ARO-C3 KOL Webinar

October 26, 2021

arrowhead pharmaceuticals

Welcome and Introductions

Vince Anzalone, CFA

Safe Harbor Statement

This presentation contains forward-looking statements within the meaning of the "safe harbor" provisions of the Private Securities Litigation Reform Act of 1995. These statements are based upon our current expectations and speak only as of the date hereof. Our actual results may differ materially and adversely from those expressed in any forward-looking statements as a result of various factors and uncertainties, including, without limitation, our developmental stage and limited operating history, our ability to successfully and timely develop products, enter into collaborations and achieve other projected milestones, rapid technological change in our markets, demand for our future products, legislative, regulatory and competitive developments and general economic conditions. Our Annual Report on Form 10-K and other SEC filings discuss some of the important risk factors that may affect our ability to achieve the anticipated results, as well as our business, results of operations and financial condition. Readers are cautioned not to place undue reliance on these forward-looking statements. Additionally, Arrowhead disclaims any intent to update these forward-looking statements to reflect subsequent developments.

Panelists

David Geffen School of Medicine at UCLA

Richard J. Glassock, MD, MACP, FRCP, FASN
Professor Emeritus

University of Auckland School of Medicine

Peter Browett, BMedSci, MBChB, FRACP, FRCPA
Professor of Pathology, Department of Molecular Medicine and Pathology

Arrowhead Pharmaceuticals

James Hamilton, MD, MBA
Senior Vice President, Discovery and Translational Medicine

Javier San Martin, MD
Chief Medical Officer

Vince Anzalone, CFA
Vice President, Investor Relations

Hamid Moradi, MD, FASN
Associate Medical Director

Agenda

- Welcome and Introductions – Vince Anzalone
- ARO-C3 Opportunity – Vince Anzalone
- Overview of Complement Cascade – Dr. Hamid Moradi
- Nephrology - IgAN and C3G – Dr. Richard Glassock
- Hematology - PNH – Dr. Peter Browett
- ARO-C3 Preclinical Data and Clinical Plan – Dr. James Hamilton
- Wrap up – Vince Anzalone
- Q & A – Panel

ARO-C3 Opportunity
Vince Anzalone

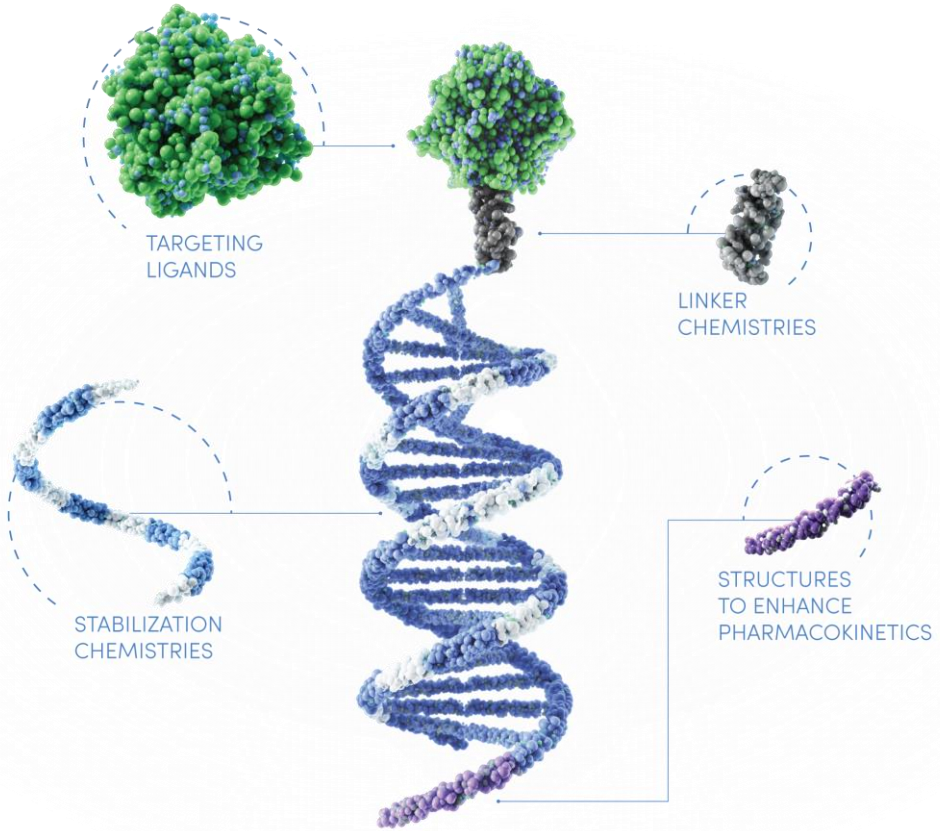
ARWR Profile

Arrowhead is a **mid-cap RNAi therapeutics platform company** with a **broad pipeline** of **wholly owned and partnered** product candidates.

Our mission is to treat intractable medical conditions by **silencing the genes** that cause them

Broad Pipeline:	• **10clinical stage programs** (4 partnered; 6 wholly-owned) • Mix of **early, mid, and later-stage** candidates targeting **rare and high prevalence diseases** • Growing pipeline with **2-3 new clinical programs planned per year**
Proprietary Platform:	• **Targeted RNAi Molecules** platform **(TRiM™)** designed for **deep and durable gene silencing** • Potential to be **best in class for liver** expressed genes • **Fulfilling the promise** of bringing RNAi therapeutics to diseases **outside of the liver** with a goal of reaching a **new tissue type every 18-24 months**
Financial Resources:	• Strong balance sheet to **push candidates towards commercialization** • **Non-dilutive capital** from Janssen, Amgen, Takeda, and Horizon as milestones are achieved • Potential for **additional** product and/or platform **deals**

Targeted RNAi Molecules - TRiM™ Platform



TRiM™ – *Target the gene*
Silence the disease

- ***Activity*** characterized by depth & duration of effect
  - Ability to unlock previously undruggable targets
- ***Specificity*** to maximize activity and innate stability with the potential for reduced off-target effects
- ***Versatility*** in formulation & ligand design offers multiple routes of administration, and access to multiple tissues
  - Facilitates rapid drug development and speed to patients
- ***Simplicity*** in design translates to relatively lower costs, and production at scale

Broad Complement C3 Opportunities

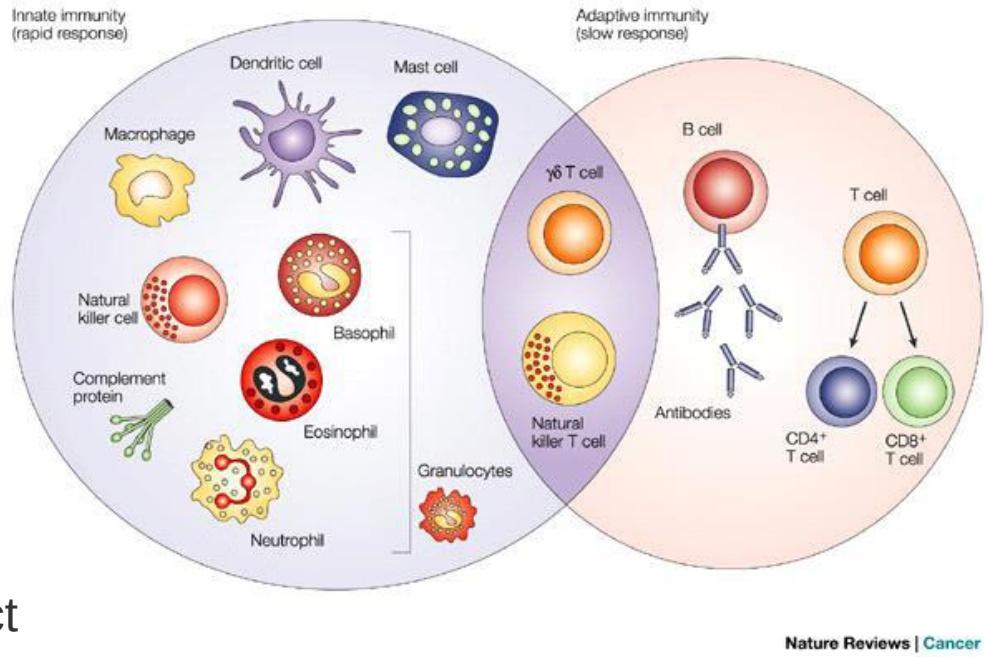
	Lupus Nephritis	IgAN	PMN	C3G	PNH	AIHA/CAD
U.S. Patient Size	130k[1]	60k[2]	60-90k[3]	4k[4]	~6k[5]	40k (WW)[6]
2026E Market Size[7]	$2-3Bn	$1.5Bn	$2-3Bn	$2.2Bn	$2.2Bn	$1.2Bn
SOC	Benlysta, Lupkynis	No approved (ACEi/ARBs)	No approved (Rituxan)	No approved (ACEi/ARBs)	Soliris, Ultomiris, EMPAVELI	Future: Sutimlimab (NDA)
SOC annual U.S. WAC per patient	$50-65k				$450-$600k	
Unmet need	Medium	High	High	High	Medium	High
Dev Program Scale[8]	800-1000pts	800-1000pts	800-1000pts	Small	300-500pts	200pts
Dev Program Comparator	Comparator likely required	None	None	None	Soliris, Ultomiris or EMPAVELI comparator	Potential Sutimlimab comparator
Anticipated Endpoint	Composite renal response	Proteinurea, EGFR	Proteinurea, EGFR	Proteinurea, EGFR	Hb, LDH, bilirubin, transfusion avoidance	
Est Dev Timeframe[8]		7-9yrs		6-7yrs	6.5yrs	7 yrs

1) Furst et al., 2013; Datamonitor; Hoover, Paul J, and Karen H Costenbader. "Insights into the epidemiology and management of lupus nephritis from the US rheumatologist's perspective." *Kidney international* vol. 90,3 (2016): 487-92. doi:10.1016/j.kint.2016.03.042; 2) https://www.kidney.org/news/hundreds-iga-nephropathy-patients-share-experience-fda-professionals-drug-makers; 3) https://www.orpha.net/consor/cgi-bin/OC_Exp.php?lng=en&Expert=97560; 4) Thomas S, Ranganathan D, Francis L, et al. Current concepts in C3 glomerulopathy. Indian J Nephrol. 2014;24:339-348 (330M*3*4=~4k); 5) Hill A, et al. *Blood*. 2006; 6) Berentsen S, et al. *Haematologica*. 2006;91(4):460-466; 7) Evaluate Pharma; 8) Biomedtracker; EvaluatePharma

Overview of Complement Cascade
Dr. Hamid Moradi

Innate and Adaptive Immune System

- **The innate immune system**: evolutionarily conserved → rapid, non-specific inflammatory responses to signals from Pattern Recognition Receptors (PRR).
- Cellular component: natural killer cells, macrophages, mast cells, neutrophils produce cytokines or interact with other cells directly in order to activate the adaptive immune system.
- Humoral Component: Complement proteins

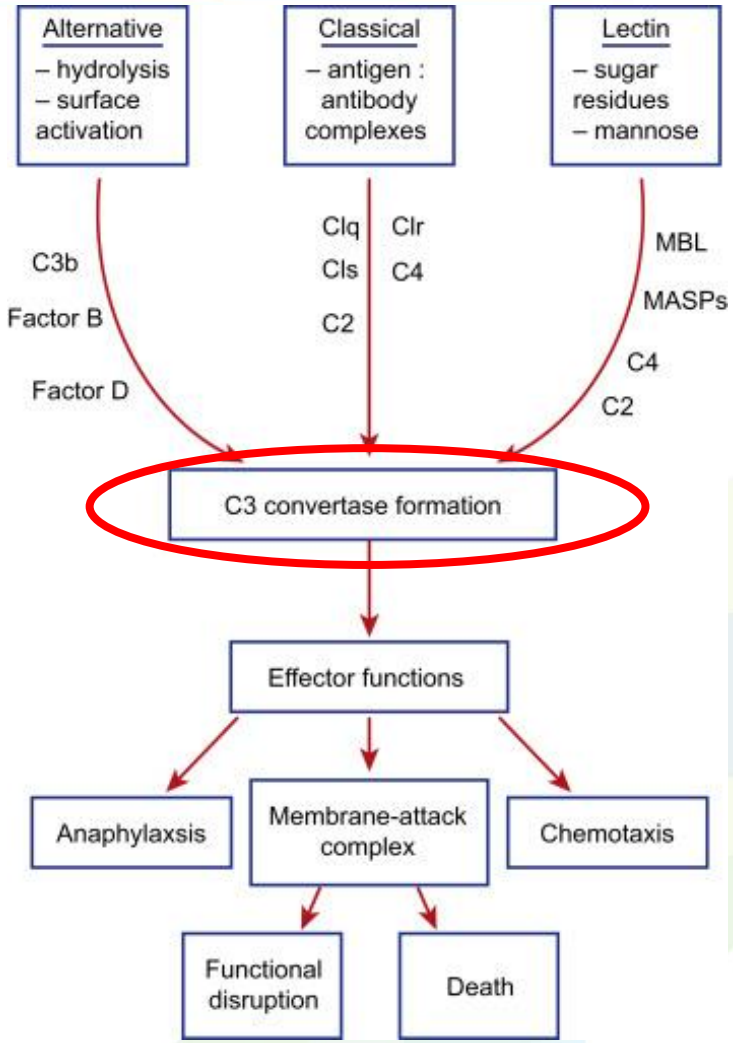


Nature Reviews Cancer, 2004; 4, 11-22.

