



Overview of C inhibitors: the pipeline

ESPN Research Conference

13th March 2026

Dr Edwin Wong

Consultant Nephrologist | Honorary Senior Clinical Lecturer
National Renal Complement Therapeutics Centre | Newcastle University

Disclosures

Received fees for consultancy and/or speakers agreements from

- Adarx, Alexion, Apellis, Arrowhead, Biocryst, Emerald, Florio, Novartis, Omeros and Sobi

Principal or sub-investigator on studies by Alexion, Apellis, ADARX, Chemocentryx, Novartis, Omeros



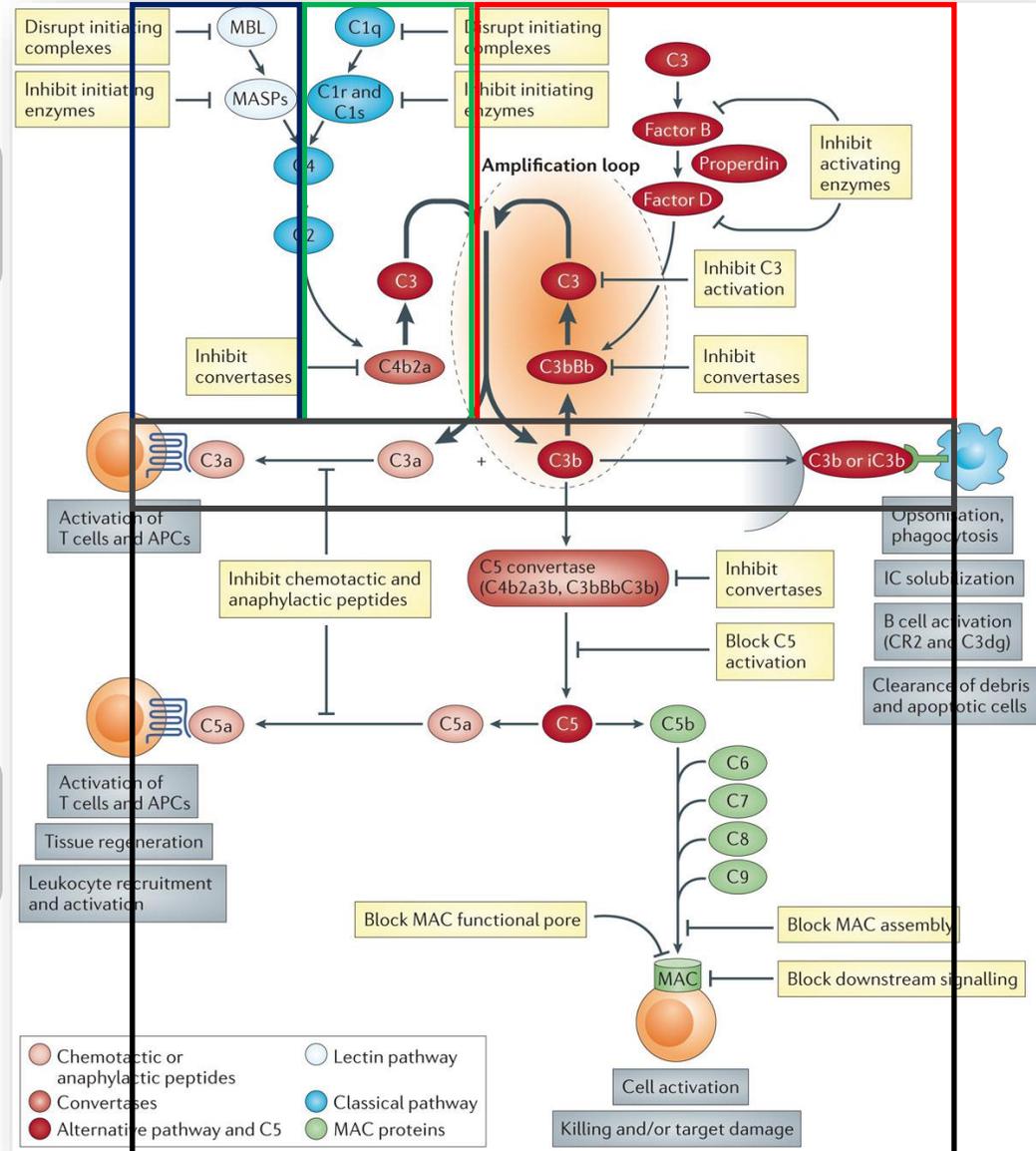
- Complement inhibitors in investigative trials
- Renal disease being considered for complement inhibition
- Other considerations in complement inhibition
 - Safety
 - Paediatric use
 - Use with other treatments

