Suppl 1:10-5.

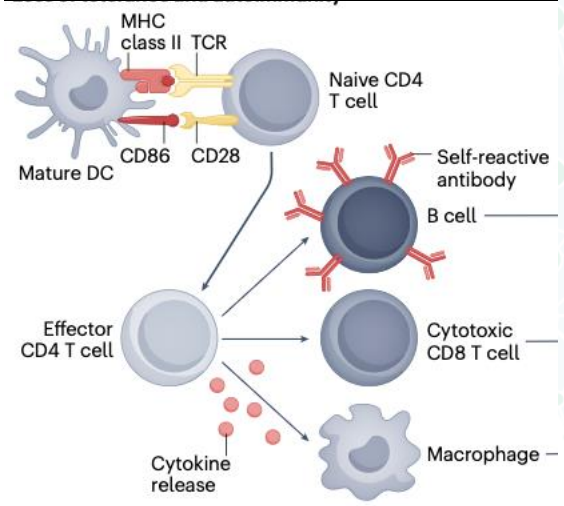
Conventional immunosuppressive drugs + complement inhibitors for GN

Conventional immunosuppressive drugs

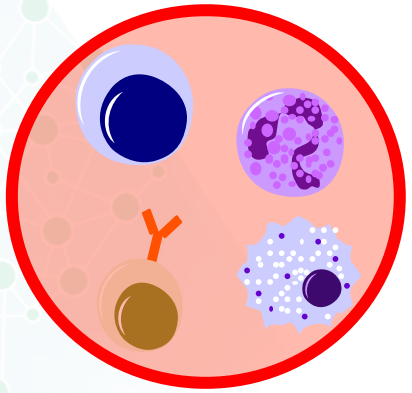
- Cyclophosphamide
- MMF
- Rituximab

Glucocorticoids

1) Loss of tolerance



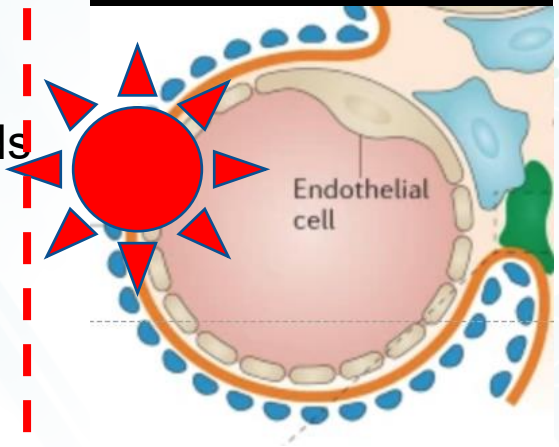
2) Immune activation



Triggers

- Cytokines
- PAMPS/DAMPS
- NETS, nucleic acids
- Molecular mimicry

3) Tissue injury



Cellular immunity

- Neutrophils
- Macrophages
- T cells/B cells

Molecular immunity

- Antibodies
- Complement
- Cytokines

Modified from:

- Feldmann and Steinman, Nature, 2005, 435: 612
- Petr and Thurman, Nature reviews Nephrology. 2023;19(12):771-87.
- Theofilopoulos et al. Nat Immunol. 2017;18(7):716-24.

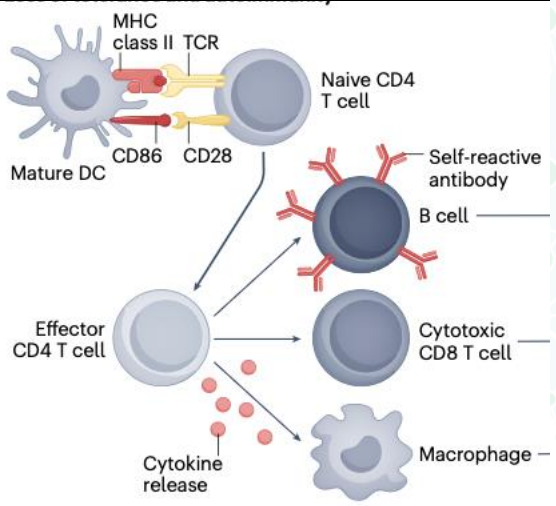
Conventional immunosuppressive drugs + complement inhibitors for GN

Conventional immunosuppressive drugs

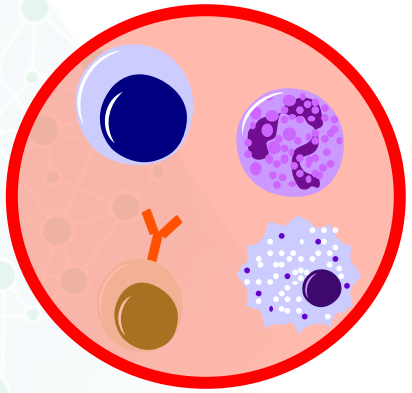
- Cyclophosphamide
- MMF
- Rituximab

Complement inhibitors

1) Loss of tolerance



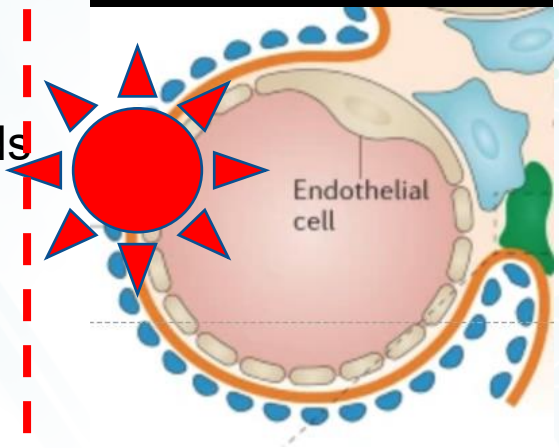
2) Immune activation



Triggers

- Cytokines
- PAMPS/DAMPS
- NETS, nucleic acids
- Molecular mimicry

3) Tissue injury



Cellular immunity

- Neutrophils
- Macrophages
- T cells/B cells

Molecular immunity

- Antibodies
- Complement
- Cytokines

Modified from:

- Feldmann and Steinman, Nature, 2005, 435: 612
- Petr and Thurman, Nature reviews Nephrology. 2023;19(12):771-87.
- Theofilopoulos et al. Nat Immunol. 2017;18(7):716-24.

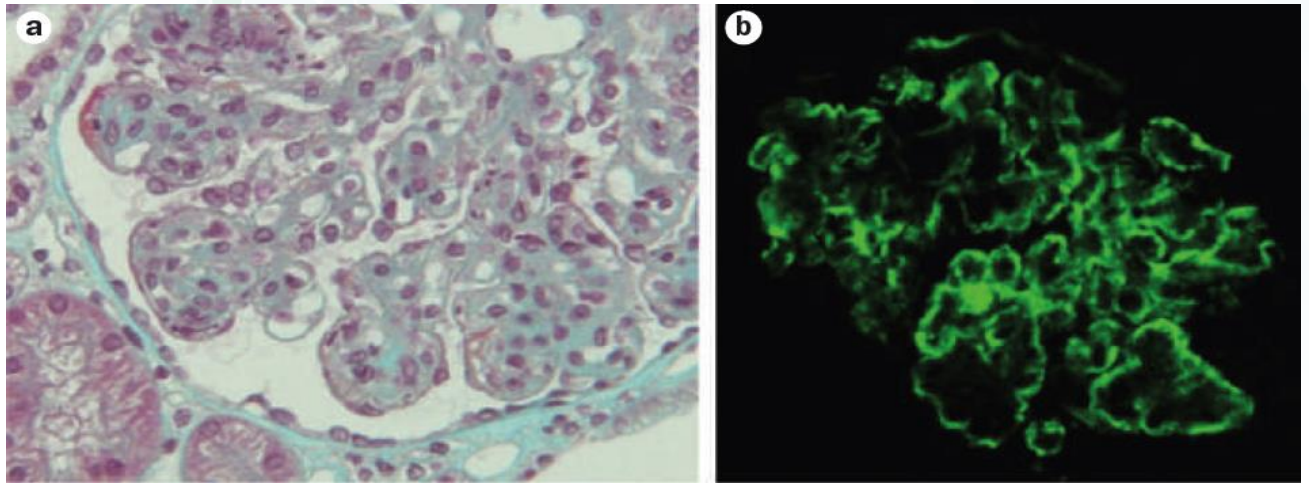
“Pure” complement-mediated kidney diseases

- C3G/(IC-MPGN)
- aHUS

Complement-inhibitors as monotherapies

Conventional immunosuppression does not target the underlying pathophysiology

C3G: Complement without the immunoglobulin.

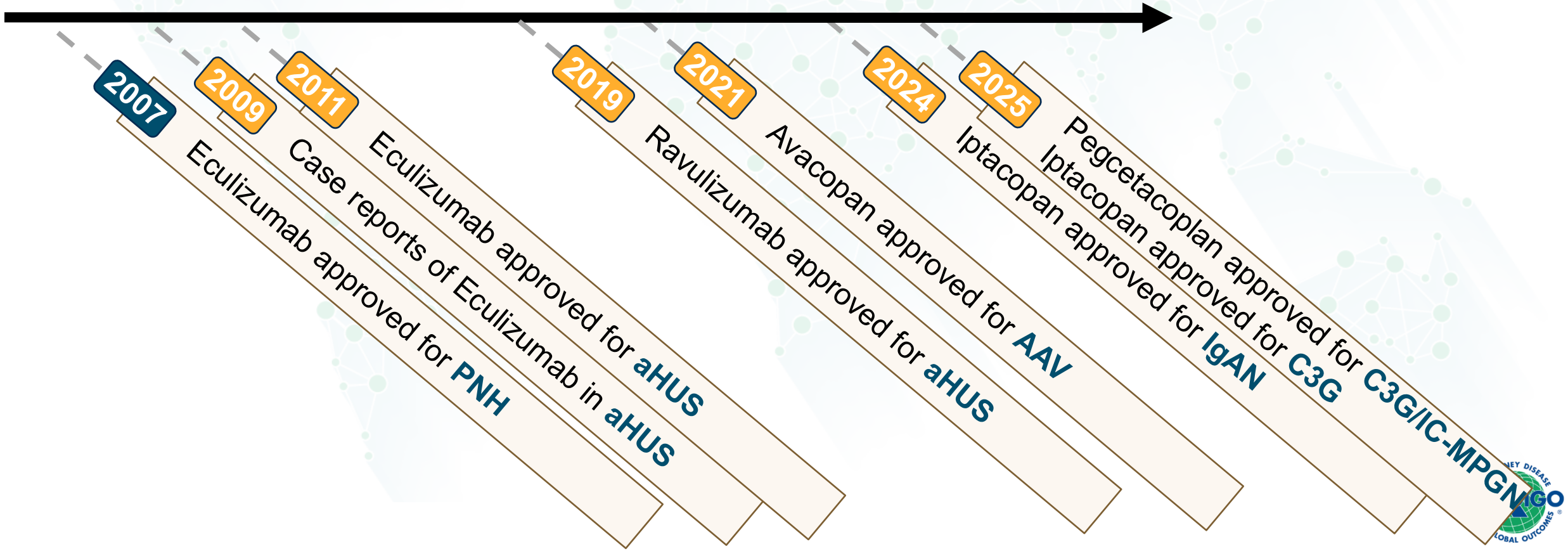


Servais et al. *Journal of medical genetics.* 2007;44(3):193-9.