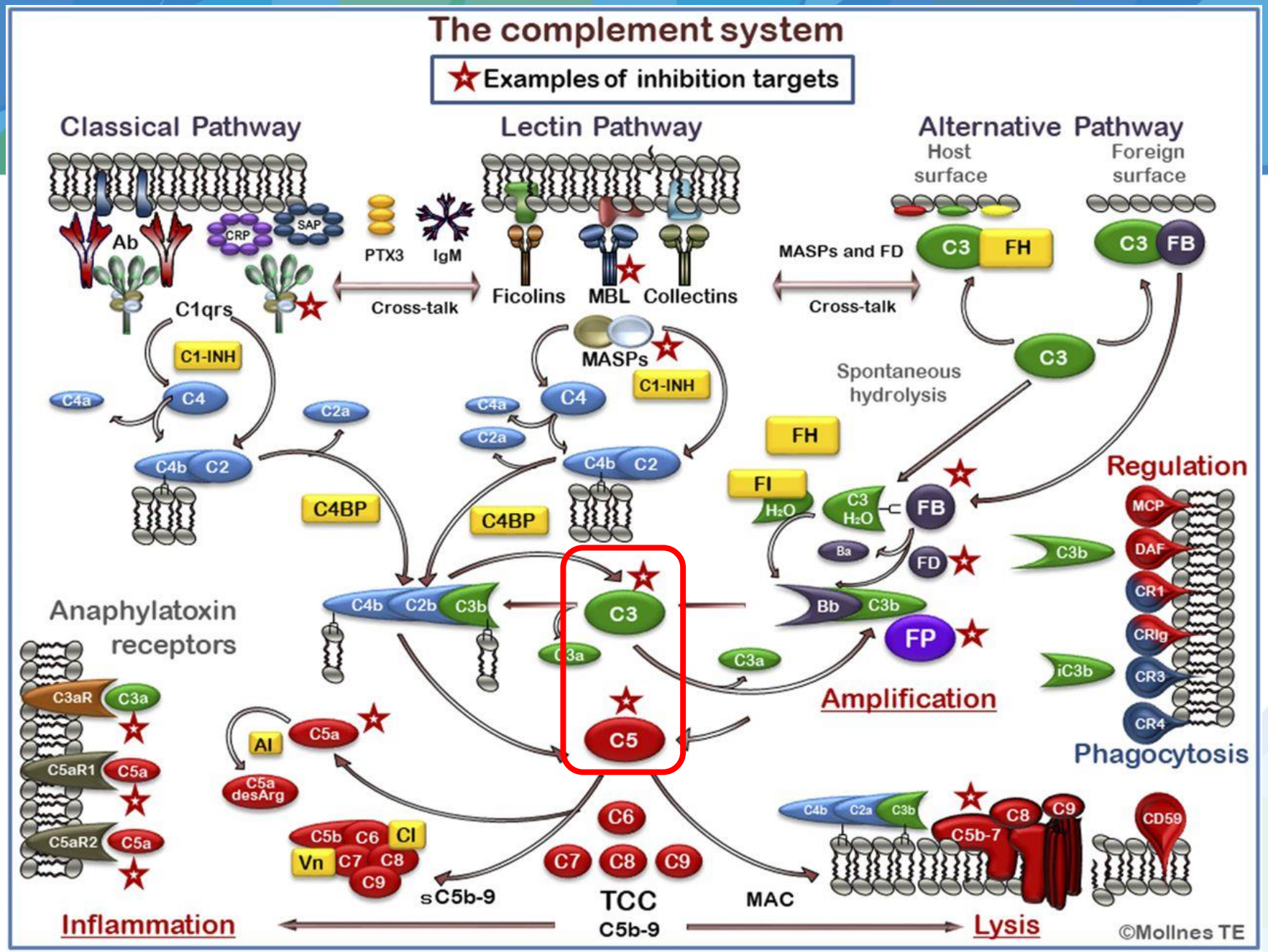
- **The adaptive immune system**
- Antigen receptors bind to antigen displayed in Major Histocompatibility Complex (MHC) molecules on antigen-presenting cells.
- Immunologic memory is the hallmark of adaptive immunity because it allows vertebrates to survive in a world where they are re-exposed to pathogens throughout their lifetimes.

Innate Immune system

- Complement cascade is a crucial part of the innate immune system.
- Some of the main functions of the complement system are
  - orchestrate opsonization,
  - facilitate cytotoxic destruction and formulate membrane attack complexes (MAC), and
  - release peptides that promote the inflammatory response.
- The complement system consists of 3 pathways, the alternative, classical, and lectin, that are initiated by distinct mechanisms.

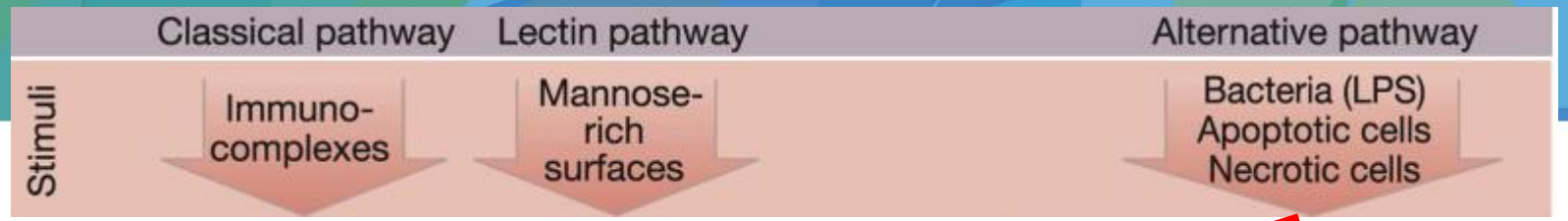


Tom P. Monie, The Innate Immune System, 2017, Pages 1-40.



Garred et. al. Pharmacol Rev 73:792–827, April 2021

Complement Activation



Opsonin
Tag for destruction

Anaphylatoxin
Proinflammatory

C3 Convertase

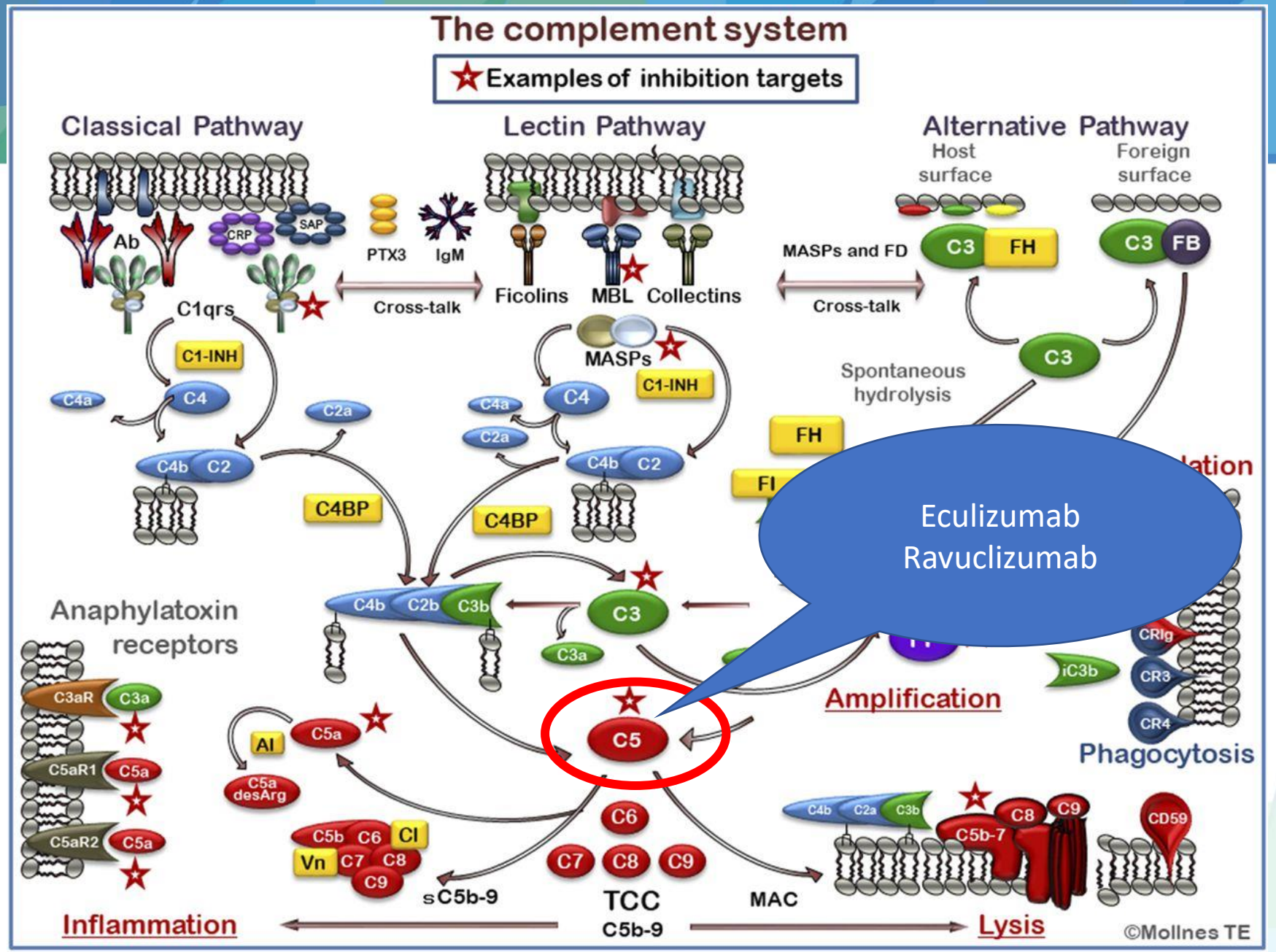
C3 inhibitor or KD

C5 Convertase

C5 inhibitor Eculizumab

C6 C9

Angioi et al. Kidney Int. 2016 Feb;89(2):278-88.



Garred et. al. Pharmacol Rev 73:792–827, April 2021

CONCLUSIONS

Pegcetacoplan was superior to eculizumab in improving hemoglobin and clinical and hematologic outcomes in patients with PNH by providing broad hemolysis control, including control of intravascular and extravascular hemolysis. (Funded by Apellis Pharmaceuticals; PEGASUS ClinicalTrials.gov, NCT03500549.)

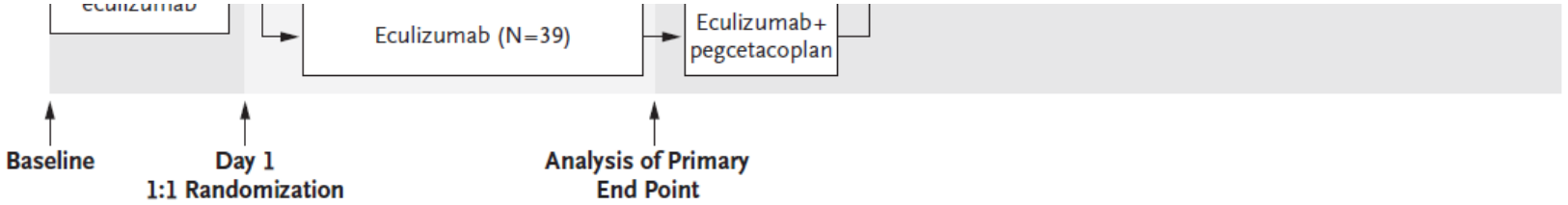


Figure 1. Trial Design.

The trial treatment period consisted of three parts: a 4-week run-in period, followed by a 16-week randomized, controlled period during which patients received either pegcetacoplan or eculizumab as monotherapy, and a 32-week open-label period during which patients received pegcetacoplan. Patients who received eculizumab during the 16-week randomized, controlled period continued to receive eculizumab in addition to pegcetacoplan for the first 4 weeks of the open-label period.

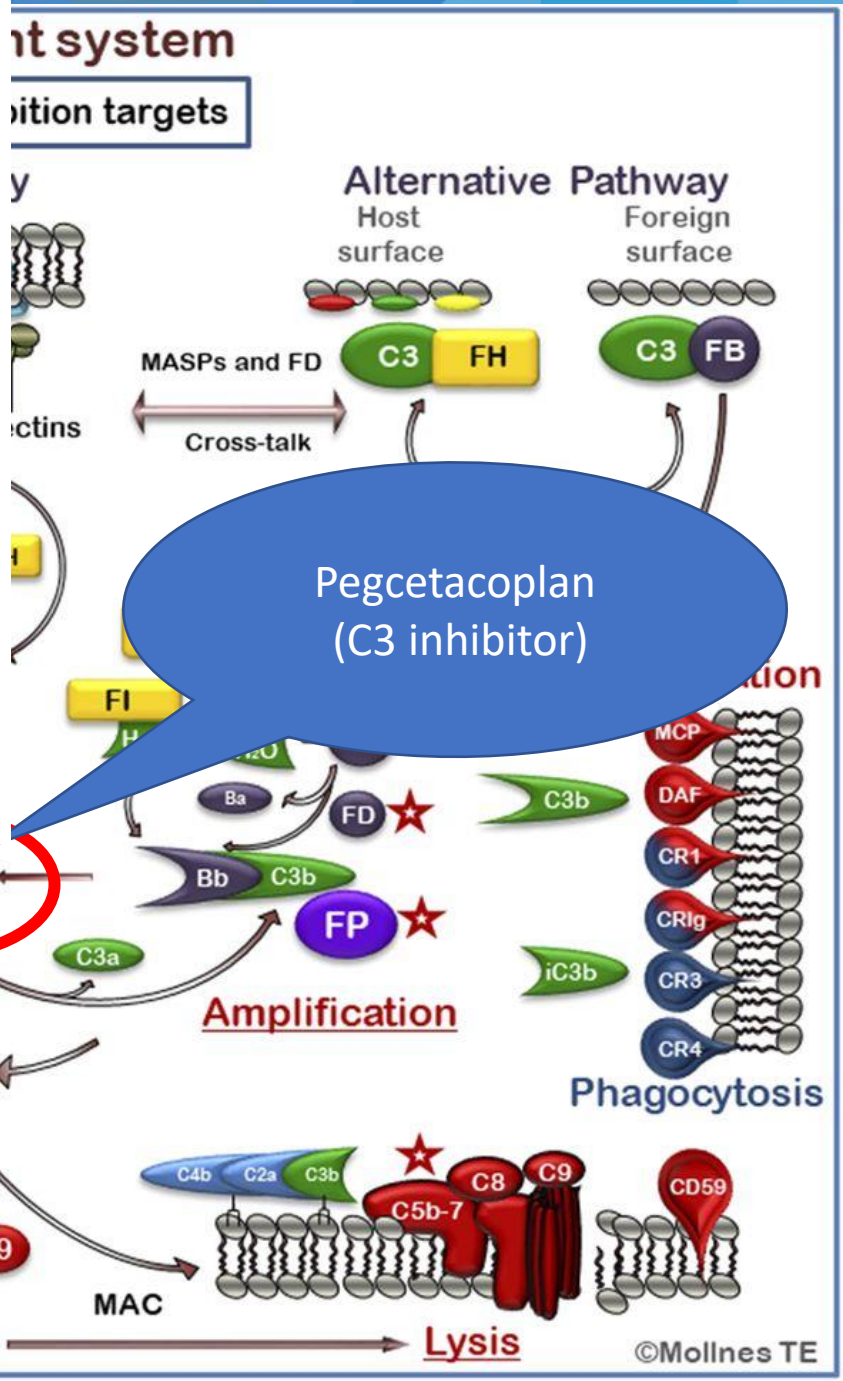
mab, we randomly assigned patients to subcutaneous pegcetacoplan monotherapy (41 patients) or intravenous eculizumab (39 patients). The primary end point was the mean change in hemoglobin level from baseline to week 16. Additional clinical and hematologic markers of hemolysis and safety were assessed.

RESULTS

Pegcetacoplan was superior to eculizumab with respect to the change in hemoglobin level from baseline to week 16, with an adjusted (least squares) mean difference of 3.84 g per deciliter ($P<0.001$). A total of 35 patients (85%) receiving pegcetacoplan as compared with 6 patients (15%) receiving eculizumab no longer required transfusions. Noninferiority of pegcetacoplan to eculizumab was shown for the change in absolute reticulocyte count but not for the change in lactate dehydrogenase level. Functional Assessment of Chronic Illness Therapy–Fatigue scores improved from baseline in the pegcetacoplan group. The most common adverse events that occurred during treatment in the pegcetacoplan and eculizumab groups were injection site reactions (37% vs. 3%), diarrhea (22% vs. 3%), breakthrough hemolysis (10% vs. 23%), headache (7% vs. 23%), and fatigue (5% vs. 15%). There were no cases of meningitis in either group.