The Complement System

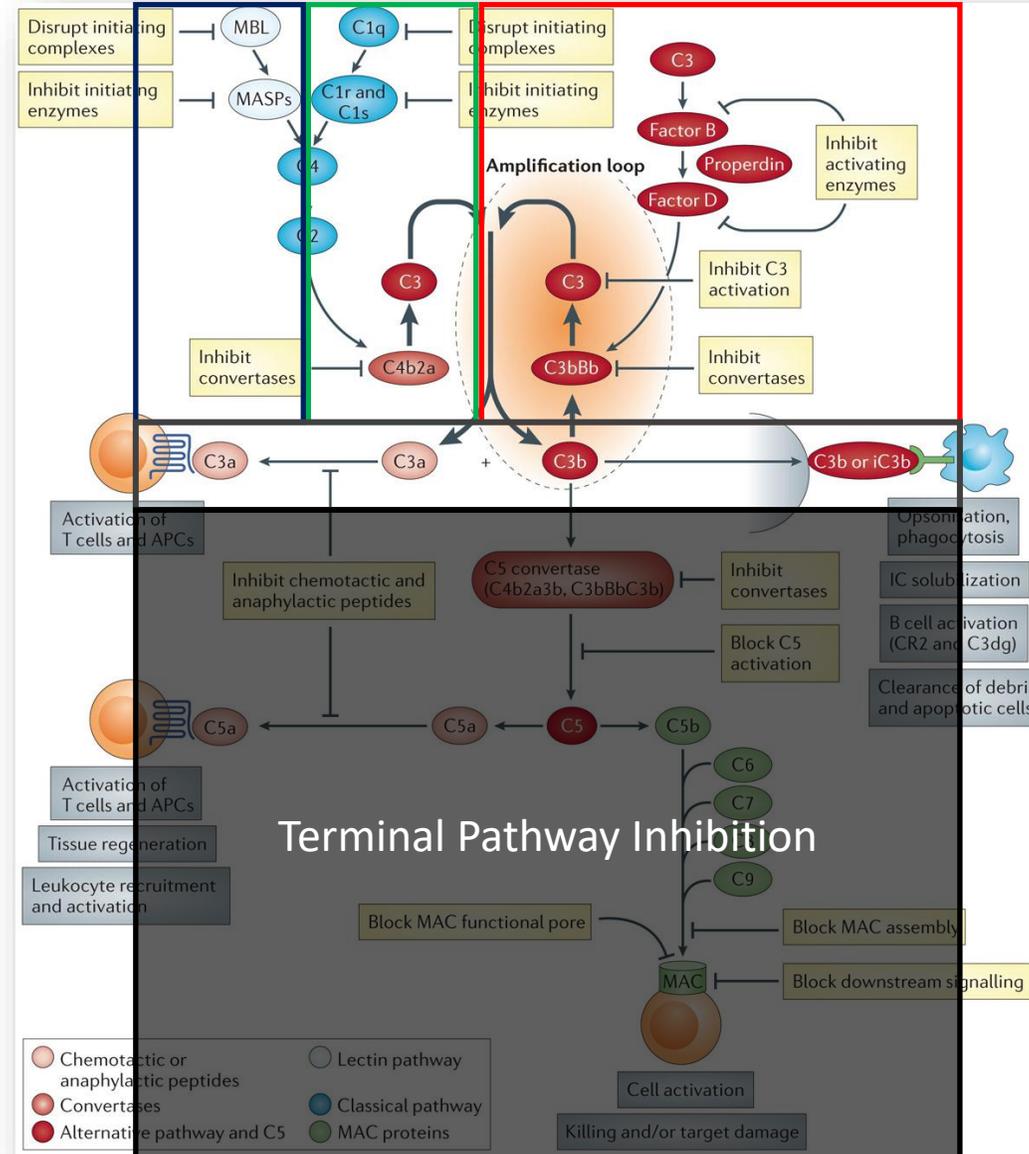


Activation Pathways

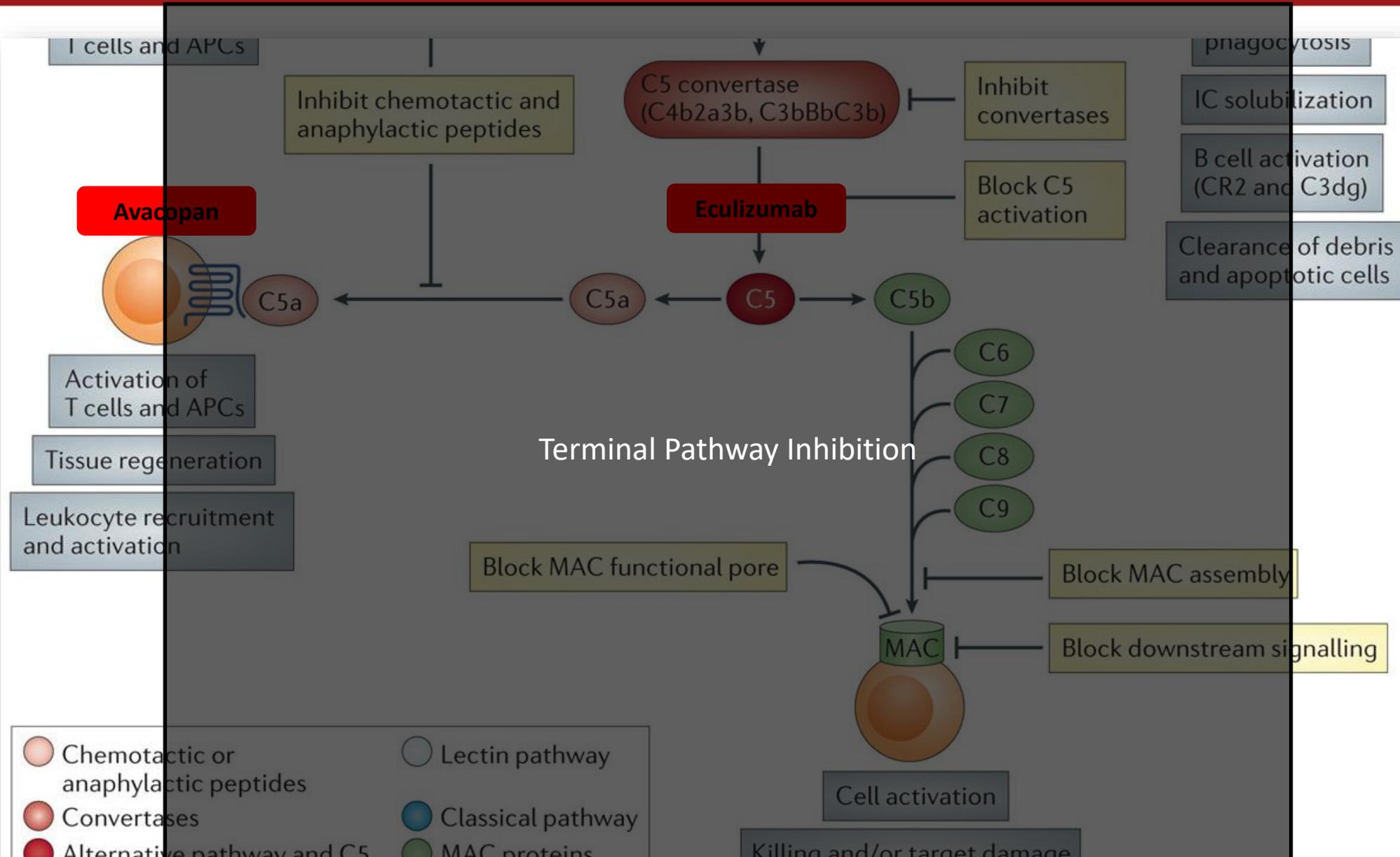
Terminal Pathway



Terminal Pathway Inhibition



Terminal Pathway Inhibition



Breadth of C5 inhibition

Drug	Type	Route	Approvals (BOLD is Renal Indication)	Investigational Trials [BOLD is Phase 3] [Withdrawn or completed]
Eculizumab [including biosimilars]	monoclonal Ab	IV	aHUS , PNH, Myasthenia Gravis, Neuromyelitis Optica Spectrum Disorder	
Ravulizumab	monoclonal Ab	IV	aHUS , PNH, Myasthenia Gravis, Neuromyelitis Optica Spectrum Disorder	AKI in Cardiac Surgery, Delayed Graft Function, IgAN, Lupus nephritis, Post-HSCT Associated TMA, Secondary TMA,
Crovalimab	monoclonal Ab	SC	PNH	aHUS
Zilucoplan	Cyclic peptide	SC	Myasthenia Gravis	Amyotrophic Lateral Sclerosis
Cemdisiran *with Pozelimab	siRNA	SC		Geographic Atrophy* , aHUS , IgAN , inclusion body myositis, Myasthenia Gravis* , PNH*
Pozelimab	Monoclonal Ab	SC	CHAPLE disease	
Gefurulimab	nanobody	SC		Myasthenia Gravis
Nomacopan	Small molecule	Oral		aHUS, Bullous Pemphigoid, PNH, Post-HSCT Associated TMA

