Dr. Thomas Nevill
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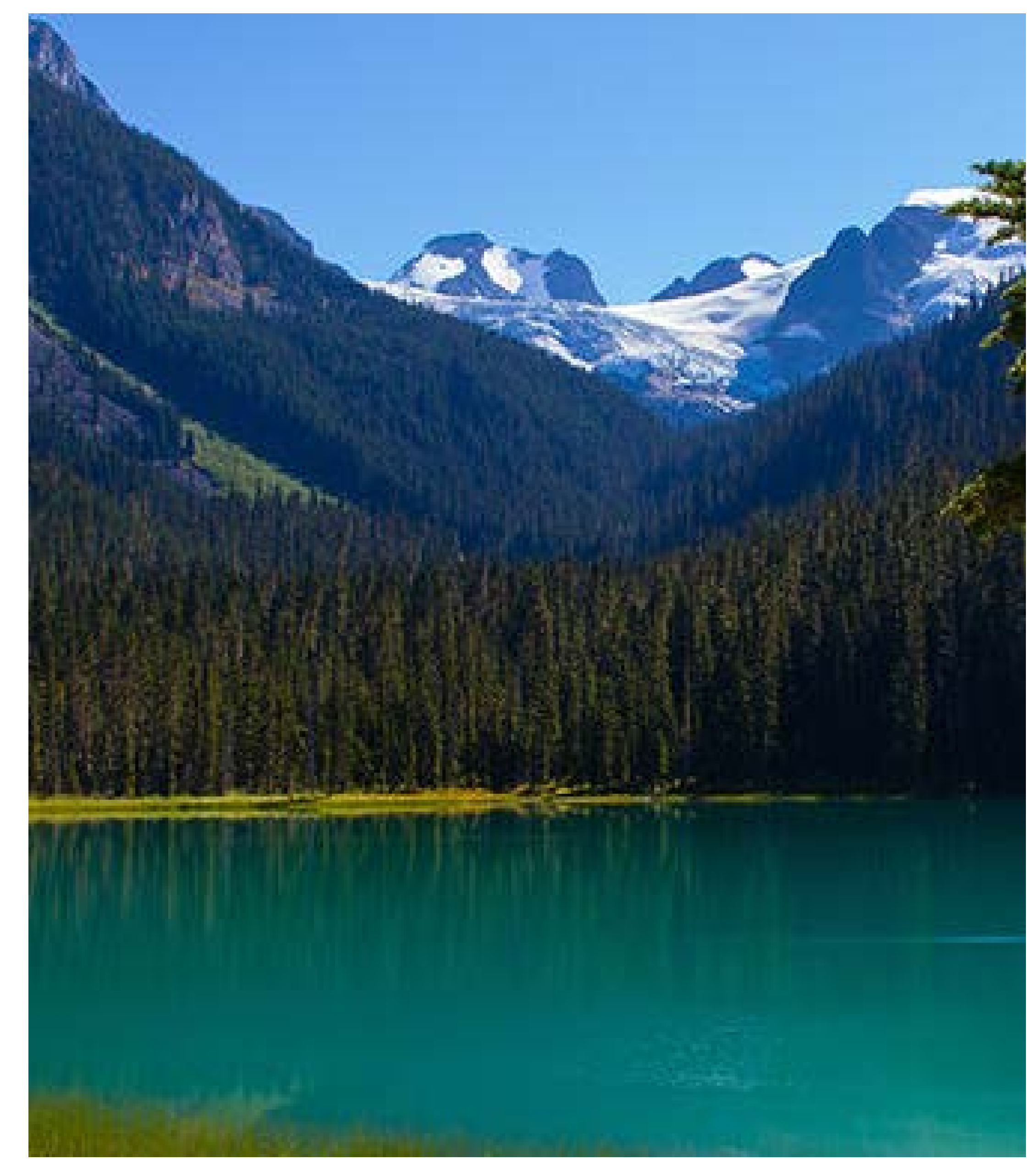
Vancouver General Hospital

New Treatment Paradigms in PNH: An Expanding Landscape



Disclosures

Advisory Boards/CME Lectures for:

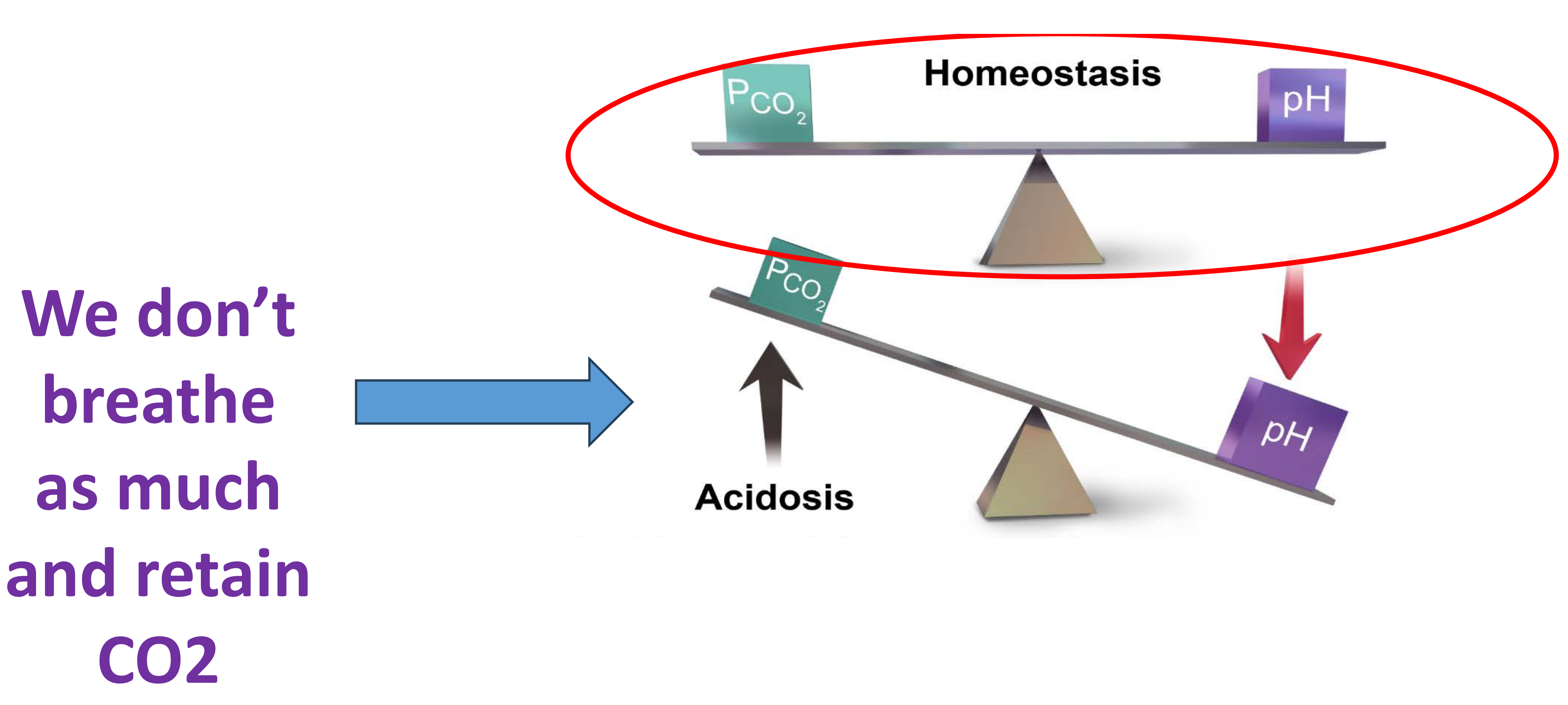
- BMS/Celgene
- Sobi
- Astra-Zeneca/Alexion
- Novartis
- Taiho
- Abbvie

What is PNH?