Complement inhibitors approved for kidney diseases

2026

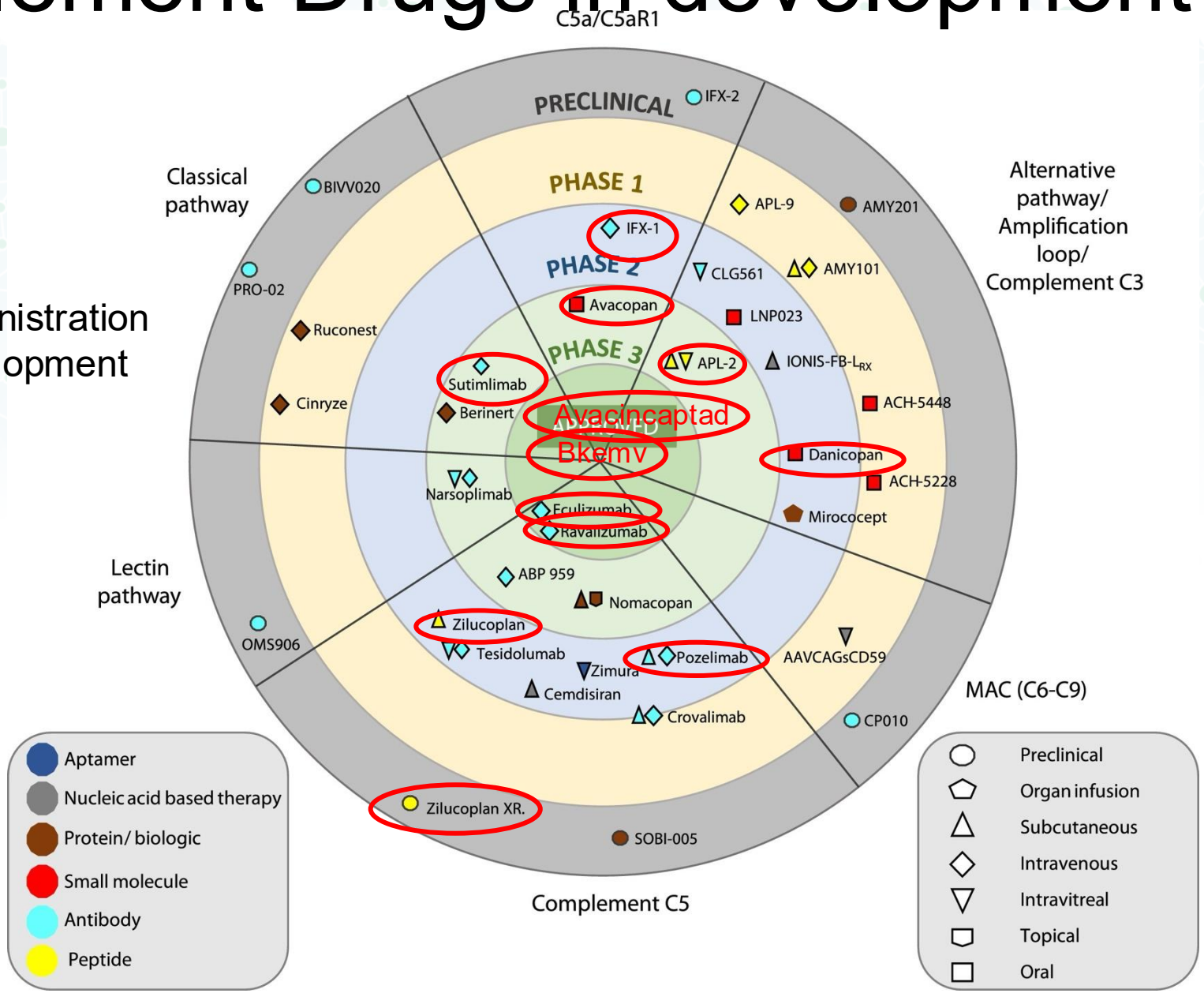
13 FDA-approved complement inhibitors
for thirteen different disease indications
6 FDA-approved complement inhibitors for 5 renal indications