Ravulizumab in IgAN and Lupus Nephritis

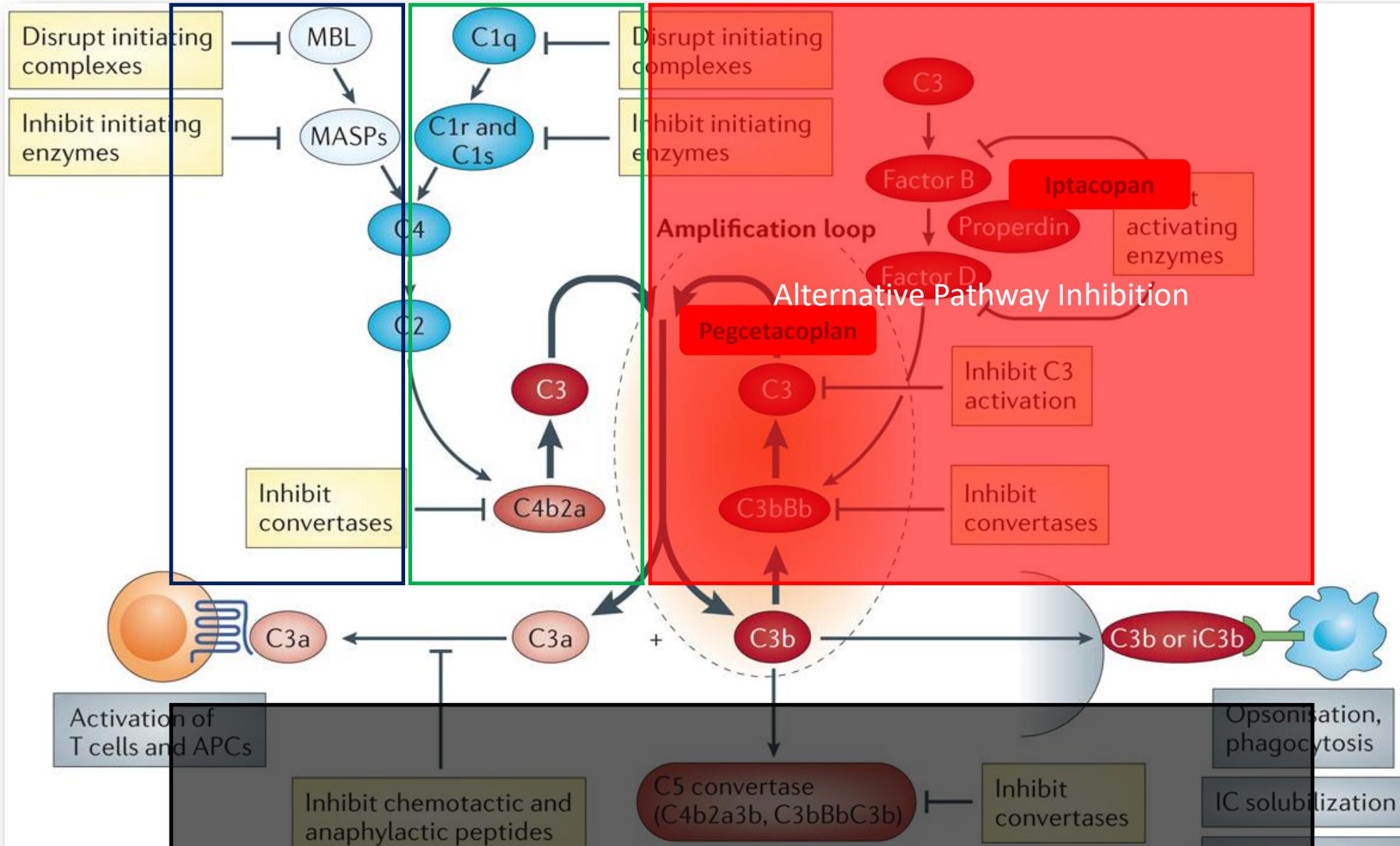


- Phase 2 trial:
 - Double-blinded Placebo-controlled trial
 - Trial has been published
 - 43 patients patients with IgAN randomised to Ravulizumab, 23 patients to placebo
 - Proteinuria reduction: 30.1% treatment effect compared to placebo $P < 0.005$
 - Phase 3 trial is ongoing
- No data on lupus nephritis patients...

Other C5a inhibitors

Drug	Type, Target	Route	Approvals (BOLD is Renal Indication)	Investigational Trials [BOLD is Phase 3][Withdrawn or completed]
Avacopan	Small molecule, C5aR	oral	ANCA-associated vasculitis	AAV – including paediatric aHUS €3G Crescentic IgA – currently recruiting Hidradenitis suppurative IgA nephropathy SLE
INF904	Small molecule, C5aR	Oral		Chronic spontaneous urticaria Hidradenitis suppurative
Vilobelimab	Monoclonal Ab, C5a	IV	COVID-19	AAV Hidradenitis suppurative Pyoderma gangrenosum

Alternative pathway inhibition



Other indications for approved AP inhibitors

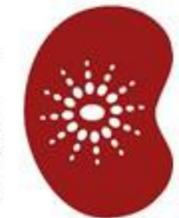
	Type, Target	Route	Approvals (BOLD is Renal Indication)	Investigational Trials [BOLD is Phase 3] [Withdrawn or completed]