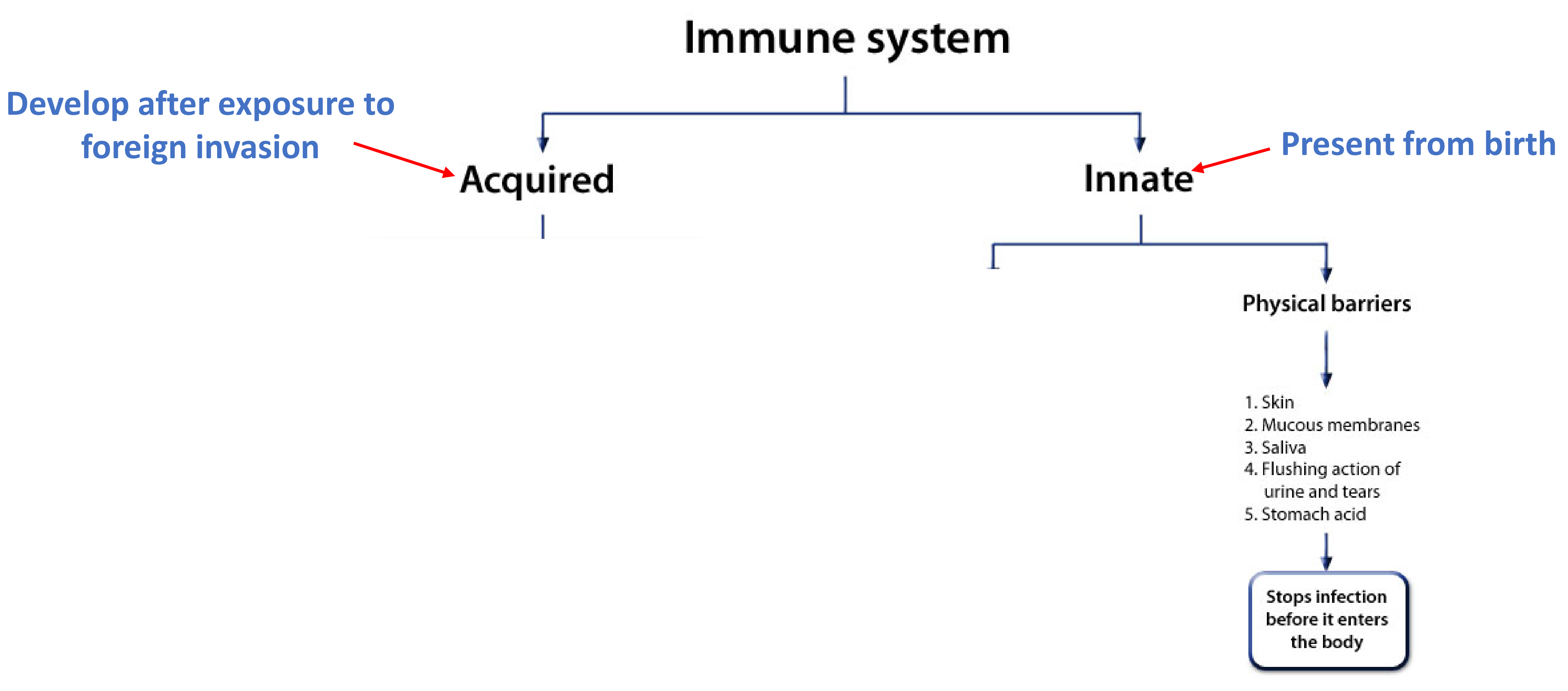
Historical Background

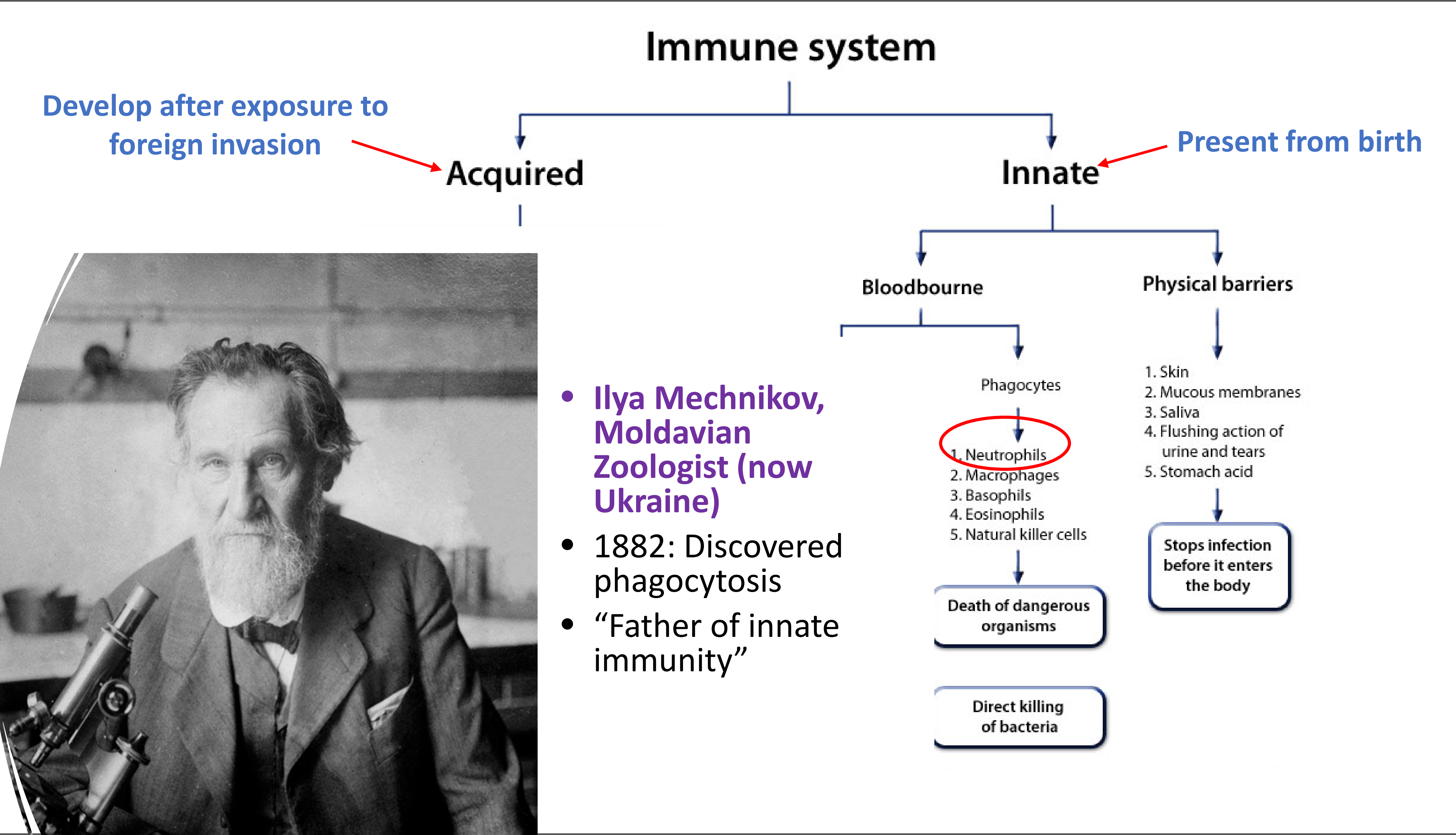
- Paroxysmal Nocturnal Hemoglobinuria
- 1882: German – Dr. Paul Strübing
- 29-year-old man
- “Voided dark urine only in the morning”
- Proposed: RBCs susceptible to destruction (“hemolysis”) when blood pH becomes “acidic”

Why does blood become more acidic at night?



But why does acidic blood destroy red cells?


Immune system
Develop after exposure to foreign invasion
Acquired
Innate
Present from birth
Physical barriers
1. Skin
2. Mucous membranes
3. Saliva
4. Flushing action of urine and tears
5. Stomach acid
Stops infection before it enters the body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Bloodbourne
Physical barriers
Phagocytes
1. Neutrophils
2. Macrophages
3. Basophils
4. Eosinophils
5. Natural killer cells
Death of dangerous organisms
Direct killing of bacteria
1. Skin
2. Mucous membranes
3. Saliva
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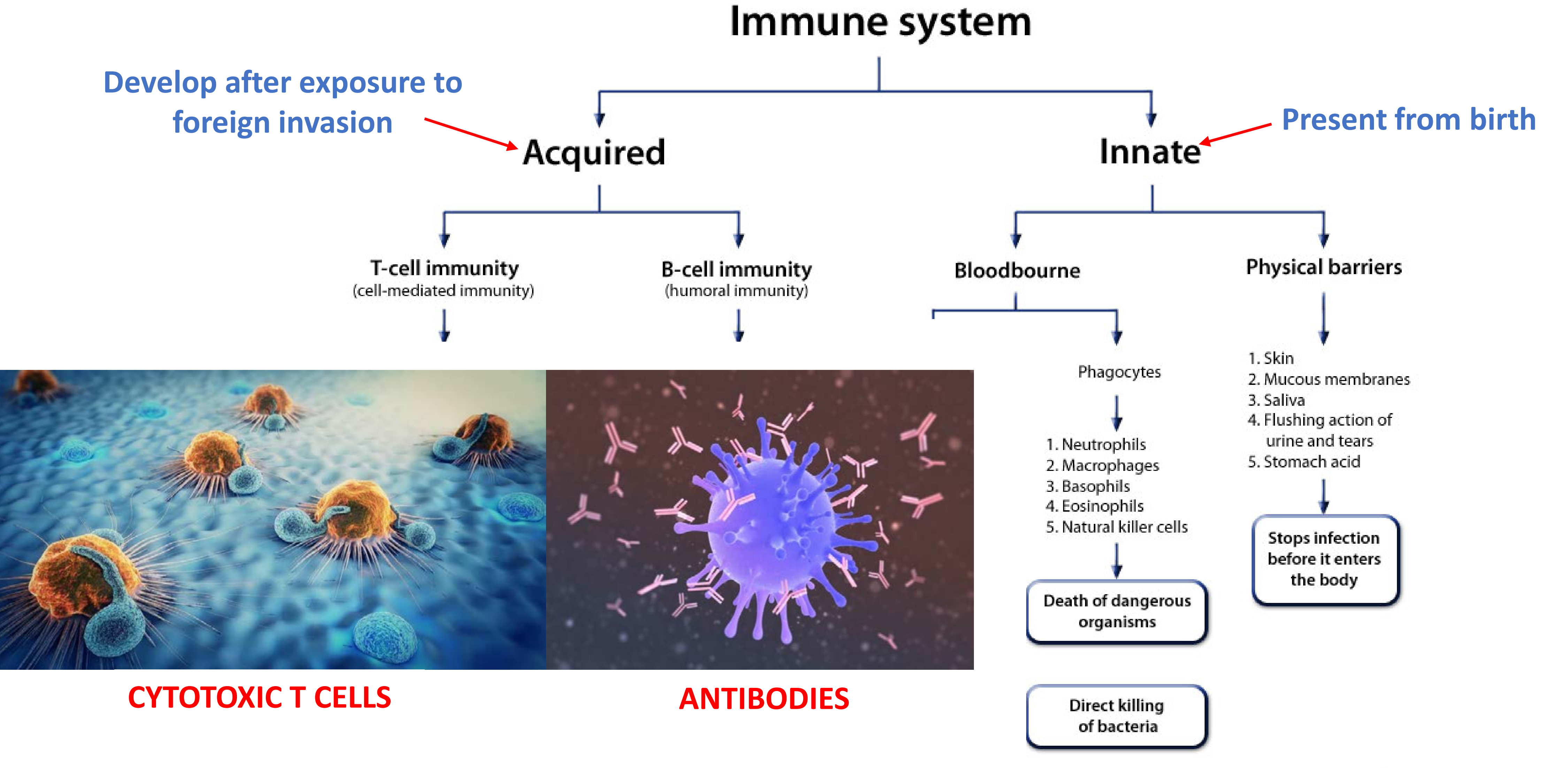
Stops infection before it enters the body
Ilya Mechnikov, Moldavian Zoologist (now Ukraine)
1882: Discovered phagocytosis
"Father of innate immunity"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(cell-mediated immunity)
B-cell immunity
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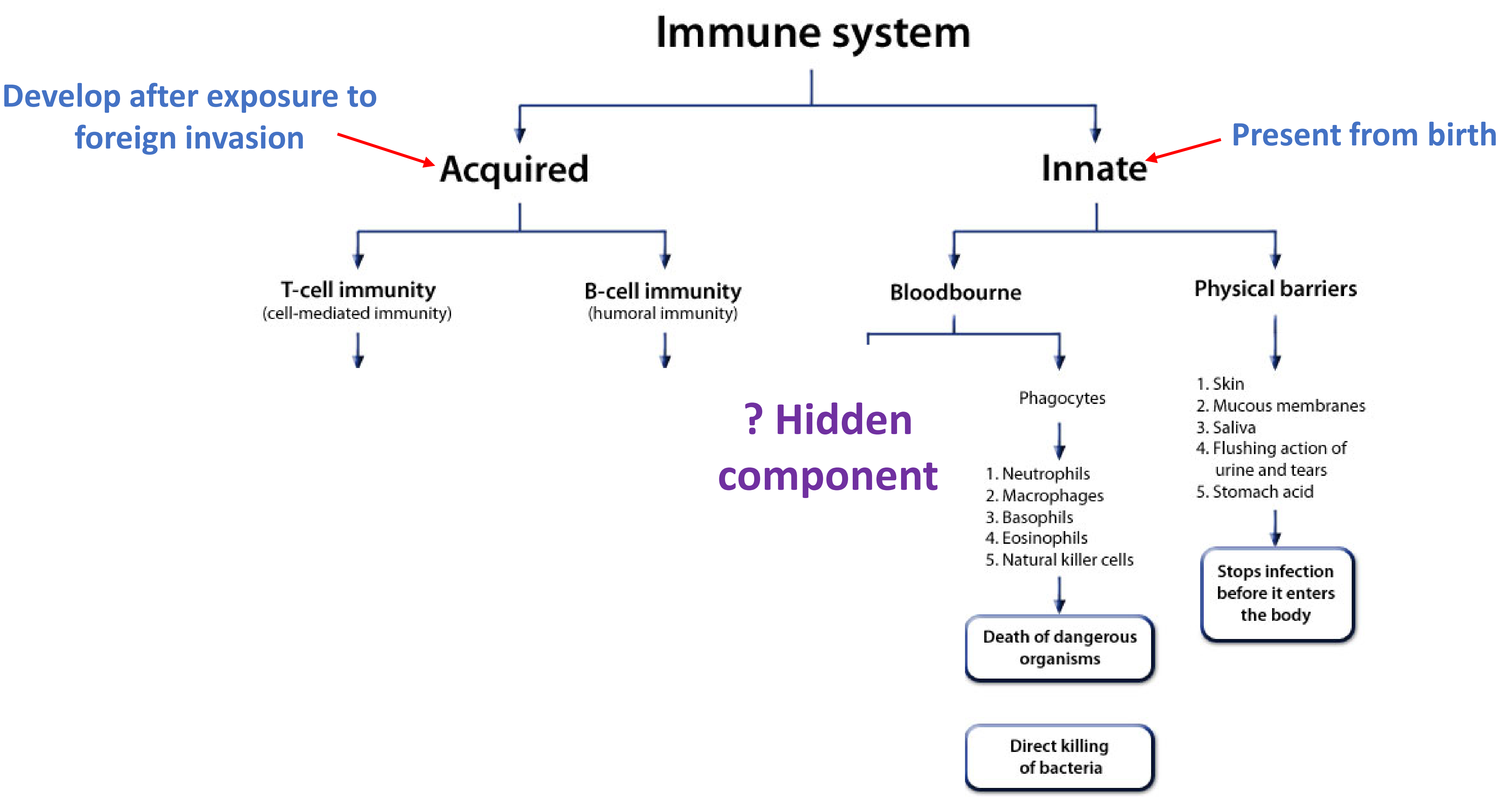
Stops infection before it enters the body
CYTOTOXIC T CELLS
ANTIBODIES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? Hidden component
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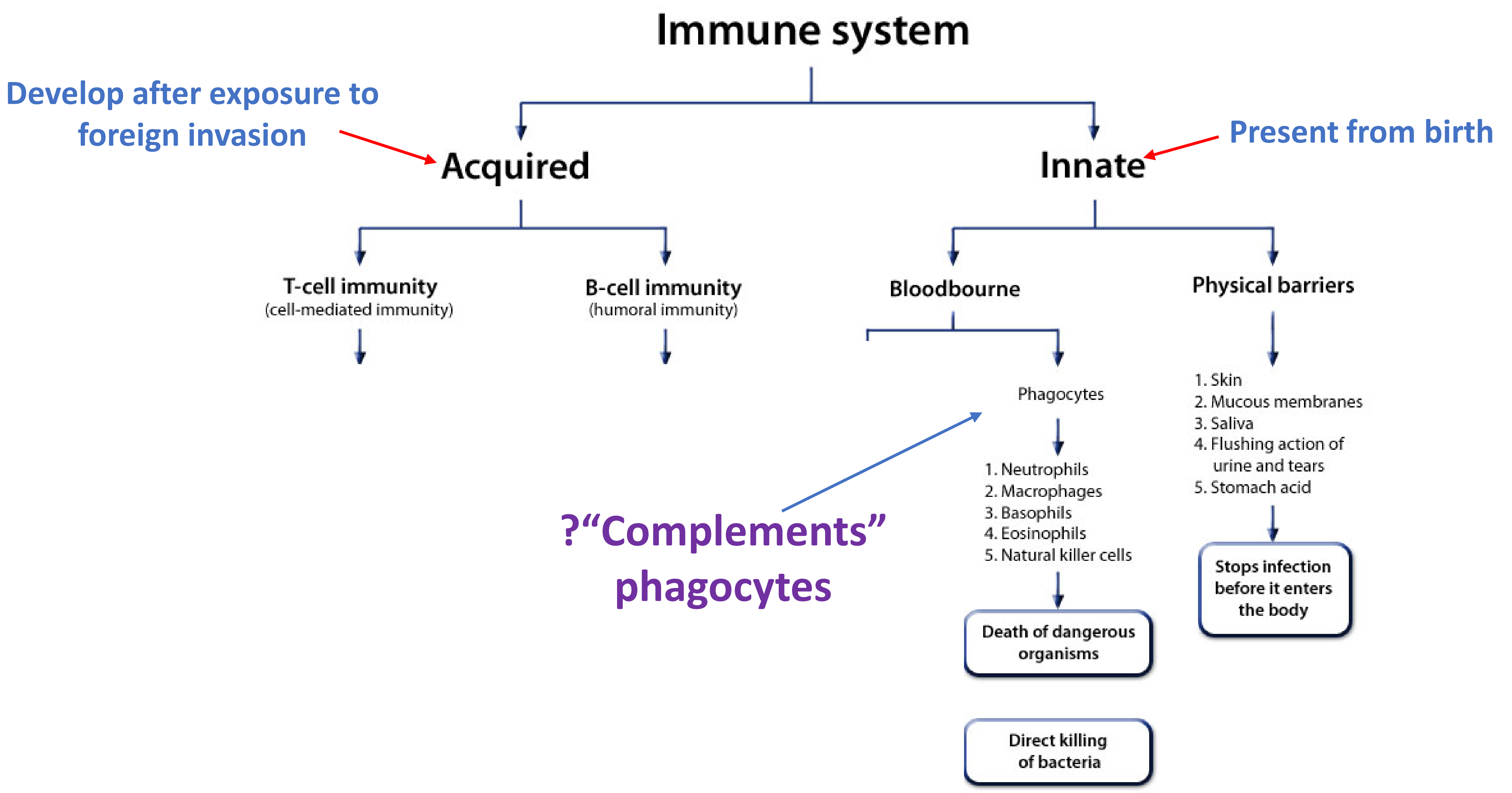
Stops infection before it enters the body



