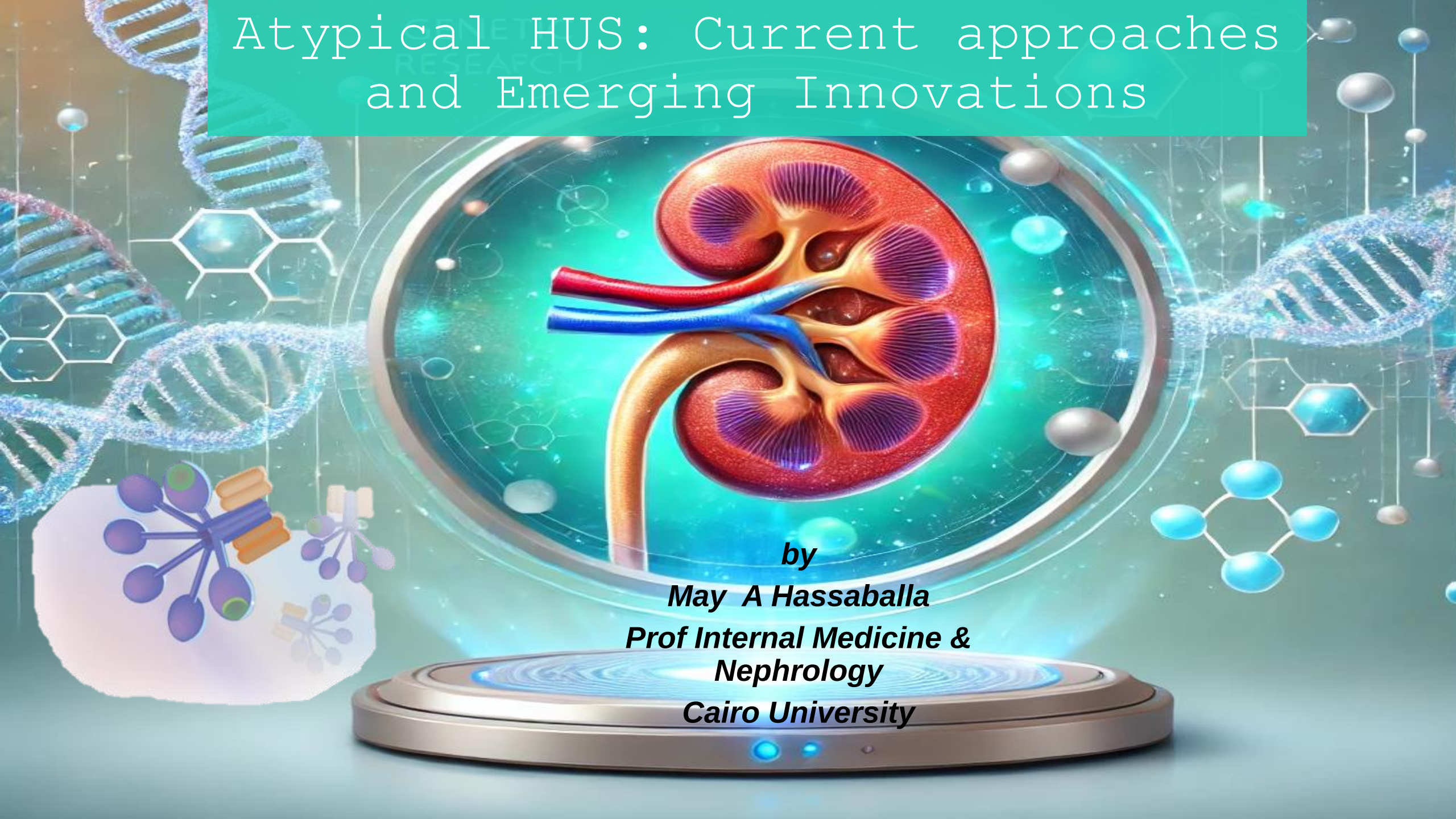
Atypical HUS: Current approaches and Emerging Innovations



by

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PROF. TAREK FAYAD

- Definition and pathogenesis
- Differential diagnosis
- Diagnostic workup and limitations
- Approach to treatment
- Importance of genetic testing
- Current Medications
- Emerging strategies
- conclusion

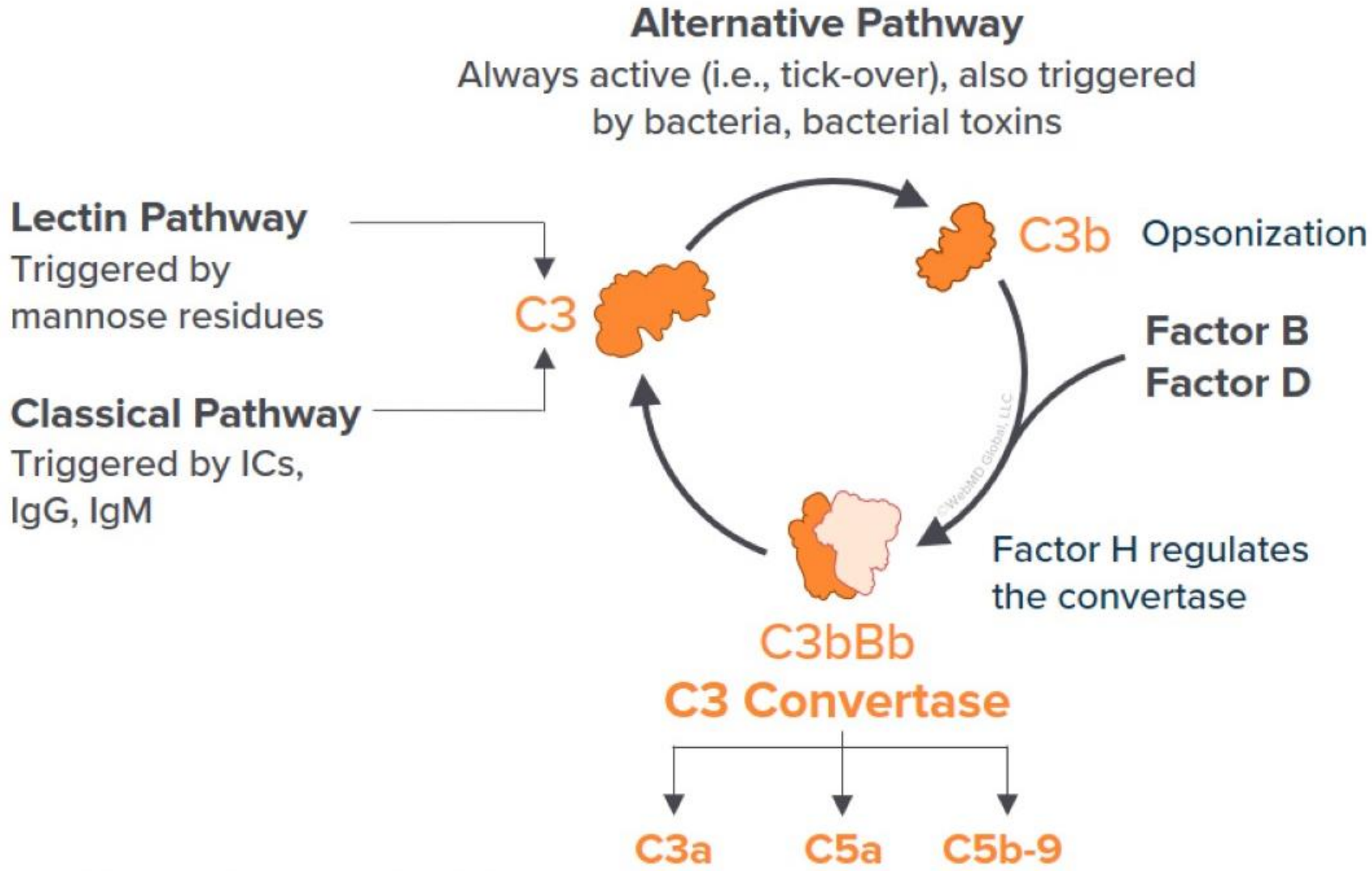
Atypical **H**aemolytic **U**raemic **S**yndrome (**aHUS**)

- **Rare** disease: 2-9 people/million
- **Complement mediated**
- **TMA**
- Untreated, it leads to **ESRD in up to 2 /3** affected shortly after onset or following relapses
- **Very high recurrence after Tx**

Atypical HUS Facts: 2024 www.atypicalHUSallianceaction.org

Shafer S, et al, Kidney Int: 94(2), 2018

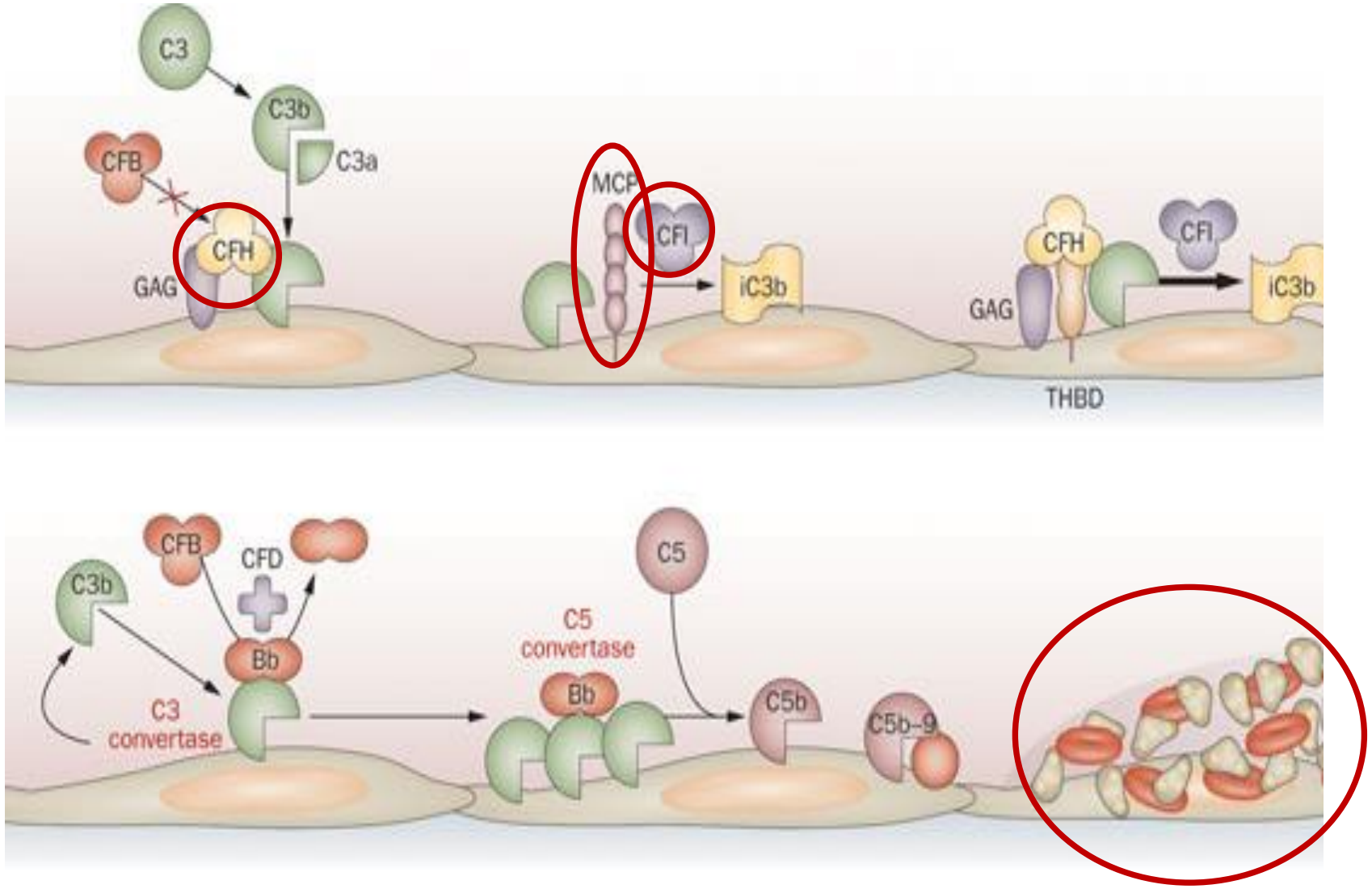
Diseases of Dysregulated Complement Activation



IC, immune complex; Ig, immunoglobulin; sMAC, soluble membrane attack complex.