Iptacopan	Small molecule, FB	oral	C3G, IgAN [Accelerated in US], PNH	AAV, Age-related Macular Degeneration, aHUS , Auto-immune haemolytic anaemia, Cold agglutinin disease , HSCT associated TMA, IC-MPGN, ITP , Lupus nephritis, Membranous nephropathy , Myasthenia gravis
Pegcetacoplan	Pegylated peptide, C3 and C3b	SC	C3G , Geographic Atrophy, IC-MPGN , PNH	Amyotrophic lateral sclerosis, Cold agglutinin disease , Delayed Graft Function , Fallopian tube carcinoma, HSCT associated TMA, Pancreatic carcinoma

Ongoing iptacopan trials in renal indications

	AAV	aHUS	IC-MPGN	Lupus
Phase	2	3	3	2
Comparator	Iptacopan vs Placebo vs Rituximab	Open Label	Iptacopan vs Placebo	Iptacopan vs Placebo
SOC	Evidenced based immunosuppression in conjunction with trial intervention	N/A	Some immunosuppression in conjunction with trial intervention	Evidenced based immunosuppression in conjunction with trial intervention
Disease Phase	Acute or Relapse	Acute (APPELHUS) Remission (APPRECIATE)	Chronic	Acute or Relapse


 Iptacopan in C3G
 Pegcetacoplan in C3G and IC-MPGN
 Ravulizumab in IgAN [No I/S]