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Stops infection before it enters the body
?“Complements” phagocytes

The Complement Pathway

- 1891 German bacteriologist Hans Buchner found a “heat-labile protein” capable of killing bacteria – **“Alexin”**

The Complement Pathway

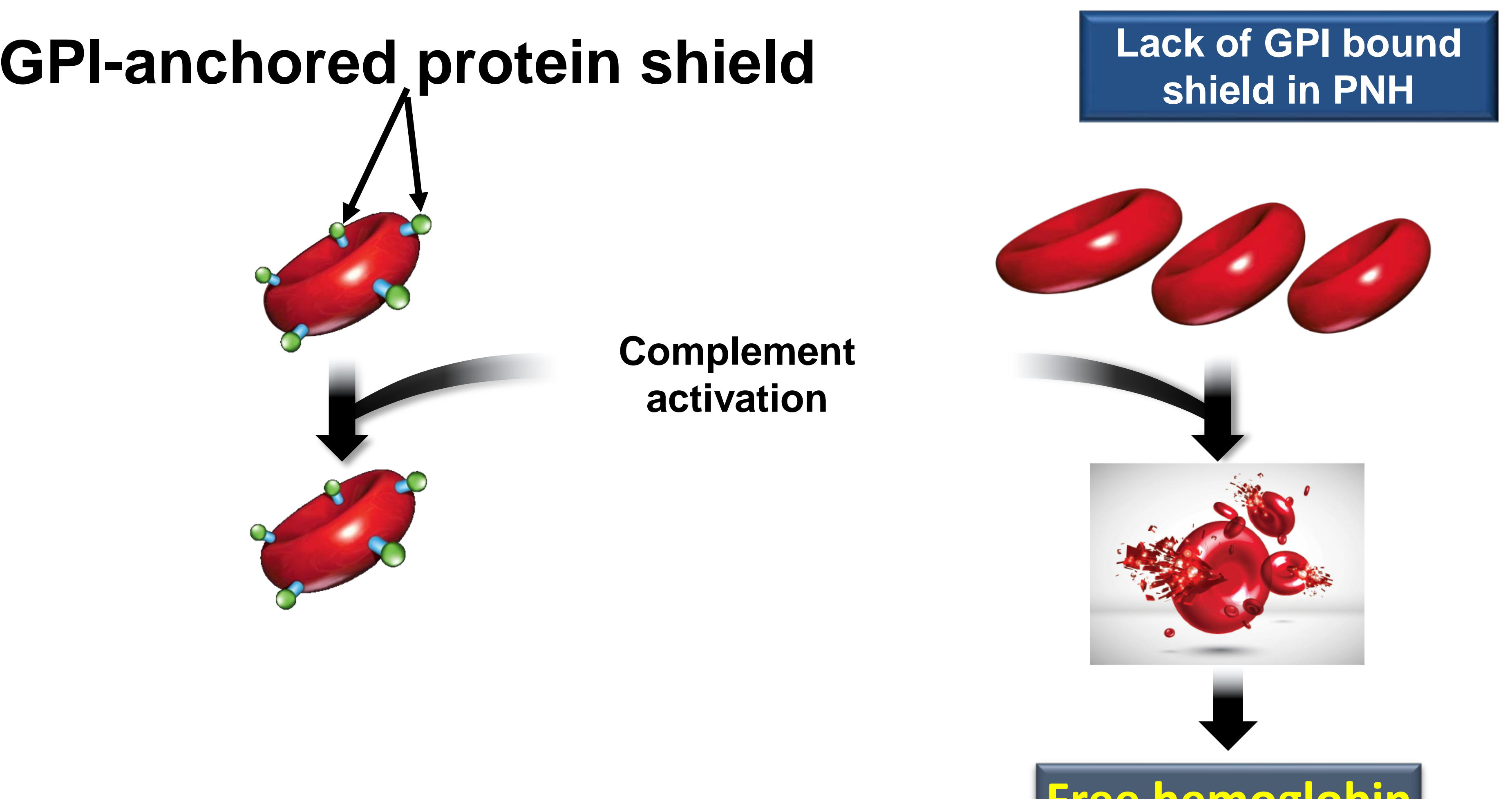
- **Paul Ehrlich, Prussian physician**
- Many contributions to Medicine
- Coined: “Chemotherapy” & “Magic bullet”
- “Antibodies” killed bacteria by recognizing their antigen target
- **Alexin** assisted the killing – **re-named “complement”**
- **1908: Awarded Nobel Prize in Medicine** (along with Ilya Mechnikov) **for their work on immunity**

Get to the point.

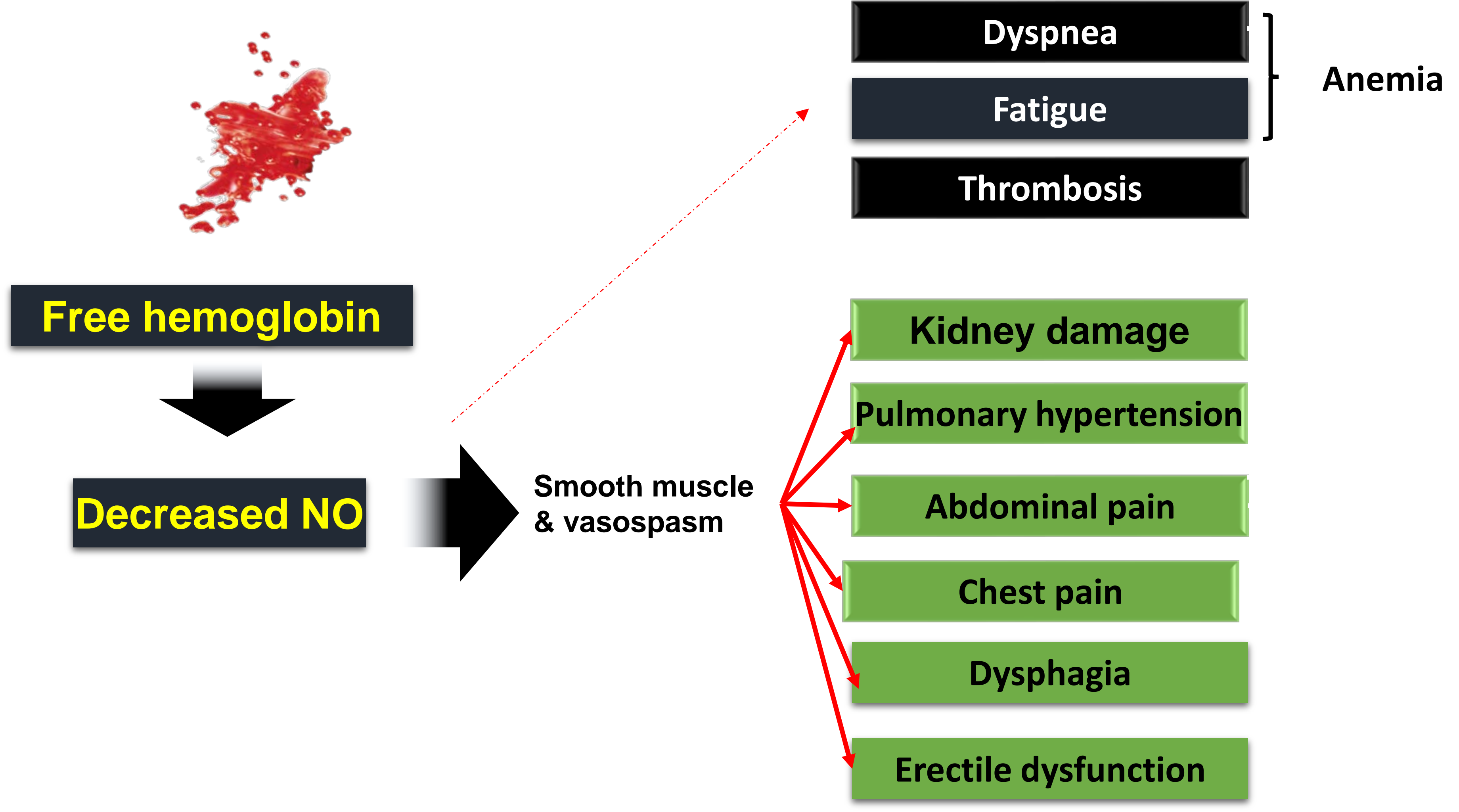
The Point.....

- Complement is activated in acidic blood
- While complement is part of our immune system it can do **bad things**
- Most red cells have a protective coat
- This coat prevents complement from destroying our own red cells
- **Those that don't have that coat have PNH**