Smith RJH, et al. Nat Rev Nephrol. 2019;15:129-143; Warwick CA, et al. J Biol Chem. 2021;297:101085.

Regulated and deregulated activation of the alternative complement pathway

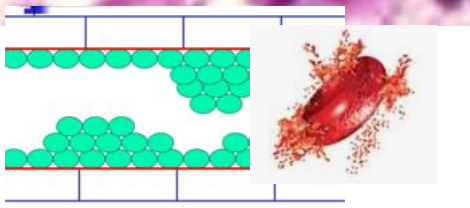


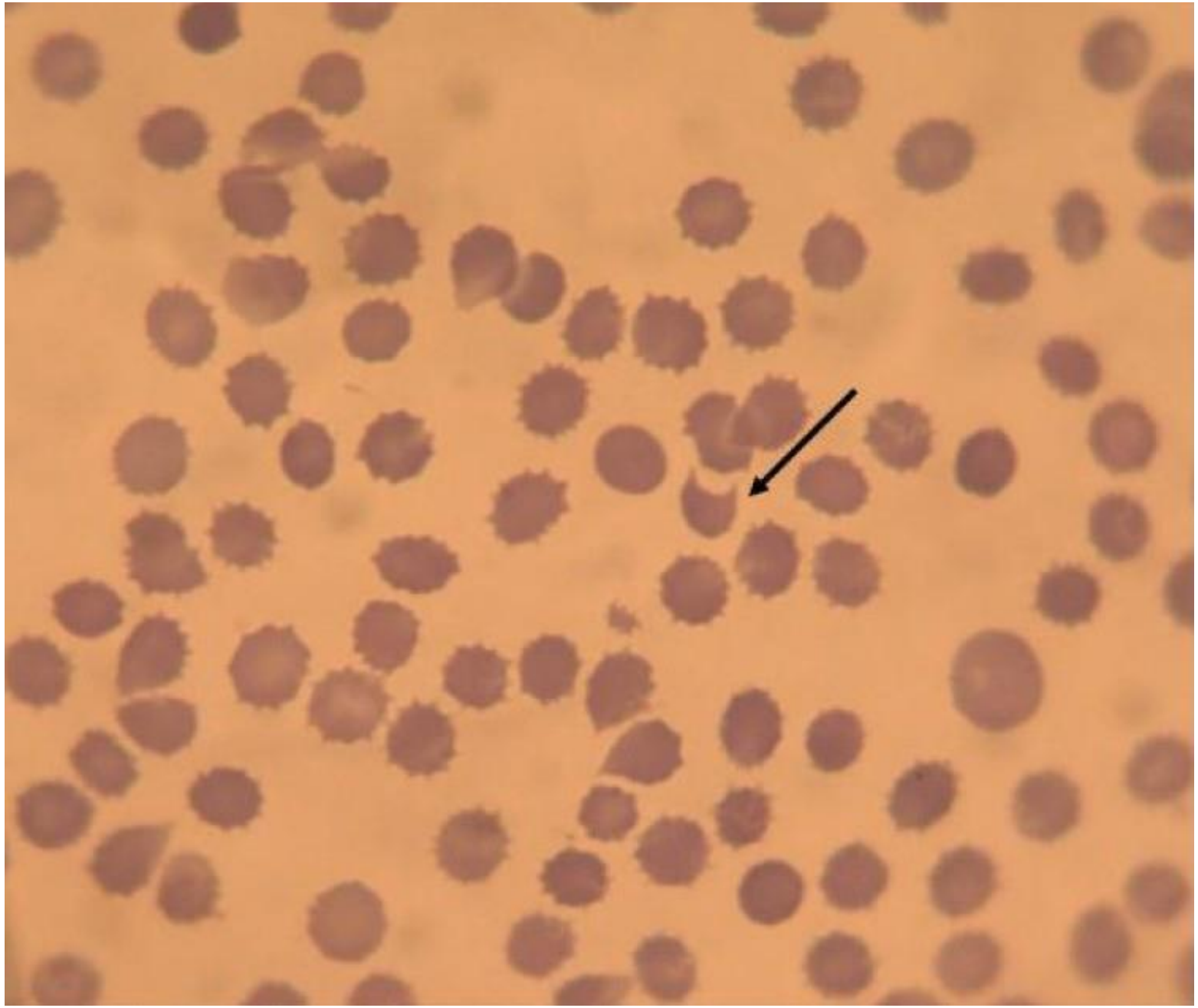
Zuber, J. *et al.* (2010) New insights into postrenal transplant hemolytic uremic syndrome
Nat. Rev. Nephrol. doi:10.1038/nrneph.2010.155

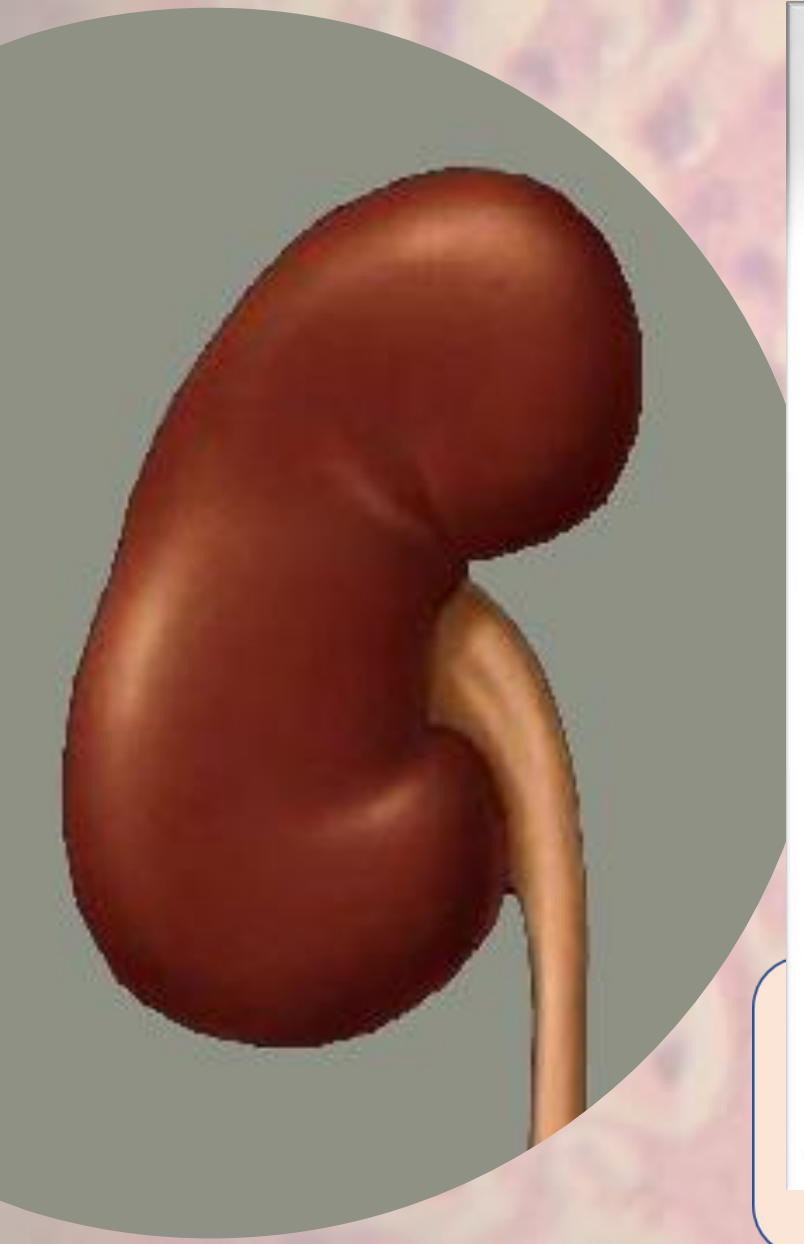
Thrombotic Microangiopathy: (TMA)

Thrombocytopenia

Microangiopathic Haemolytic Anaemia (MAHA)







Complement-Mediated TMA (aHUS) Can Affect Multiple Organs, Tissues

Renal
- Edema, malignant hypertension
- Elevated creatinine
- Decreased eGFR
- Proteinuria

CNS
- Confusion
- Stroke
- Encephalopathy
- Seizures

Blood
- Thrombocytopenia
- Decreased hemoglobin
- Elevated LDH
- Decreased haptoglobin
- Schistocytes

Cardiovascular
- Diffuse vasculopathy
- Hypertension
- Myocardial infarction
- Peripheral gangrene

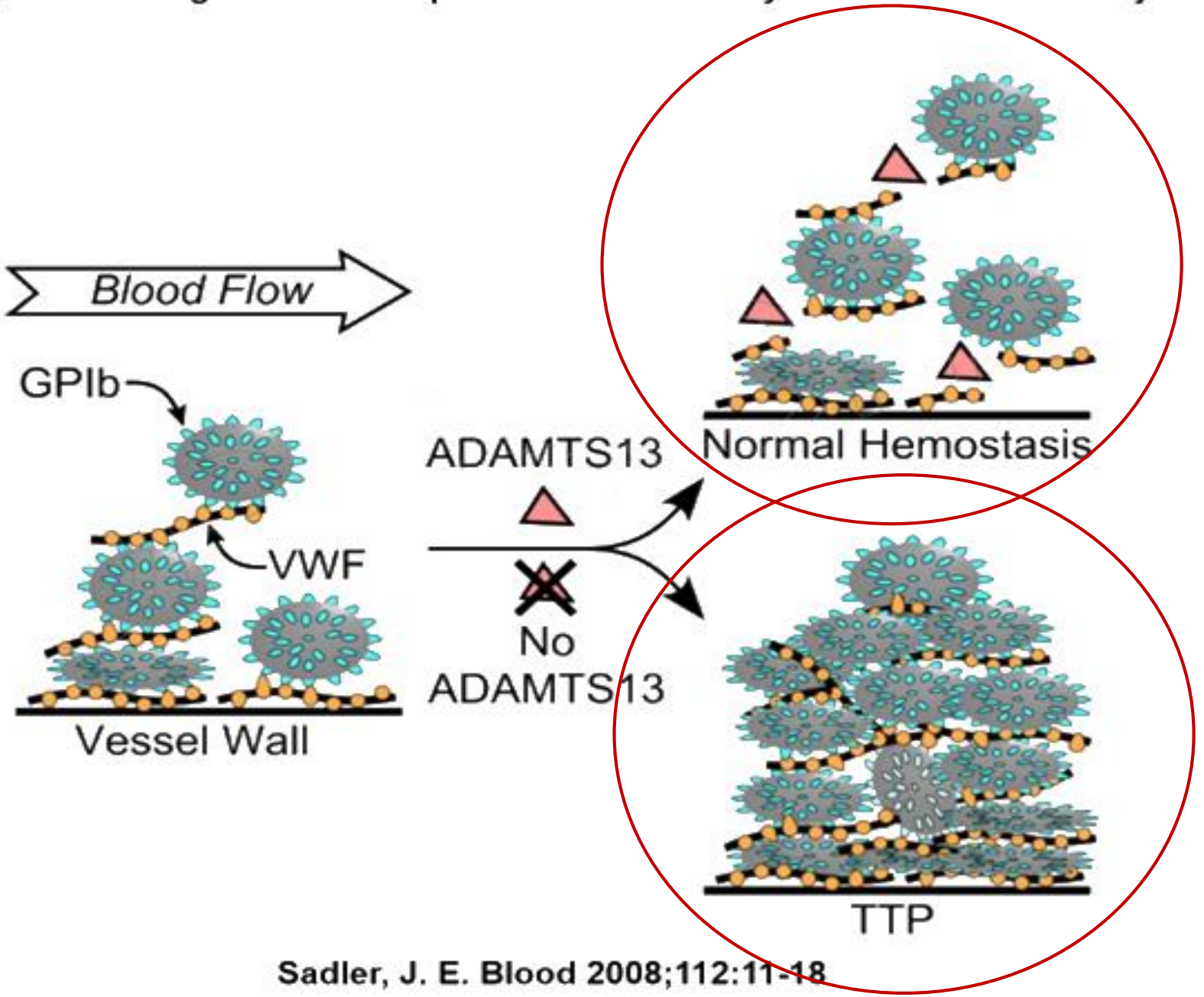
Gastrointestinal
- Abdominal pain
- Colitis
- Gastroenteritis
- Liver necrosis
- Nausea/vomiting
- Pancreatitis