Complement Drugs in development

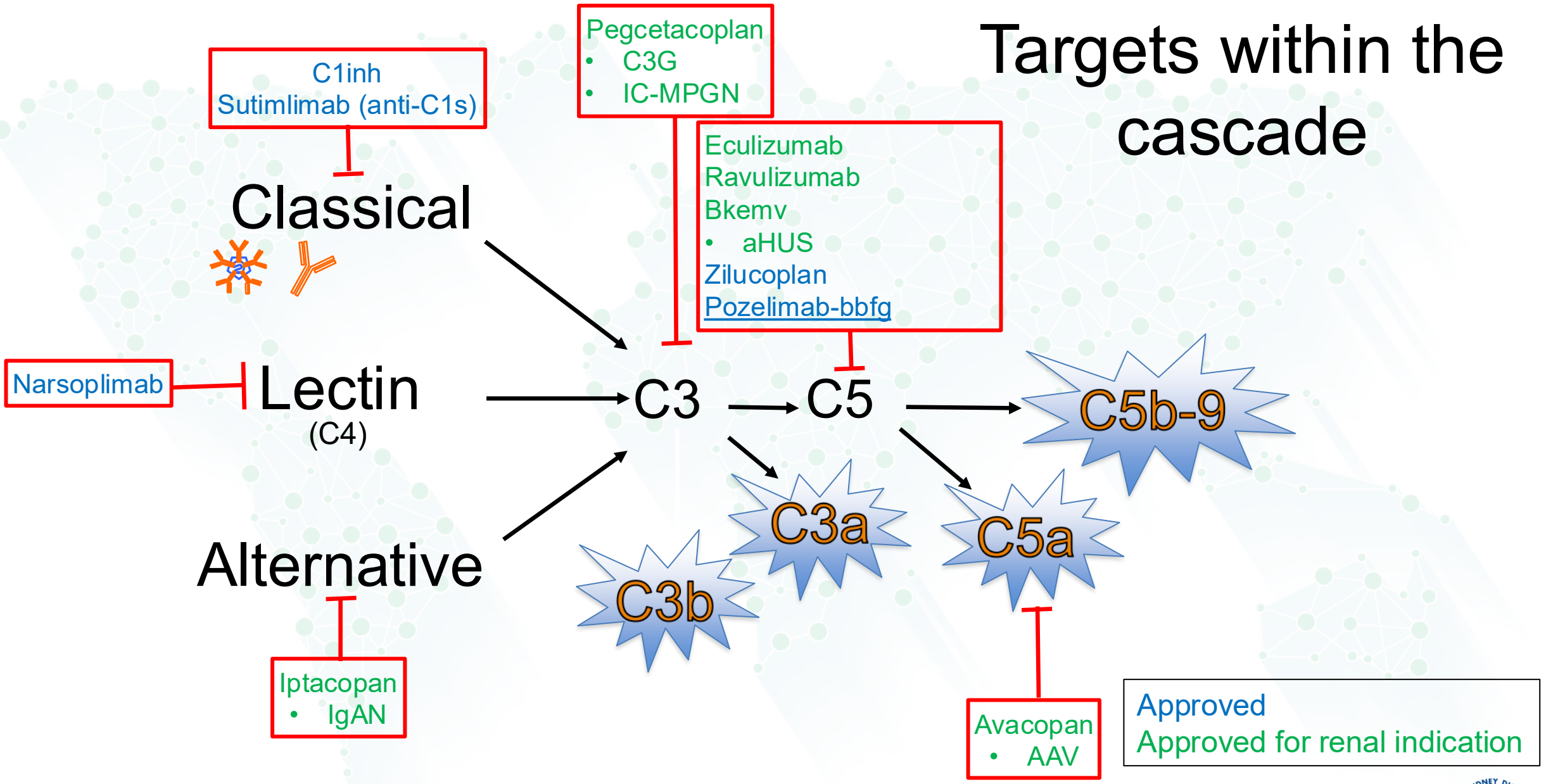
Variety in:

- Target
- Molecule
- Route of administration
- Stage of development



Zelek et al. *Mol Immunol,* 114: 341-352, 2019

Targets within the cascade



Modified from: Thurman and Le Quintrec, Kidney International, 2016.

Molecular types:

Molecular type	Example	Advantages	Disadvantages
Monoclonal antibody	Eculizumab	• Defined target • Duration weeks-months • Safe (many mAbs in use)	• Intravenous • Abundance of complement proteins • Cost
Small molecule	Avacopan	• Can be administered orally • Cost	• Hepatotoxicity • Cost • Daily administration
Recombinant proteins	Conestat alfa (C1est inhib) ADX-097	• Can leverage naturally occurring complement inhibitors • Targeted therapy • Duration days/weeks	• Intravenous/SQ • Cost
siRNA	Cemdisiran	• SQ • Duration weeks/months	• Long duration limits reversibility • Incomplete reduction

Established renal indications:

Disease	Drug	Target	Type (administration)
Atypical haemolytic syndrome (aHUS)	Eculizumab[1] Ravulizumab[1] Bkemv	C5 C5 C5	Monoclonal antibody (IV) Monoclonal antibody (IV) Monoclonal antibody (IV)
C3 glomerulopathy (C3G)	Iptacopan Pegcetacopoan	Factor B C3	Small-molecule (PO) Pegylated peptide (SQ)
Anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis	Avacopan	C5aR	Small-molecule (PO)
IgA Nephropathy (IgAN)	Iptacopan	Factor B	Small-molecule (PO)
Immune-complex membranoproliferative glomerulonephritis (IC-MPGN)	Pegcetacoplan	C3	Pegylated peptide (SQ) Small-molecule (PO) Monoclonal antibody (IV)

Keeping it simple

Use an approved drug according to the recommendations

1. Diagnosis
2. Recommended prophylaxis
3. Treat

A “personalized medicine” approach to complement inhibition

	Factor	Low	Medium	High
Risks	Age	18-60	< 18	> 60
	In			cted
	In			ted
Benefits				
	Ta			ysiology
	G			ssive
	O			ments
				available

Pragmatic considerations:

- Cost, availability
- Irreversible damage (do no harm) vs. the need to try something
- If treatment is stopped, can the patient tolerate another flare?
- Is there reason to think that the other therapies will eventually reduce complement activation?