COMPLEMENT CAUSES HEMOLYSIS IN PNH

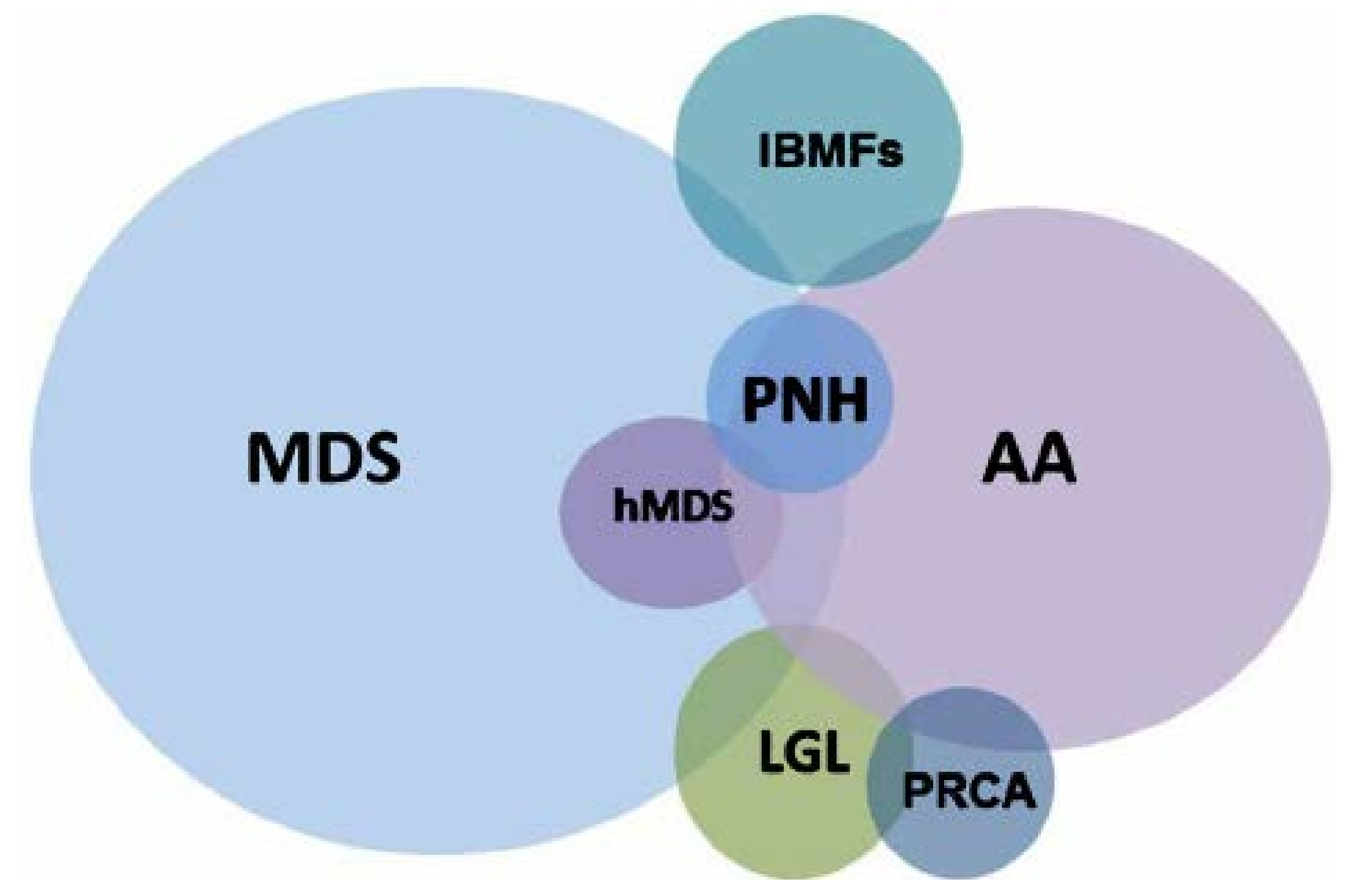


FREE HEMOGLOBIN CAUSES SYMPTOMS



Did You Forget You're Talking at AAMAC?

Bone Marrow Failure Disorders Overlap

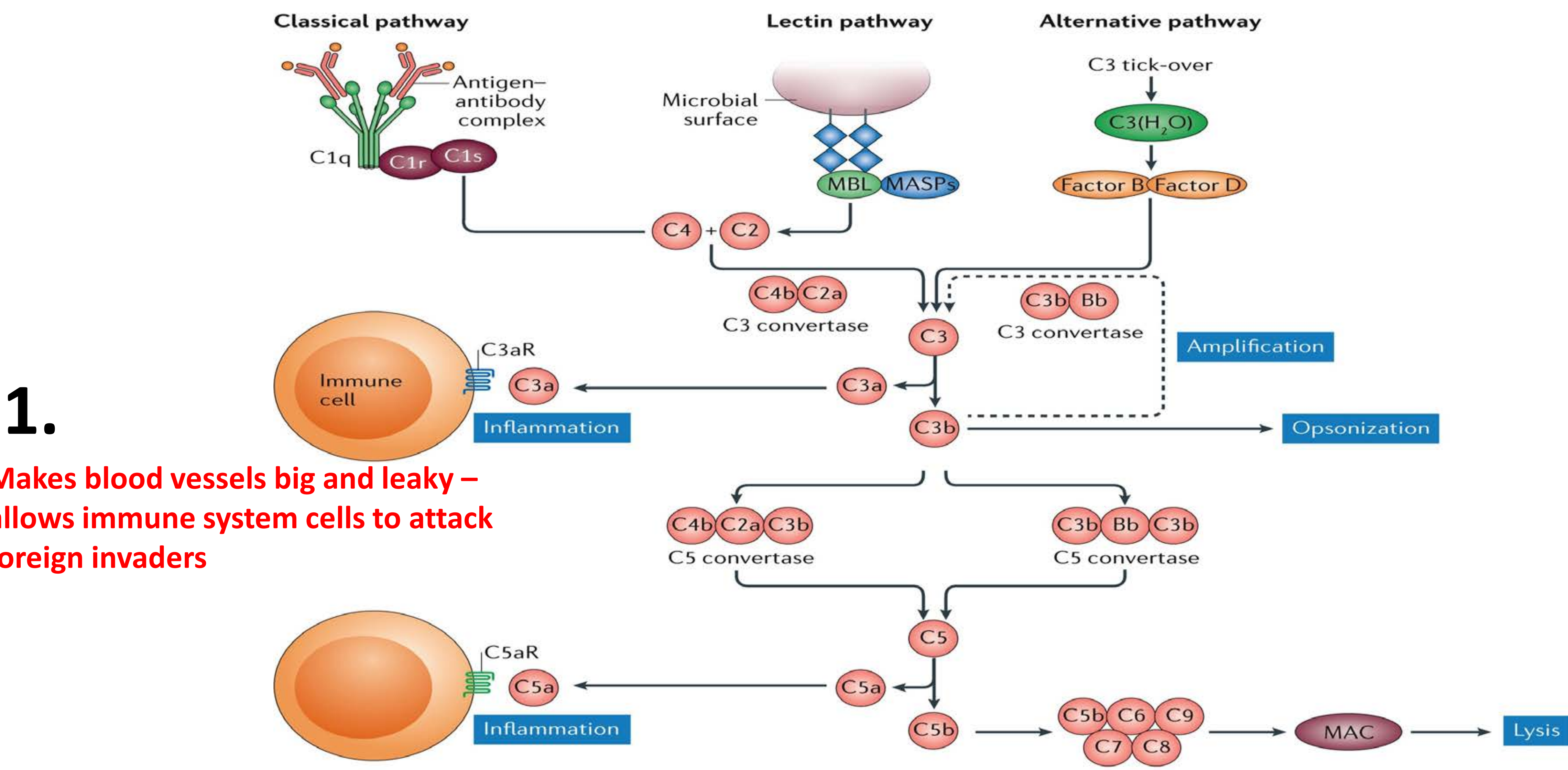


A common root cause is an immune system abnormality….

PNH Basics

- **Acquired** disorder of stem cells
- **Most healthy individuals have 0.001% PNH clones**
- 1% of healthy people have 0.02% clones
- Larger clones are RARE
- Only seen in immune-mediated bone marrow disorders – WHY?
- **PNH cells are more RESISTANT to immune attack**
- 50% of Aplastic Anemia patients have PNH clones
- 15% of MDS patients have PNH clones
- Isolated “classic” PNH - Incidence - 5 cases/million/year
- Median age: Early 30s
- **To reiterate: PNH is a complement-mediated disease!**

The Complement Pathway in 1 minute:
3 Methods of Activation and 3 Major Functions

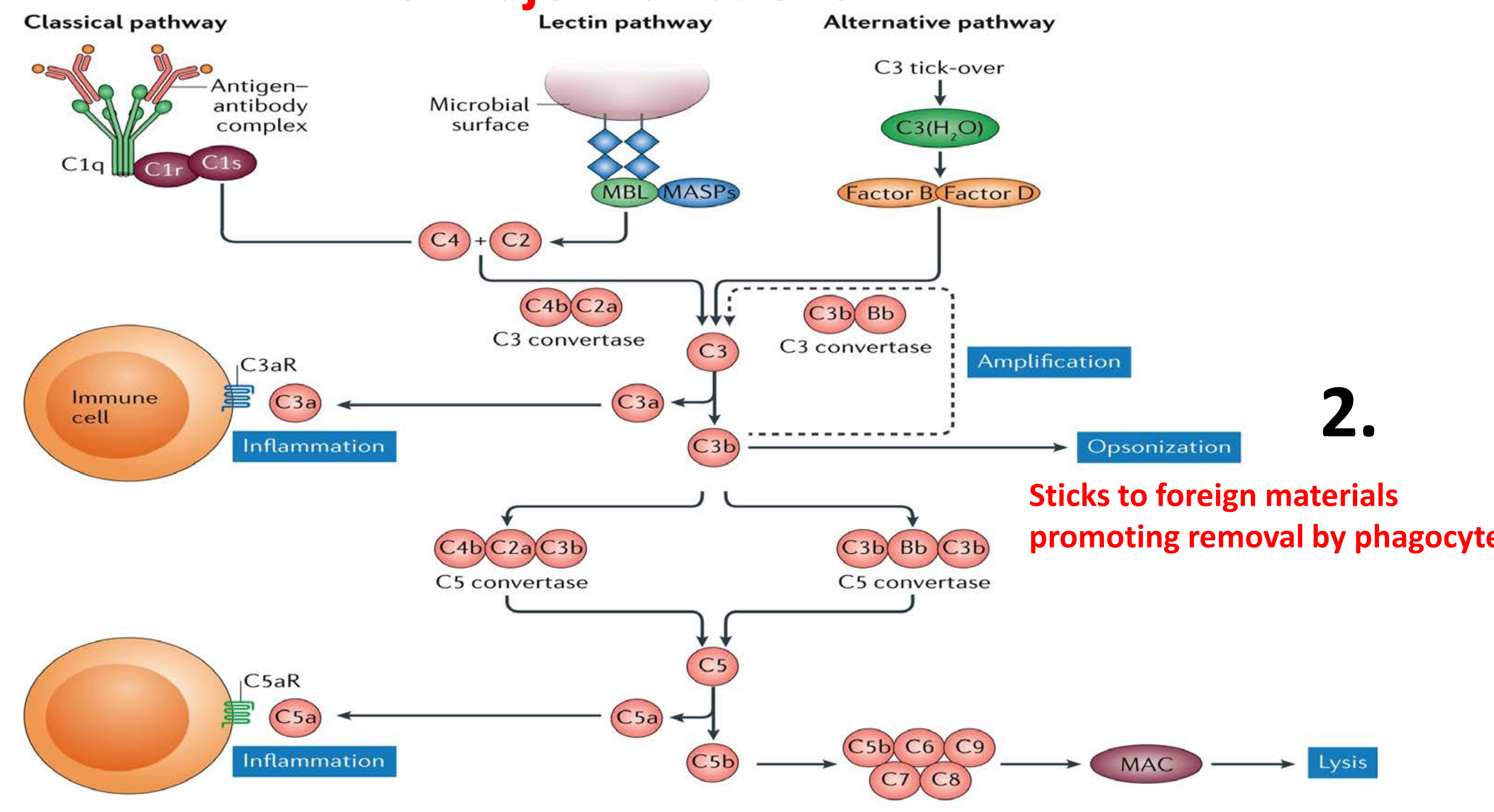


1.

Makes blood vessels big and leaky – allows immune system cells to attack foreign invaders

Trouw et al, 2017

The Complement Pathway in 1 minute:
3 Major Functions

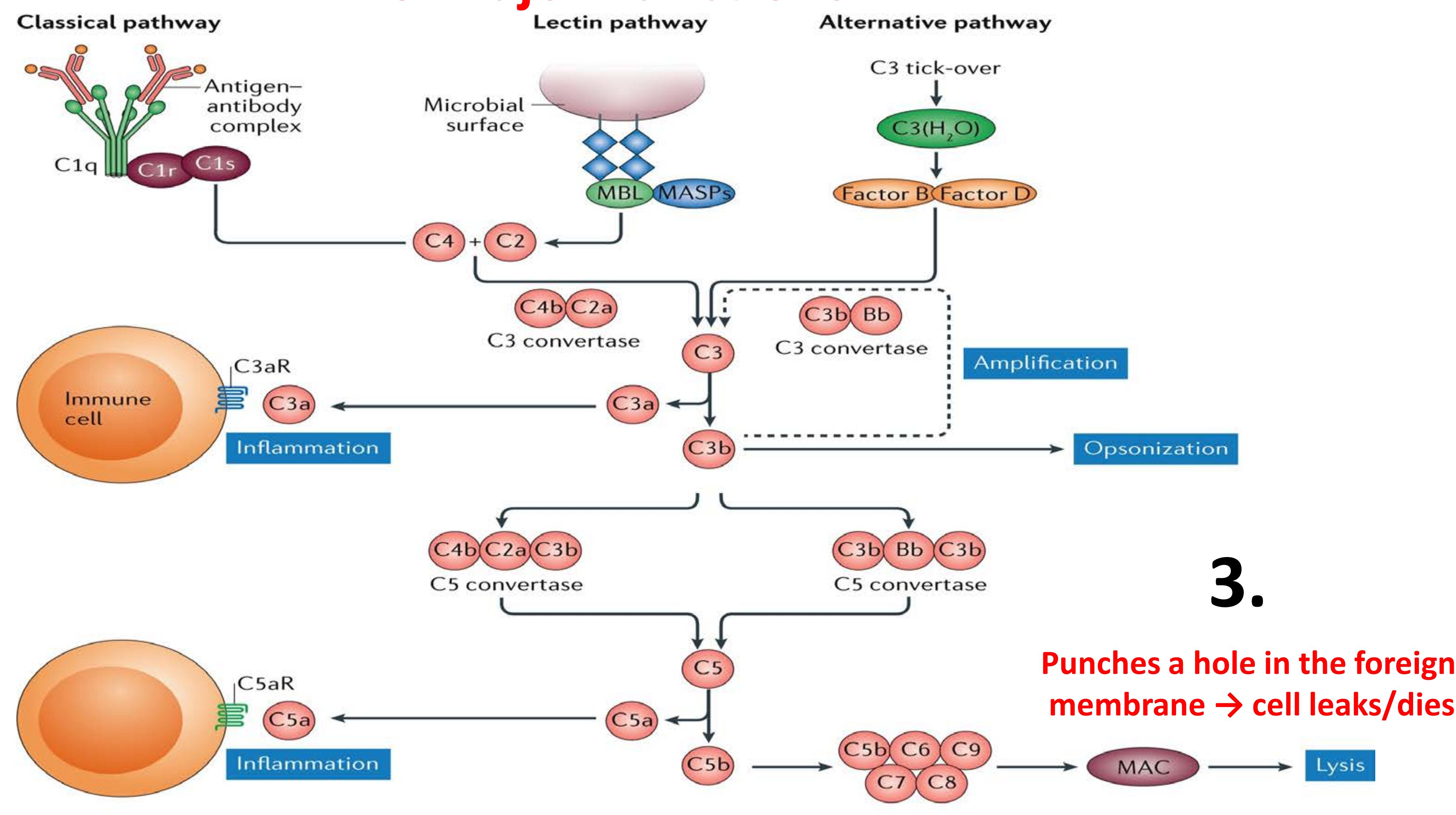


2.