Pulmonary
- Dyspnea
- Pulmonary edema
- Pulmonary hemorrhage

Neuhaus TJ, et al. *Arch Dis Child*. 1997;76:518-521[6]; Noris M, et al. *N Engl J Med*. 2009;361:1676-1687.[1]

TTP

Figure 2 Pathogenesis of idiopathic TTP caused by ADAMTS13 deficiency



Sadler, J. E. Blood 2008;112:11-18

a HUS

Lemaire et al., CJASN 16: 942–956, 2021

All renal TMAs

Infection-associated HUS
- Shiga toxin-associated HUS (STEC-HUS)
- Pneumococcus-associated HUS (P-HUS)

Atypical HUS (aHUS)

Complement-mediated aHUS
- Genetics (*CFH, C3, CFB, CFI, MCP, CFHRs*)
- Autoimmunity (anti-CFH)

Complement-independent aHUS
- Genetics (*DGKE, cblC, INF2*)

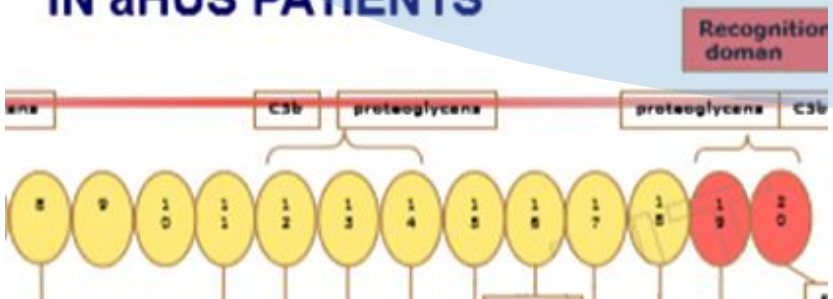
HUS with coexisting conditions
- Malignancy
- Bone marrow transplantation
- Medications (e.g., VEGF inhibitors)

Autoimmune disease
- Antiphospholipid syndrome
- Systemic lupus erythematosus
- Vasculitis
- Scleroderma
- Neoplasms
- Malignant hypertension
- Glomerulonephritis
- IBD

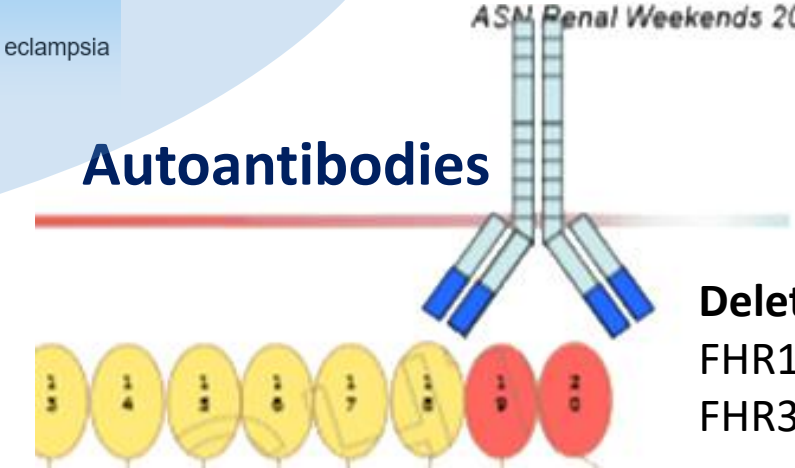
Pregnancy
- HELLP syndrome
- Preeclampsia and eclampsia
- Postpartum TMA

Idiopathic (unclear etiology)

CFH MUTATIONS IN aHUS PATIENTS



Autoantibodies



Deletions
FHR1
FHR3

Kidney International 106, 326–336, 2024

An expert discussion on the atypical hemolytic uremic syndrome nomenclature—identifying a road map to precision: a report of a National Kidney Foundation Working Group

Check for updates

OPEN

Carla M. Nester[1], David L. Feldman[2], Richard Burwick[3], Spero Cataland[4], Shruti Chaturvedi[5], H. Terence Cook[6], Adam Cuker[7], Bradley P. Dixon[8], Fadi Fakhouri[9], Sangeeta R. Hingorani[10], Anuja Java[11], Nicole C.A.J. van de Kar[12], David Kavanagh[13,14], Nelson Leung[15,16], Christoph Licht[17], Marina Noris[18], Michelle M. O'Shaughnessy[19], Samir V. Parikh[20], Flora Peyandi[21,22], Giuseppe Remuzzi[18], Richard J.H. Smith[1], C. John Sperati[23], Meryl Waldman[24], Patrick Walker[25] and Marina Vivarelli[26]

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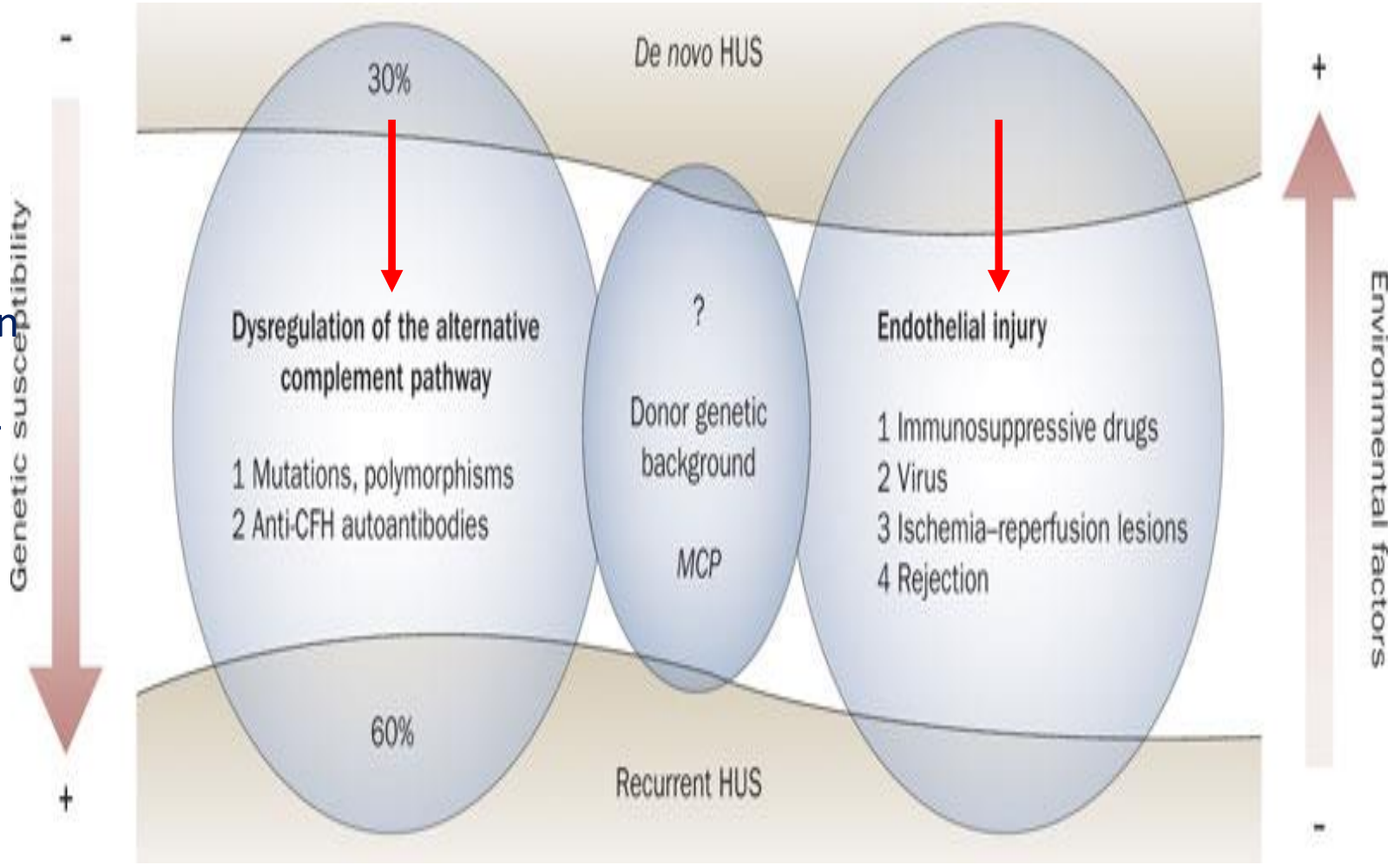
The term *atypical hemolytic uremic syndrome* has been in use since the mid-1970s. It was

Interrelation between **genetics** and **environmental** factors

Incomplete penetrance

- Additional genetic mutation
- Environmental triggering factor



Trigger aHUS

Self-perpetuating, progressive TMA

Transient activation of complement
Transient self limiting TMA

Direct endothelial damage

Zuber, J. *et al.* (2010) New insights into postrenal transplant hemolytic uremic syndrome *Nat. Rev. Nephrol.* doi:10.1038/nrneph.2010.155

Diagnostic Workup

- **Levels of complement factors**

  C3 (660–1,250 mg/l; nephelometry), C4, CH50

  CFH (338–682 mg/l; ELISA)

  CFI (42–78 mg/l; ELISA)

  CFB (90–320 mg/l; nephelometry)

- Testing can be unreliable.
- Complement pathways can be activated in other disorders.
- Levels are normal in most patients with aHUS.

- **MCP expression on peripheral blood leukocytes**

- **Autoantibody Screening**
- **Genotyping**

- 30% to 50% of patients with aHUS have no identified genetic mutation

- **Rule out TTP (ADAMTS13 activity)**
- **Rule out infection & other secondary causes:** PCR for Shigatoxin in the stools, Plasma homocystein, Tests for anti-dsDNA, anti-ENA, anti-β2 GPI, anticardiolipin antibodies, lupus anticoagulant, test for monoclonal gammopathy (> 50 years)

Dilemma in aHUS DIAGNOSIS[1]

Lack of a definitive biomarker for aHUS[2]

No single test can positively diagnose aHUS; complement gene variants are not detected in 40%-60% of patients with aHUS with currently available tests

Overlapping clinical features[3]

Clinical features of aHUS, such as thrombocytopenia and hemolytic anemia, are characteristic of other conditions as well

Underlying conditions that trigger aHUS[3]

aHUS may be triggered by underlying conditions with overlapping symptoms, which may mask aHUS and complicate diagnosis

Progressive onset[4]

Patients may have a progressive onset, with subclinical or fluctuating laboratory values and a gradual increase in SCr that can eventually result in CKD

A clinical diagnosis is required for aHUS, using diagnostic tests available for other causes of TMA[1,3]

aHUS is a diagnosis of exclusion and a condition that may lead to irreversible organ damage[1]

aHUS, atypical hemolytic uremic syndrome; **CKD**, chronic kidney disease; **SCr,** serum creatinine; **TMA,** thrombotic microangiopathy.