Other AP inhibitors in clinical development



	Type, Target	Route	Approvals (BOLD is Renal Indication)	Investigational Trials [BOLD is Phase 3] [Withdrawn or completed]
ADX038	siRNA, CFB	SC		PNH, C3G, IgAN, IC-MPGN, Geographic Atrophy
ARO-C3	siRNA, C3	SC		C3G, IgAN
ARO-CFB	siRNA, CFB	SC		IgAN
BCX9930	Small molecule, FD	Oral		C3G, IgAN, PNH
BCX10013	Small molecule, FD	Oral		PNH
Danicopan	Small molecule, FD	Oral	PNH *add on with Ecu	C3G, IC-MPGN
KP104	Mab Fusion protein, C5 and FH	SC		C3G, IgAN, Lupus, PNH
Roxuprubart	mAB, FBb	IV		AAV, aHUS, C3G, Dermatomyositis, IgAN, PNH
Safexersen	ASO, CFB	SC		Geographic Atrophy, IgAN
SGB9768	siRNA, C3	SC		C3G, IC-MPGN, IgAN,
Vemircopan	Small molecule, FD	Oral		IgAN, Lupus nephritis, MG, PNH
Zaltenibart	MAB, MASP3	IV		C3G, IC-GN, PNH

Classical and Lectin Pathway inhibitors



- ANX009 – C1q inhibitor, previous trial in lupus nephritis
- Narsoplimab – MASP2 inhibitor, previous trials in aHUS, IgAN and Transplant-associated TMA
 - recently FDA approved in Hematopoietic Stem Cell Transplant Associated TMA
- CM338 – MASP2 inhibitor, recruiting as of 2024 in IgAN, phase 2.

Complement Protein Replacement



- C1 esterase inhibitor replacement in Hereditary Angioedema approved since 2009

Early phase studies emerging:

- Puresprings Therapeutics
- Adeno-associated viral vector containing the human Complement Factor I (CFI) gene in IgAN
- Eleva biologics
- Moss derived recombinant factor H in C3G

Role of complement in kidney disease

Prototypical rare diseases

Complement dysfunction
has primary role

Complement dysfunction
is secondary driver of injury

Common multifactorial diseases

aHUS
C3G
Primary IC-MPGN

AAV, SLE
IgAN, IgAVN
APS, MN

Secondary TMA
Secondary MPGN

Diabetic nephropathy

FSGS

Potential impact of complement inhibition

aHUS studies



Drug	Type, Target	Route	Stage	Pathway
Eculizumab [including biosimilars]	monoclonal Ab, C5	IV	Approved	Terminal
Ravulizumab	monoclonal Ab, C5	IV	Approved	Terminal
Crovalimab	monoclonal Ab, C5	SC	Phase 3	Terminal
Iptacopan	Small molecule, FB	oral	Phase 3	Alternative
Roxuprubarb	Monoclonal Ab, FBb	IV	Phase 2	Alternative
Avacopan	Small molecule, C5aR	oral	Discontinued	Terminal
Cemdisaran	siRNA, C5	SC	Discontinued	Terminal
Narsoplimab	Monoclonal Ab, MASP2	IV	Discontinued	Lectin
Nomacopan	Small molecule, C5	Oral	Discontinued	Terminal

C3G (+ IC-MPGN) studies

Drug	Type, Target	Route	Stage	Pathway
Iptacopan	Small molecule, FB	oral	Approved	Alternative
Pegcetacoplan	Cyclic Peptide, C3/C3b	SC	Approved	Alternative
ADX038	siRNA, CFB	SC	Phase 2	Alternative
KP104	Mab Fusion protein, C5 and FH	SC	Phase 2	Alternative
Roxuprubart	mAB, FBb	IV	Phase 2	Alternative
SGB9768	siRNA, C3	SC	Phase 2	Alternative
Zaltenibart	MAB, MASP3	IV	Phase 2	Alternative / Lectin
ARO-C3	siRNA, C3	SC	Phase 1/2	Alternative
CPV-104	Recombinant FH		Phase 1	Alternative
Avacopan	Small molecule, C5aR	oral	Discontinued	Terminal
BCX9930	Small molecule, FD	Oral	Discontinued	Alternative
Danicopan	Small molecule, FD	Oral	Discontinued	Alternative