Sticks to foreign materials promoting removal by phagocytes

Trouw et al, 2017

The Complement Pathway in 1 minute:
3 Major Functions



3.

Punches a hole in the foreign membrane → cell leaks/dies

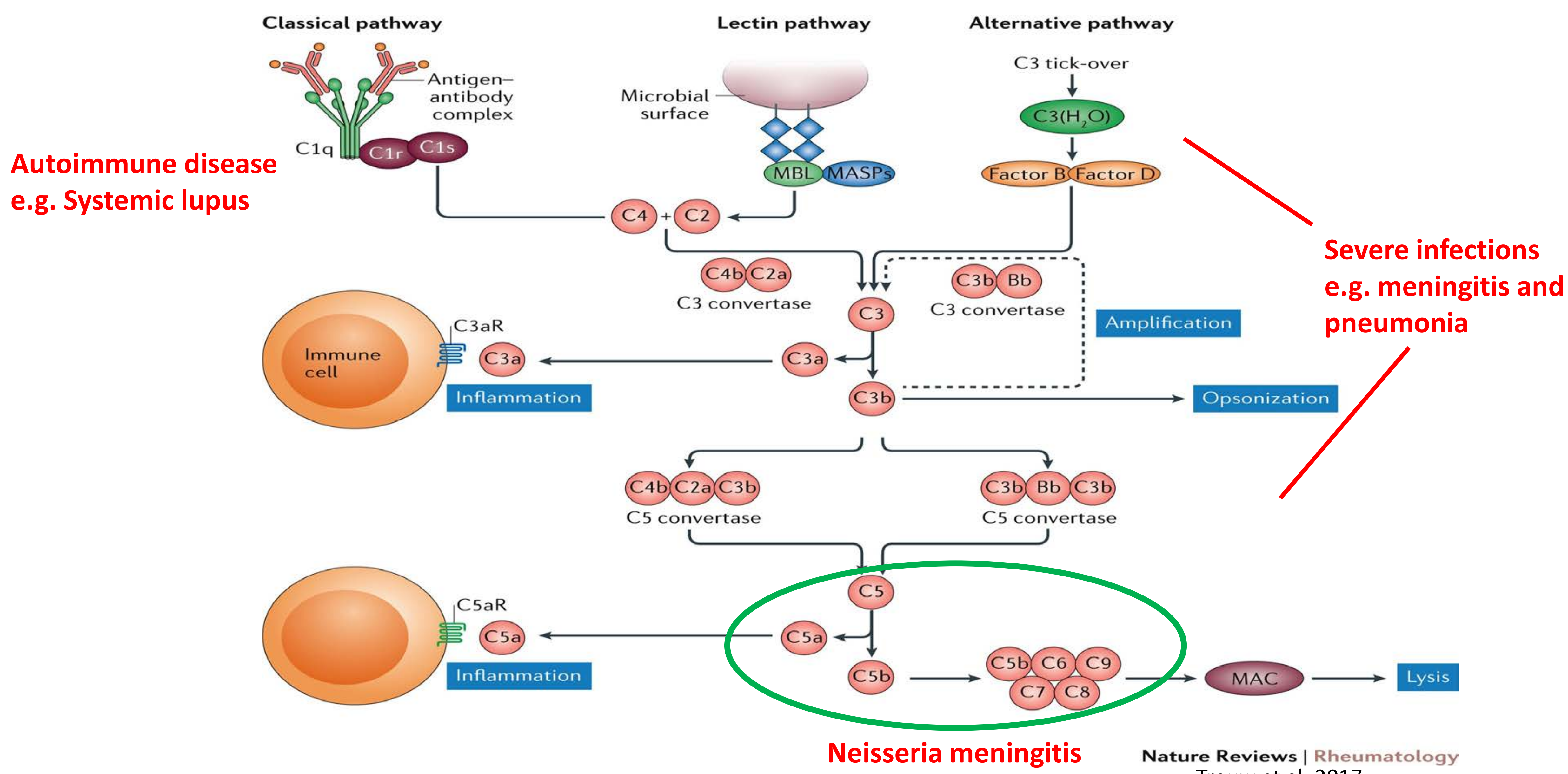
Trouw et al, 2017

SUPPORTIVE TREATMENTS FOR PNH

- **Hemolysis** - Blood transfusions
  - Steroids/Prednisone
- **Thrombotic events** - Anticoagulation/Blood thinners
- **Bone marrow failure** - Immunosuppression (CSA/ATG)
  - Bone marrow transplantation

MODERN (SMART) TREATMENTS FOR PNH

Complement Pathway: Deficiency syndromes



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Development of Complement Inhibitors

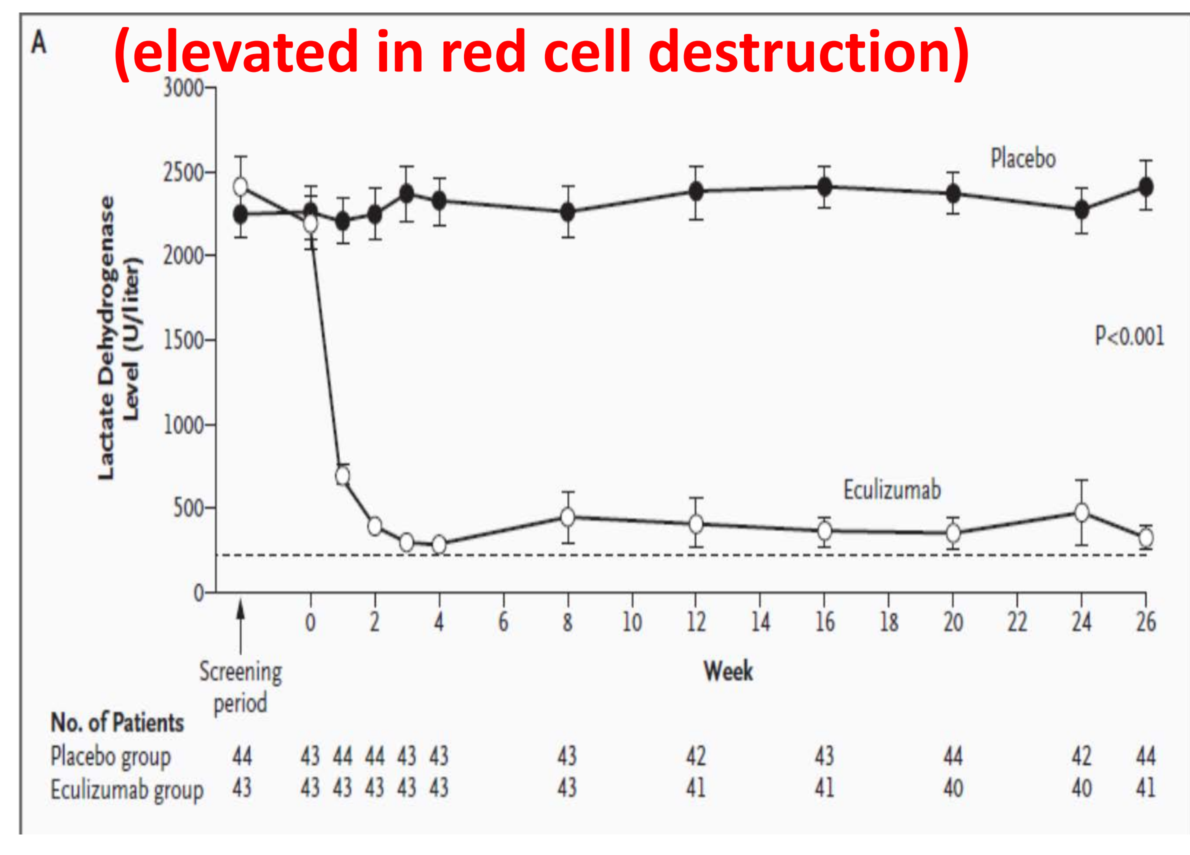
Mid 1990s:

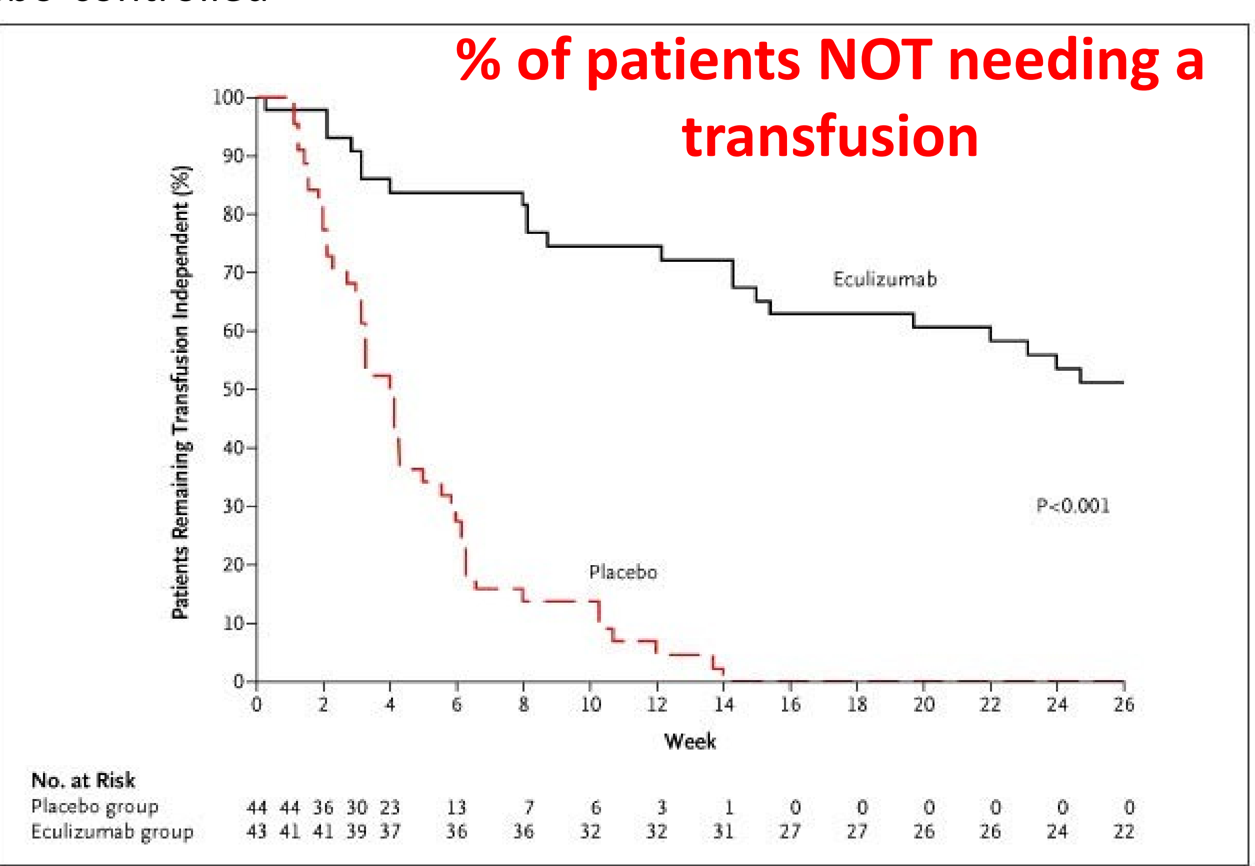
- Focus was on **C5 inhibition**
- Common to all pathways
- Protective function of early complement components PRESERVED
- Panels containing **30,000** anti-C5 antibodies screened
- Two selected for human testing – Pexelizumab and Eculizumab
- Eculizumab was attractive – $t_{1/2}$ = 11 days given INTRAVENOUSLY
- 1999: Testing began in Rheumatoid arthritis, Lupus and heart disease!
- **PNH studies in UK began in May 2002**