1. Campistol JM, et al. *Nefrologia*. 2015;35(5):421-447. **2.** Fakhouri F, Frémeaux-Bacchi V. *Nat Rev Nephrol*. 2021;17(8):543-553.
3. Laurence J, et al. *Clin Adv Hematol Oncol*. 2016;14(11)(suppl 11):2-15. **4.** Loirat C, Frémeaux-Bacchi V. *Orphanet J Rare Dis*. 2011;6:60. doi:10.1186/1750-1172-6-60

Fakhouri,et al., Blood, VOLUME 141, NUMBER 9, 2023

Approach to Treatment

MAHA, thrombocytopenia, organ dysfunction

Apparent Secondary Cause

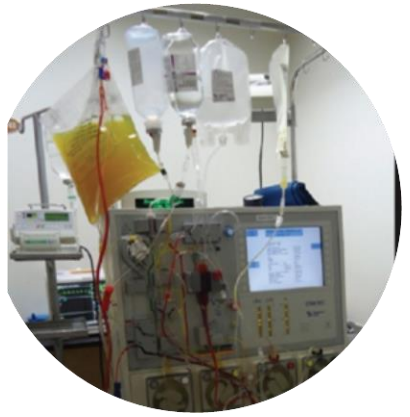
Unexplained

Treat the cause

If persistent

Plasma Exchange

Treat as primary while waiting for lab results



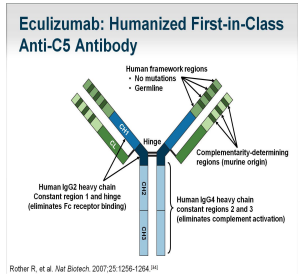
anti–factor H antibody–associated aHUS

Start Eculizumab (Urgency)

Family history of aHUS/Relapse
Severe oliguric AKI
postpartum AKI
PE dependent/Refractory hemolysis persists despite maximum doses of PE therapy

TTP
Plasma
Exchange

aHUS
Eculizumab



Complement Abnormalities

Complement abnormality	Frequency (%)	NO. of Tx pts	Recurrence (% of pts)	No. of grafts	Recurrence % of grafts	Graft failure
CFH mutations	20 - 30	42	76 (32/42)	51	71 (36/51)	86 (31/36)
CFI mutations	4 - 10	12	92 (11/12)	17	88 (15/17)	85 (11/13)
MCP mutations	10 - 15	10	20 (2/10)	12	17 (2/12)	1/2
CFH autoantibodies	6	5	20 (1/5)	9	22 (2/9)	2/2
C3 mutations	5 - 10	7	57 (4/7)	14	50 (7/14)	80 (4/5)
CFB mutations	1 - 2	3	3/3	3	3/3	2/3
THBD mutations	5	1	1/1	1	1/1	1/1

Noris & Remuzzi, Am J of Transplant, 10 : 1517, 2010

Variants Risk Stratification

- joint consensus of the American College of Medical Genetics (ACMG)
- Association of Molecular Pathology

  - Level 1: pathogenic
  - level 2: likely pathogenic
  - level 3: variants of uncertain clinical significance (VUS)
  - level 4: likely benign
  - level 5: benign.

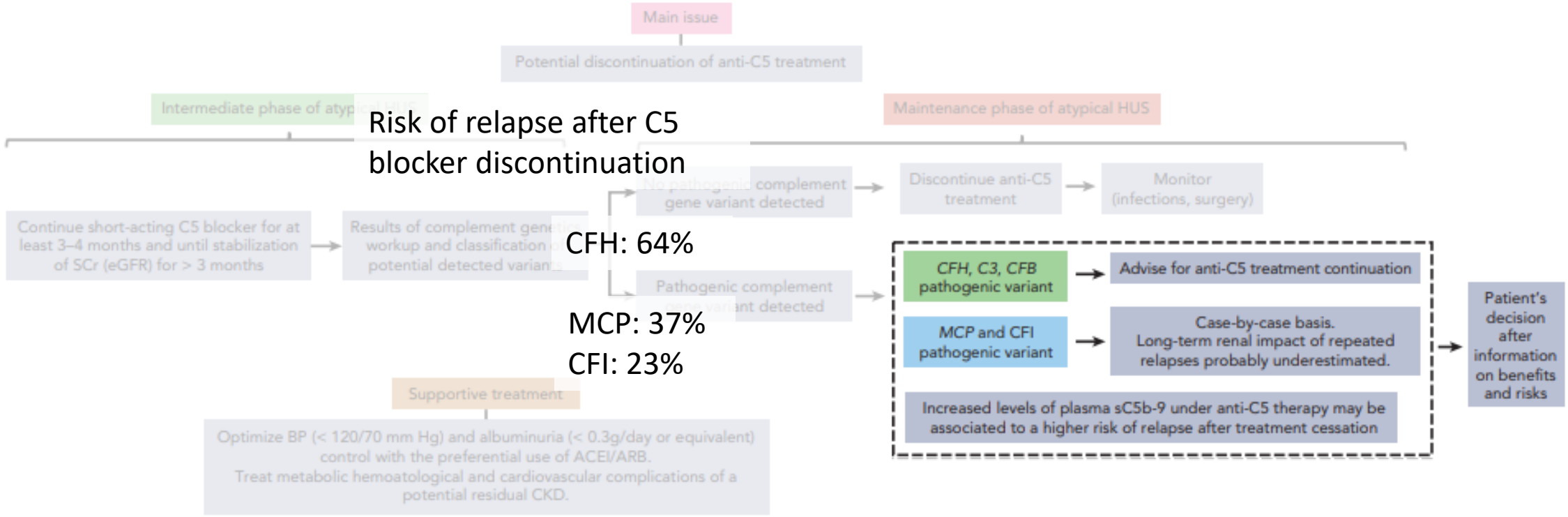
Richards et al. Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology. Genet Med. 2015;17(5):405-424.

Importance of Genetic Testing

- Predict progression to dialysis and recurrence after Tx
- Longterm management of aHUS & treatment discontiuation
- Directing prophylactic treatment before transplantation

Fakhouri,et al., Blood, VOLUME 141, NUMBER 9, 2023
Kidney International 106, 369–391, 2024

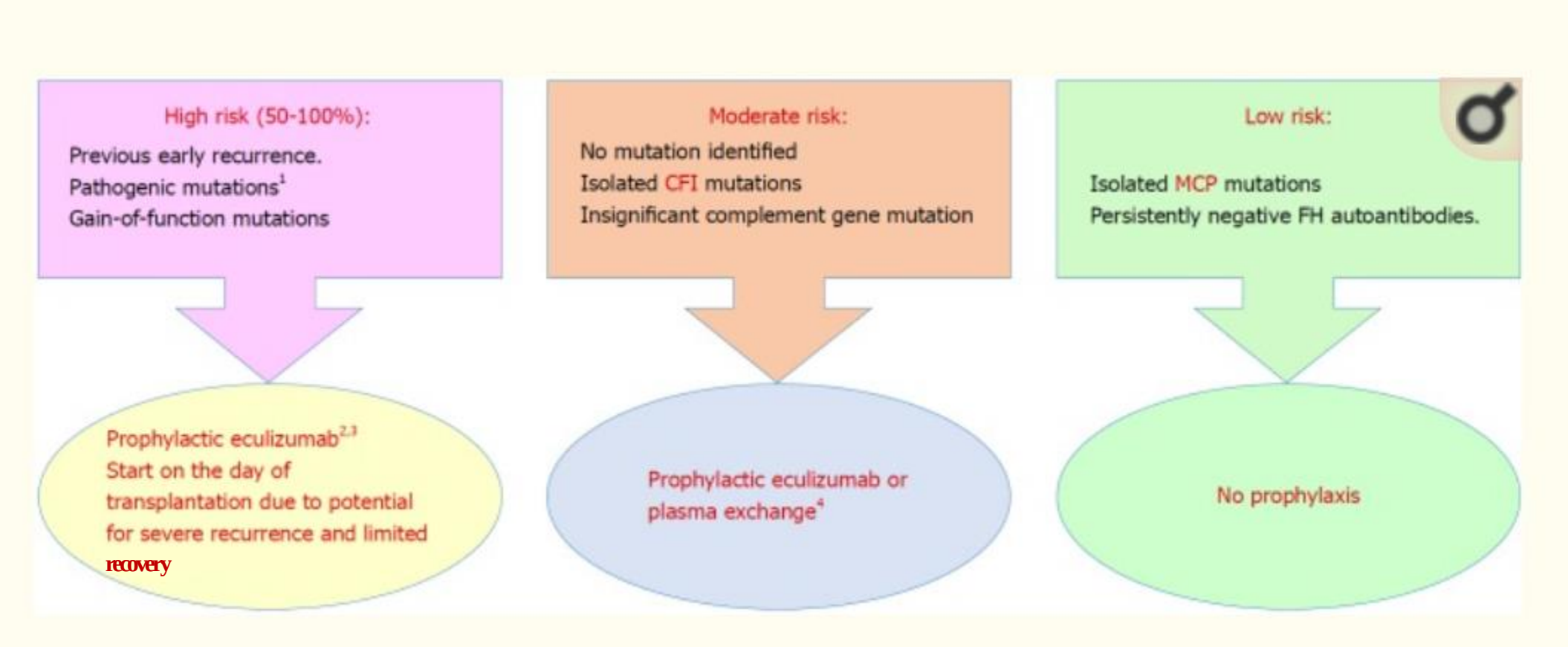
Discontiuation of Therapy



Patients with no detected pathogenic complement variants: the risk relapse <5%: safe to discontinue treatment

