PNH Overview: New Treatment Options

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Disclosures

Advisory Boards/CME Lectures for:

- BMS/Celgene
- Sobi
- Astra-Zeneca/Alexion
- Novartis
- Taiho
- Abbvie

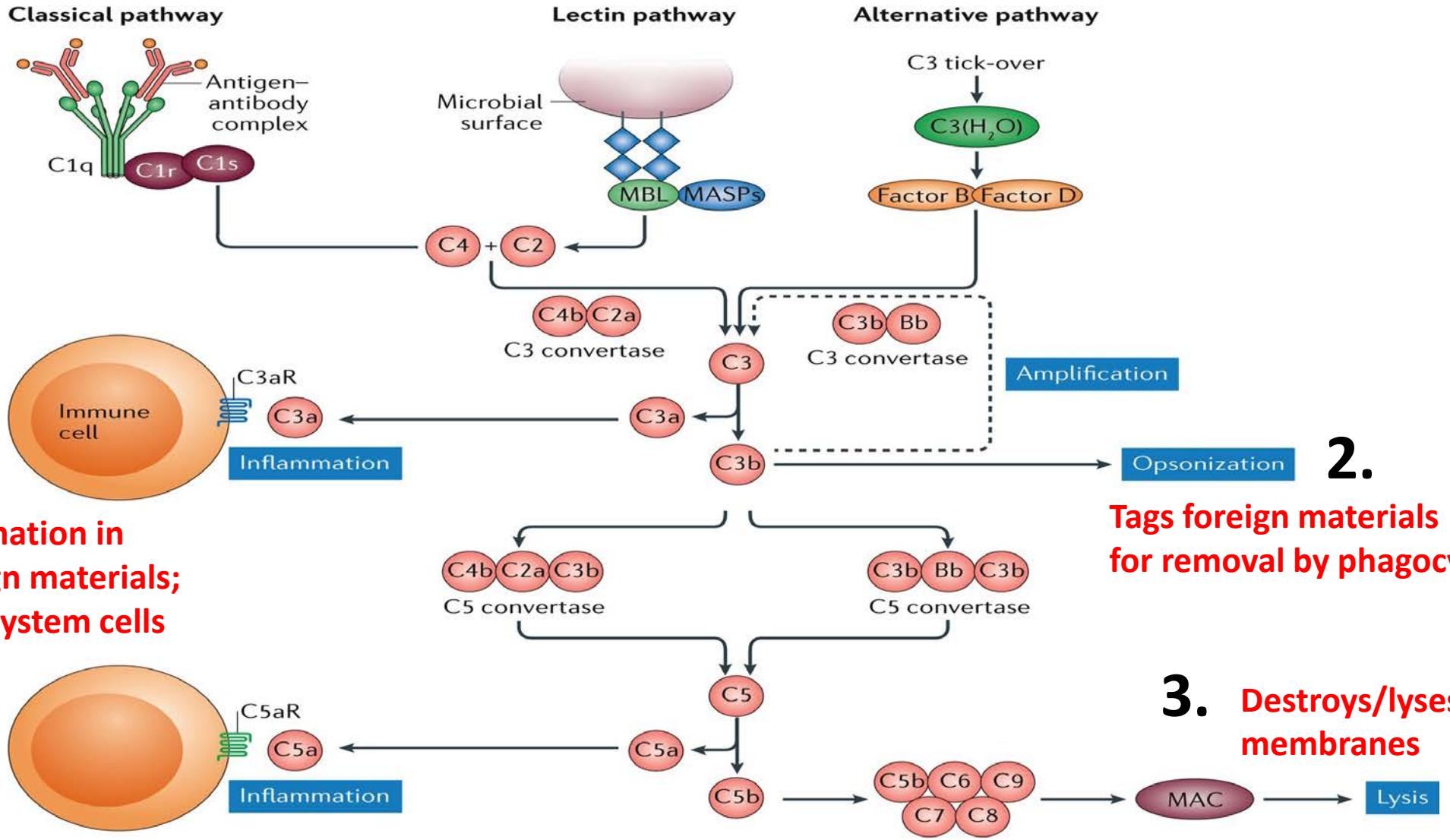
What is PNH?

- Paroxysmal Nocturnal Hemoglobinuria was first described by German physician, Dr. Paul Strübing in 1882
- A 29-year-old man that “voided dark urine only in the morning”
- Dr. Strübing proposed that red blood cells were susceptible to destructive hemolysis in an acid environment

PNH Basics

- **Acquired** disorder
- Affects bone marrow **stem cells** and all 3 cell lines (red, white, platelets)
- **Rare** (4 cases per million)
- Median age: Early 30s
- Key contributor to manifestations is the **complement system**

The Complement Pathway: 3 Major Functions



1.

Promotes inflammation in response to foreign materials; attracts immune system cells

2.