ECULIZUMAB: THE FIRST C5 INHIBITOR

(Hillmen; NEJM, 2006)

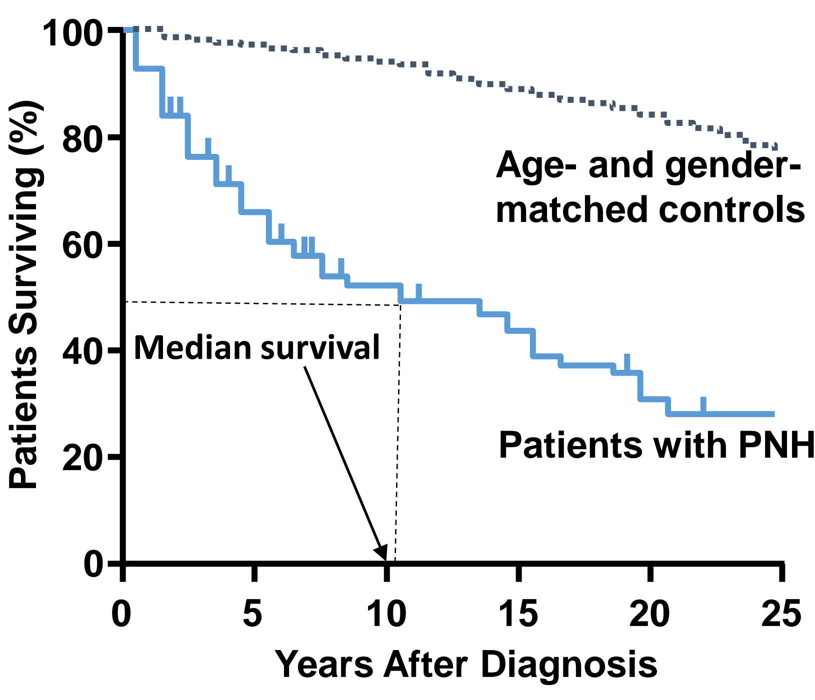
Phase III placebo-controlled



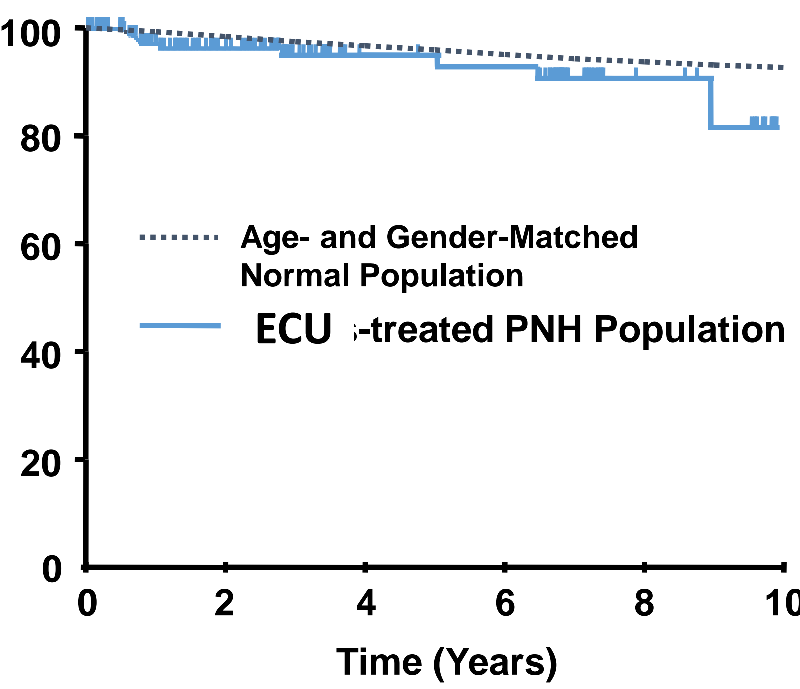


PNH Survival: Then and Now

Pre-Eculizumab Era



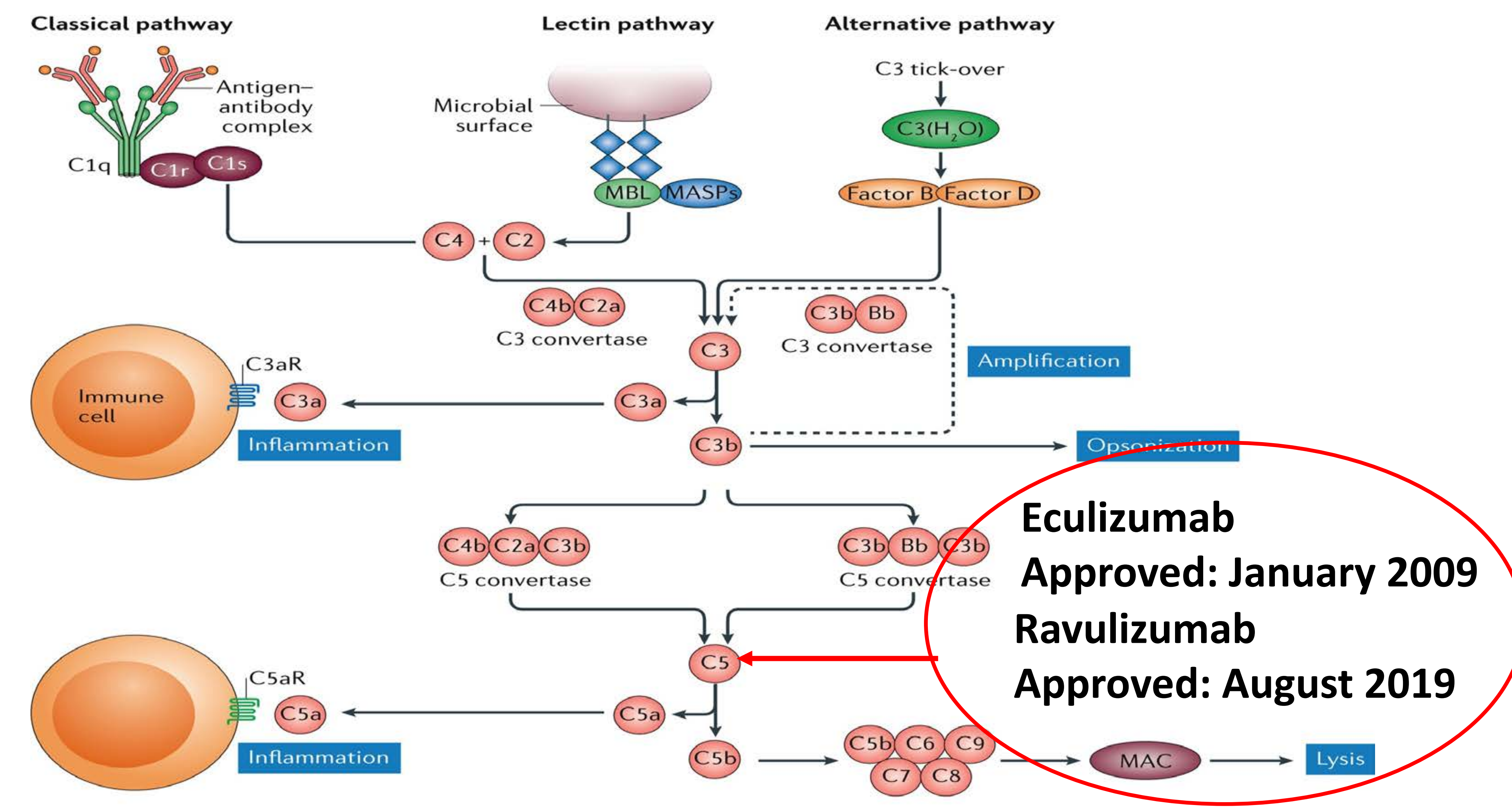
Post-Eculizumab Era



LONG-ACTING C5 INHIBITOR: RAVULIZUMAB

- **Ravulizumab** – C5i with 4 amino acid substitution
- Promotes internal drug RECYCLING (a Green C5 inhibitor!!)
- Extends its $t_{1/2}$ to over 7 weeks!
- A 2018 study compared ECU every 2 wks to RAVU every 8 wks
- RAVU was "non-inferior" to ECU
- No new side effects

The Complement Pathway



Trouw et al, 2017

So….

SO CLOSE

A New Problem…..

<u>Despite C5i, 25-50% of patients remain anemic and fatigued!</u>

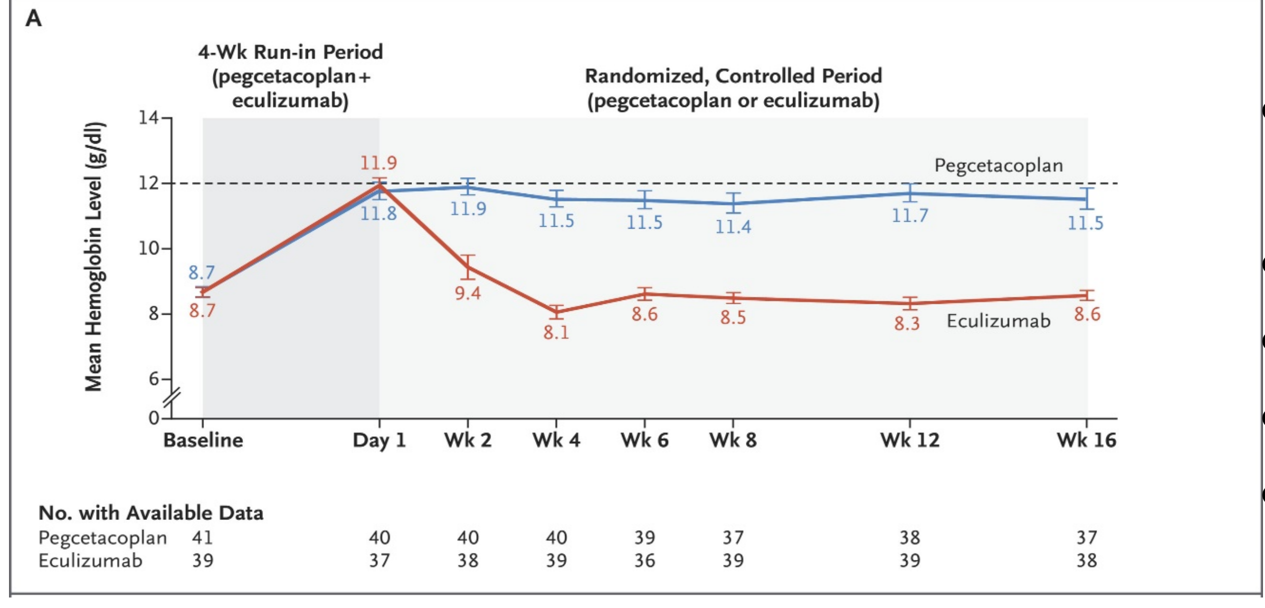
- “Breakthrough” hemolysis triggered by infection, vaccination, stress
- “Extravascular” hemolysis from buildup of earlier complement components (C3)

  → C3 coats the red cells and the spleen pulls these cells from the blood
- Some PNH patients have underactive bone marrows (concurrent aplastic anemia)