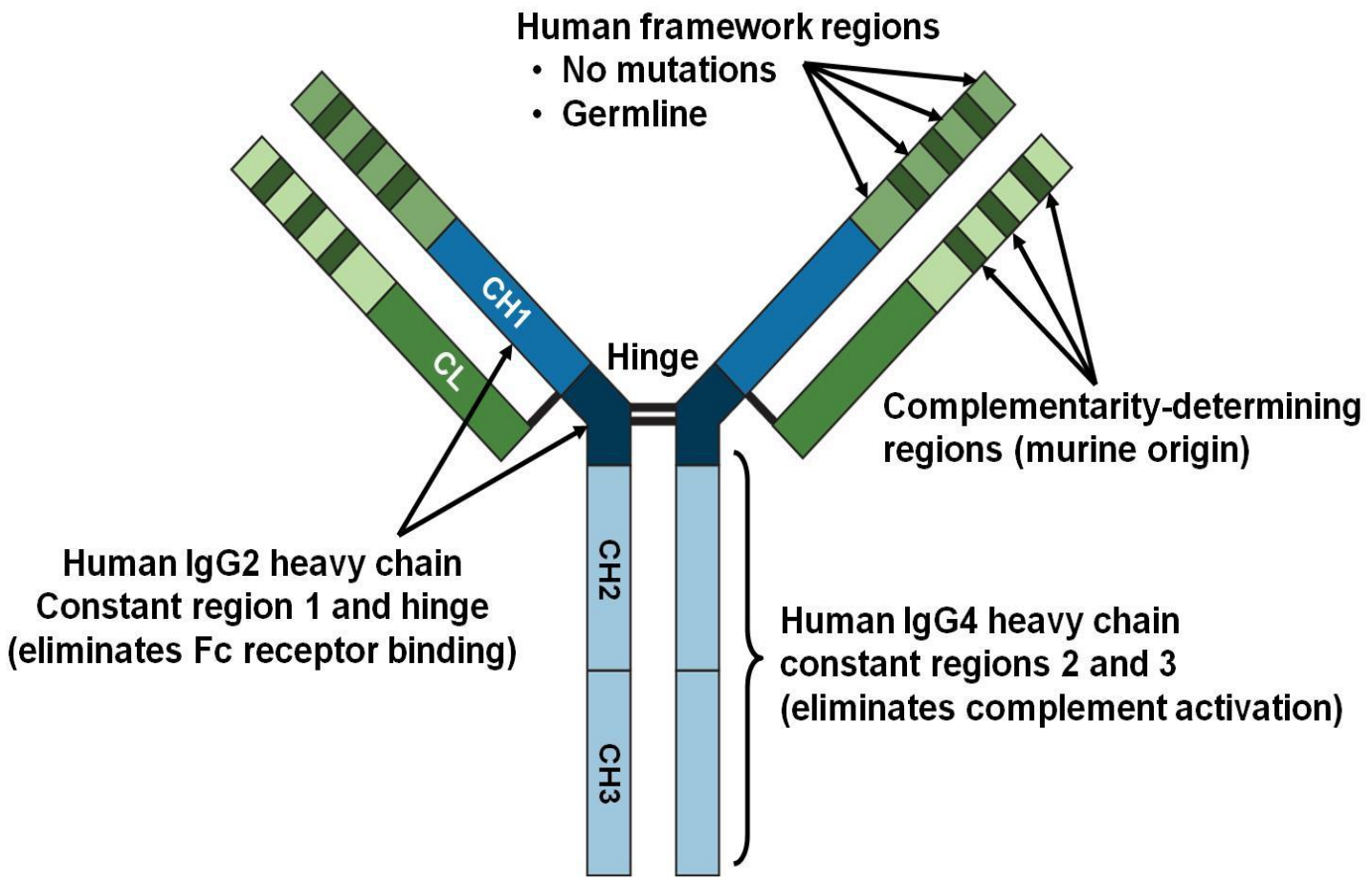
Extreme caution in stopping is warranted in patients with chronic kidney disease stages G3b–G5 and in kidney transplant recipients.

Atypical hemolytic uremic syndrome and C3 glomerulopathy: conclusions from a "Kidney Disease: Improving Global Outcomes" KDIGO) Controversies



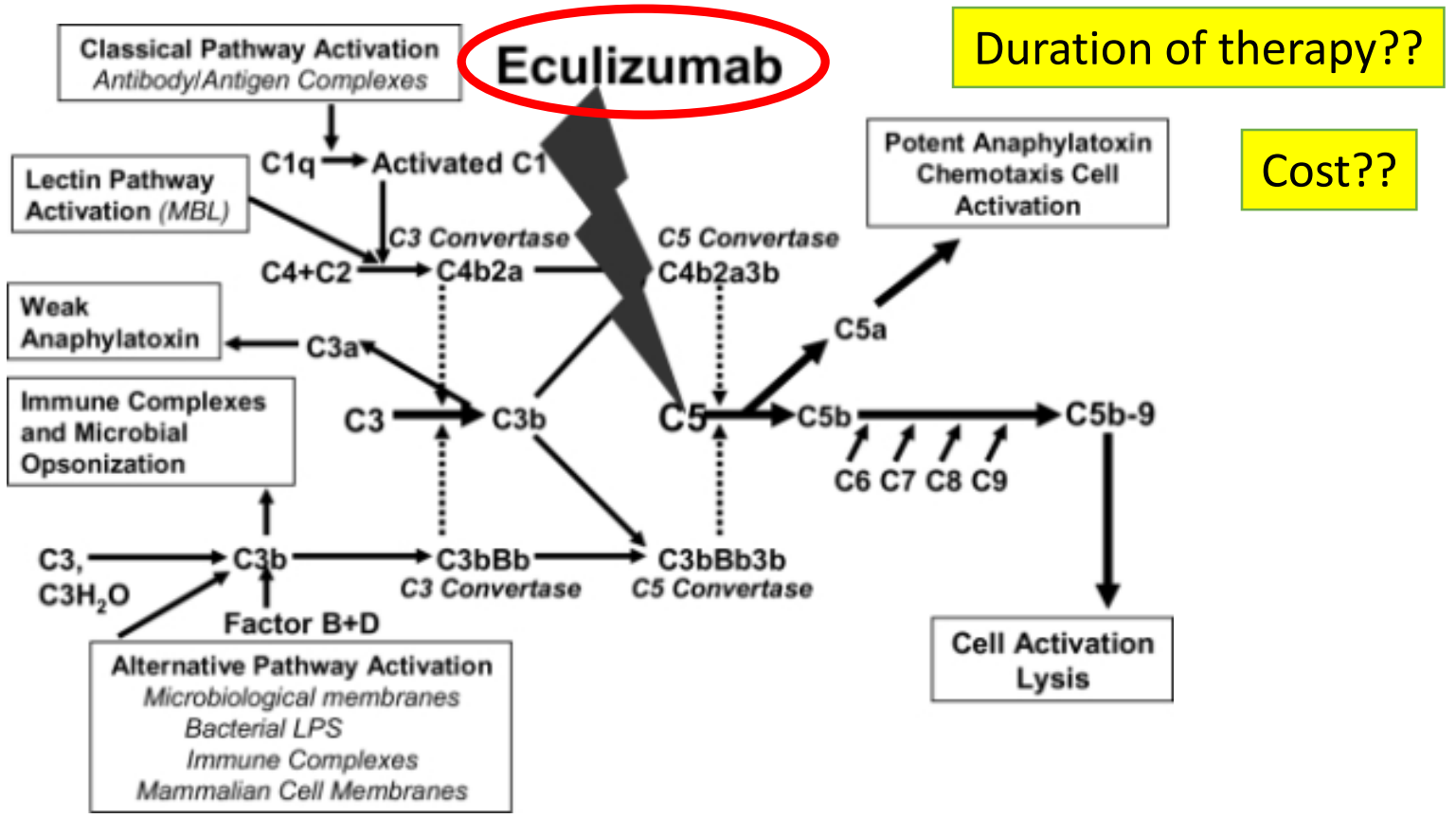
Kidney Int.; 91(3):539-551, 2017

Eculizumab: Humanized First-in-Class Anti-C5 Antibody



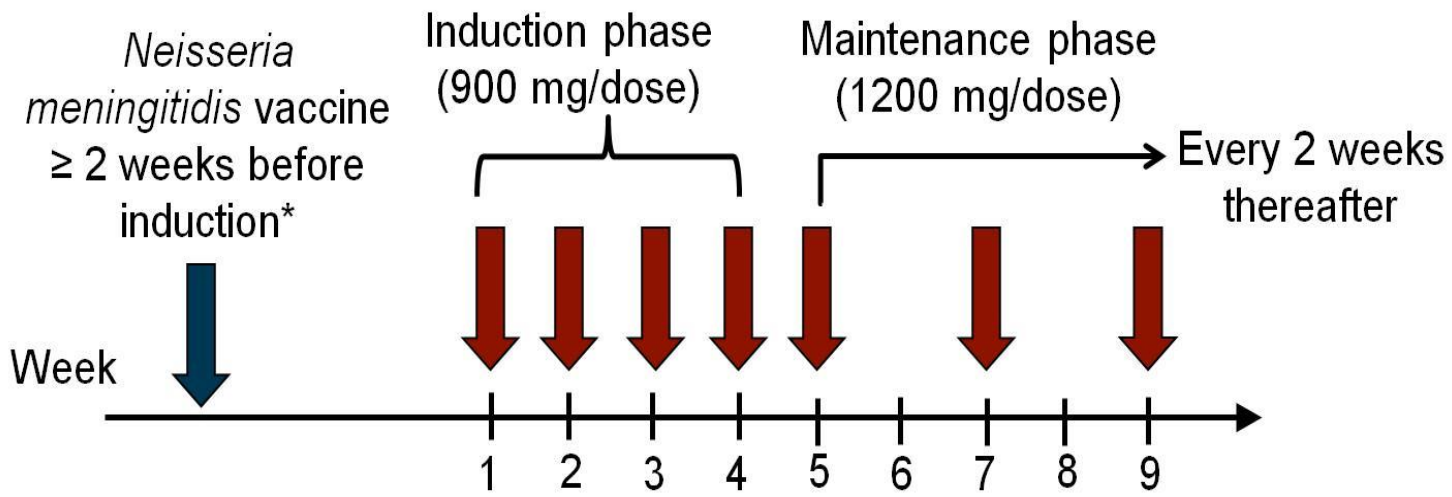
Rother R, et al. *Nat Biotech*. 2007;25:1256-1264.[34]

Atypical HUS Treatment



Licht C et al. J Am Soc Nephrol. 2011;22:197A.
Greenbaum LA et al. J Am Soc Nephrol. 2011;22:197A.

Eculizimab Dosing Schedule: Adults



- Administered via IV infusion over 35 minutes every 7 days during induction and every 14 days during maintenance
- Dose adjustment to every 12 days may be necessary.

*Patients not receiving vaccination at least 2 weeks before eculizumab received prophylactic antibiotics until 2 weeks after vaccination.

Legendre CM, et al. *N Engl J Med*. 2013;368:2169-2181[30]; Soliris® (eculizumab). PI. April 2014.[35]

Table 2. Comparison of eculizumab and ravulizumab in 3 prospective noncontrolled trials in adults with aHUS

	Eculizumab (n = 17) (Legendre et al)[5] n, (%)	Eculizumab (n = 41) (Fakhouri et al)[6] n, (%)	Ravulizumab (n = 58) (Rondeau et al)[46] n, (%)
Age, >65 y	Not available (range, 17-68)	2 (5)	8 (14.3) >60
≥1 variant in complement gene (or anti–factor H antibodies)	13 (76)	21 (51)	8 (20.5)
Dialysis requirement at inclusion	6 (35)	24 (59)	29 (51.8)
Patients requiring dialysis at last follow-up	1 (6)		
Death	0	0	4 (7)

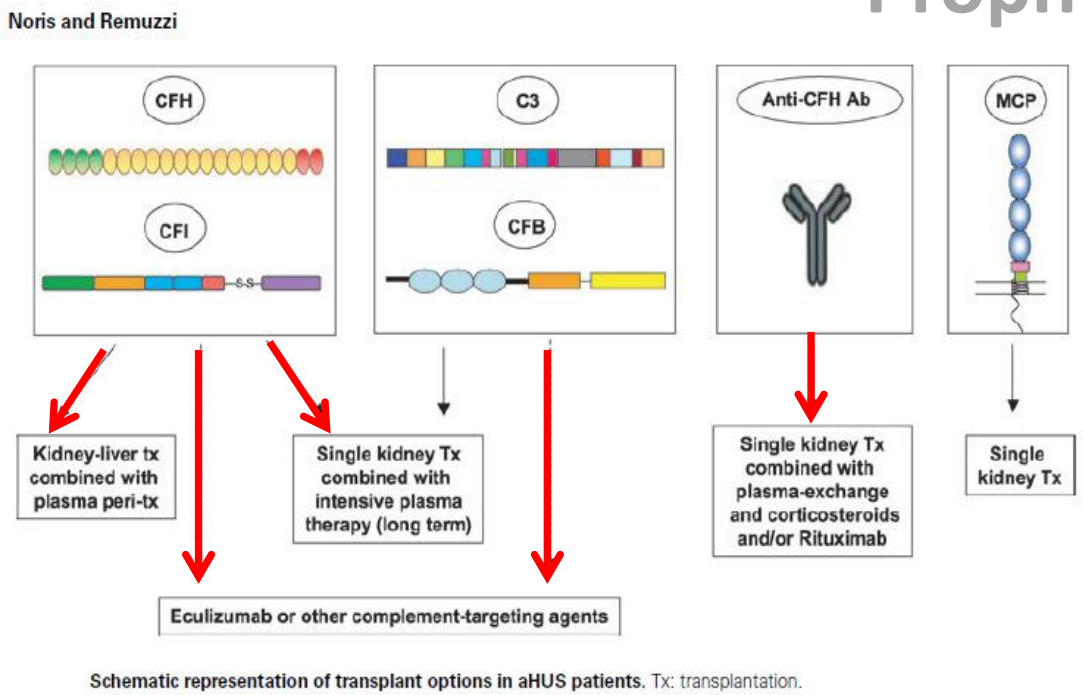
Advocated to use a short-acting C5 blocker during the initial acute phase of aHUS, owing to the remaining uncertainties regarding the diagnosis of aHUS and to extensive experience

Patients in whom C5 blockade discontinuation is not feasible or desired, a switch to a long-acting C5 blocker is an option to decrease the inconvenience of repeated infusions

In routine practice, only CH50 and eculizumab trough levels are used to assess the degree of terminal complement blockade for FU

Fakhouri,et al., Blood, VOLUME 141, NUMBER 9, 2023
Kidney International (2024) 106, 369–391

Prophylactic Treatment



Schematic representation of transplant options in aHUS patients. Tx: transplantation.