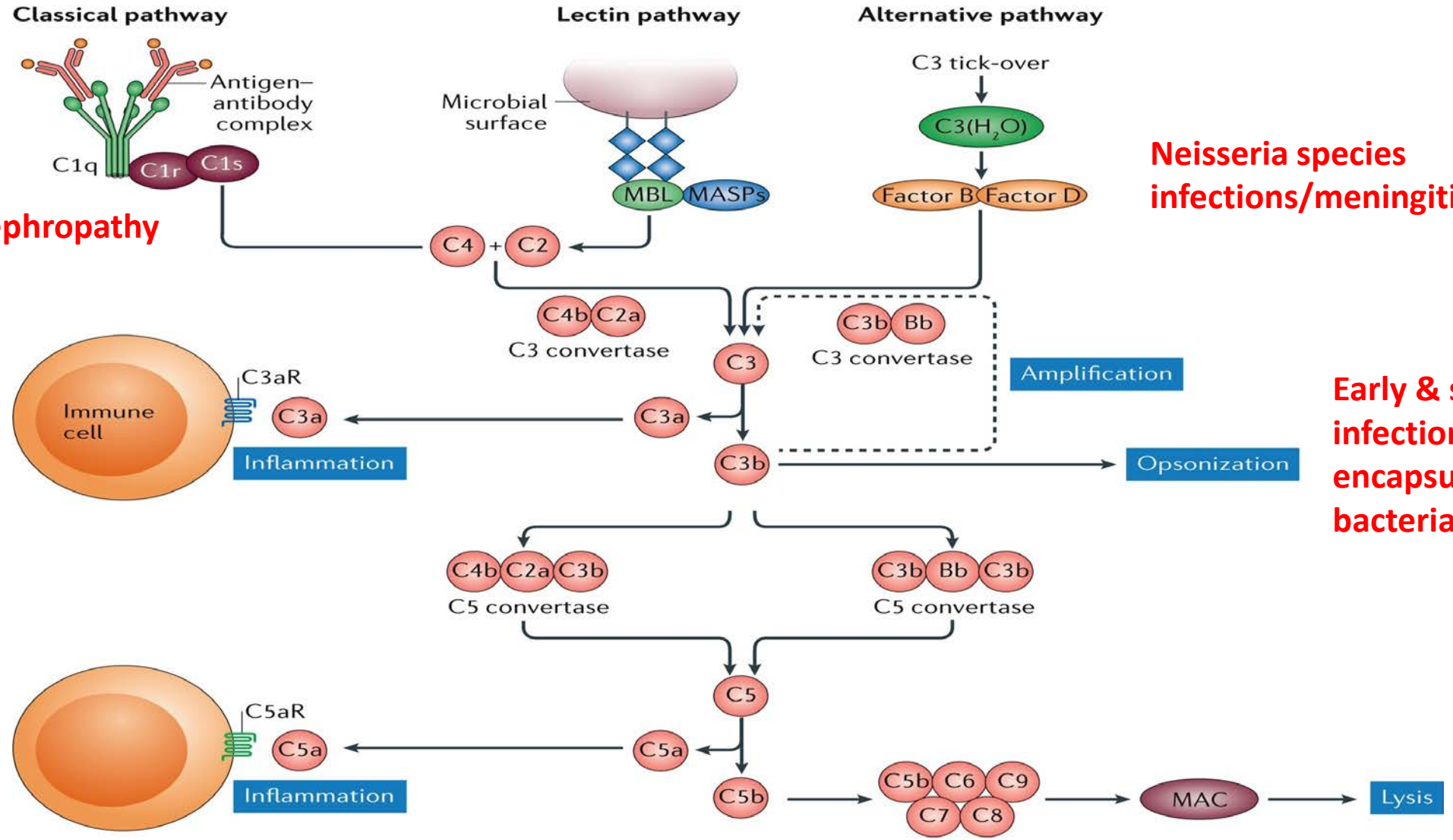
Tags foreign materials for removal by phagocytes

3. **Destroys/lyses foreign membranes**

Nature Reviews | Rheumatology
Trouw et al, 2017

Complement Pathway Deficiencies

- SLE
- Scleroderma, nephropathy & vasculitis



Neisseria species infections/meningitis

Neisseria species infections/meningitis

Early & severe infections with encapsulated bacteria

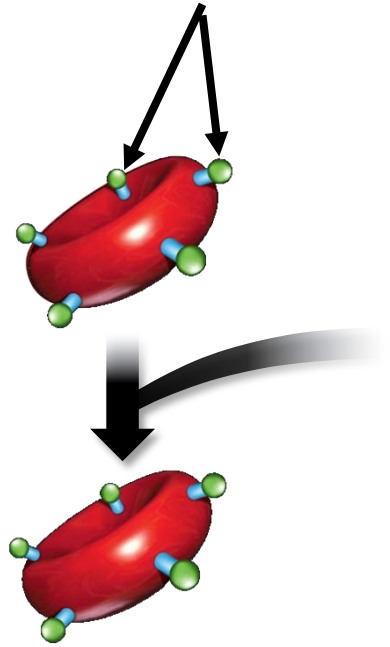
Nature Reviews | Rheumatology
Trouw et al, 2017

THE “ABC” FEATURES OF PNH

- **A**nemia – Destruction (hemolysis) of red blood cells
- **B**one marrow failure – Underproduction of red cells
  “Aplastic” / “hypoplastic” marrow due to autoimmune attack of healthy cells (PNH cells relatively resistant)
- **C**lotting - Venous or arterial thrombosis (unusual sites)