CONCLUSIONS

Pegcetacoplan was superior to eculizumab in improving hemoglobin and clinical and hematologic outcomes in patients with PNH by providing broad hemolysis control, including control of intravascular and extravascular hemolysis. (Funded by Apellis Pharmaceuticals; PEGASUS ClinicalTrials.gov, NCT03500549.)



Garred et. al. Pharmacol Rev 73:792–827, April 2021

Potential RNAi Advantage

- Eculizumab and Ravulizumab
  - Require 2-3-hour IV infusion every 2 weeks to 2 months.
  - Only block terminal complement pathway, many of the proximal complement actions remain intact.

- Pegcetacoplan
  - ~1 gm of drug in 20 mL to be given SQ with infusion pump.
  - Infused over one hour every 2-3 days.

- ARO-C3
  - Administration of ~1 mL of drug SQ every 3-6 months.

Pegcetacoplan
20 mL (~1 gram) via SQ infusion every 3 days

ARO-C3
~1 mL SQ every 3-6 months

Nephrology, IgAN and C3G
Dr. Richard Glassock

COMPLEMENT and IgA Nephropathy and C3 Glomerulopathy

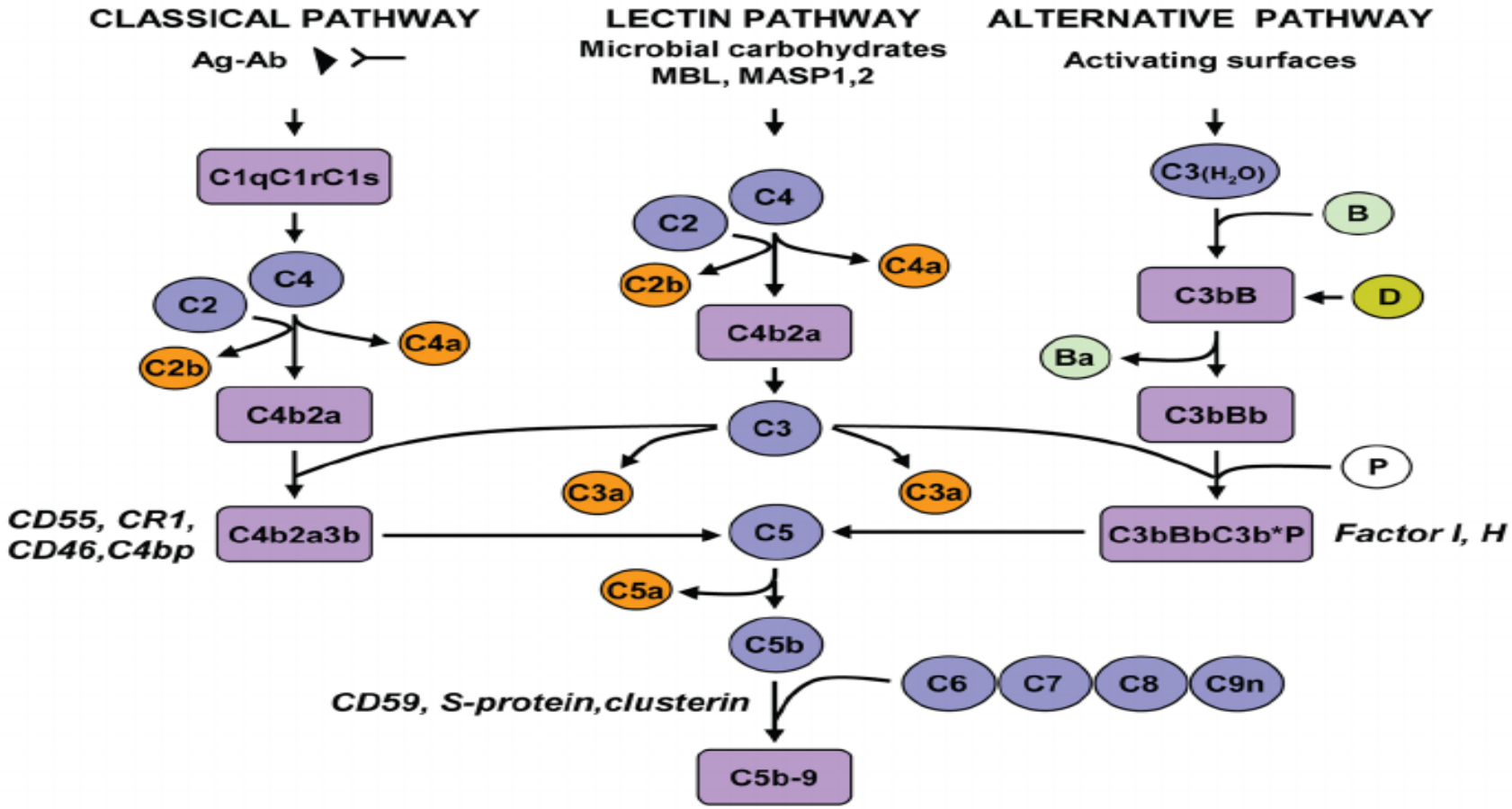
Richard J. Glassock, MD, MACP, FASN

ARROWHEAD Webinar

October 26, 2021

Virtual

THE COMPLEMENT CASCADE



ALL THREE MAJOR PATHWAYS OF COMPLEMENT ACTIVATION PLAY *IMPORTANT ROLES* IN THE PATHOGENESIS OF GLOMERULAR DISEASES,

BUT TO DIFFERING EXTENT IN A DISEASE SPECIFIC MANNER

IgA NEPHROPATHY

IgA N –
Commonest form of "Primary" Glomerulonephritis in World

Can only be *diagnosed* by Kidney Biopsy (no reliable non-invasive diagnostic test)

Incidence= *14-50* cases diagnosed/million population per year (highest in Asia lowest in Africa)

Routine urinalysis screening *increases* incidence as more kidney biopsies are performed

IgA Nephropathy-
Presenting Features- Clinical

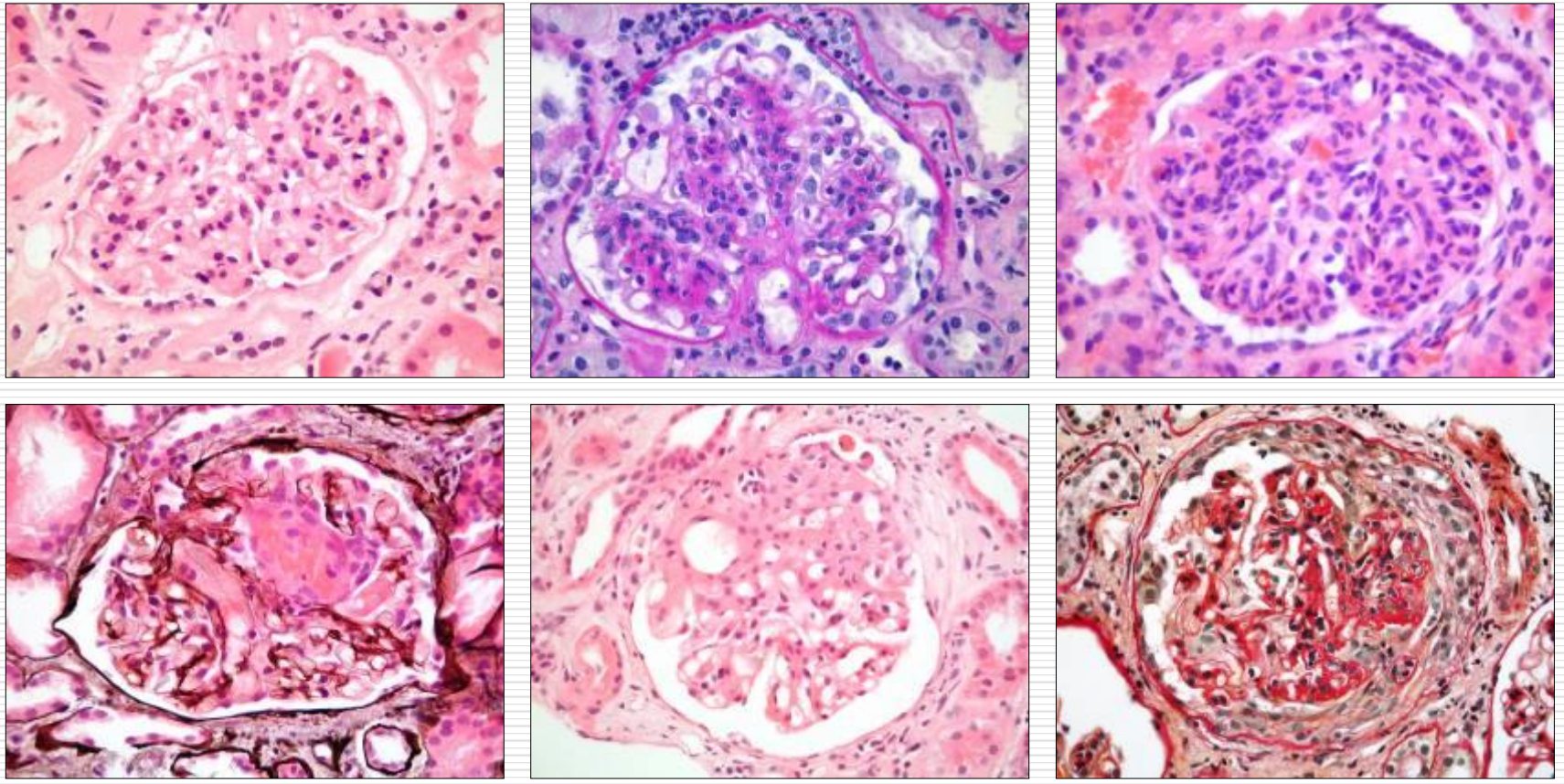
- Isolated Hematuria (persistent or episodic; microscopic or gross)
- Asymptomatic proteinuria (with or without hematuria)
- Slowly progressive CKD
- Acute or Rapidly progressive GN (<10%)
- Nephrotic Syndrome (<10%)
- Acute Renal Failure
- Malignant Hypertension
- Acute thrombotic micro-angiopathy (atypical HUS)- rare

Commonest Presentation is "Symptomless" Hematuria and Proteinuria

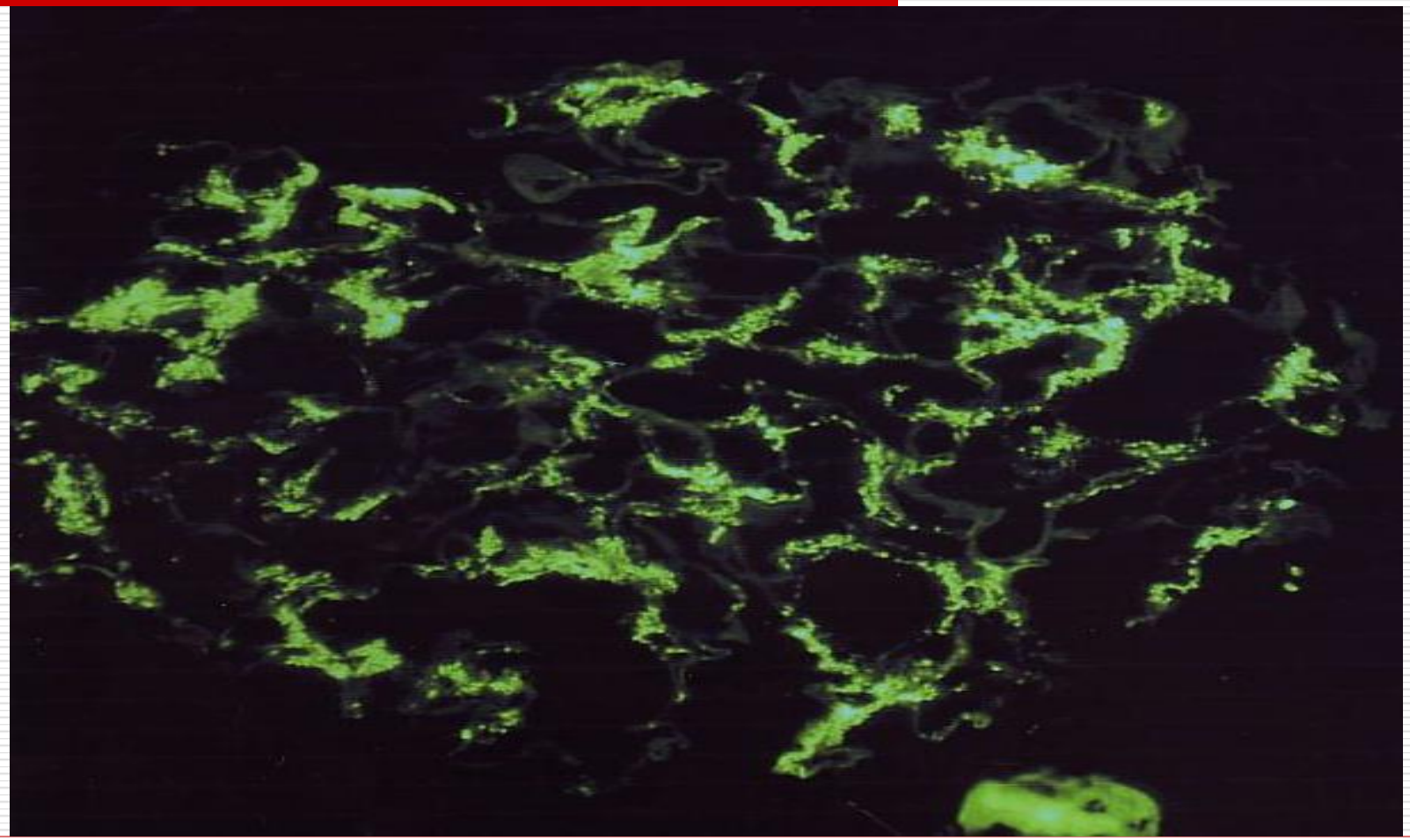
IgA Nephropathy:

Pathologically heterogeneous

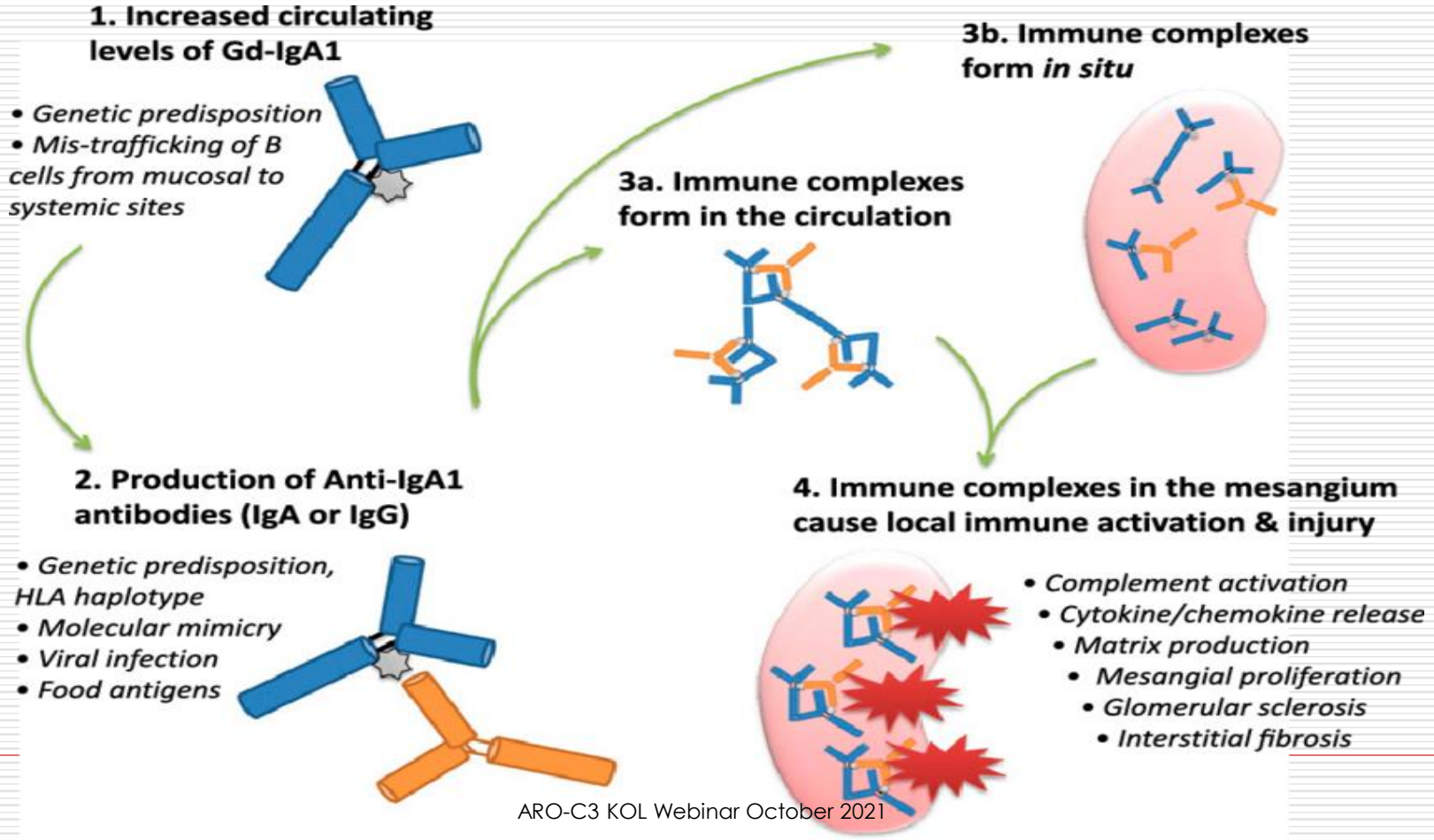
(Roberts, et al ASN CNC. 2008)



IgA Nephropathy:
Immunohistochemically Uniform



Pathogenesis of IgAN
(After Novak J,et al 2018)

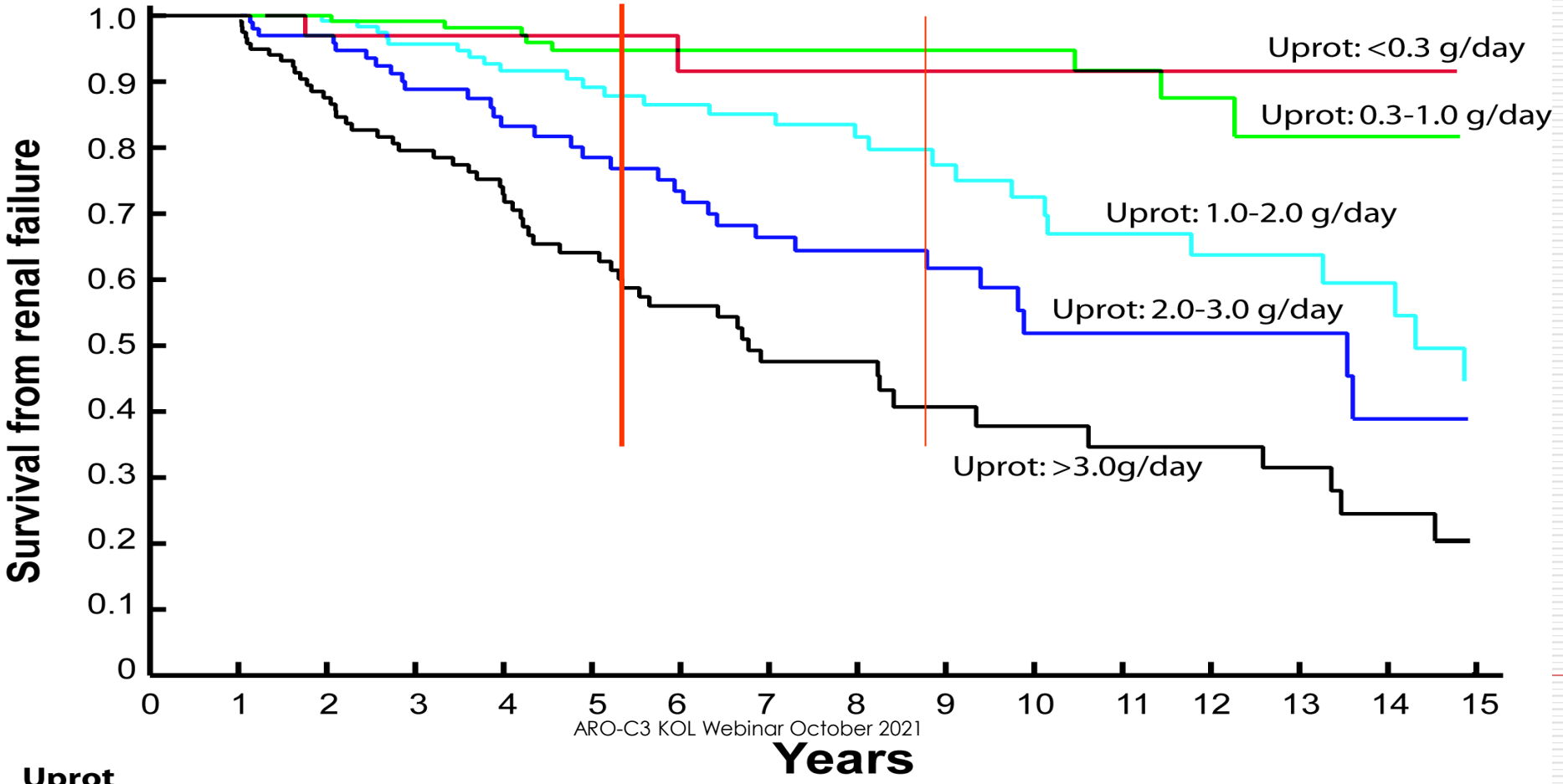


IgA Nephropathy:

Effect of Remission of Proteinuria on Outcome

(Time Averaged Proteinuria, gm/d)

(Reich, H et al.JASN 18:3177, 2007)



RISK STRATIFICATION IN IgA N

(Barbour SJ, et al JAMA- Intern Med, 2019)

Table 3. Rate of Kidney Function Decline and the Mean Predicted 5-Year Risk of the Primary Outcome In Subgroups Based on the Linear Predictor

Risk Subgroup[a]	Mean Predicted 5-Year Risk, %	Rate of eGFR Decline, Mean (95% CI), mL/min/1.73 m^2/y	*P* Value[b]
Full Model With Race/Ethnicity			
Low risk	1.5	−1.24 (−1.63 to −0.85)	<.001
Intermediate risk	4.7	−1.76 (−2.01 to −1.50)	
Higher risk	13.9	−2.35 (−2.35 to −2.10)	
Highest risk	46.5	−3.43 (−3.80 to −3.06)	
Full Model Without Race/Ethnicity			
Low risk	1.6	−1.64 (−2.01 to −1.27)	<.001
Intermediate risk	4.5	−1.82 (−2.07 to −1.57)	
Higher risk	12.0	−2.12 (−2.36 to −1.87)	
Highest risk	40.9	−3.54 (−3.91 to −3.16)	

IgA Nephropathy;
Conventional Treatment

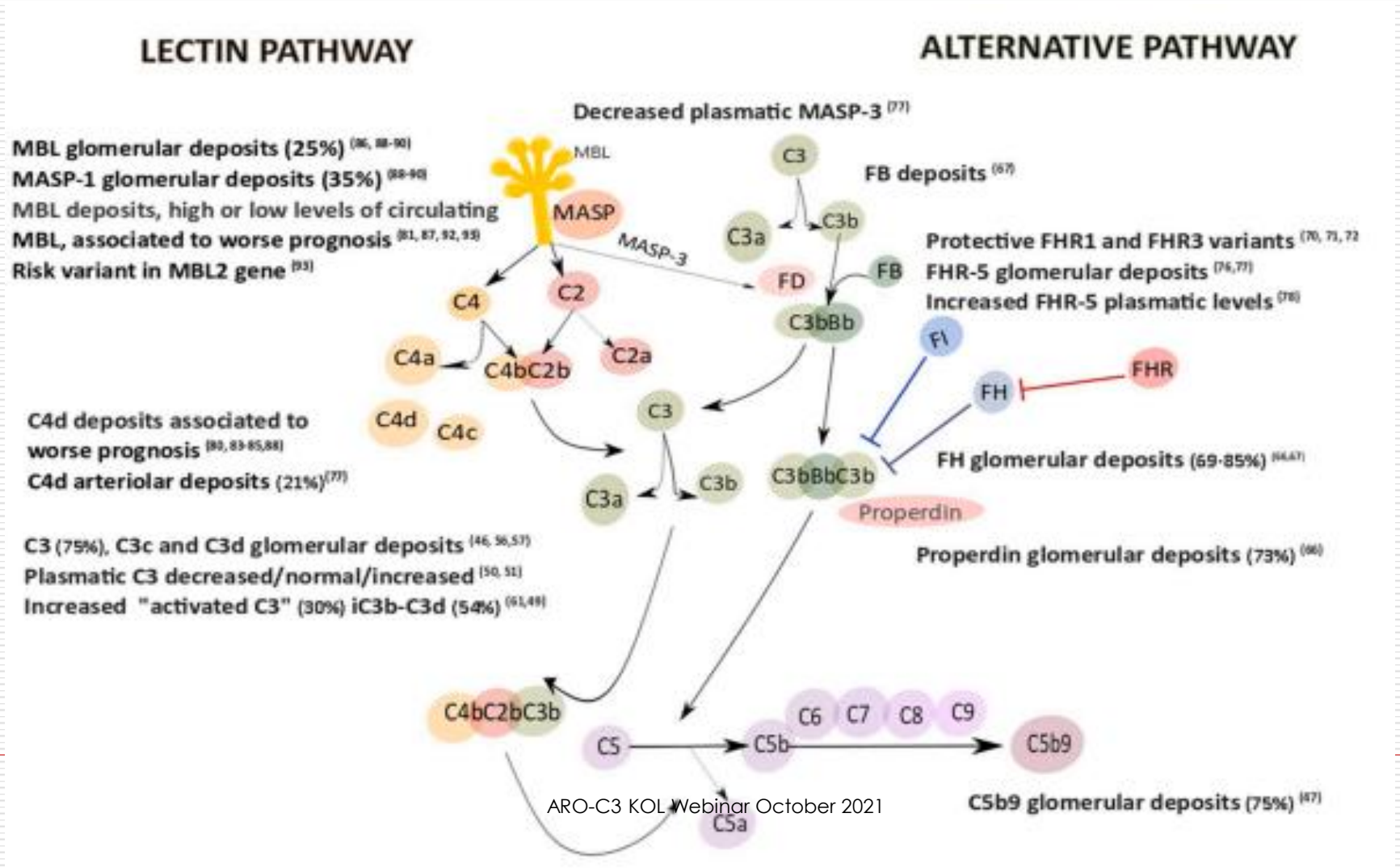
- ***Renin-Angiotensin System Inhibitors:*** (RASi)- Angiotensin Converting Enzyme Inhibitors, Angiotensin Receptor Blockers, Direct Renin inhibitors
- **Sodium Glucose Co Transporter 2 *inhibitors*** (SGLT2i)- Dapagliflozin?

- ***Glucocorticoids (? Dose, duration, formulation)***

Strong and Compelling Evidence
exists that Activation of the Complement Cascade (Lectin and Alternate Pathways) Contribute importantly to Kidney Injury and Progression in IgA N

THE COMPLEMENT CASCADE in IgA N

(From Le Stang M-B, et al, Mol Immunol, 2021)



INVESTIGATIONAL AGENTS

- Blys/April inhibitors (B-Cell therapy)
- Mesenchymal Stem Cells
- Endothelin antagonists (+ RASi)
- *Complement Inhibition (C3, Factor B, Factor D, MASP, C5a, C5a receptor)*
- NRf2 agonist (Bardoxolone)

C3 GLOMERULOPATHY

C3 GLOMERULOPATHY

- **Uncommon disorder <1/million/year**
- **Can only be diagnosed by kidney *biopsy*, including immunofluorescence and electron microscopy**
- **Very likely *heterogeneous* in pathogenesis, but activation of Alternate Pathway key in most cases**

C3 Glomerulopathy:
Clinical Features

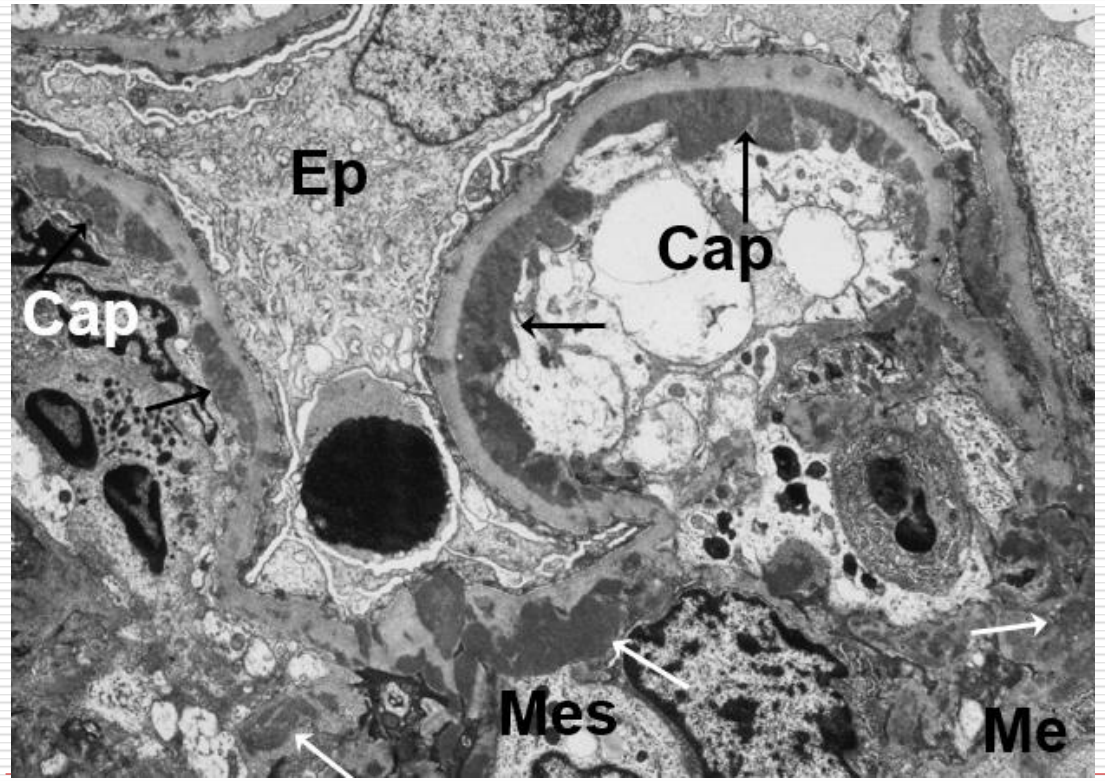
- **Asymptomatic hematuria and proteinuria**
- **Nephrotic Syndrome**
- **Rapidly Progressive GN (uncommon)**