Development of a C3 Inhibitor: Pegcetacoplan

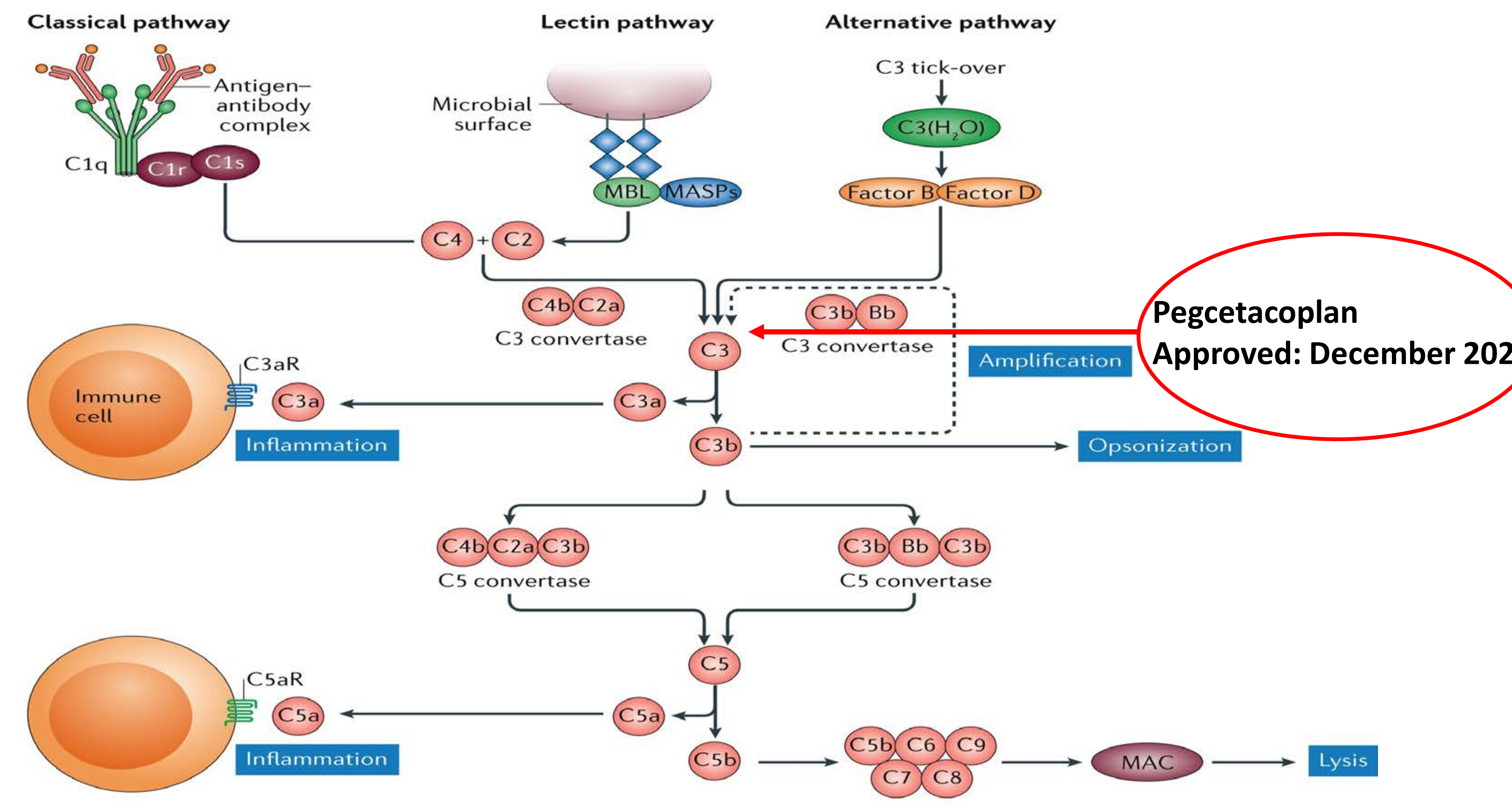
- PEGASUS Trial, 2021 - PNH patients on ECU with persistent anemia (avg 87 g/L)
- Randomized to **Pegcetacoplan** s.c. b.i.w. (½-1h) vs. continuing ECU

RESULTS:



- Less fatigue, H/A, hemolysis with PEG
- PEG had new side effects
- 1/3 injection site reactions
- 1/4 had diarrhea
- NO DIFFERENCE IN INFECTIONS

The Complement Pathway



Pegcetacoplan
Approved: December 2022

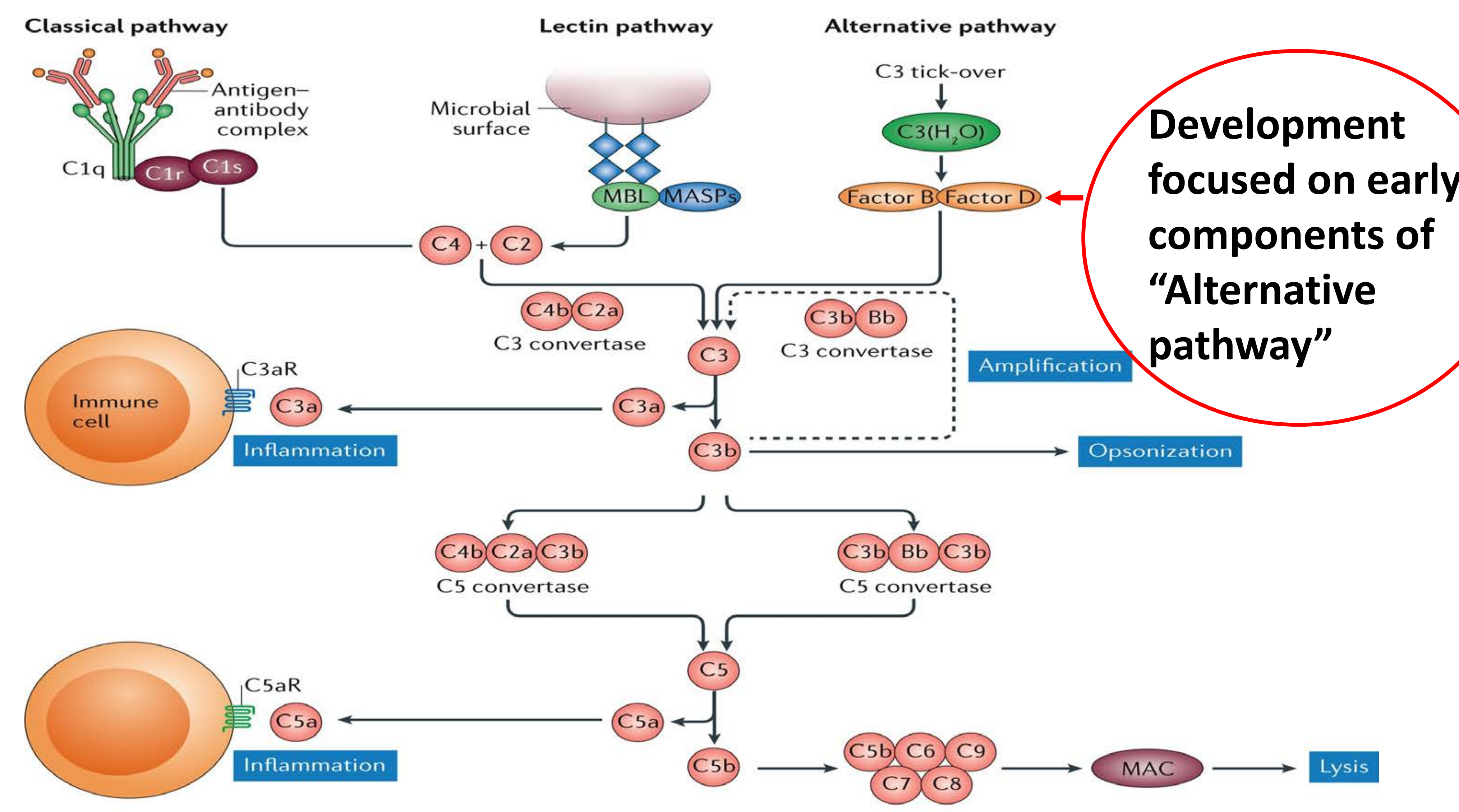
Trouw et al, 2017

Are we done now?

Remaining PNH Treatment Issues

- Breakthrough hemolysis – dramatic BTH with Pegcetacoplan
- **Inconvenient** – IV infusion every 2 weeks or s.c. infusion twice weekly
- Heightened infection prevention measures needed (vaccination, Penicillin)
- EXPENSIVE (400-500K/year) – high interest in alternatives…..

The Complement Pathway



Development focused on early components of "Alternative pathway"

Trouw et al, 2017

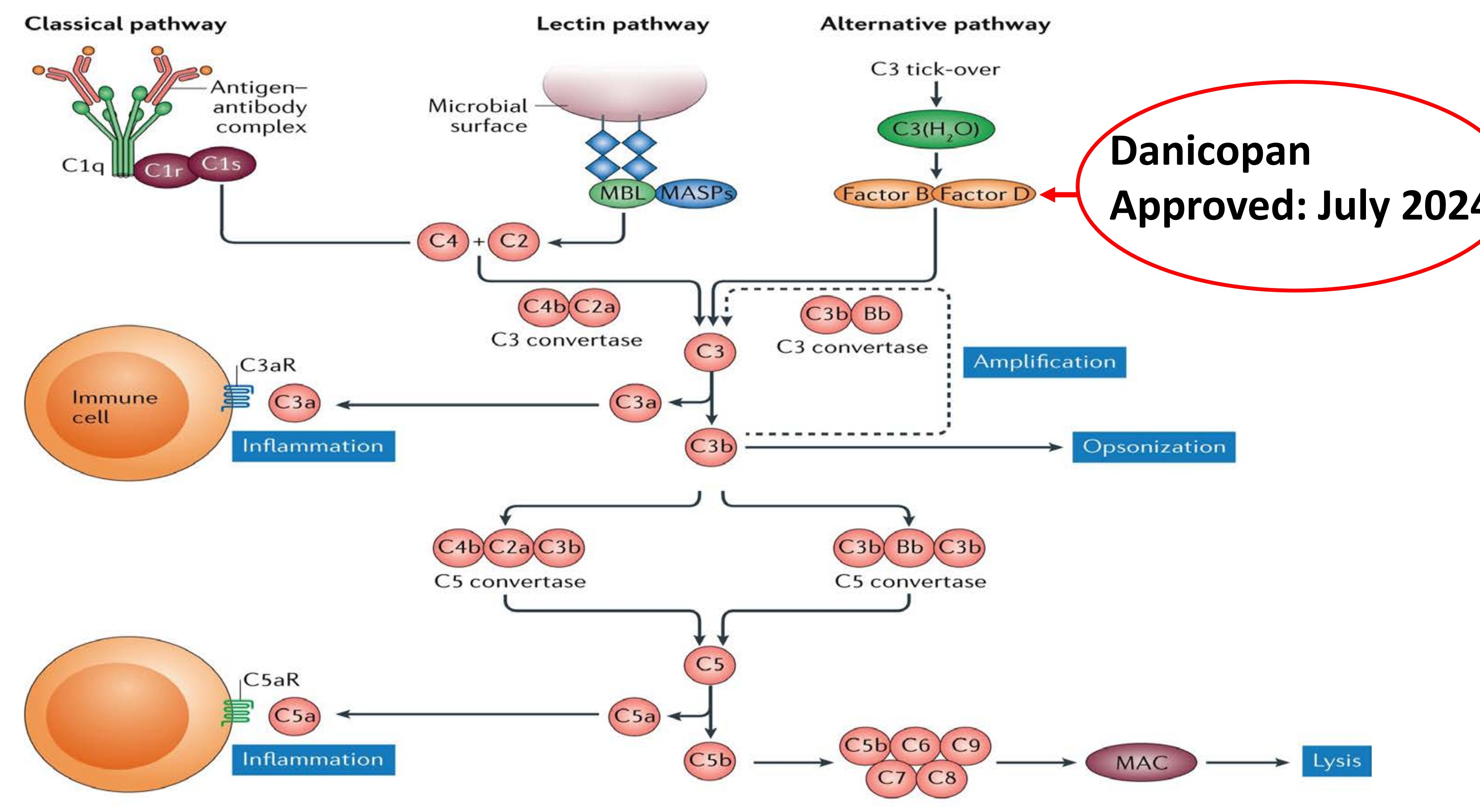
Factor D Inhibitor: Oral Danicopan

- **First trialed in 2021**
- Danicopan pills three times daily
- 10 Rx-naive PNH patients and all responded well - ↓ hemolysis ↑ hemoglobin

Led to ALPHA Trial reported in 2023

- ECU/RAV with Hb $\leq$ 95 g/L
- **Danicopan added for 3 months**
- **Improved hemoglobin and reduced symptoms**
- Side effects: H/A, mild liver abnormalities