COMPLEMENT CAUSES HEMOLYSIS IN PNH

Normal RBCs protected from complement by GPI-anchored proteins shield



Complement activation

Lack of GPI bound shield in PNH

Free hemoglobin

HEMOLYSIS CAUSES SYMPTOMS IN PNH

Free hemoglobin

Decreased NO

Smooth muscle/Vaso spasm

- **Dyspnea**
- **Fatigue**

Anemia

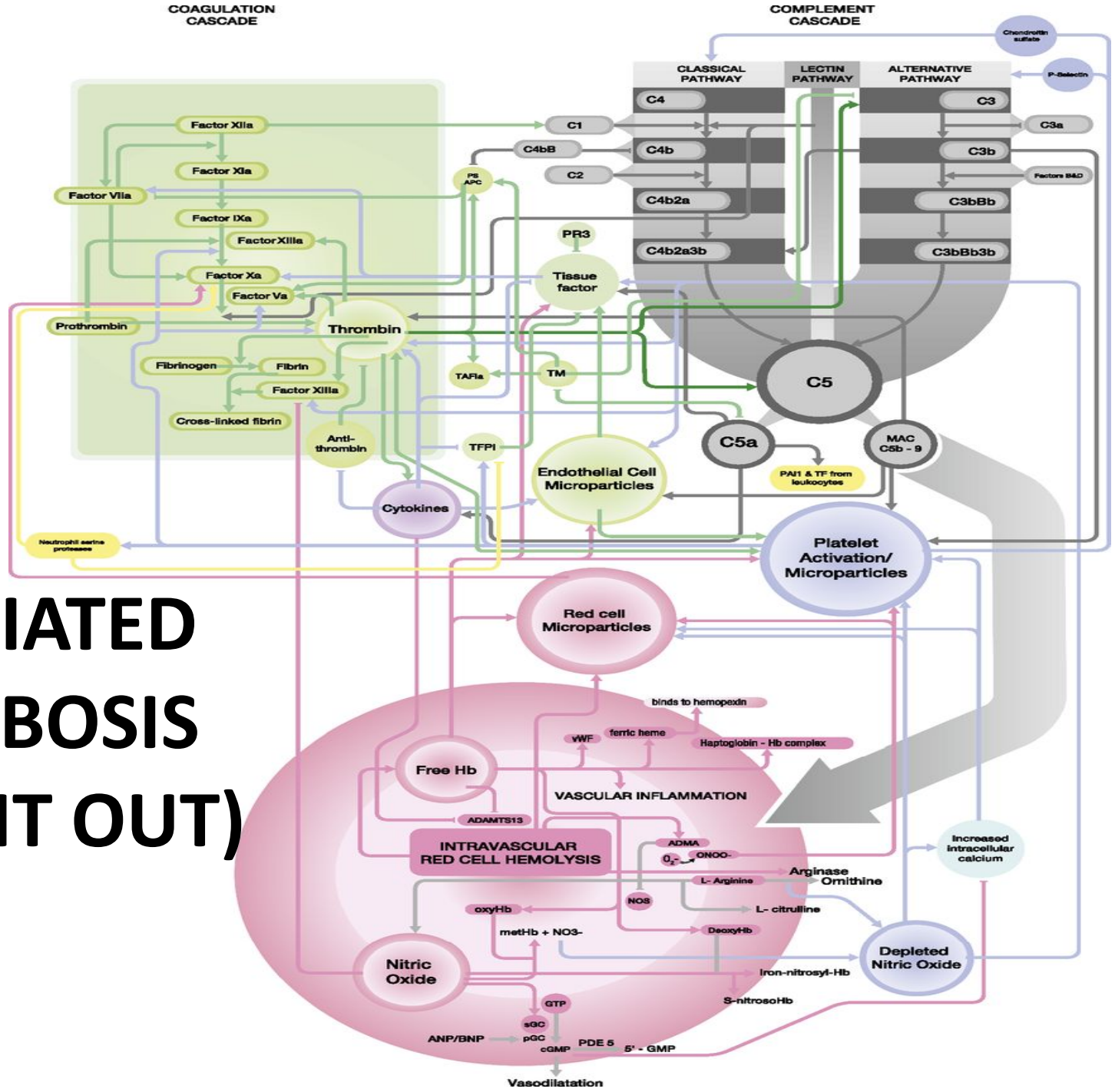
- **Thrombosis**

***COMPLEX!**

- **Kidney damage**
- **Pulmonary hypertension**
- **Abdominal pain**
- **Chest pain**
- **Dysphagia**
- **Erectile dysfunction**

+ deposition of heme

PNH IS ASSOCIATED WITH THROMBOSIS (YOU FIGURE IT OUT)



Hill et al, Blood 2013

SUPPORTIVE TREATMENTS FOR PNH (?HISTORICAL)

- **Hemolysis - Red cell transfusion**
  - Narcotic analgesia
  - Corticosteroids
- **Arterial/venous thrombotic events (unusual sites)**
- **Hypoplastic bone marrow failure**

SUPPORTIVE TREATMENTS FOR PNH

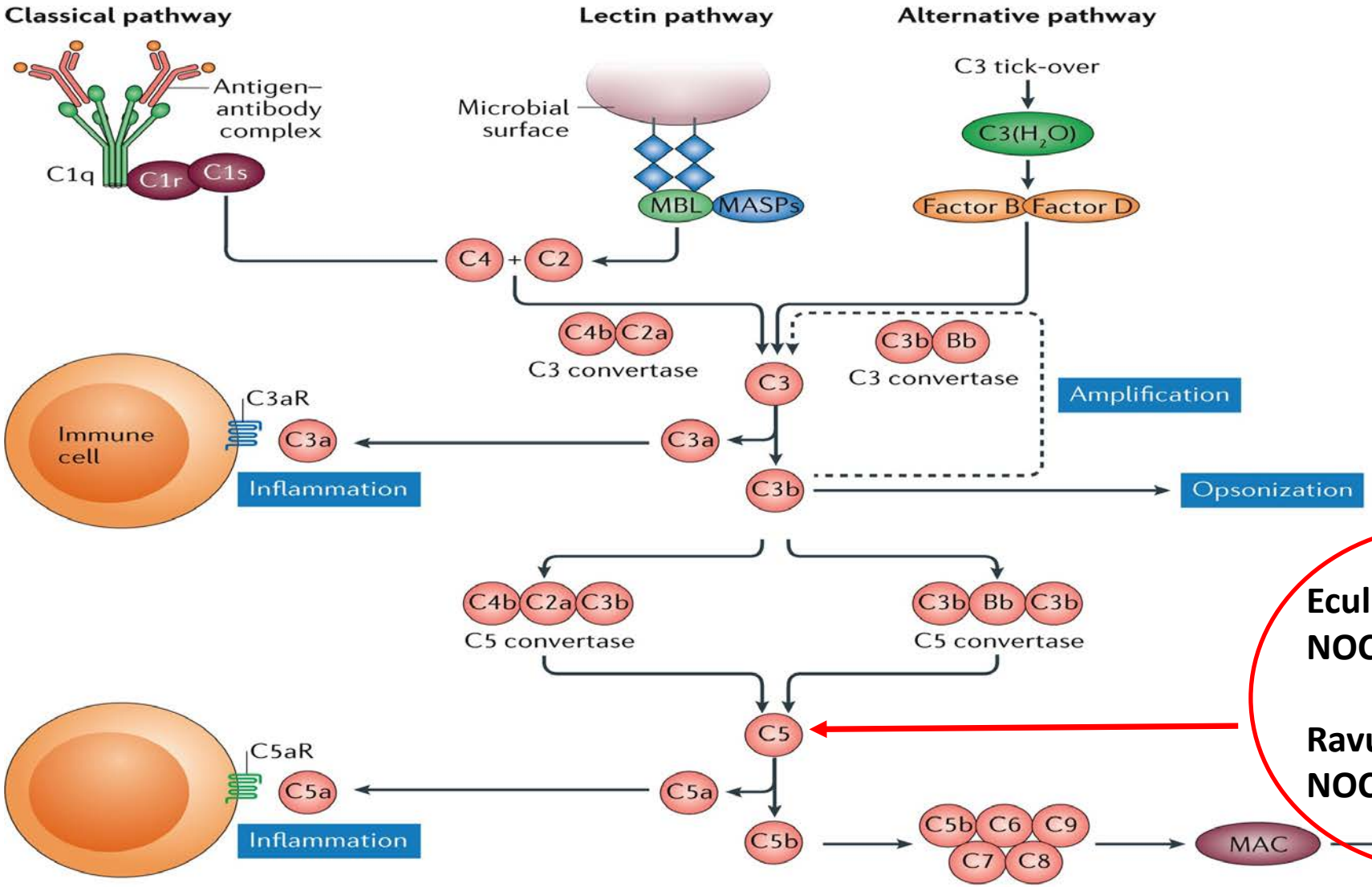
- **Hemolysis** - Red cell transfusion
  - Narcotic analgesia
  - Corticosteroids
- **Arterial/venous thrombotic events (unusual sites)**
  - **Anticoagulation**
  - **Surgical/transjugular shunting**
  - **Thrombolysis**
- **Hypoplastic bone marrow failure**