C3 GLOMERULOPATHY:
Pathology

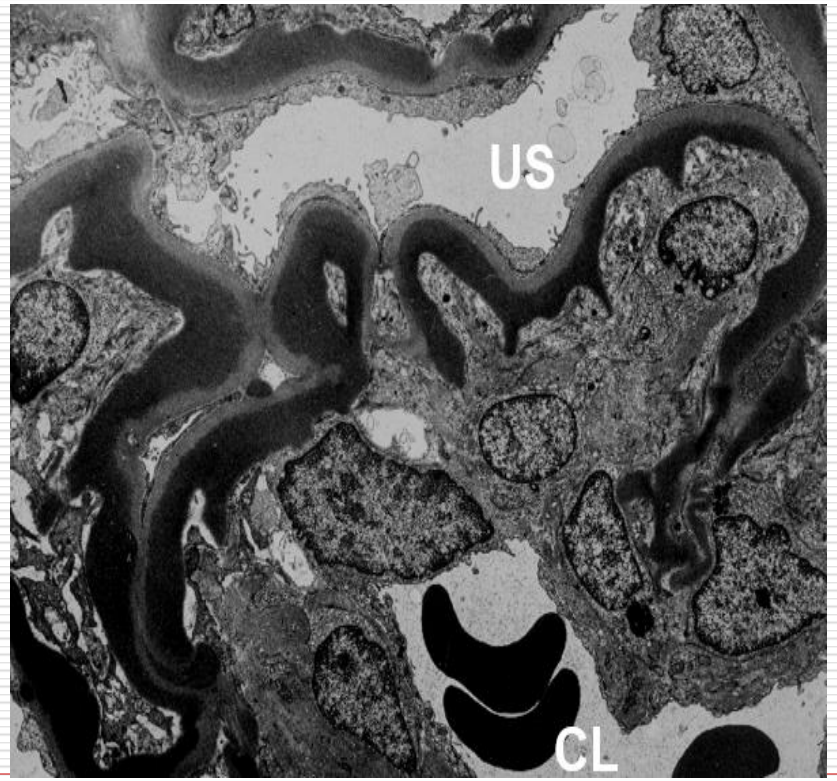
- **LM- Mesangial Proliferative , Membrano-Proliferative or Crescentic glomerulonephris**
- ***IF*- exclusively or dominant C3 deposition, usually without C4 or C1q deposition**
- ***EM*- either sub-endothelial ED deposits (C3GN- 85%)or intramembranous ED deposits (DDD- 15%). Occasional "hump-like" sub-epithelial deposits**

C3 Glomerulopathy:
Electron Microscopy

C3 Glomerulonephritis



Dense Deposit Disease



C3 Glomerulopathy:
Pathogenesis

- Genetic complement regulatory mutation (CfH, CFHR-5, others)
- Light chain monoclonal gammopathy that inhibits action of CfH on C3b
- Auto-antibody to CfH
- Infections (bacterial, viral)
- Other

C3 GLOMERULOPATHY
Treatment

- **UNCERTAIN – NO RCT.**
- **Steroids with or without Mycophenolate Mofetil may be effective in some cases**
- **Eculizumab may be effective is selected cases (severe or recurrent disease in kidney transplants)**

C3 GLOMERULOPATHY

Investigational Agents

- **Complement inhibition; C3, Factor B, Factor D, C5, C5a Receptor**
- **Monoclonal ant0CD20 antibody**
- **Chemotherapy for monoclonal Light Chain Disorders**
- **Liver transplantation (for CfH mutations)**

SUMMARY and CONCLUSIONS

- **Both IgA Nephropathy and C3 Glomerulopathy are *attractive target disease* for Complement Inhibitor therapy**

- **Multiple targets within the Complement Cascade are *viable candidates* for testing of efficacy and safety of novel agents**

Hematology - PNH
Dr. Peter Browett

Paroxysmal Nocturnal Haemoglobinuria

-addressing the unmet needs-

Peter Browett
Molecular Medicine and Pathology
Leukaemia and Blood Research Unit
University of Auckland

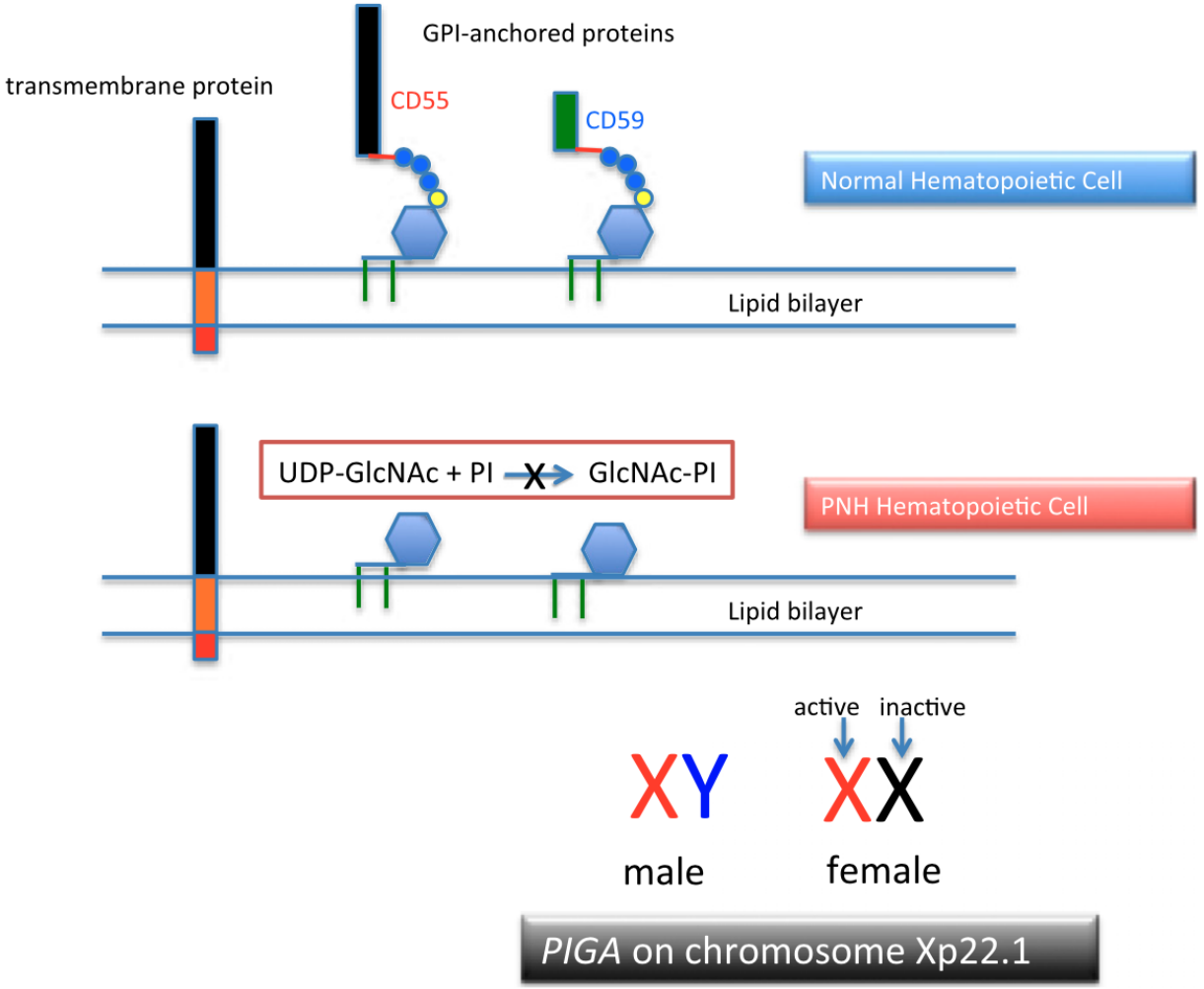
Paroxysmal Nocturnal Haemoglobinuria (PNH)

Rare acquired blood cell disorder due to loss of complement regulatory proteins CD55 and CD59

Considered an “ultra-orphan” disease with prevalence of 16 per million population

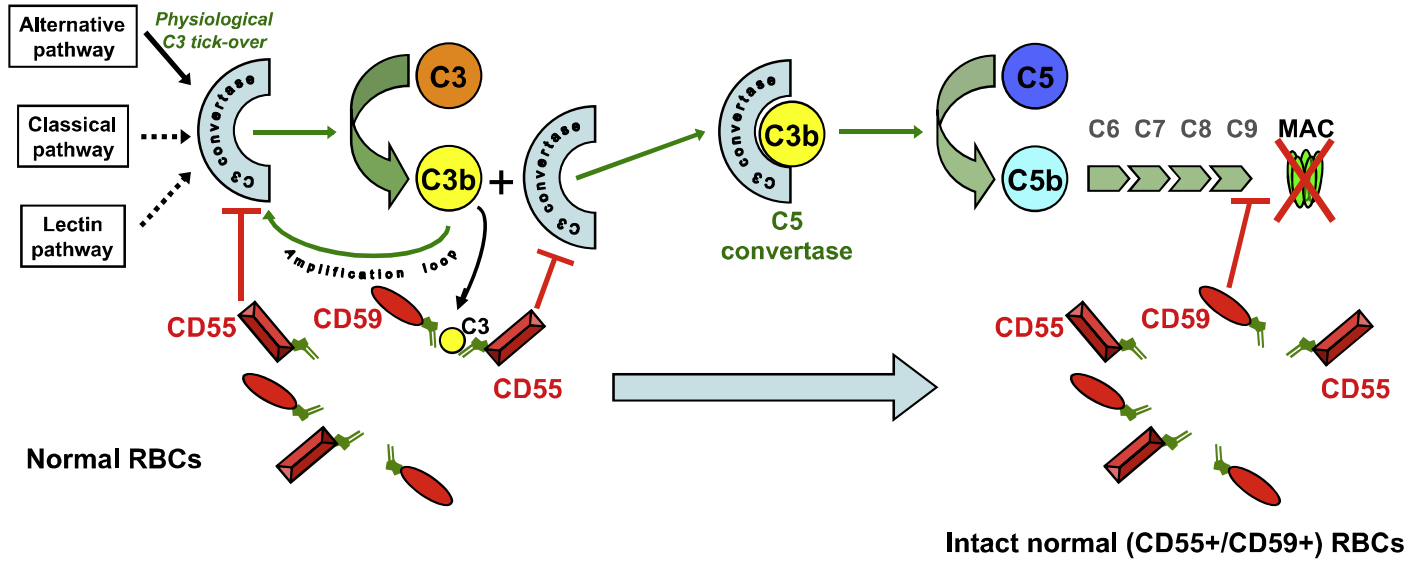
Neither paroxysmal, nocturnal and not all patients have haemoglobinuria