Am J Kidney Dis. 2022;79(4):570-81.

aHUS - challenges

All complement-mediated TMA should be treated with a complement inhibitor

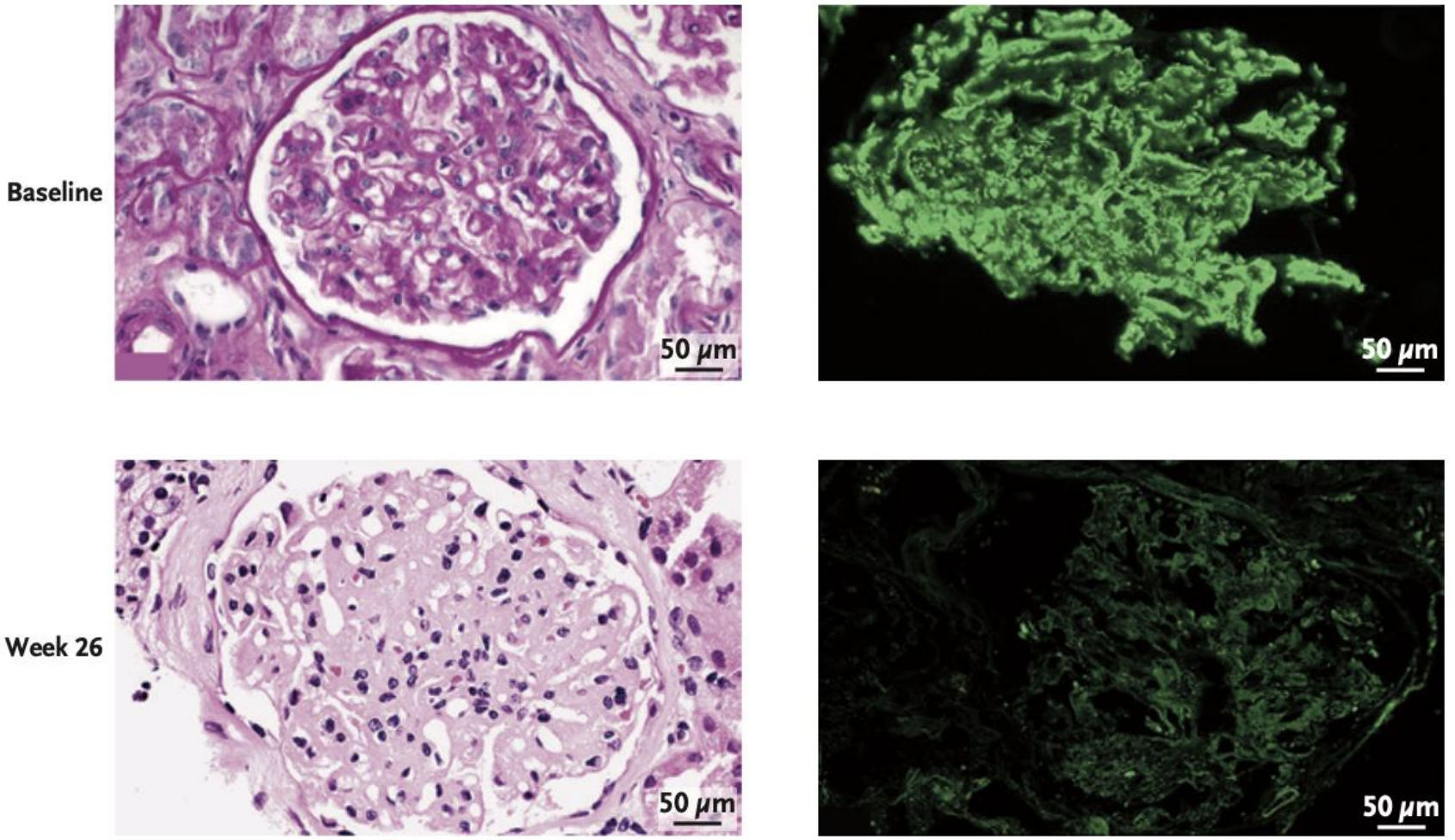
But…

- How make a rapid diagnosis?
  - Distinction of “triggers” versus other ”secondary TMA”
- How long to continue?
  - Any role for reduced dose?
- Infectious prophylaxis
  - Stop complement inhibition during infection
- Overlap diseases (aHUS and C3G)

Conversano and Vivarelli
J Clin Med 2025 Vol. 14 Issue 12

C3G/IC-MPGN - challenges

C3G/IC-MPGN should be treated with iptacopan or pegcetacoplan



Fakhouri et al. N Engl J Med 2025 Vol. 393 Issue 22 Pages 2210-2220

C3G/IC-MPGN - challenges

C3G/IC-MPGN should be treated with iptacopan or pegcetacoplan

But…

- Infectious prophylaxis
- Pregnancy
- How long to continue?

AAV - challenges

It is great to have an alternative to glucocorticoids

Is it possible that C5a blockade can replace steroids in other kidney diseases?