- **Eculizumab:** anti C5 Mab

The introduction of eculizumab, an anti-C5 monoclonal antibody, has favorably changed the outcomes and challenged the role of TPE

- **PE + IS with steroids &/or Rituximab**
  anti CFH autoantibodies

- **Living donation in combination with a protocol to reduce endothelial injury**
  Avoid ischemia-reperfusion injury, viral infection , consider Belatacept

- **Intensive Plasma Exchange**
  Mutations affecting Plasma complement proteins

- **Liver Kidney Transplant**
  CFH mutations

Noris & Remuzzi, Am J of Transplant, 10 : 1517, 2010
Kidney International, 106, 369–391, 2024

What's New in aHUS Research – June 2024

Biomarkers to diagnose and monitor complement-Mediated forms of TMA

Newly developed assays such as ex vivo cell-based tests

- Modifies Ham: (mHam)
- Human dermal microvascular endothelial cells-1 assay: HMEC-1, staining for C5b-9
- Complement biosensor (Autonomously bioluminescent HEK293)
  - Regardless of AP dysregulation, there is a **CP stimulus** in CM-HUS, explaining the mystery of why 40% of CM-HUS lack complement specific variants or autoantibodies, and suggests a breakdown in IgM immunologic tolerance as a key driver of CM-HUS
- **All tests , require further validation before implementation in the clinic.**

bioRxiv preprint doi: https://doi.org/10.1101/2024.05.29.596475;

The role of complement in kidney disease: conclusions from a Kidney Disease: Improving Global Outcomes (KDIGO) Controversies Conference

OPEN

Marina Vivarelli[1], Jonathan Barratt[2], Laurence H. Beck Jr[3], Fadi Fakhouri[4,5], Daniel P. Gale[6], Elena Goicoechea de Jorge[7,8], Marta Mosca[9], Marina Noris[10], Matthew C. Pickering[11], Katalin Susztak[12], Joshua M. Thurman[13], Michael Cheung[14], Jennifer M. King[14], Michel Jadoul[15], Wolfgang C. Winkelmayer[16] and Richard J.H. Smith[17,18,19]; for Conference Participants[20]

[1]Laboratory of Nephrology, Bambino Gesù Children's Hospital, IRCCS, Rome, Italy; [2]Department of Cardiovascular Sciences, University of Leicester, Leicester, UK; [3]Section of Nephrology, Department of Medicine, Boston University Chobanian & Avedisian School of Medicine and Boston Medical Center, Boston, Massachusetts, USA; [4]Department of Nephrology, Centre Hospitalier Universitaire, Nantes, France; [5]INSERM UMR S1064, Nantes, France; [6]Centre for Kidney and Bladder Health, University College London, UK; [7]Department of Immunology, Ophthalmology and ORL, Complutense University, Madrid, Spain; [8]Area of Chronic Diseases and Transplantation, Research Institute Hospital 12 de Octubre (imas12), Madrid, Spain; [9]Department of Clinical and Experimental Medicine-Rheumatology Unit, University of Pisa, Pisa, Italy; [10]Clinical Research Center for Rare Diseases Aldo e Cele Daccò, Istituto di Ricerche Farmacologiche Mario Negri IRCCS, Ranica, Italy; [11]Centre for Inflammatory Disease, Department of Immunology and Inflammation, Imperial College,

Kidney International 106, 369–391, 2024

Emerging

Various C5 inhibitors are available or in development, including antibodies, small, interfering RNA, and short- and long-acting drugs with multiple modes of administration.

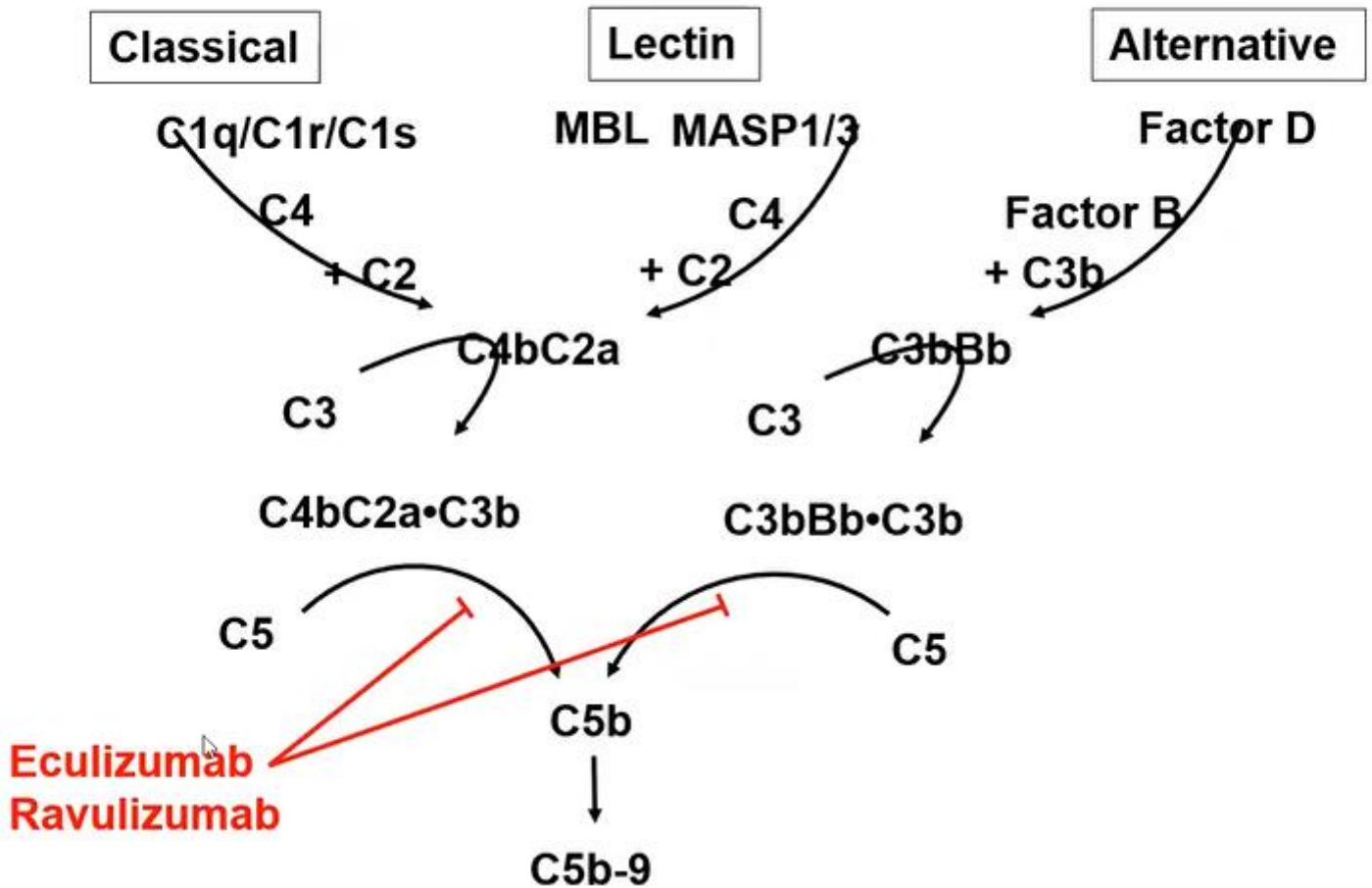
Targeting the **C3 convertase**

C3/FB/factor D inhibition is a potential alternative

. Selective **C5a** or C5a receptor blockade is a potential approach that carries the advantage **of preserving C5b-dependent killing of encapsulated pathogens**. However, in an animal model, genetic C5a receptor invalidation did not prevent aHUS

Kidney International 106, 369–391, 2024

What is on the horizon for aHUS treatment?



Dixon B, Webinar, Rare Disease, 2022

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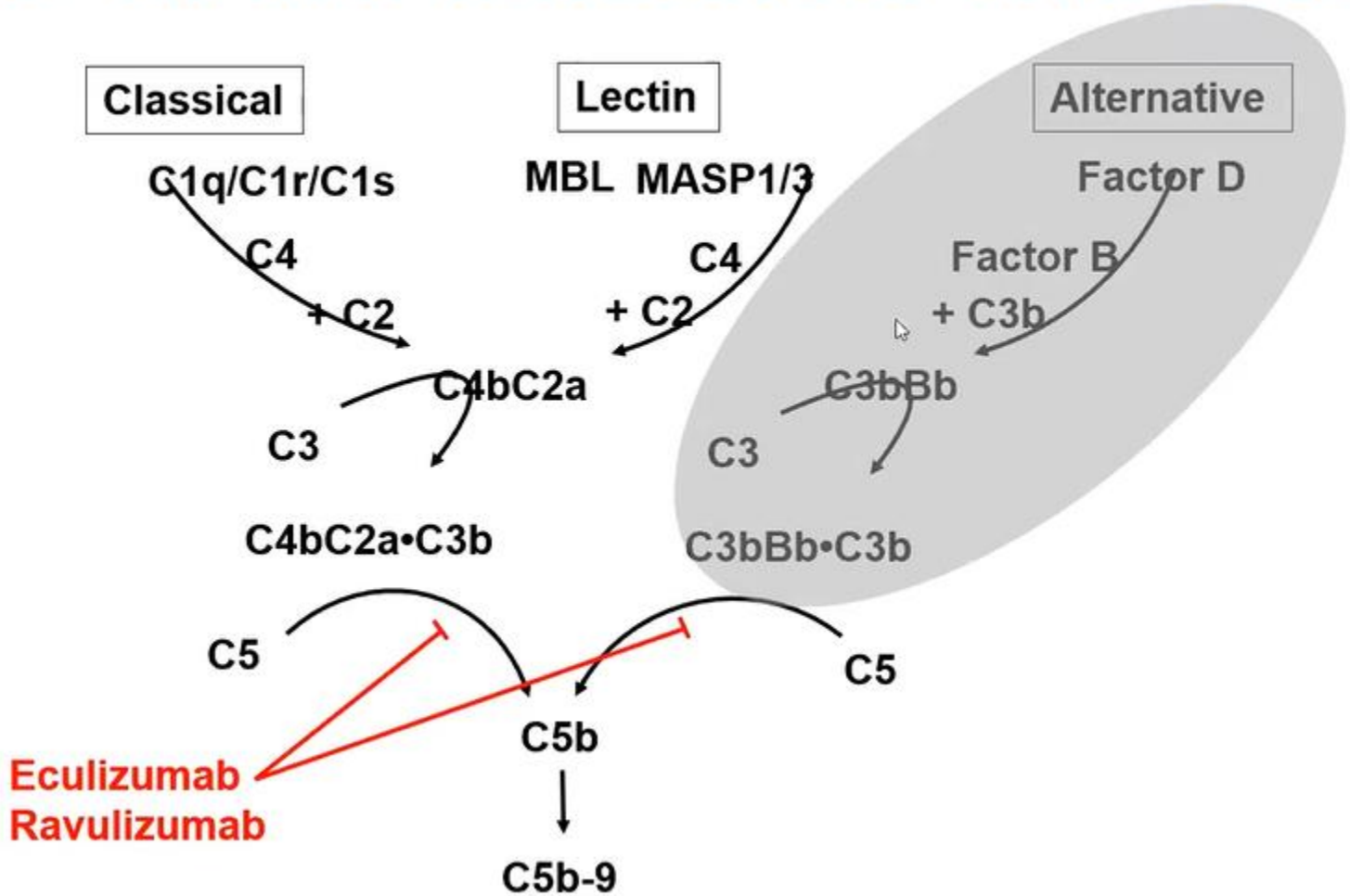