PNH is caused by loss of GPI anchored proteins



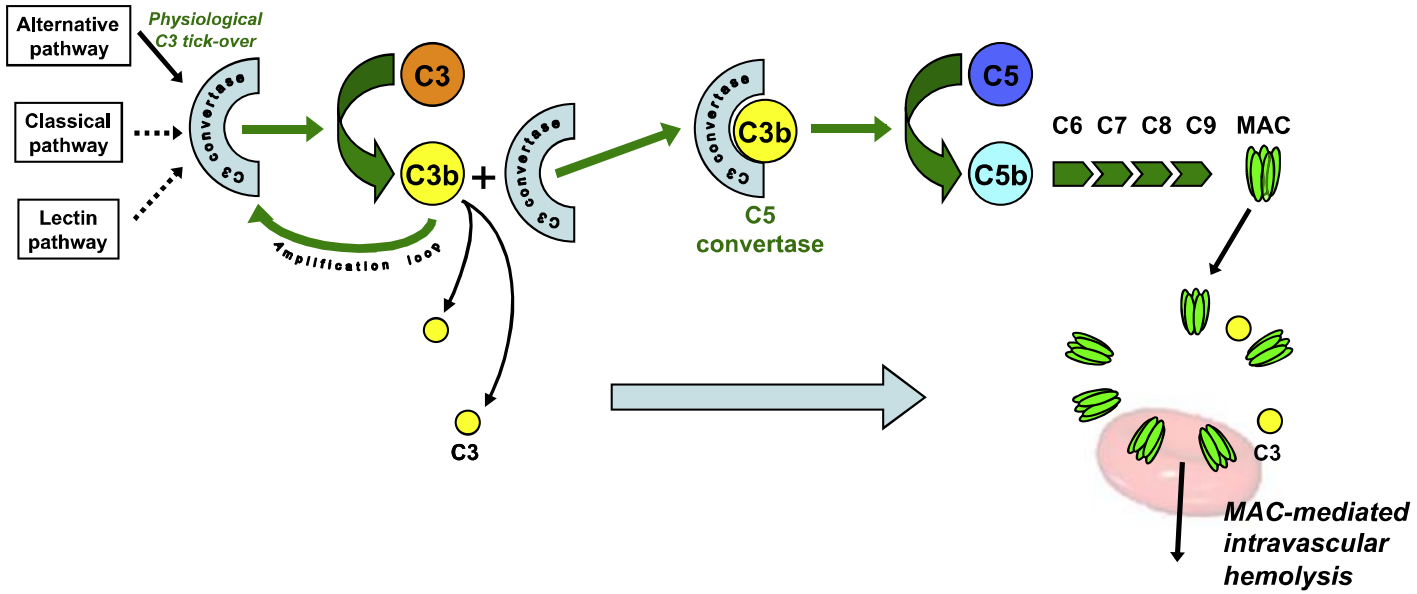
Parker et al Blood 2016

Loss of GPI anchored proteins predisposes intravascular haemolysis



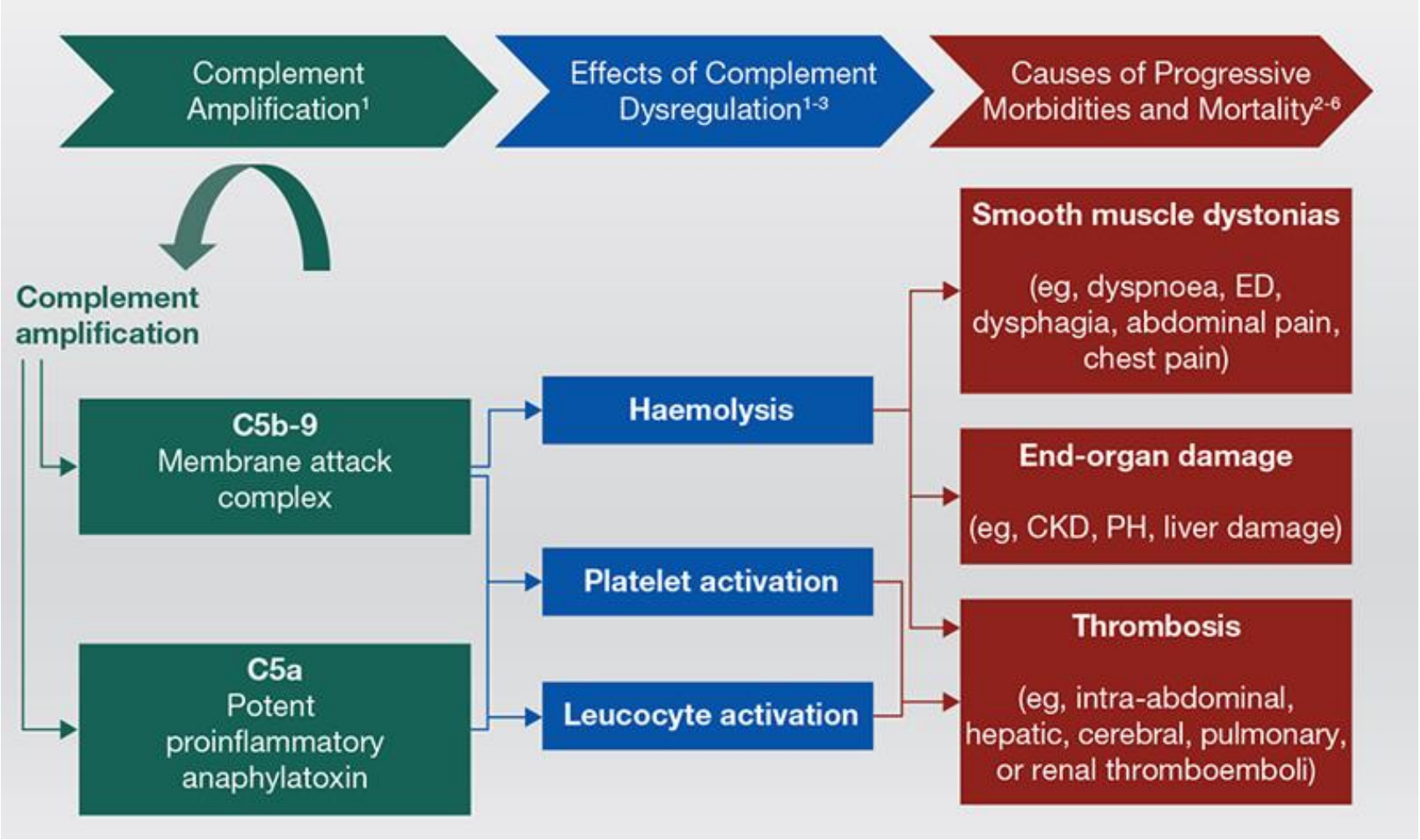
Notaro and Sica Seminars in Hematology 2018