The Complement Pathway



Danicopan
Approved: July 2024

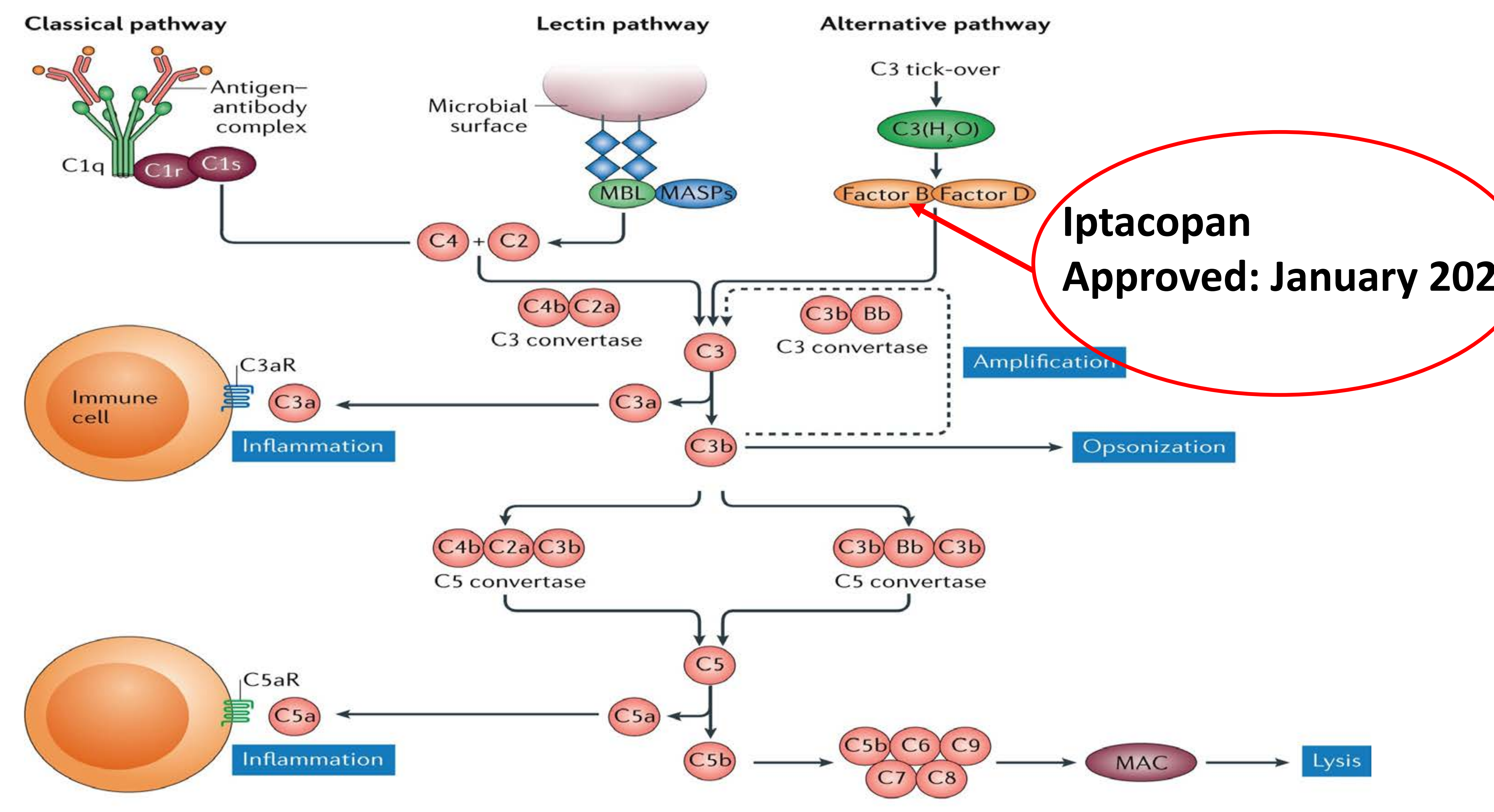
Trouw et al, 2017

FACTOR B INHIBITOR: ORAL IPTACOPAN

NEJM March 2024

- **Oral agent given TWICE daily as a “stand-alone” treatment**
- Tried in NEW PNH patients [APPOINT-PNH Trial]
- Tried in patients already on ECU/RAVU with Hb <100 [APPLY-PNH]
- Excellent response to Iptacopan in both studies
- 2/3 of Iptacopan patients had Hb ≥ 120 g/L (vs none with ECU/RAVU)
- **Rapid (2 wks) and unprecedented level of response!**
- Side effects: H/A and nausea/diarrhea

The Complement Pathway



Iptacopan
Approved: January 2025

Trouw et al, 2017

Oral complement inhibitors that are highly effective and have no significant side effects

But.....

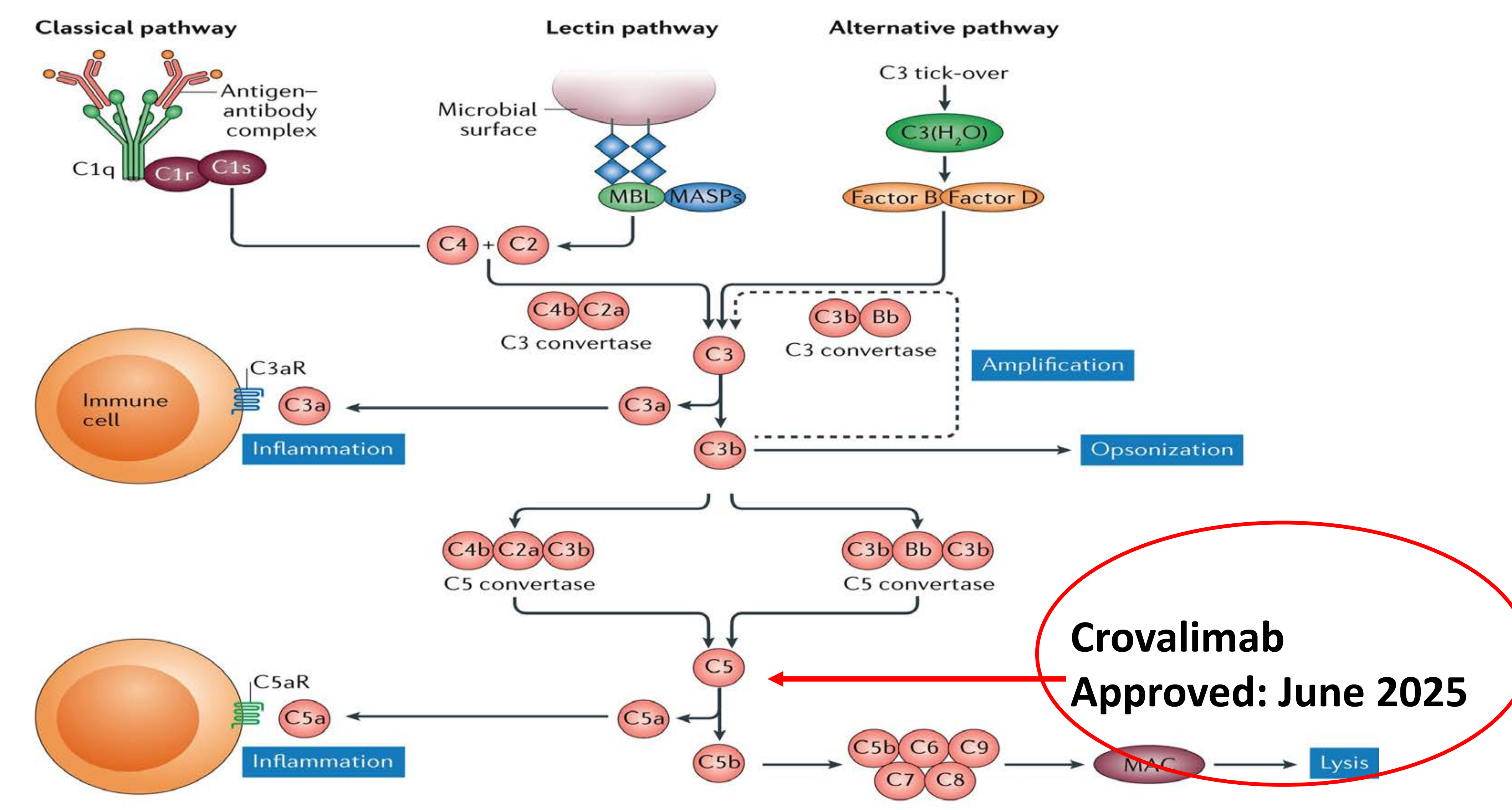
- **Danicopan** is marketed as an ADD-ON to Eculizumab/Ravulizumab in patients with suboptimal response to C5i
- Mark-up of 100K/year as you cannot stop ECU/RAVU
- Canada's Drug Agency (CDA) issued a final recommendation to reimburse Danicopan with certain conditions
- Negotiations with the pan-Canadian Pharmaceutical Alliance (pCPA) “were concluded without an agreement.”
- **Iptacopan,** as a stand-alone drug treatment, more recently suffered a similar fate….

I'M NOT DONE YET!

LONG-ACTING SUBCUTANEOUS C5 INHIBITOR: CROVALIMAB

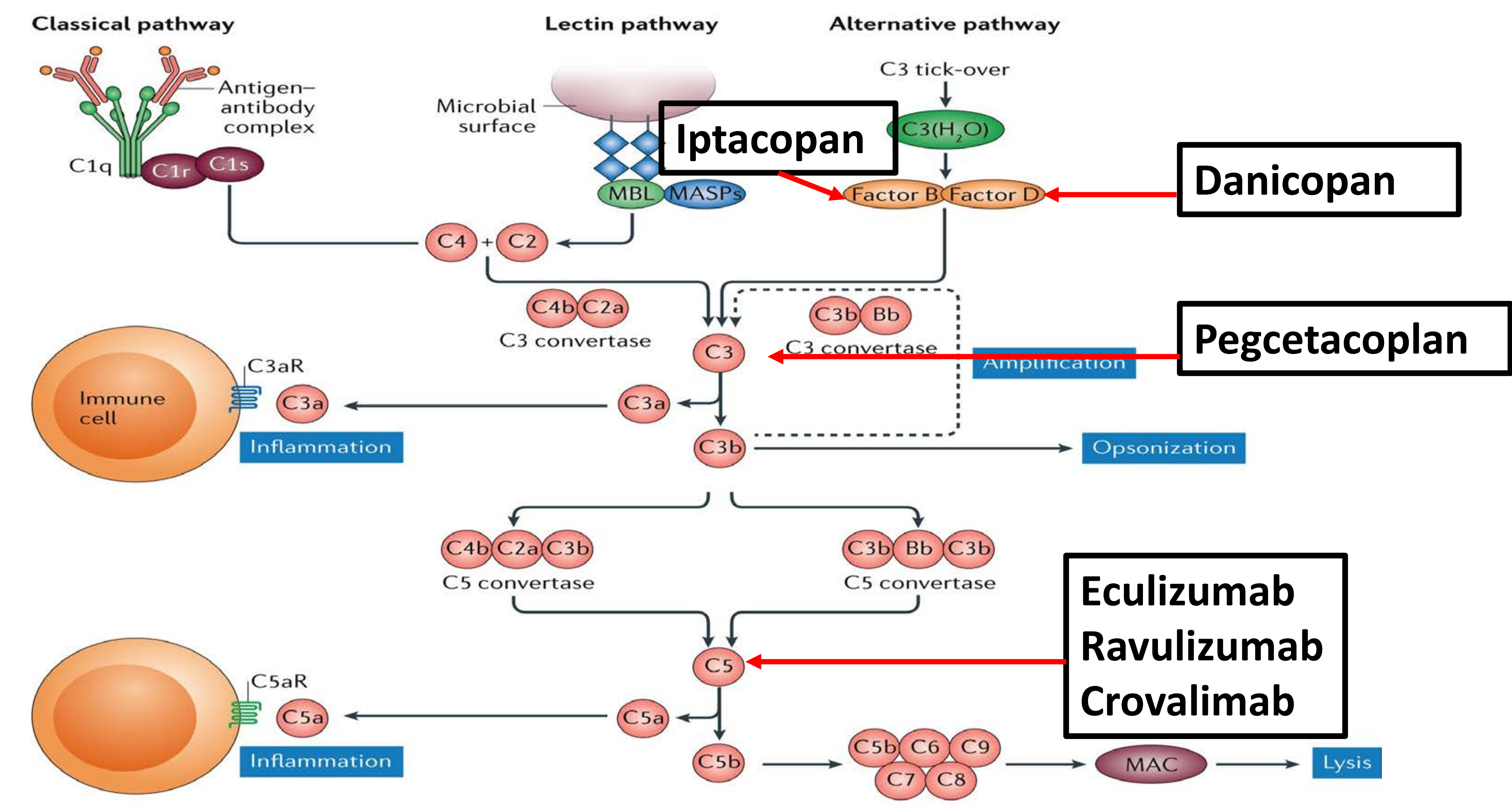
- **Given s.c. every 4 weeks**
- COMMODORE trials comparing Crovalimab to IV Eculizumab every 2 weeks
- Crovalimab found to be “non-inferior”
- 84% of patients who received both preferred Crovalimab
- One unique side effect: When switching from ECU to CROVA, 15% of patients have a Type III hypersensitivity reaction – generally mild/limited
- Skin rash, fever, joint pain, swollen glands +/- lung or kidney involvement

The Complement Pathway



Trouw et al, 2017

The Complement Inhibitor Landscape



Trouw et al, 2017

THE PNH TREATMENT LANDSCAPE