SUPPORTIVE TREATMENTS FOR PNH

- Hemolysis - Red cell transfusion
  - Narcotic analgesia
  - Corticosteroids
- Arterial/venous thrombotic events (unusual sites)
  - Anticoagulation
  - Surgical/transjugular shunting
  - Thrombolysis
- **Hypoplastic bone marrow failure**
  - **Immunosuppression (CSA+ATGAM)**
  - **Allogeneic stem cell transplantation**

MODERN (SMART) TREATMENTS FOR PNH

The Complement Pathway



Eculizumab
NOC: January 2009

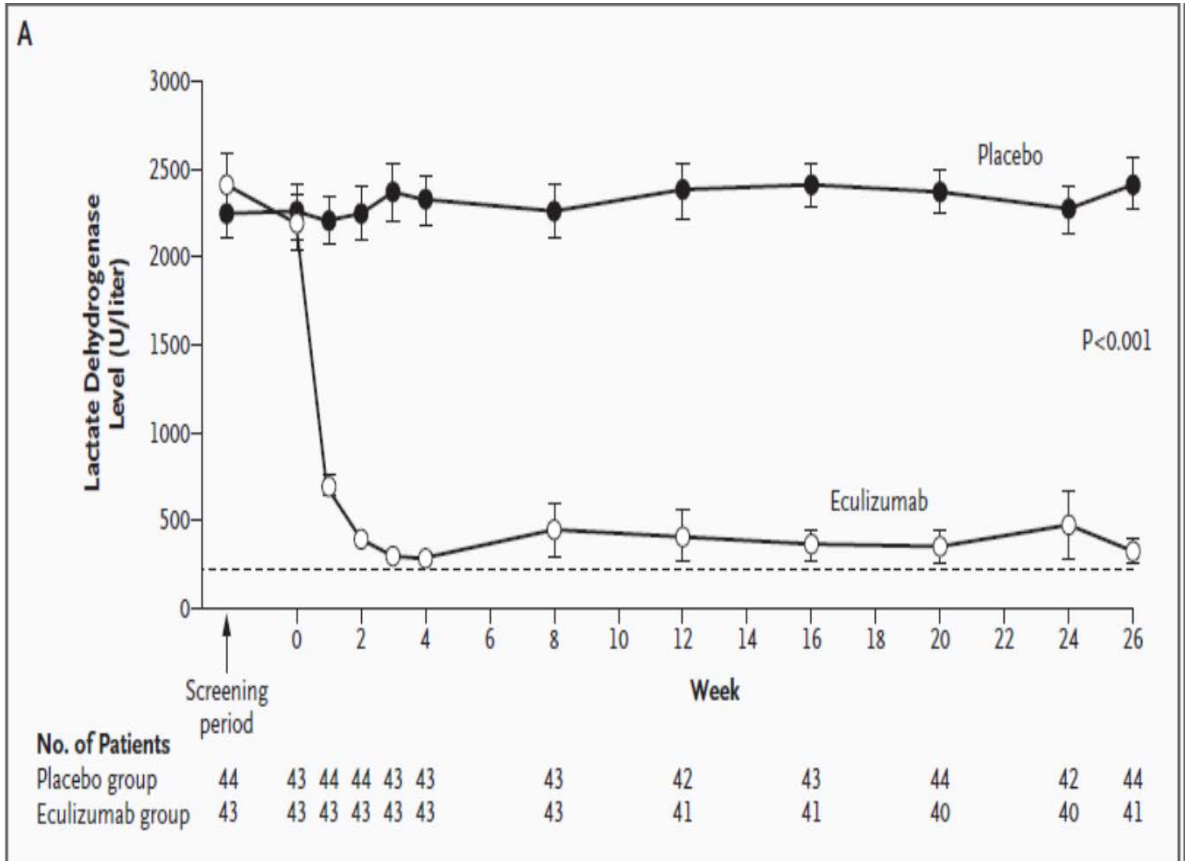
Ravulizumab
NOC: August 2019

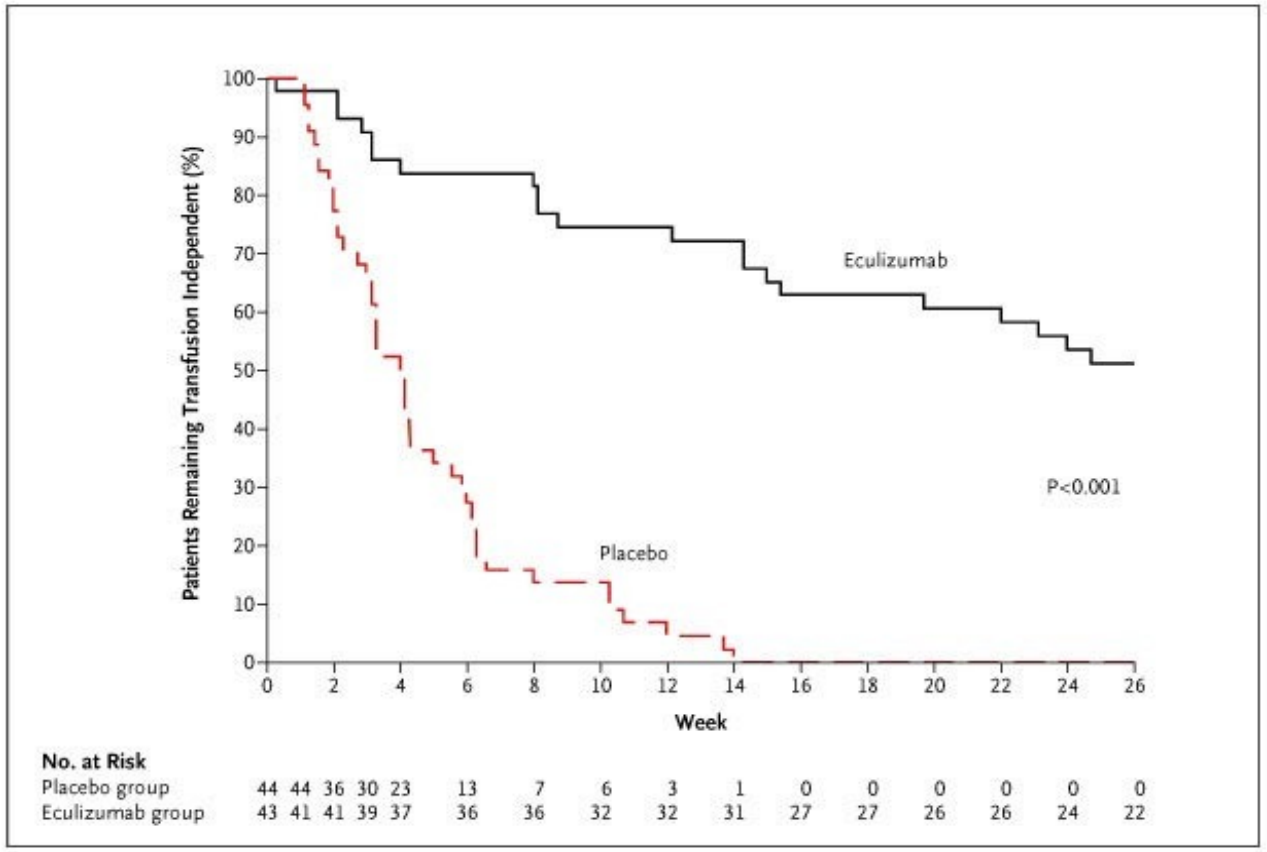
Nature Reviews | Rheumatology
Trouw et al, 2017