Loss of GPI anchored proteins predisposes intravascular haemolysis

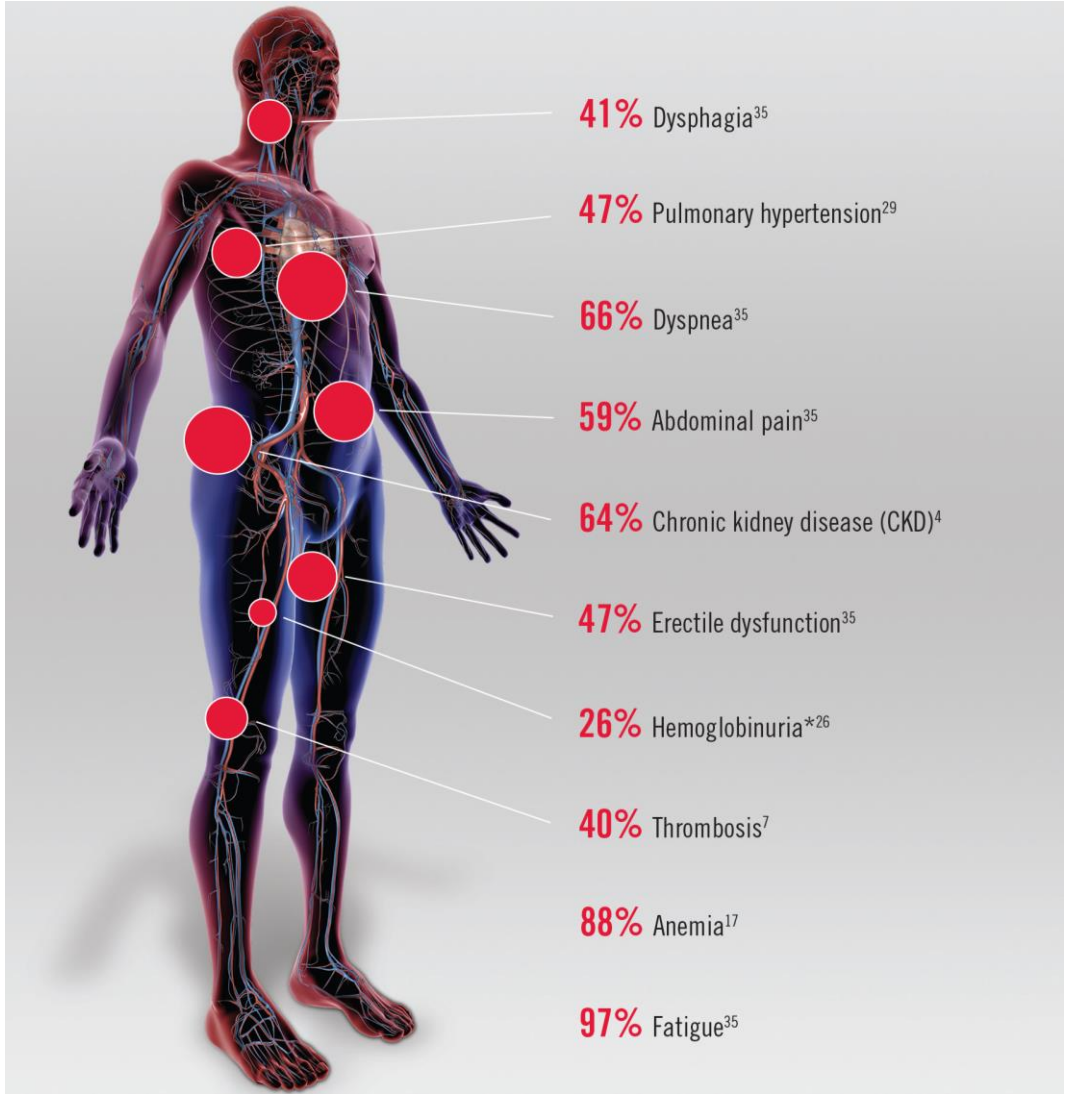


Notaro and Sica Seminars in Hematology 2018

PNH is a multisystem disease

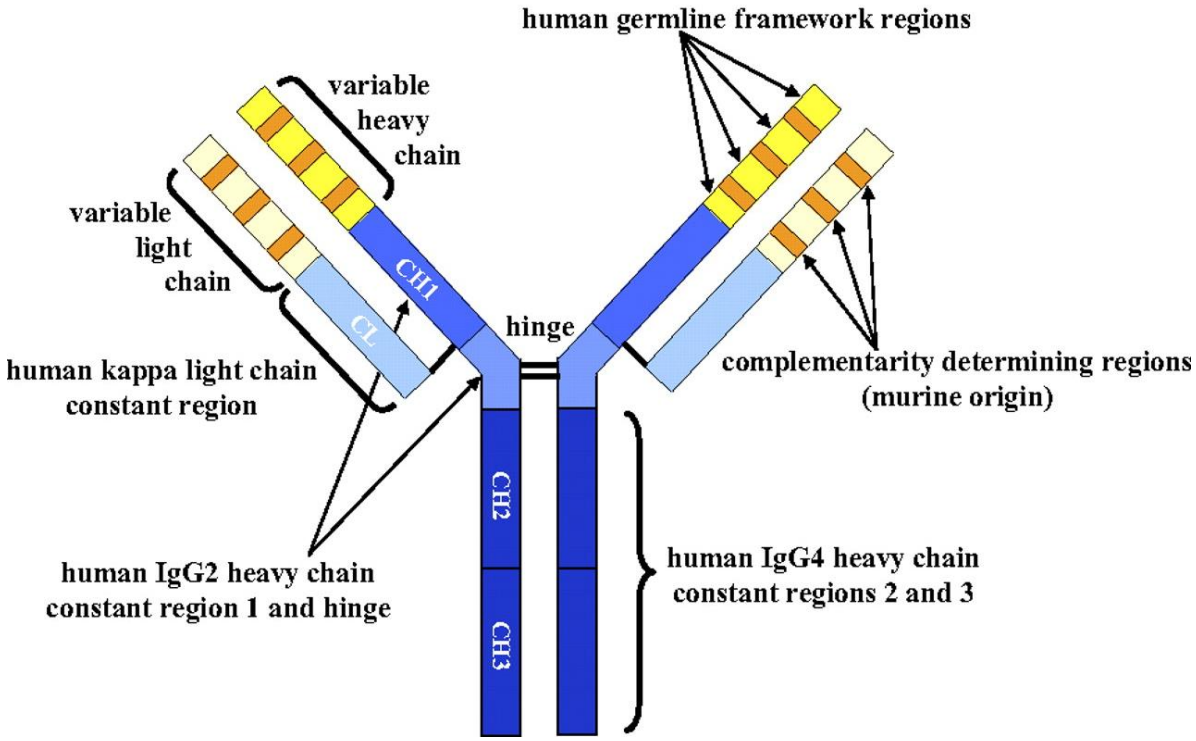


Symptoms often non specific

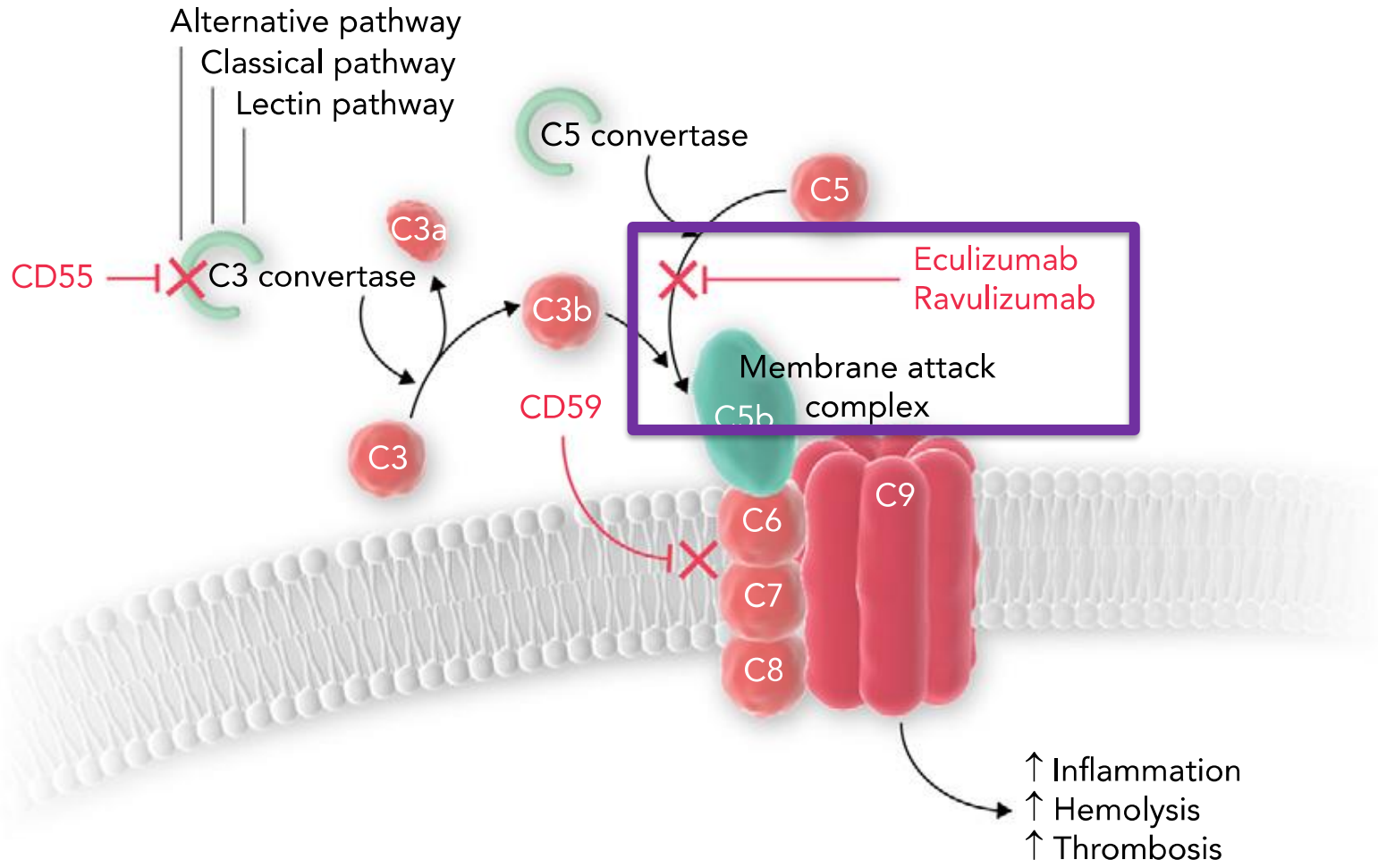


Disease modifying therapy in PNH

Eculizumab C5 inhibitor

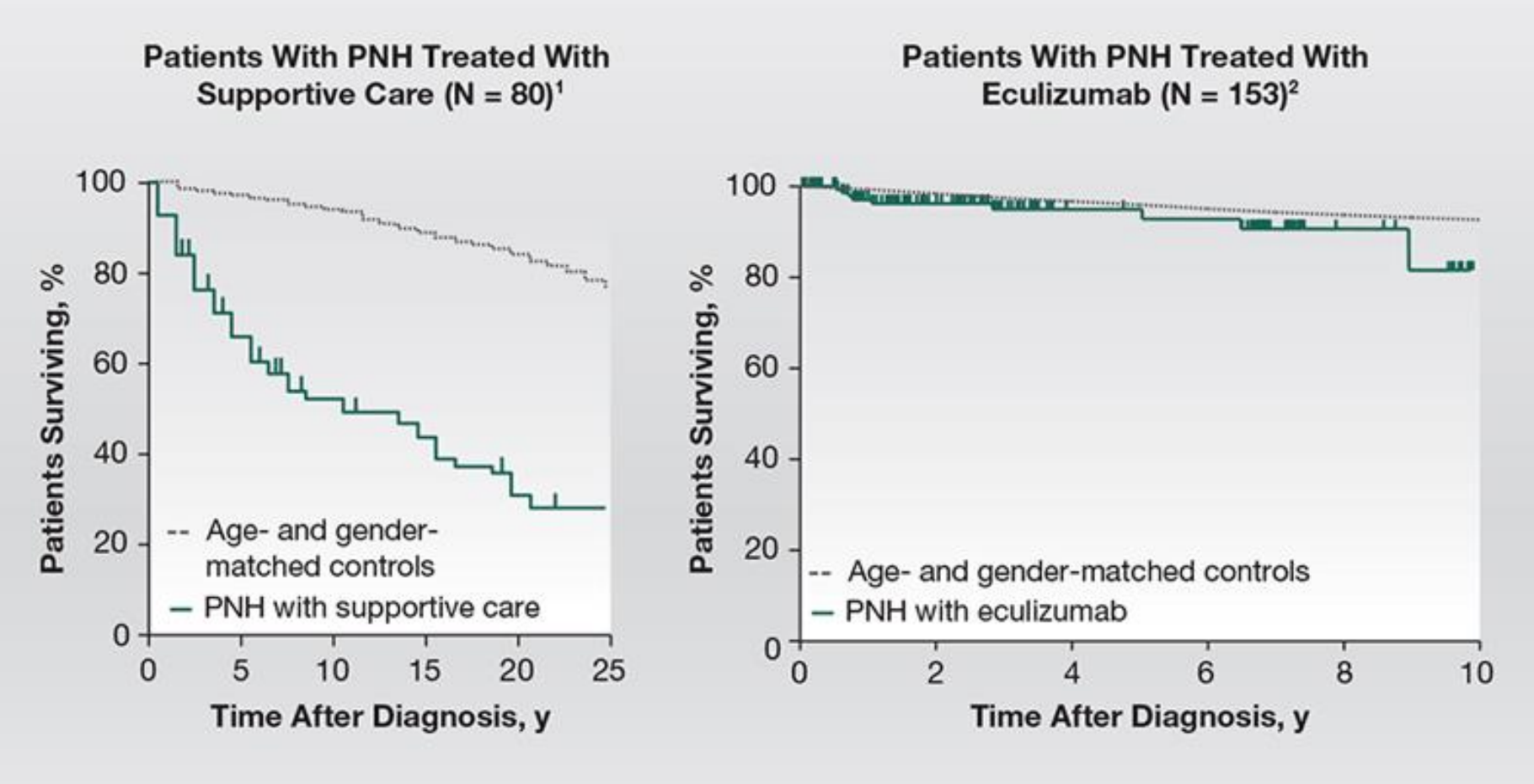


Disease modifying therapy in PNH



Connell Blood 2019

Improved quality of life and overall survival on Eculizumab



Unmet needs in treating PNH

Breakthrough intravascular haemolysis

Emergence of extravascular haemolysis

The requiremnt for lifelong intravenous infusions of antibody

Risk of meningococcal infection

Unmet needs in treating PNH

Breakthrough intravascular haemolysis

Reason	Cause	Prevalence	Mechanism	Clinical impact on hematological response
Intravascular hemolysis	Inherited C5 variants	Ultra-rare (<1%, usually in Japanese patients)	Intrinsic resistance due to impaired binding of eculizumab (and of ALXN1210)	Minimal (but very significant for the few patients for whom there is no available treatment)
	Recurrent pharmacokinetic breakthrough	10–15% of patients	Inadequate plasma level of eculizumab	Significant
	Sporadic pharmacodynamics breakthrough	May occur in any patients	Massive complement activation due to concomitant clinical events	Minimal

Risitano et al Frontiers in Immunology 2019

Unmet needs in treating PNH

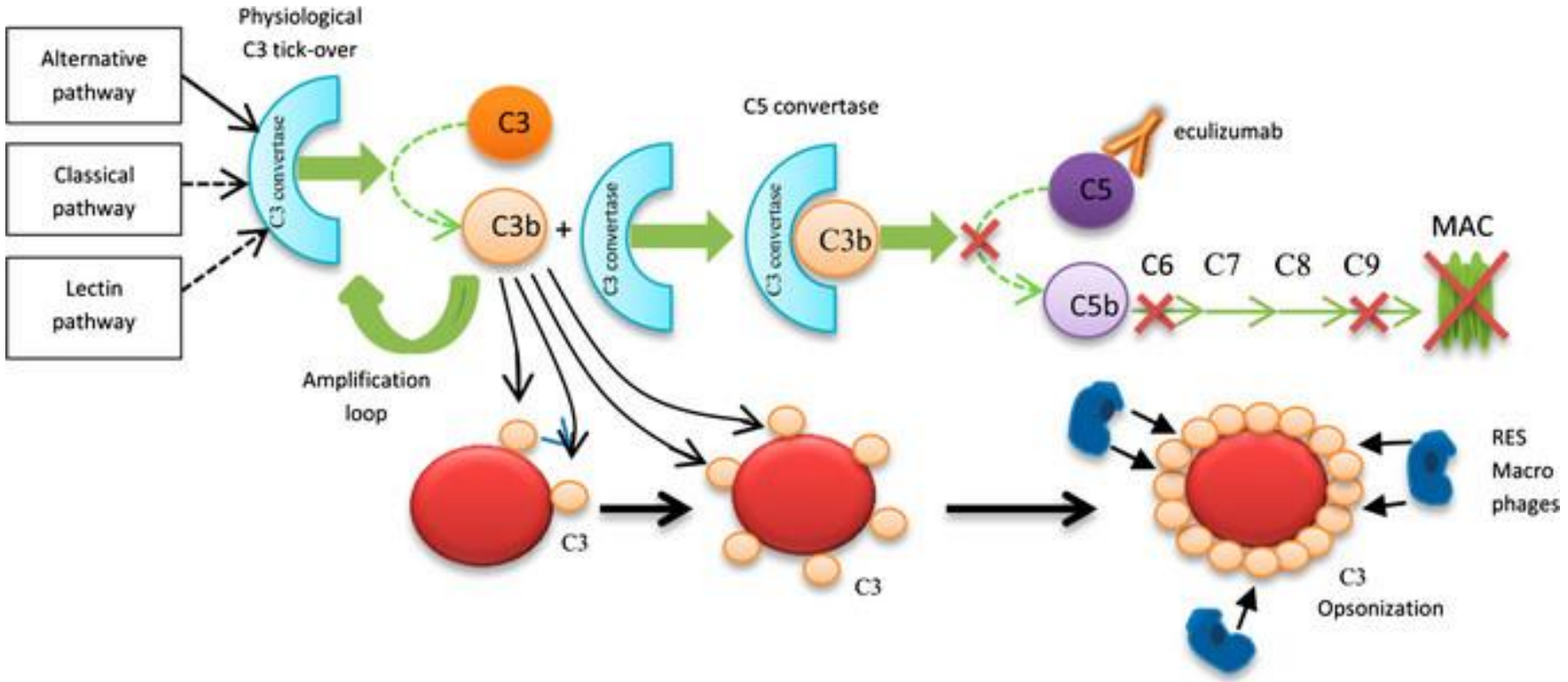
Breakthrough intravascular haemolysis

Emergence of extravascular haemolysis

The requirment for lifelong intravenous infusion of antibody 2 weekly

Risk of meningococcal infection

Breakthrough extravascular haemolysis



C3 mediated extravascular haemolysis
25% of patients

Unmet needs in treating PNH

Breakthrough intravascular haemolysis

Breakthrough extravascular haemolysis

The requirment for lifelong intravenous infusions of antibody

Risk of meningococcal infection

CLINICAL TRIALS AND OBSERVATIONS

Ravulizumab (ALXN1210) vs eculizumab in C5-inhibitor–experienced adult patients with PNH: the 302 study

Austin G. Kulasekararaj,[1] Anita Hill,[2] Scott T. Rottinghaus,[3] Saskia Langemeijer,[4] Richard Wells,[5] F. Ataulfo Gonzalez-Fernandez,[6] Anna Gaya,[7] Jong Wook Lee,[8] Emilio Ojeda Gutierrez,[9] Caroline I. Piatek,[10] Jeff Szer,[11] Antonio Risitano,[12] Shinji Nakao,[13] Eric Bachman,[3] Lori Shafner,[3] Andrew I. Damokosh,[3] Stephan Ortiz,[3] Alexander Röth,[14] and Regis Peffault de Latour[15-17]

CLINICAL TRIALS AND OBSERVATIONS

Ravulizumab (ALXN1210) vs eculizumab in adult patients with PNH naive to complement inhibitors: the 301 study

Jong Wook Lee,[1] Flore Sicre de Fontbrune,[2] Lily Wong Lee Lee,[3] Viviani Pessoa,[4] Sandra Gualandro,[5] Wolfgang Füreder,[6] Vadim Ptushkin,[7] Scott T. Rottinghaus,[8] Lori Volles,[8] Lori Shafner,[8] Rasha Aguzzi,[8] Rajendra Pradhan,[8] Hubert Schrezenmeier,[9,10] and Anita Hill[11]

Ravulizumab every 8 weeks is non inferior to eculizumab every 2 weeks in C5 inhibitor naïve and eculizumab treated PNH patients

Blood February 2019

Unmet needs in treating PNH

Breakthrough intravascular haemolysis

Breakthrough extravascular haemolysis

Lifelong intravenous infusion of antibody 2 weekly

Risk of meningococcal infection

IMMUNOBIOLOGY AND IMMUNOTHERAPY

Eculizumab treatment and impaired opsonophagocytic killing of meningococci by whole blood from immunized adults

Monica Konar and Dan M. Granoff

Center for Immunobiology and Vaccine Development, UCSF Benioff Children's Hospital Oakland, Oakland, CA

43 cases of meningococcal disease reported in in patients treated with eculizumab

- Estimated annual incidence 330 per 100,000
- Annual rate general population 0.5 per 100.000
- Almost all eculizumab population immunized