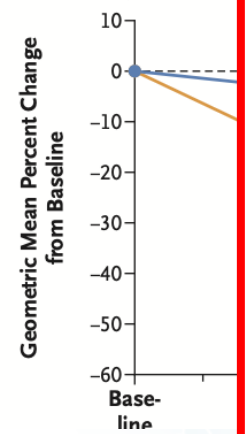
But…

- Steroid sparing effect has not been tested/shown in other diseases
- The FDA requested voluntarily withdrawal of avacopan from the U.S. market, citing concerns over the re-adjudication process of clinical trial data for nine patients and potential hepatotoxicity risks.

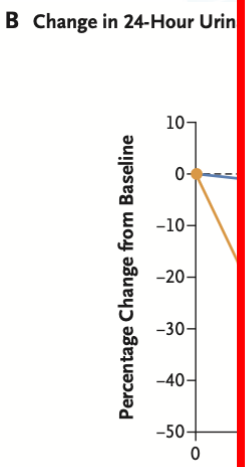
IgAN - challenges

Acceptance of proteinuria as an endpoint in clinical trials has facilitated approval of new drugs.

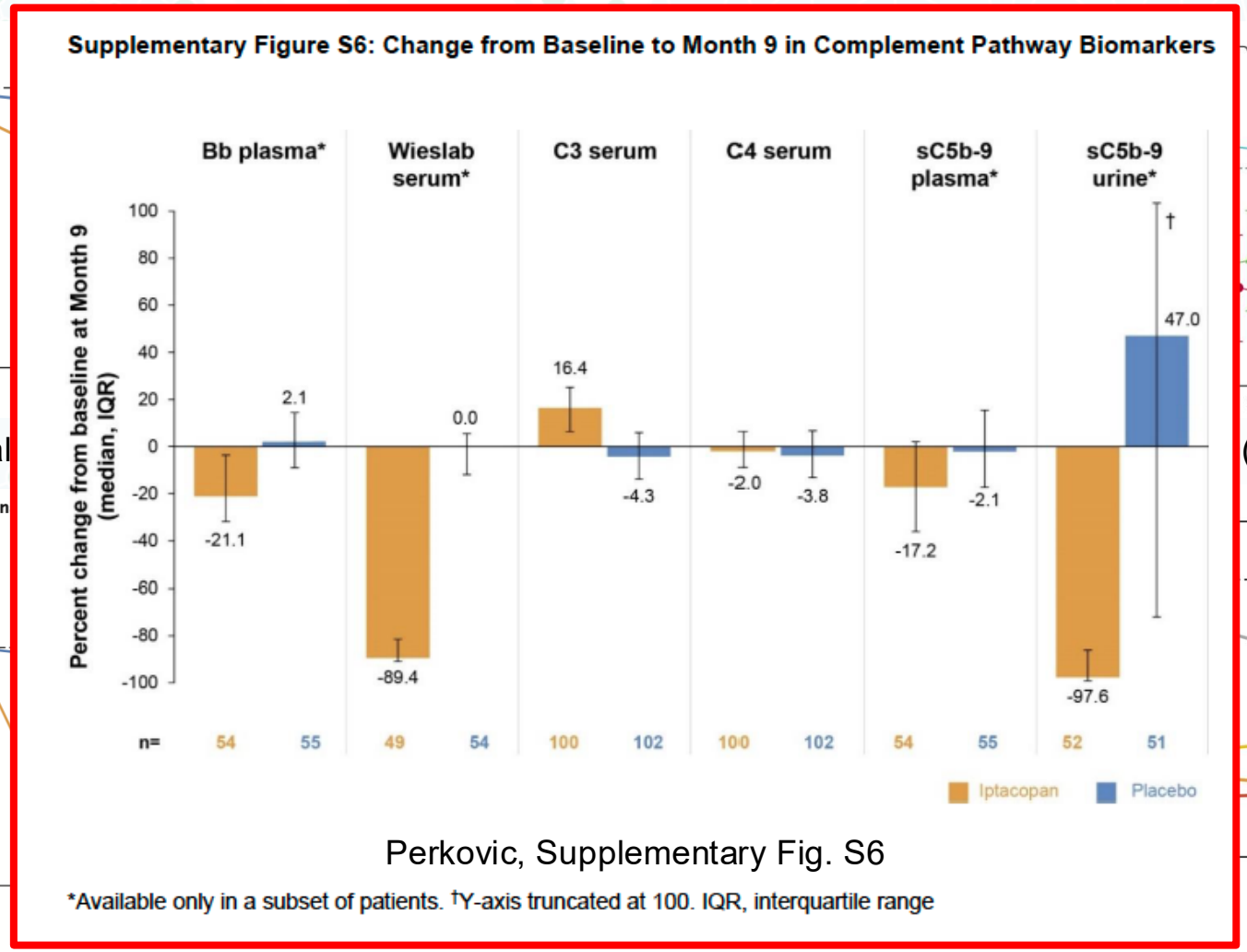
Iptacopan



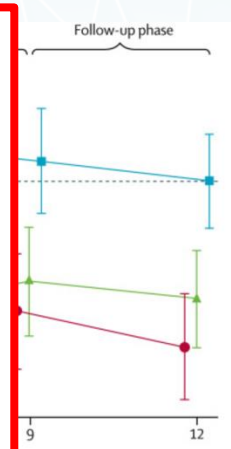
Perkovic et al



Atrasentan

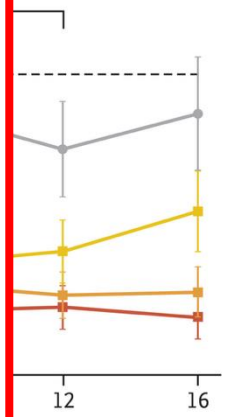


Perkovic, Supplementary Fig. S6



Budesonide

(10084): 2117-2127



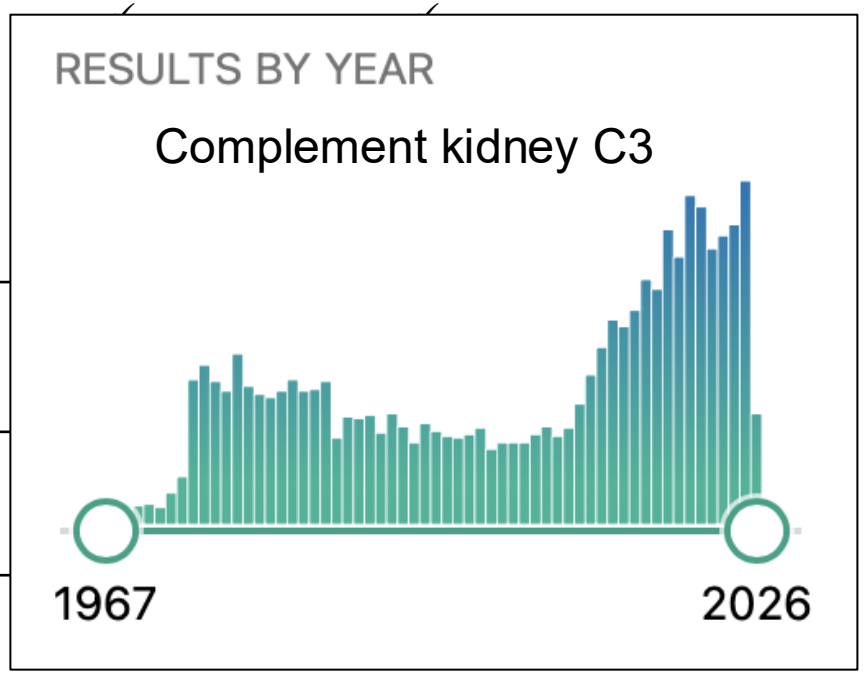
Sibeprenlimab

Heerspink et al. N Engl J Med. 2025;392(6):544-54.

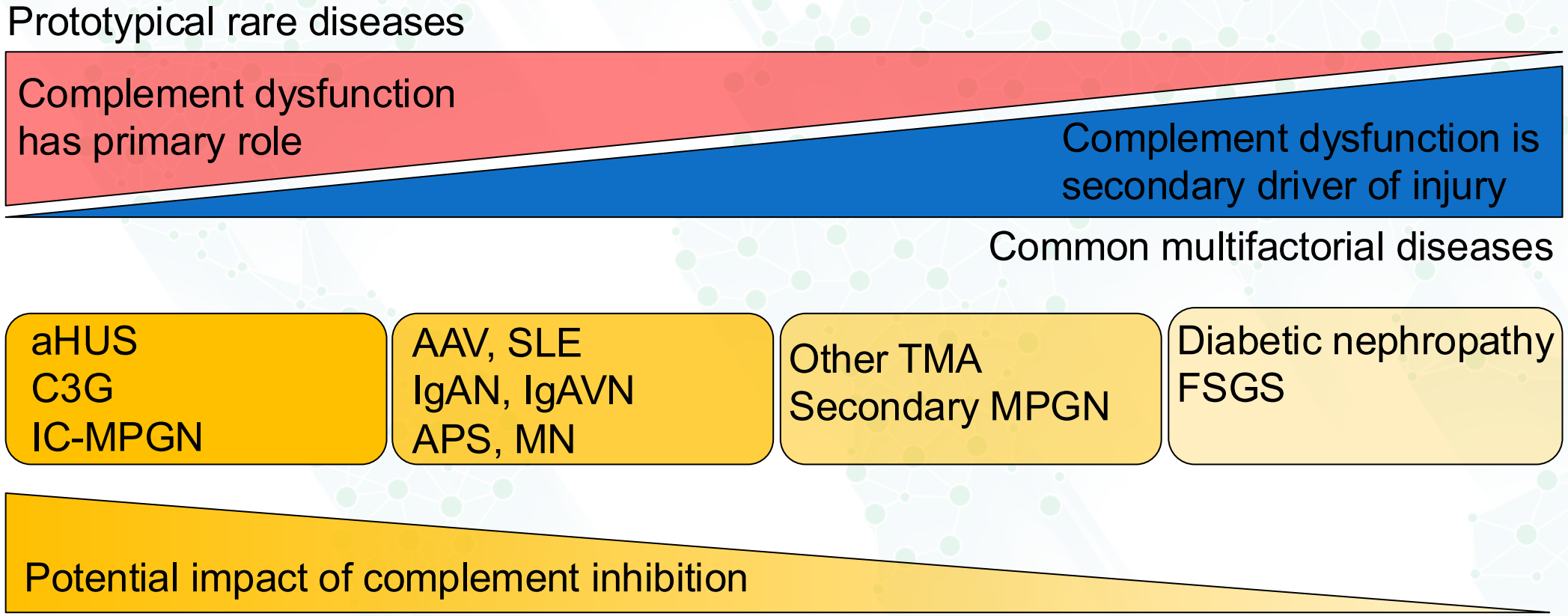
Mathur et al. N Engl J Med 2024 390(1): 20-31