ECULIZUMAB: THE FIRST C5 INHIBITOR

(Hillmen et al; NEJM, 2006)

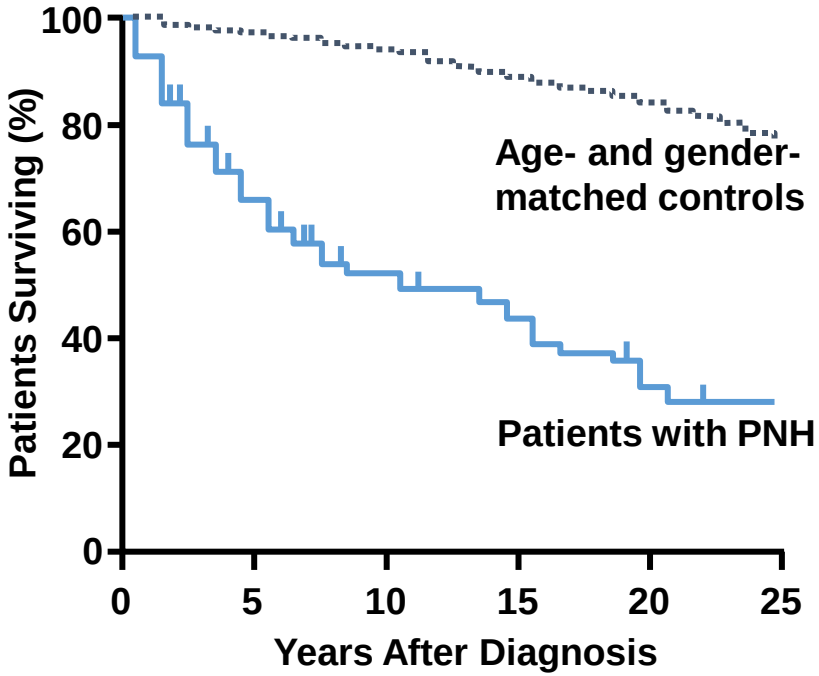
Phase III placebo-controlled trial in PNH