Konar and Granoff Blood 130(17): 891; 2017

How do we address the unmet needs in treating PNH

Breakthrough intravascular haemolysis

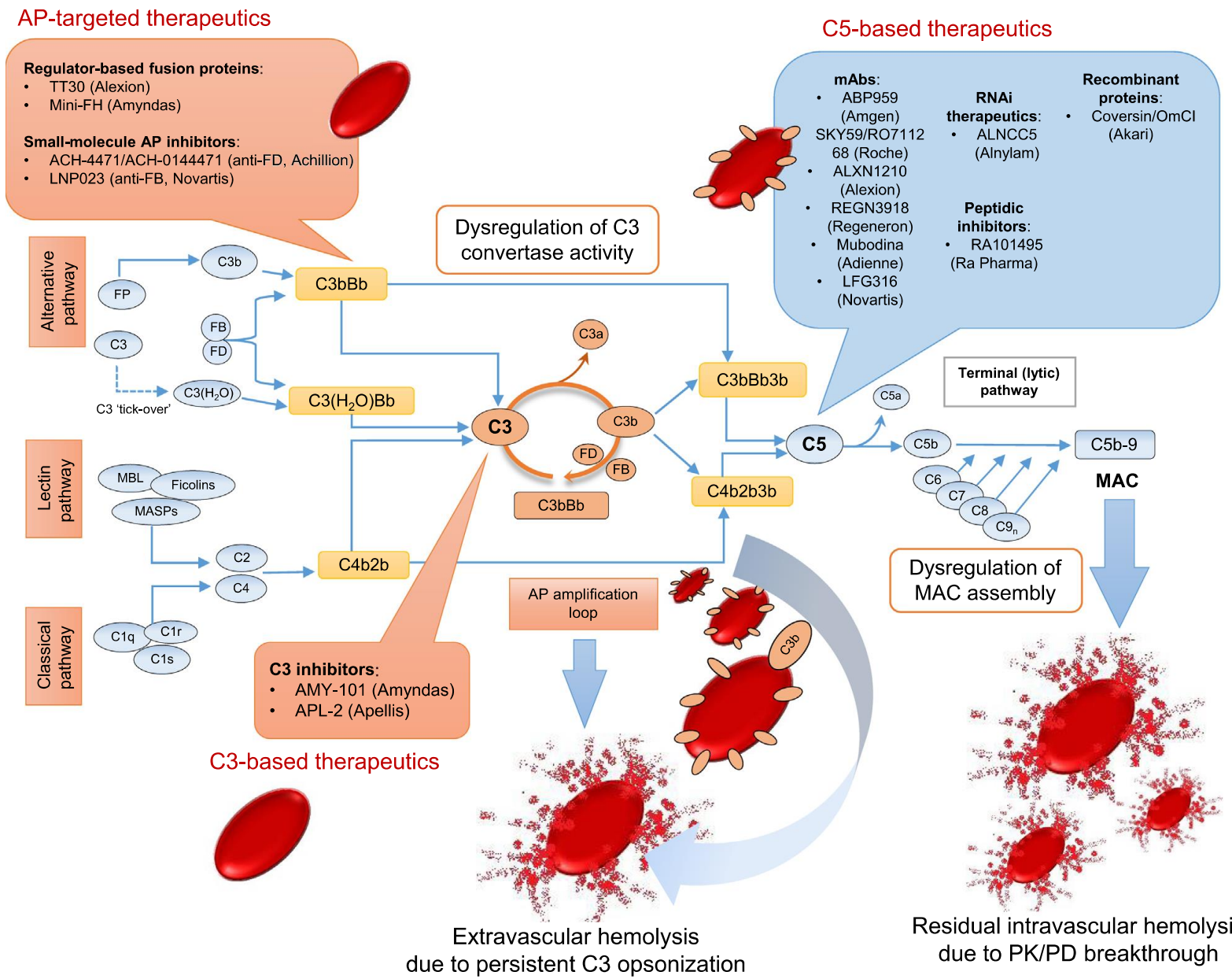
More effective complement blockade

Emergence of extravascular haemolysis

Proximal inhibition of complement

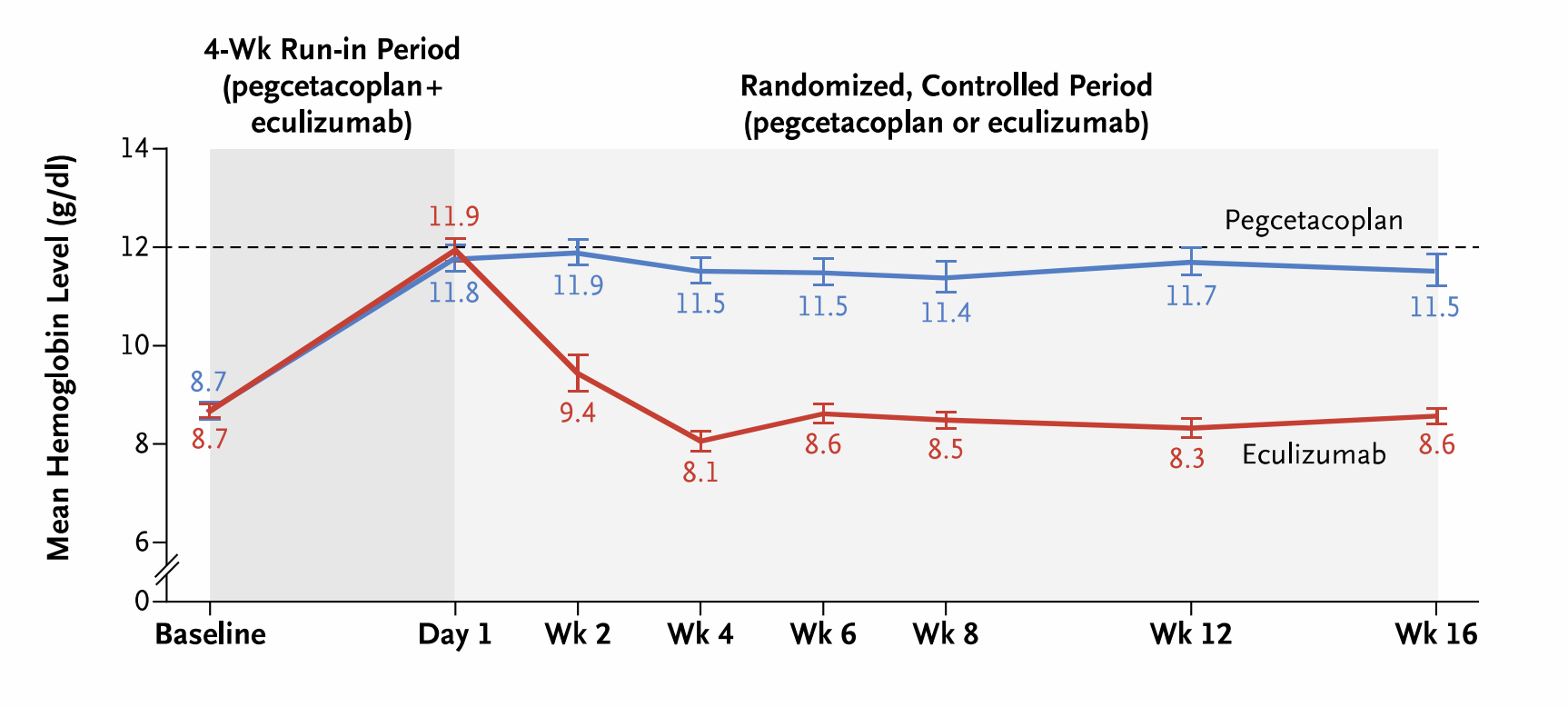
The requiremnt for lifelong intravenous infusions of antibody

Longer acting therapy



Mastellas et al Seminars in Hematology 2018

Proof of Principle: C3 inhibition in PNH with Pegcetacoplan



PEGASUS Trial Hillmen et al New Engl J Med 2021

The unmet needs in PNH

PNH is a multisystem disease of complement dysregulation

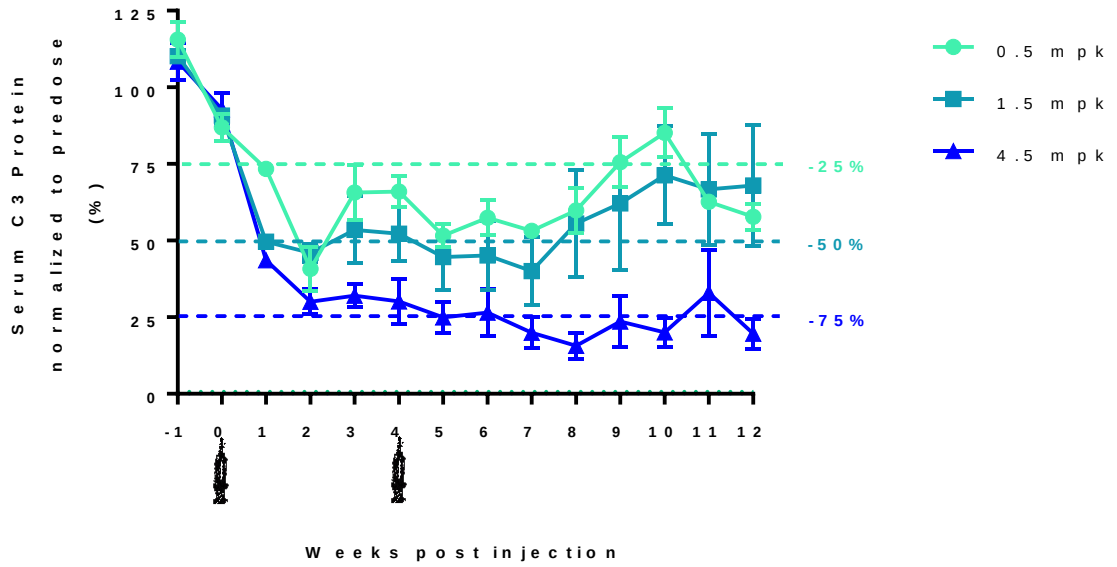
C5 inhibition has improved survival and quality of life for PNH patients but breakthrough extravascular haemolysis in up to 25% of patients

Potential benefit for proximal C3 inhibition as a target in PNH

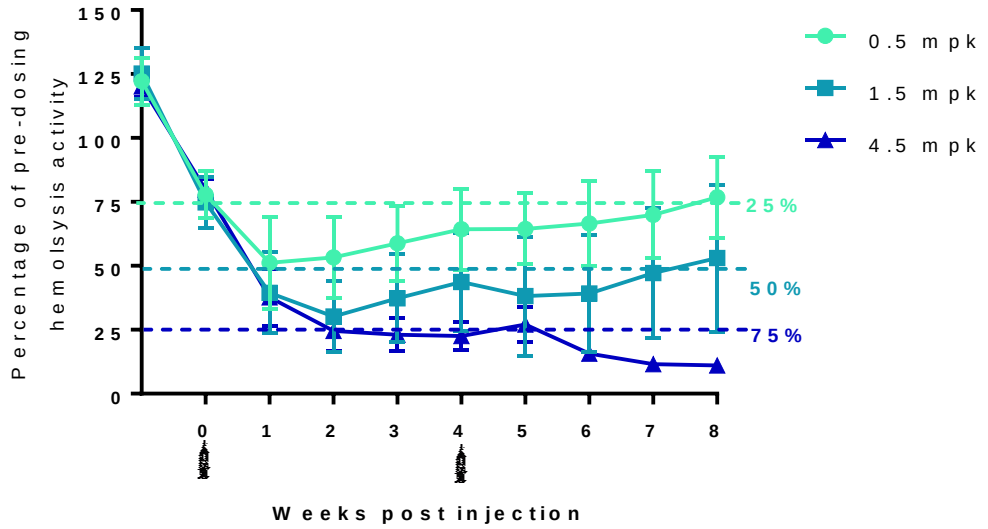
ARO-C3 Preclinical Data and Clinical Plan
Dr. James Hamilton

ARO-C3 Potently Decreases Serum C3 Levels and C3 Function in Cynomolgus Monkeys

Serum C3 level



Hemolysis



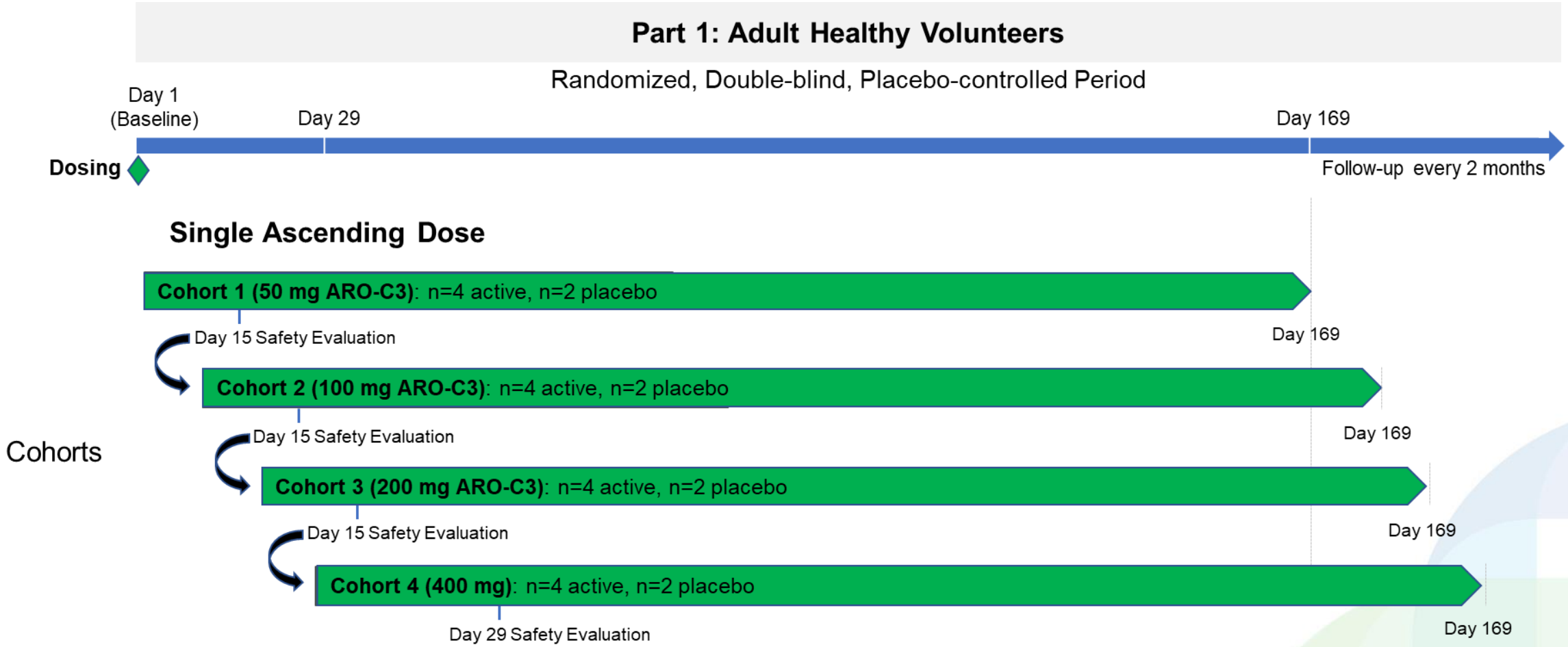
Male cynomolgus monkeys
N=3/group
ARO-C3 was administrated subcutaneously

Maximum serum C3 reduction of 90% with associated reduction in hemolytic activity and long duration of effect

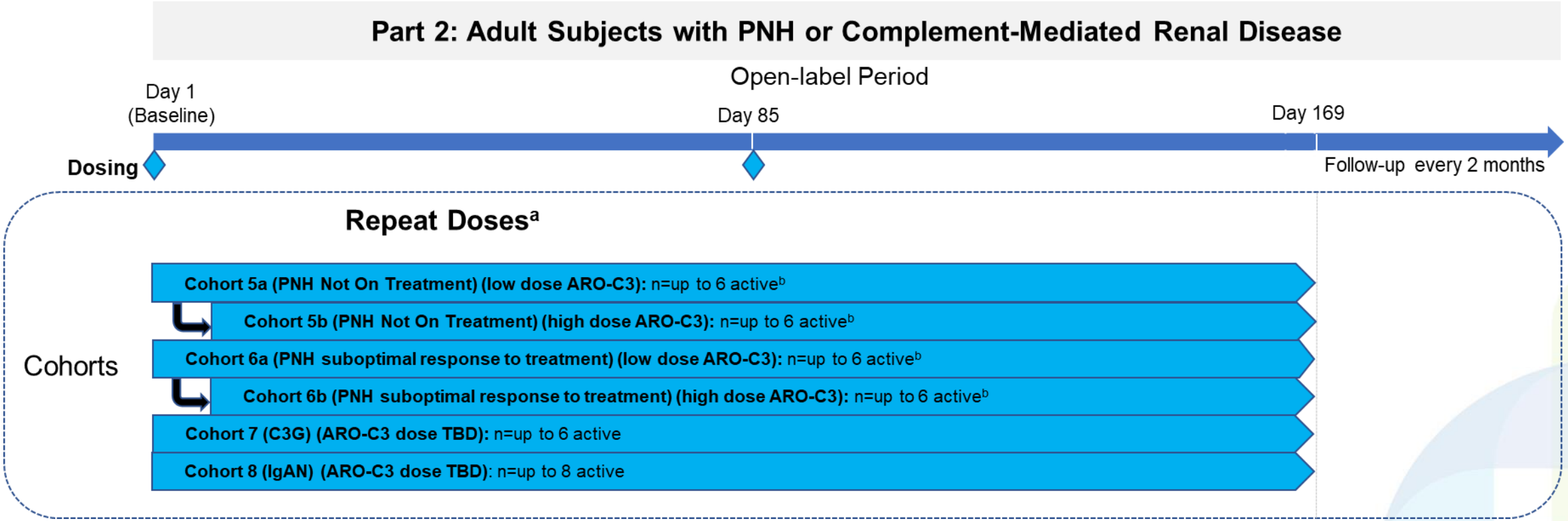
AROC3-1001 Clinical Study

- Phase 1/2a dose-escalating study to evaluate the safety, tolerability, pharmacokinetics, and pharmacodynamics of ARO-C3
- Part 1 - Single Ascending Doses
  - 24 healthy volunteer subjects
  - 4 cohorts
  - Placebo controlled
- Part 2 – Dose selection based on Part 1
  - 38 subjects with PNH, IGaN, C3G
  - 6 cohorts
  - Open label
- CTA filed
- Dosing expected to begin Q1 2022

Part 1: Healthy Volunteer Cohorts 1-4 (24 subjects)



Part 2: Patient Cohorts 5-8 (38 subjects)



Wrap Up
Vince Anzalone

What Do We Know?

- Complement C5 inhibitors are disease modifying
- Substantial unmet medical need remains in:
  - Nephrology
  - Hematology
- Clinical validation exists for C3 inhibitors

Why We're Confident in ARO-C3

- Proximal C3 inhibition may confer advantages over C5
- Multiple commercially attractive opportunities
- RNAi-based C3 inhibition has dosing advantages over other MOAs
- ARO-C3 is the first clinical stage RNAi-based candidate
- TRiM™-based candidate targeting liver-expressed protein
  - A proven hepatocyte delivery platform
  - Deep and durable knockdown of target genes
  - Consistent safety and tolerability
- Potential for rapid clinical proof of concept

Q&A Session
Panel