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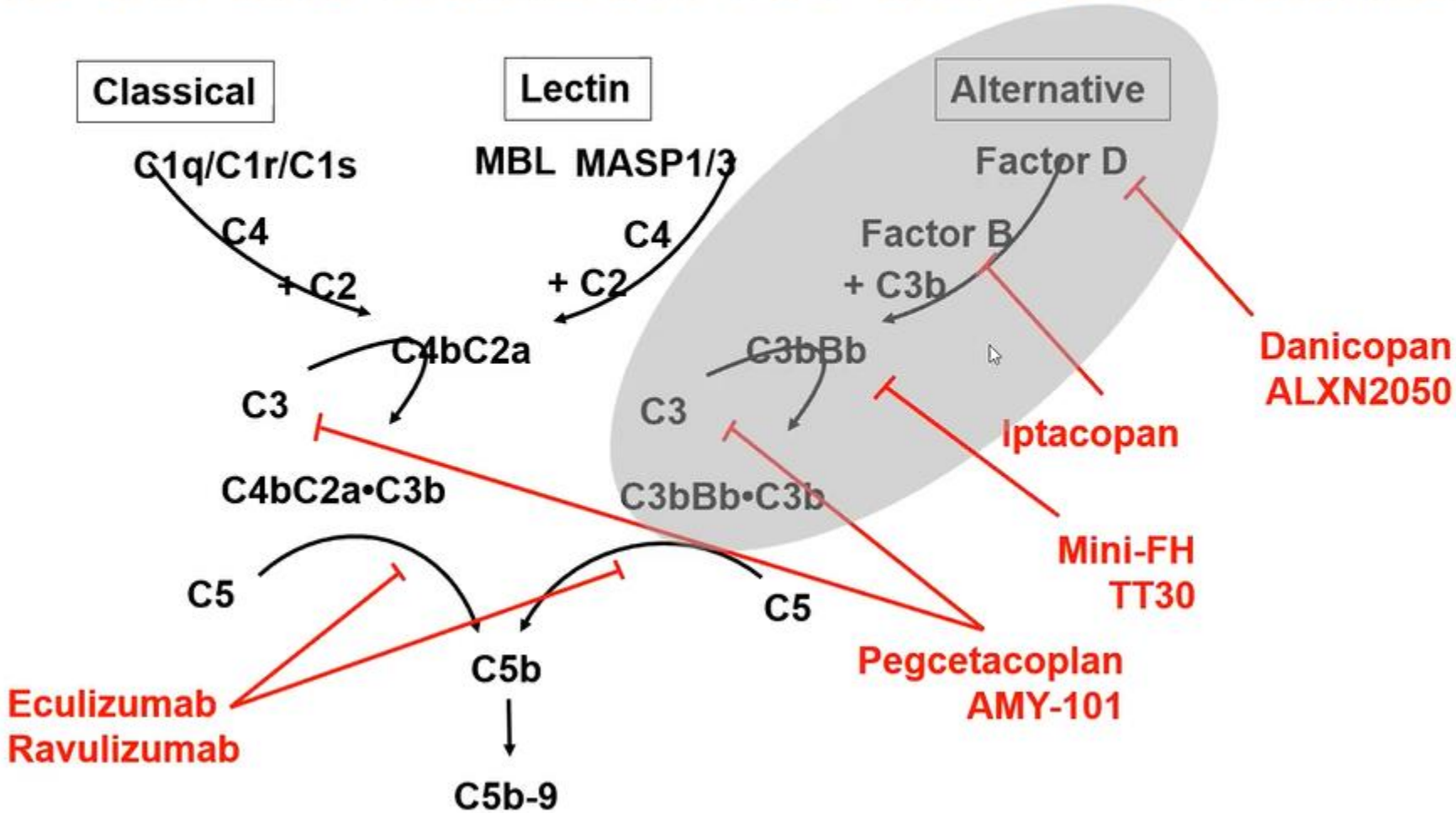
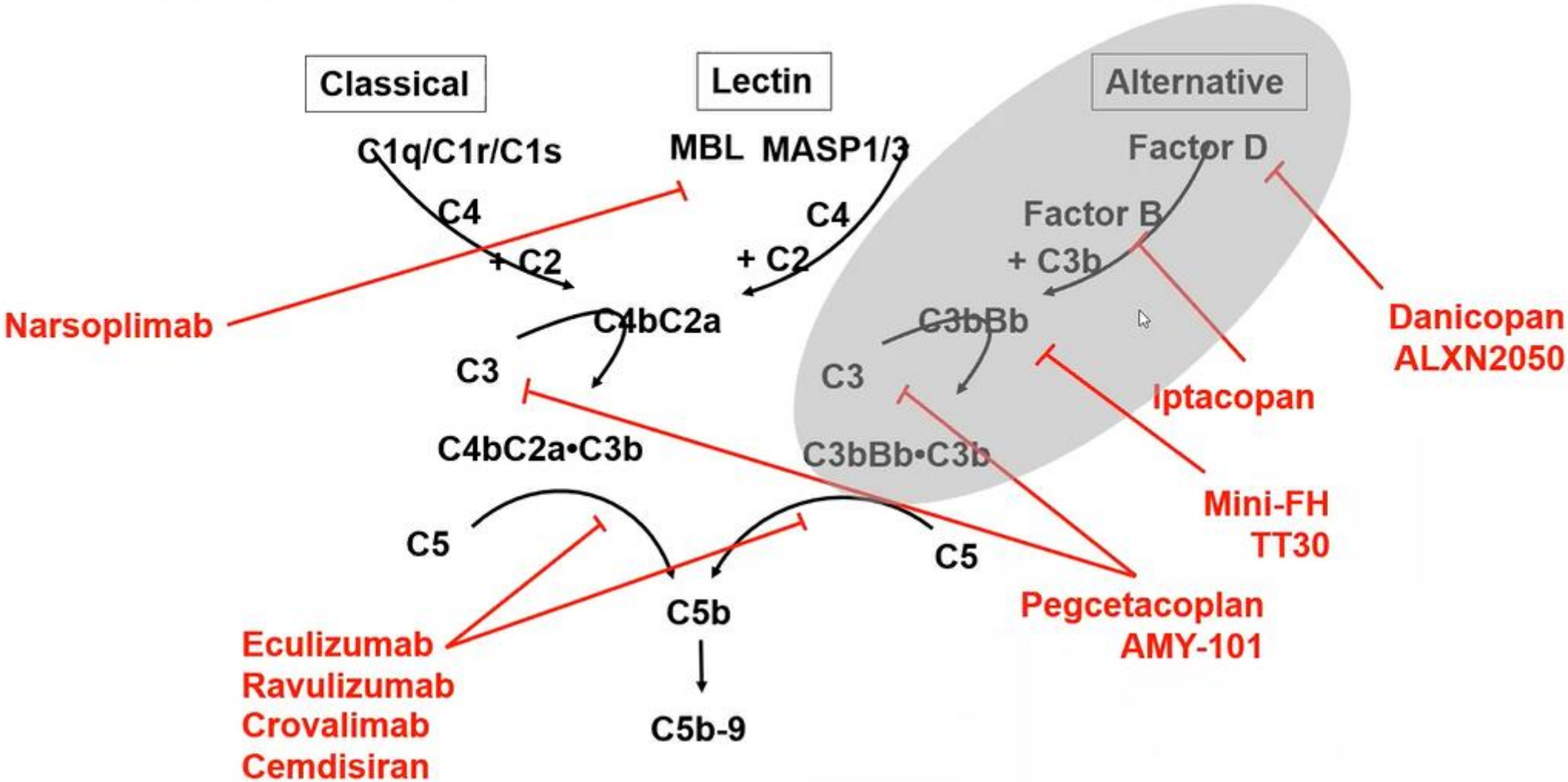


Dixon B, Webinar, Rare Disease, 2022

What is on the horizon for aHUS treatment?



Dixon B, Webinar, Rare Disease, 2022

The role of complement in kidney disease: conclusions from a Kidney Disease: Improving Global Outcomes (KDIGO) Controversies Conference,

Kidney International 106, 369–391, 2024

Table 1 | Complement inhibitors in clinical development[a] for kidney diseases

Target of inhibition	Drug	Inhibitor type	Mechanism	Route	Clinical trials
C1	ANX009	Antibody	Inhibits C1q substrate interactions	SC	NCT05780515 (lupus nephritis, phase 1, recruiting)
C3, C3b	Pegcetacoplan	Peptides conjugated to polyethylene glycol	Binds C3 and C3b and prevents interaction and activity of the C3 and C5 convertases of the classical, lectin, and alternative pathways	SC twice weekly	NCT05148299 (post-BMT TMA, phase 2, recruiting) NCT04572854 (post-transplant recurrence C3G or IC-MPGN, phase 2, active not recruiting) NCT03453619 (C3G) (basket in glomerulopathies, phase 2, completed)[4] NCT05067127 (C3G or IC-MPGN, phase 3, active not recruiting) NCT05809531 (C3G or IC-MPGN, phase 3 open-label extension of a previous study, recruiting)
C3	AMY101	Small peptide	Binds C3 and blocks its binding to and cleavage by C3 convertases into C3a and C3b	IV	NCT03316521 (phase 1 healthy male volunteers, completed)
C3	ARO-C3	Small, interfering RNA	Inhibits C3 synthesis in the liver	SC	NCT05083364 (phase 1/2a dose-escalating: healthy volunteers, adult patients with C3G and IgAN, recruiting)
C3b, C5	KP104	Antibody plus factor H regulatory domain	Blocks the alternative and terminal pathways	IV	NCT05517980 (IgAN and C3G phase 2, not yet recruiting) NCT05504187 (lupus nephritis phase 2, not yet recruiting)
C5	Cemdisiran	Small, interfering RNA	Inhibits C5 synthesis in the liver	SC	NCT03841448 (IgAN, phase 2, completed)[5]
C5	Crovalimab	Antibody	Prevents cleavage of C5 by the C5 convertase	IV, then SC	NCT04958265 (aHUS, phase 3, recruiting, children between 28 days and 17 years of age) NCT04861259 (aHUS, phase 3, recruiting)
C5	Eculizumab	Antibody	Prevents cleavage of C5 by the C5 convertase	IV	NCT03518203 (HUS post-BMT with multiple organ dysfunction syndrome, phase 2, completed) NCT01029587 (CAPS to enable kidney transplant, phase 2, completed) NCT05702996 (HUS secondary to gemcitabine, phase 2, not yet recruiting) NCT05726916 (HUS secondary to hypertensive emergency, phase 2, not yet recruiting) NCT02205541 (STEC-HUS, phase 3, completed)[6] NCT05876351 (aHUS in China, phase 3, recruiting)
C5	Gefurulimab (ALXN1720)	Bispecific minibody	Binds C5, inhibiting its cleavage into C5a and C5b. It also binds to albumin, which increases its half-life	SC	NCT05314231 (proteinuria, phase 1B, completed)
C5	Ravulizumab	Antibody	Prevents cleavage of C5 by the C5 convertase	IV, SC	NCT04564339 (IgAN and LN, phase 2, recruiting) NCT04743804 (trigger-associated TMA, phase 2, terminated) NCT04543591 (adult and adolescent post-BMT HUS, phase 3, recruiting) NCT04557735 (pediatric post-BMT HUS, phase 3, recruiting)