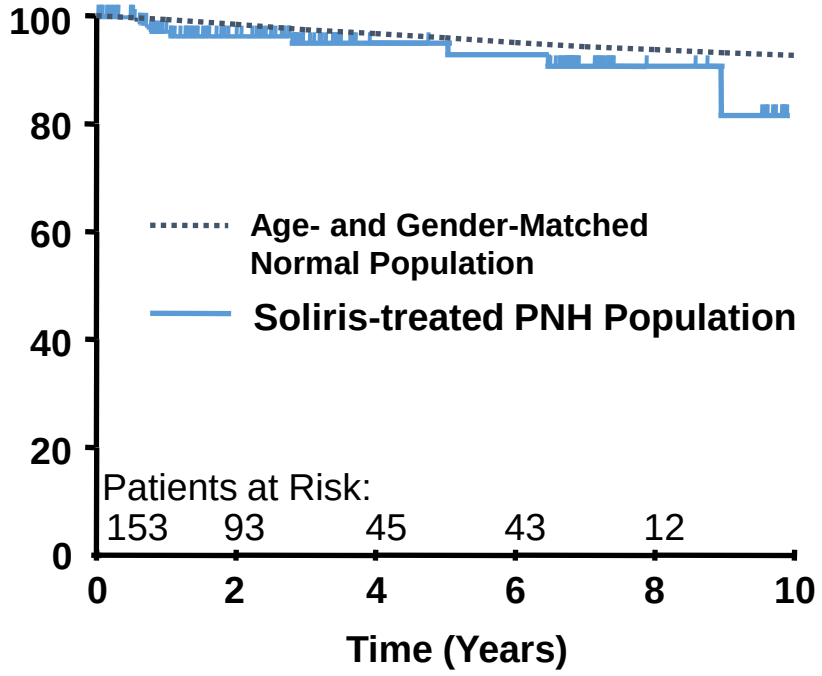


PNH Survival: Then and Now

Pre-Eculizumab from Time of Diagnosis in 80 Patients With PNH



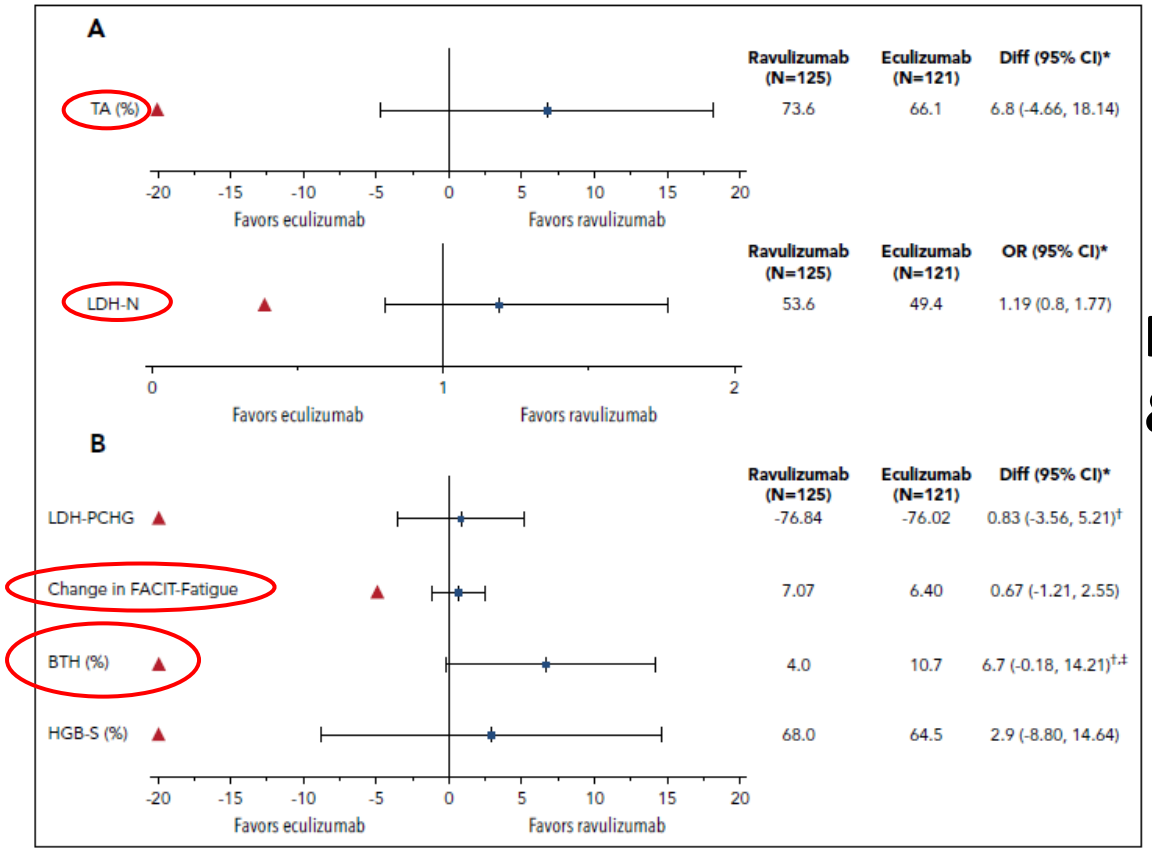
PNH Patients on Eculizumab Compared with Matched Controls



LONG-ACTING C5 INHIBITOR: RAVULIZUMAB

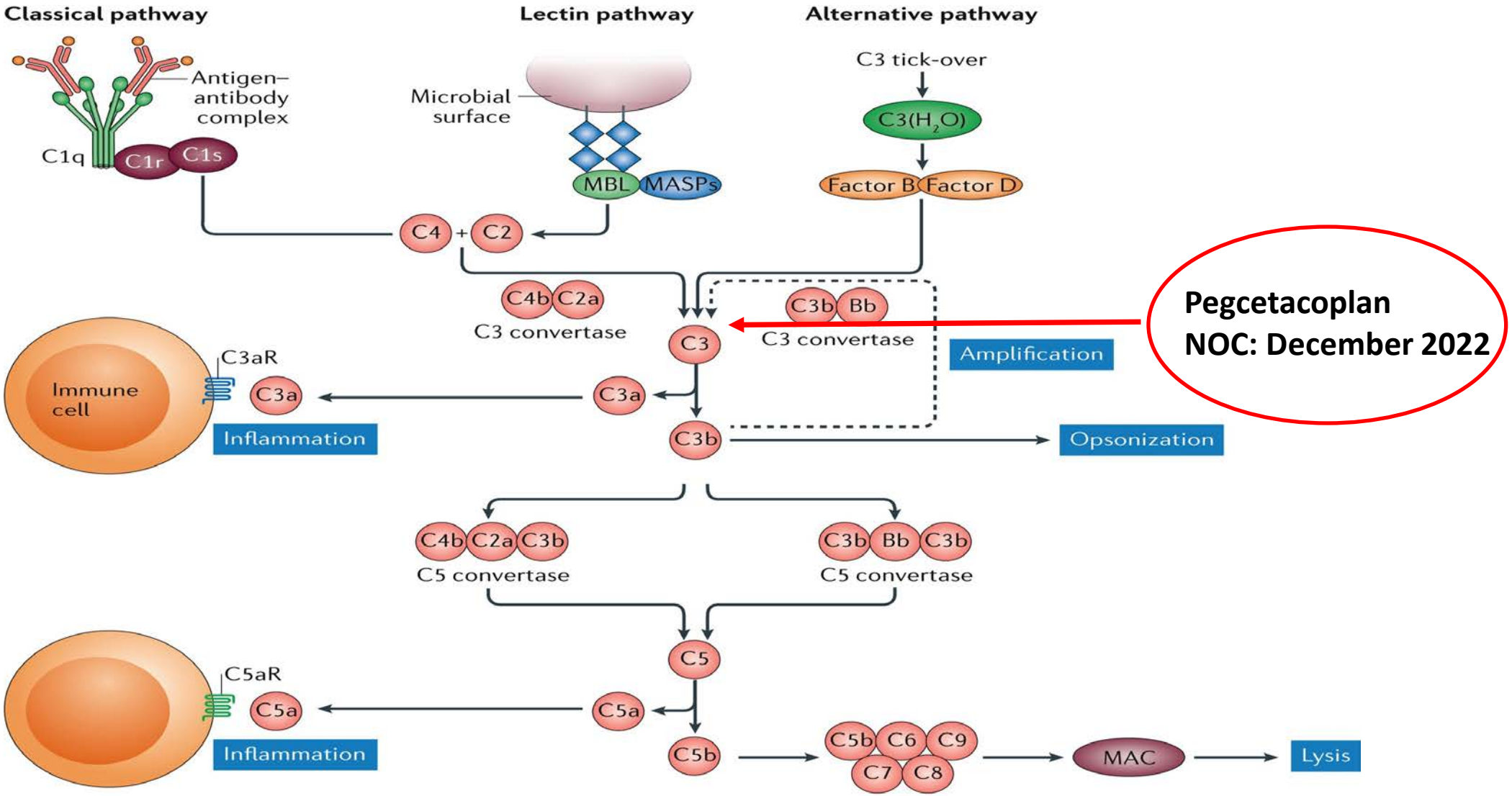
The 301 Study (Blood, 2019)