IgAN studies



Drug	Type, Target	Route	Stage	Pathway
Iptacopan	Small molecule, FB	oral	Accelerated Approval	Alternative
Ravulizumab	monoclonal Ab, C5	IV	Phase 3	Terminal
Safexersen	ASO, CFB	SC	Phase 3	Alternative
ADX038	siRNA, CFB	SC	Phase 2	Alternative
KP104	Mab Fusion protein, C5 and FH	SC	Phase 2	Alternative
Roxuprubarb	mAB, FBb	IV	Phase 2	Alternative
SGB9768	siRNA, C3	SC	Phase 2	Alternative
Vemircopan	Small molecule, FD	Oral	Phase 2	Alternative
ARO-C3	siRNA, C3	SC	Phase 1/2	Alternative
ARO-CFB	siRNA, CFB	SC	Phase 1/2	Alternative
PS002	AAV Gene Therapy, CFI	IV	Phase 1	Alternative
Avacopan	Small molecule, C5aR	oral	Discontinued	Terminal
BCX9930	Small molecule, FD	Oral	Discontinued	Alternative
Cemdisiran	siRNA	SC	Discontinued	Terminal
Narsoplimab	Monoclonal Ab, MASP2	IV	Discontinued	Lectin

Lupus and Vasculitis studies

- **Lupus**

Drug	Type	Route	Stage	Pathway
Iptacopan	Small molecule, FB	oral	Phase 2	Alternative
KP104	Mab Fusion protein, C5 and FH	KP104	Phase 2	Alternative
Ravulizumab	monoclonal Ab, C5	IV	Phase 2	Terminal
Vemircopan	Small molecule, FD	Oral	Phase 2	Alternative
Avacopan	Small molecule, C5aR	oral	Discontinued	Terminal

- **AAV**

Drug	Type	Route	Stage	Pathway
Avacopan	Small molecule, C5aR	oral	Approved	Terminal
Iptacopan	Small molecule, FB	oral	Phase 2	Alternative
Roxuprubarb	mAB, FBb	IV	Phase 2	Alternative

Safety of Complement Inhibition



- Meningococcal risk:
- Up to 2000-fold risk compared to general population
- Vaccinations should include Tetravalent ACWY and Bexsero for Meningococci
- Pneumonia risk:
- Vaccinations against Pneumococci and Haemophilus influenzae type b in alternative pathway inhibitors and under 18s [for terminal pathway]

- Consideration of long-term prophylactic antibiotics
- Patient vigilance
- Main exception is C5a / C5aR blockade

Paediatric dosing

- Approved

Drug	Age
Eculizumab	All ages
Narsoplimab	2+
Pegcetacoplan	12+
Pozelimab	1+
Ravulizumab	All ages

- Pipeline

Drug	Age
Avacopan	Ongoing study from 6+ in AAV
Avacopan (discontinued)	From 12+ in C3G trial
Danicopan (discontinued)	From 12+ in C3G and IC-MPGN trial
Iptacopan	Ongoing study from 12+ in C3G and IC-MPGN



- Complement inhibition alongside Immunosuppression as standard of care
 - Avacopan and other complement inhibition trials in AAV
 - Trials of complement inhibition in lupus nephritis
- Complement inhibition in combination
 - Eculizumab and add-on Danicopan in PNH
 - Pozelimab and Cemdisiran in studies of Geographic atrophy, Myasthenia Gravis an PNH

Summary



Breadth of therapeutics targeting the whole of the complement system

Multiple types of molecule to target the same complement protein

Approved complement inhibitors mostly targeting the terminal pathway

Emerging treatments and indications mostly in the alternative pathway

Complement [inhibitor] protein replacement also emerging

Wide range of (renal) diseases being studied for complement therapies – progress in disease developing at different speeds

Summary



Protection against meningococci and certain forms of pneumonia remain the key safety concern for most complement inhibitors

There are licensed complement inhibitors and trials for children

Complement inhibitors are being used alongside other forms of immunosuppression and other complement inhibitors