COMPLEMENT IS INVOLVED IN ~~MANY~~ all? KIDNEY DISEASES

Syndrome	Disease	Systemic levels	Biopsy	Genetic association	Animal model	Response to treatment
Nephritic syndrome	Lupus nephritis	✓	✓	✓	✓	✓
	MPGN	✓	✓	✓		
	C3 Glomerulopathy	✓	✓	✓		
	IgA Nephropathy	✓	✓	✓		
	ANCA associated vasculitis	✓				
	Post-strep GN	✓	✓			
Nephrotic syndrome	Membranous GN		✓	✓		
	FSGS/glomerulosclerosis	?	✓	✓		
	Diabetic Nephropathy		✓			
Tubular injury	Ischemic AKI		✓			
	Tubular injury in proteinuric dz		✓			
Allograft rejection	Humoral		✓			
	Cellular					
TMA	Atypical HUS	✓	✓	✓	✓	✓
	TA-TMA	✓		✓		✓
	TTP					
	HELLP					

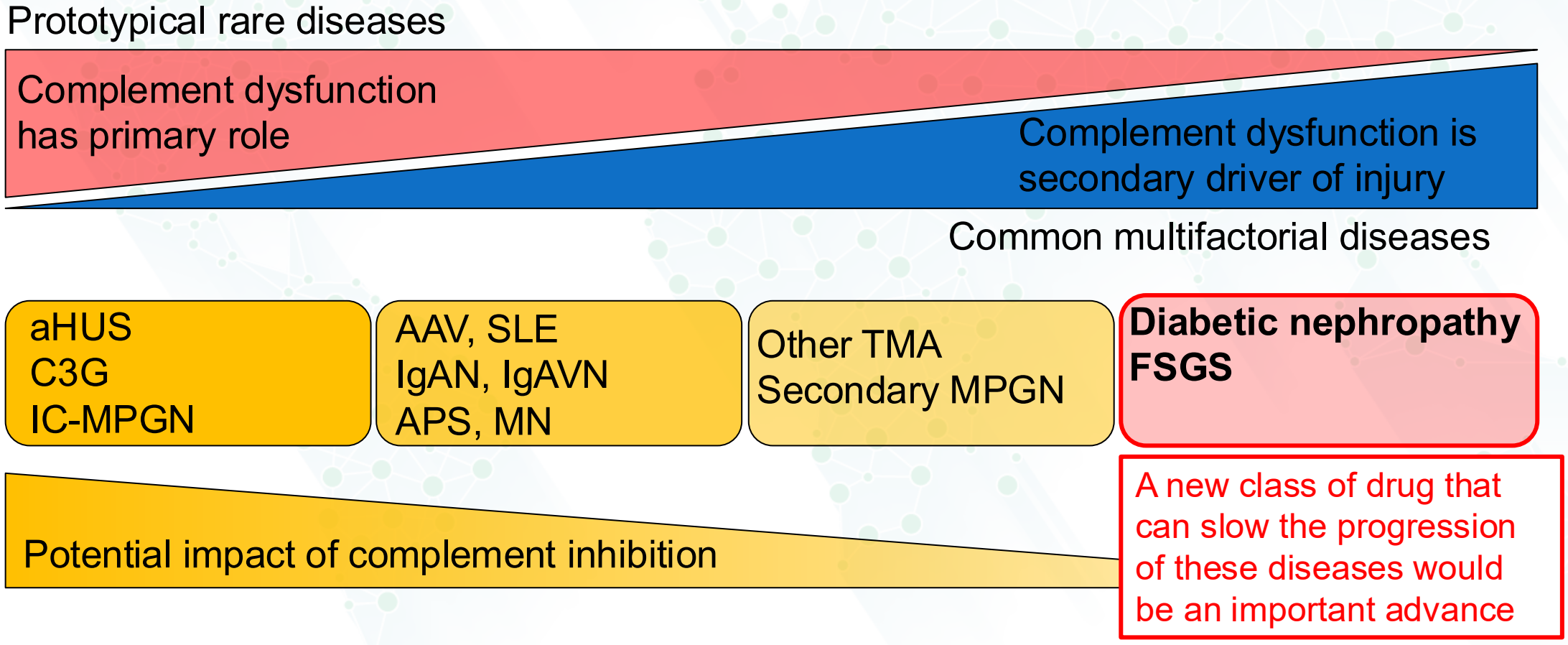


Risk/benefit



Vivarelli et al., Kidney Int 2024 Vol. 106 Issue 3 Pages 369-391

Risk/benefit



Vivarelli et al., Kidney Int 2024 Vol. 106 Issue 3 Pages 369-391

The risks of getting too fancy…

- A nephrologist in Colorado reaches out to one of my colleagues for help
- A patient with RPGN has a biopsy showing 3+ glomerular C3, and no IgM, IgG, IgA, C1q
- Colleague 1 recommends rituximab
- The original nephrologist is not satisfied and reaches out to another of my colleagues, and he shows me the biopsy report
- When I tell him that it fulfills criteria for C3G, he asks whether he should recommend eculizumab

The challenge:

- Complement is complicated. We will be lucky if busy physicians can figure out how to use even one anti-complement drug.

The opportunity:

- We can treat complement-mediated kidney diseases with precision.
  - Biomarkers
- The field of oncology has been successful at testing and adopting tailored therapies for rare diseases.
- THE IMPORTANCE OF MEETINGS SUCH AS THIS!

Thank you!