- Treatment-naïve PNH patients
- Randomized to 6 months of Eculizumab (q2wk) or Ravulizumab (q8wks)



Ravulizumab "non-inferior" & no new safety signals

The Complement Pathway



Nature Reviews | Rheumatology
Trouw et al, 2017

PEGASUS TRIAL

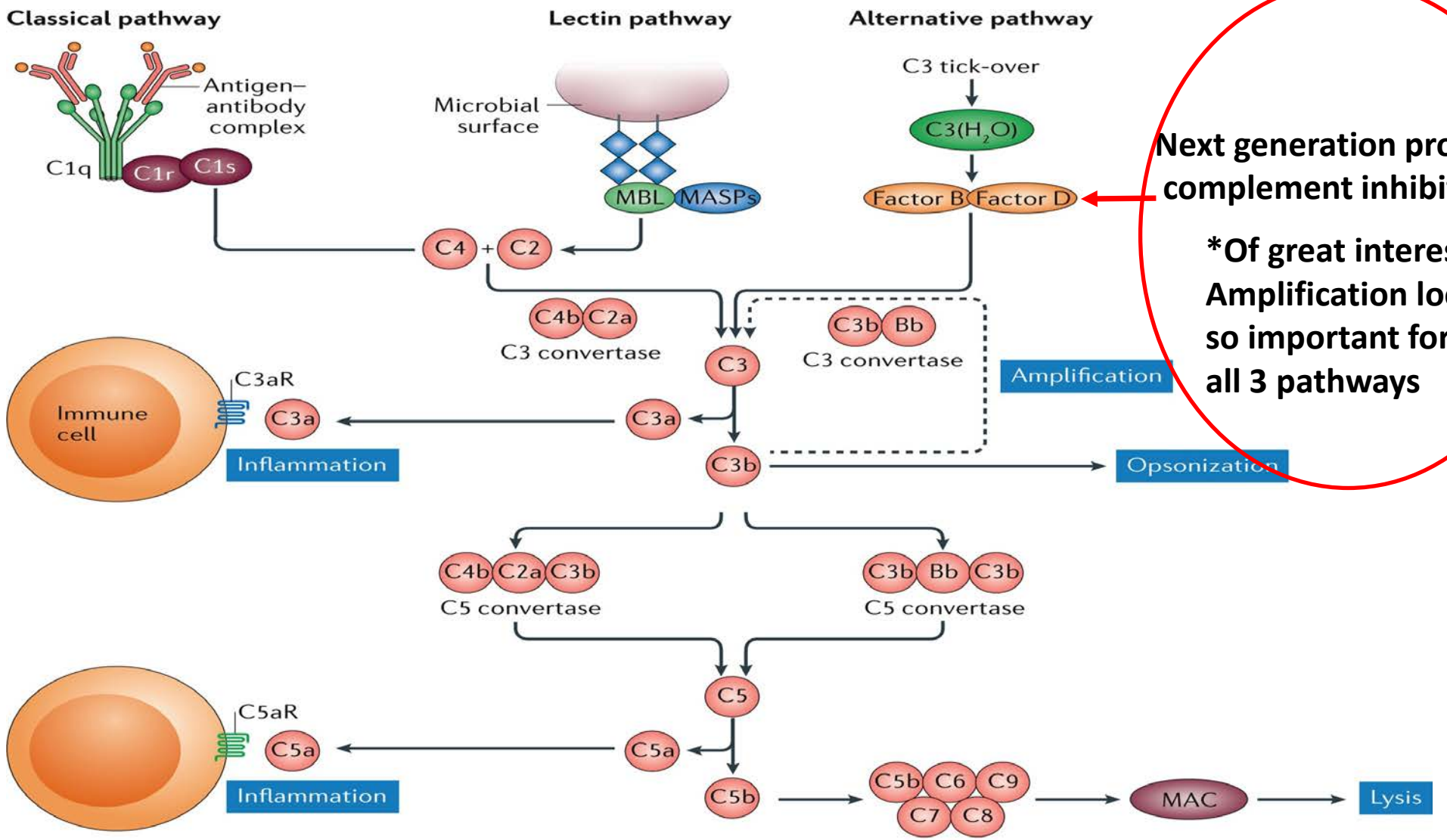
(NEJM March 2021)

- PNH patients on Eculizumab with Hb <105 g/L (mean was 87 g/L)
- Randomized to Pegcetacoplan s.c. b.i.w. (½-1h) vs. Eculizumab IV q2wk

RESULTS:

- Mean Hb at 16 wks: PEG 115 g/L vs ECU 86 g/L (p<.001)
- Over 16 wks, 85% of PEG transfusion-free (15% of ECU)
- PEG: less fatigue, less headache, less breakthrough hemolysis
- PEG did have new AEs – 37% injection site reaction, 22% diarrhea
- No difference in infections

The Complement Pathway



Next generation proximal complement inhibitors

***Of great interest as Amplification loop is so important for all 3 pathways**

Nature Reviews | Rheumatology
Trouw et al, 2017

Factor D Inhibitors: Danicopan

(Haematologica, December 2021)

- 10 untreated PNH patients: oral Danicopan TID x 84 days
- 8 patients completed treatment
- 1 patient developed elevated liver transaminases + hemolysis
- 2nd patient stopped for personal (non-safety) reasons

RESULTS:

- Day 28: LDH decreased in all patients (40% normal)
- Mean hemoglobin increased from 98 g/L → 115 g/L at day +84
- Concerns: Low level residual intravascular hemolysis especially around pre-dose period
- Led to development of *Vemircopan:* More potent BID Factor D inhibitor