Table 1 | (Continued) **Complement inhibitors in clinical development[a] for kidney diseases**

Target of inhibition	Drug	Inhibitor type	Mechanism	Route	Clinical trials
C5	Nomacopan or coversin (rVA576)	Small protein	Inhibits terminal complement activation by tightly binding to C5 and preventing C5a release and C5b-9 formation, and inhibits leukotriene B4 by capturing the fatty acid within the body of the nomacopan protein	SC	NCT04784455 (pediatric post-BMT HUS, phase 3, recruiting)
C5a	Vilobelimab (IFX-1)	Antibody	Selectively inhibits C5a activity leaving the MAC intact	IV	NCT03712345 (GPA and MPA, phase 2, terminated) NCT03895801 (GPA and MPA, phase 2, completed)
C5aR1	Avacopan	Small molecule	Blocks the binding of the anaphylatoxin C5a with the C5aR1 receptor	Oral twice daily	NCT02464891 (aHUS on dialysis, phase 2, terminated) NCT03301467 (C3G, phase 2, completed) NCT02384317 (IgAN, phase 2, completed)[7] NCT02994927 (AAV, phase 3, completed)[8] NCT01363388 (AAV, phase 2, completed) NCT02222155 (AAV, phase 2, completed)
Factor B	IONIS-FB-LRx	Antisense oligonucleotide	Inhibits liver synthesis of factor B	SC	NCT04014335 (IgAN, phase 2, active not recruiting, ASN poster SA-PO926)[8a] NCT05797610 (IgAN, phase 3 recruiting)
Factor B	Iptacopan (LNP023)	Small molecule	Prevents activity of C3 and C5 convertases of the alternative pathway	Oral twice daily	NCT04889430 (aHUS, phase 3, recruiting) NCT03832114 (C3G, phase 2, adults with native or transplanted kidney,[9] extension NCT03955445) NCT04817618 (C3G, phase 3, adults and adolescents >12 years, recruiting, for adults interim results reported) NCT05755386 (IC-MPGN, phase 3, adults and adolescents >12 years, recruiting) NCT03373461 (IgAN, phase 2, completed)[10] NCT04578834 (IgAN, phase 3, recruitment completed, interim results reported) NCT04154787 (MN, phase 2, terminated) NCT05268289 (LN, phase 2, recruiting)
Factor Bb	NM8074	Monoclonal antibody	By binding Bb, it is able to inhibit both C3 and C5 convertases and the MAC formation	IV	NCT06226662 (AAV, phase 2, not yet recruiting) NCT05647811 (C3G, phase 1b/2a, not yet recruiting) NCT05684159 (aHUS, phase 2, not yet recruiting)
Factor D	BCX10013	Small molecule	Prevents formation of C3 and C5 convertases of the alternative pathway more efficiently than BCX9930	Oral once daily	NCT06100900 (PNH, phase 1, dose escalation)

Factor D	Danicopan (ALXN2040, ACH-4471)	Small molecule	Prevents formation of C3 and C5 convertases of the alternative pathway	Oral twice daily	NCT03124368 (C3G or IC-MPGN, phase 2, completed)[11,12] NCT03369236 (C3G or IC-MPGN, phase 2, completed)[11,12] NCT03459443 (C3G or IC-MPGN, phase 2, terminated)
Factor D	Vemircopan (ALXN2050, ACH-0145228)	Small molecule	Prevents formation of C3 and C5 convertases of the alternative pathway	Oral	NCT05097989 (IgAN or LN, phase 2, recruiting)
MASP-2	CM338	Monoclonal antibody	Blocks initiation of the lectin pathway	SC	NCT05775042 (IgAN, phase 2, recruiting)
MASP-2	Narsoplimab (OMS721)	Antibody	Blocks initiation of the lectin pathway	IV	NCT05855083 (pediatric post-BMT HUS, phase 2, recruiting) NCT03205995 (aHUS, phase 3, status unknown) NCT02682407 (C3G, IgAN, LN, MN, phase 2, status unknown) NCT03608033 (IgAN, phase 3, terminated)
MASP-3	OMS906	Antibody	Blocks initiation of the lectin pathway	IV	NCT06209736 (C3G, IC-MPGN, phase 2, not yet recruiting)
Renin[b]	Aliskiren	Small molecule	Blocks renin-mediated C3 cleavage	Oral	NCT04183101 (C3G, phase 2, recruiting)

AAV, antineutrophil cytoplasmic antibody–associated vasculitis; aHUS, atypical hemolytic uremic syndrome; BMT, bone marrow transplant; C3G, complement component 3 glomerulopathy; CAPS, catastrophic antiphospholipid syndrome; GPA, granulomatosis with polyangiitis; HUS, hemolytic uremic syndrome; IC-MPGN, immune-complex membranoproliferative glomerulonephritis; IgAN, IgA nephropathy; IV, intravenous; LN, lupus nephritis; MAC, membrane attack complex (C5b-9); MASP, mannan-binding lectin-associated serine peptidase; MN, membranous nephropathy; MPA, microscopic polyangiitis; PNH, paroxysmal nocturnal hematuria; SC, subcutaneous; STEC, Shiga toxin-producing *Escherichia coli*; TMA, thrombotic microangiopathy.

[a]As of March 1, 2024. For eculizumab, completed and published studies are not listed. For all agents, only studies evaluating the diseases covered in this paper are listed, and withdrawn studies are not listed. Studies on generic/biosimilar agents or in phase 4 are also not listed. The studies enroll adults only unless specified.

[b]Recent data do not support a role for renin in the cleavage of C3 and suggest that the use of aliskiren as a renin inhibitor to decrease complement activity and C3 convertase formation is misguided.[13]

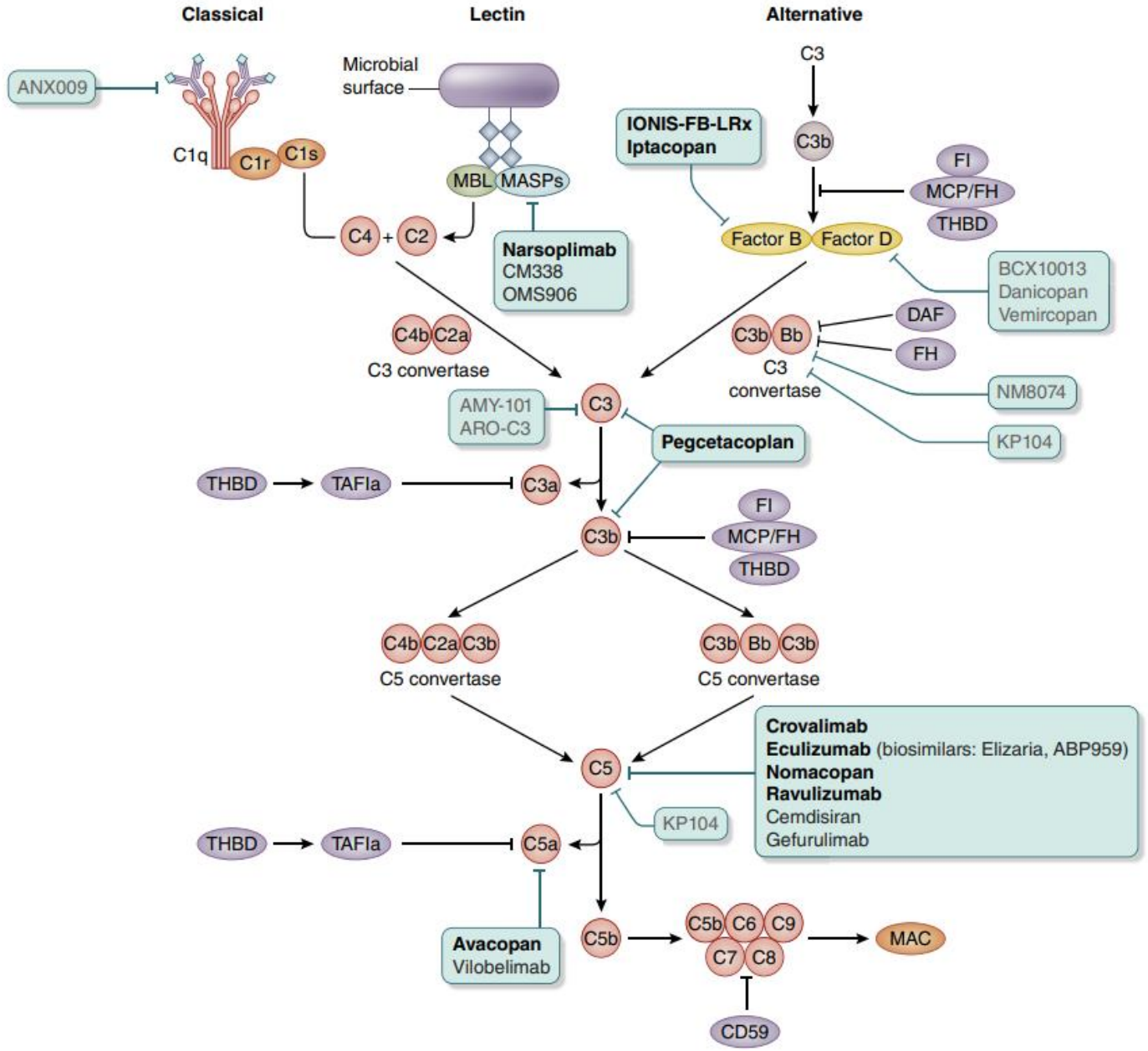


Figure 3| Therapeutic inhibitors of complement activity. In the near future, multiple drugs that target the complement system will be

Emerging:

Gene Therapy and Targeted Complement System Modulation

- Gene therapy holds great promise for aHUS as it addresses the underlying genetic causes of the condition & provide a **more permanent solution** compared to current treatments like complement inhibitors
- **Gene Identification:** to identify the specific genetic mutations responsible for aHUS in an individual. This requires comprehensive genetic testing to pinpoint the exact genetic variations contributing to the condition.
- **Gene Modification:** eg: Hundreds of errors are identified in just CFH alone so far so each will have to be changed individually. Several approaches can be used, such as **introducing functional genes or repairing mutations**.
- **Delivery Method:** to transport the modified genes into the patient's cells. These **delivery methods** can include viral vectors, nanoparticles, or other techniques.
- **This is still an evolving field, and ongoing research is needed to refine**

Len Woodward, Cure – aHUS Agenda Topic 9,

Conclusion

- **aHUS is a genetic disease that is potentially life-threatening, can affect all organ systems, and has a poor prognosis if not recognized quickly and appropriately treated**
- There are still many knowledge gaps across aHUS
- No single test can positively diagnose aHUS & it is still a diagnosis of exclusion
- Much is unknown about how certain circumstances regarding genetics and environmental factors may combine to trigger atypical HUS disease activity
- Eculizumab and Ravulizumab have proved effective in suppressing disease activity, but no definite cure, price prohibiting
- Research is ongoing to find a definite diagnostic test, and also explore other alternative or combined treatment strategies
- Encouraging the use of registries, biobanks, and open data sharing will enhance our understanding, enabling us to provide our patients with early and accurate diagnoses, as well as safe and affordable treatments.


THANK YOU