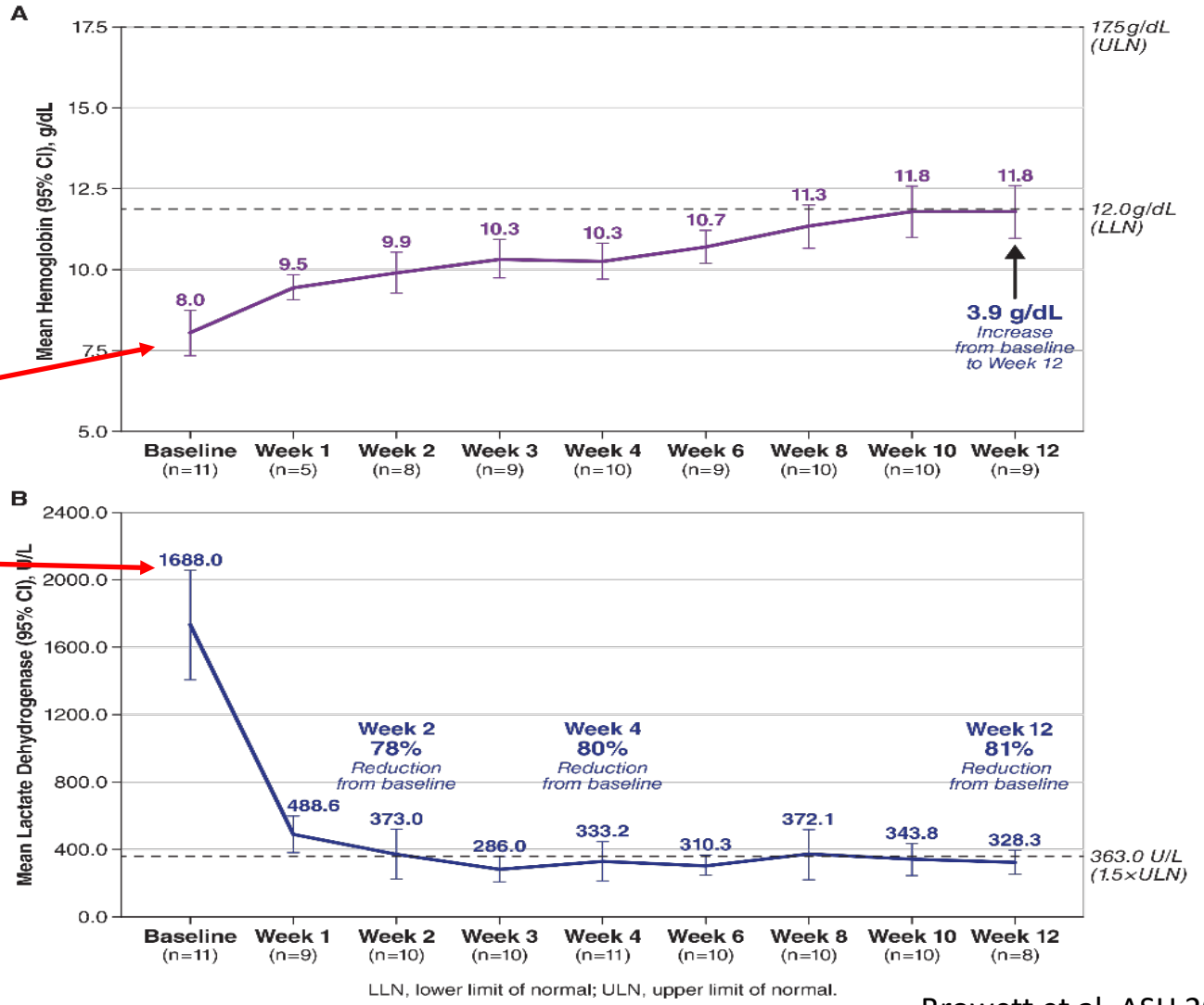
FACTOR D INHIBITOR: VEMIRCOPAN

- Phase II study of Vemircopan
- 120 mg-160 mg BID
- 11 treatment-naïve PNH pts

- **Mean Hb increased by 39 g/L**

- **Mean LDH declined rapidly –**
  (71% in first week)

- Only 1 PRBC given (on day 2)
- No serious TEAE
- 36% reported headaches



Browett et al, ASH 2022
Courtesy of American Society of Hematology

FACTOR B INHIBITOR: IPTACOPAN

(APPLY-PNH STUDY; ASH 2022)

- Randomized patients with residual anemia on Eculizumab/Ravulizumab
- Continue ECU/RAVI or switch to oral Iptacopan
- Mean hemoglobin level at 24 weeks: Increased 36 g/L on Iptacoplan
- Stable (-0.4 g/L) on ECU/RAVI
- 2/3 of Iptacopan had Hb ≥ 120 g/L (vs none in the ECU/RAVI arm)
- AE: Headaches and diarrhea

IS THE FUTURE ORAL THERAPY?.....

COMBINATION THERAPY IN PNH: THE ALPHA TRIAL

(in progress)

- PNH patients on ECU/RAVI with “evident extravascular hemolysis”
- i.e. Hemoglobin ≤95 g/L + reticulocytes > 120 x 10^9/L
- Randomized to receive “ADD-ON” Danicopan or placebo
- Primary endpoint: Change from baseline Hemoglobin at 12 weeks
- Recruitment finished – 2nd 12 wk Rx phase + 1-yr extension phase ongoing
- Study completion at end of 2023
- Prespecified interim analysis results announced September 2022:

  Addition of Danicopan *significantly improved* hemoglobin levels, reduced transfusion needs & improved fatigue score @ 12 weeks

LONG-ACTING SUBCUTANEOUS C3 INHIBITOR: CROVALIMAB

- COMMODORE trials are comparing q4week s.c. C5 inhibitor (Crovalimab) with standard q2wk IV Eculizumab
- *Will this treatment find a niche if found to be "non-inferior"*?

- Study published in *Advances in Therapy* (2023) randomized patients to weekly subcutaneous Ravulizumab vs. IV Ravulizumab
- Drug trough concentrations: s.c & IV arms did not differ
- All clinical endpoints remained equivalent through a 10-week follow-up: Transfusions, breakthrough hemolysis, change in LDH

THE PNH TREATMENT LANDSCAPE

CHALLENGES & UNMET NEEDS IN PNH MANAGEMENT

1. Currently only have access to Eculizumab – drug cost a significant impediment
2. Even when funded, access can be slow and tedious – government & 3rd party red tape
3. Eculizumab-treated patients that remain anemic can be very symptomatic
4. Options limited for persistent anemia (PRBCs, Prednisone, Eprex, SCT)
5. Treatments can be onerous and impactful on lifestyle – IV infusions q2wk, PRBCs, twice weekly subcutaneous injections
6. Serious/life-threatening infections can occur (e.g. meningitis)
7. Pregnancy is relatively contraindicated for women of child-bearing age
8. Patients with concurrent marrow failure often struggle with pancytopenia despite complement inhibition
9. Diagnosis of PNH often delayed; when serious thrombosis has already occurred, return to satisfactory health may not be achievable