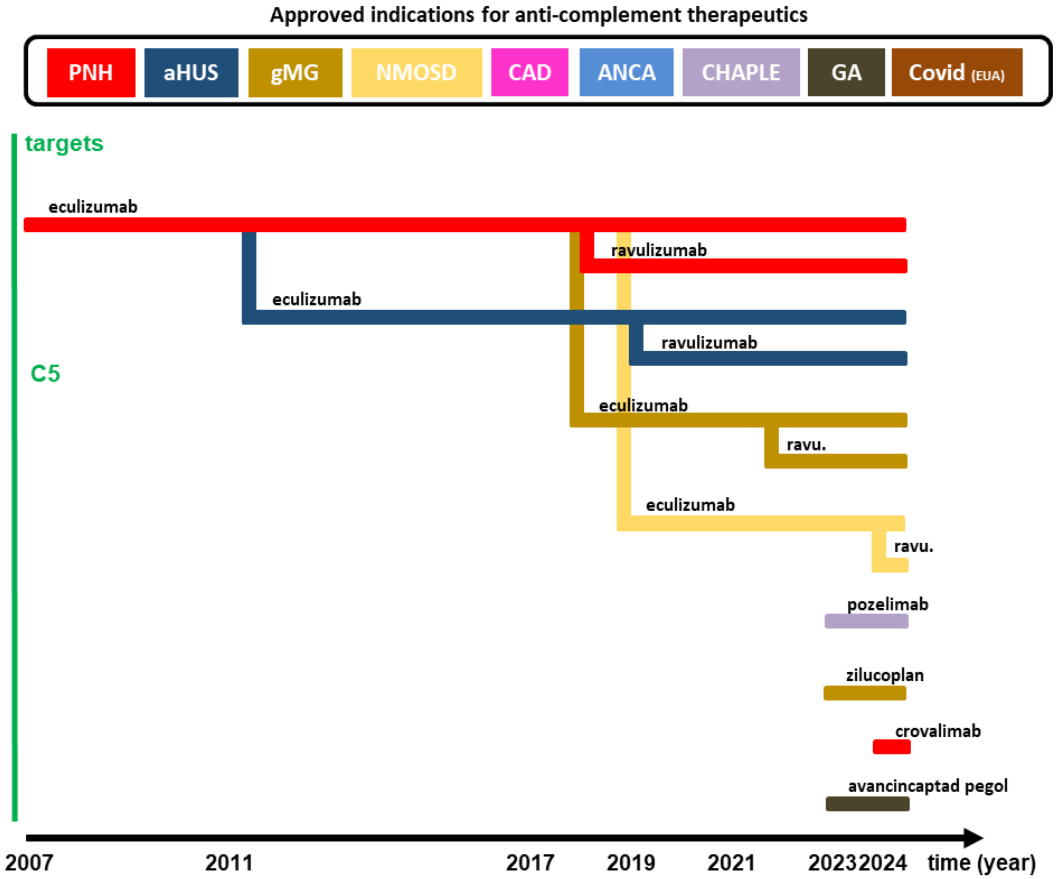
The biology of complement inhibition in PNH

Schmidt, Christoph
University of Ulm Medical Centre

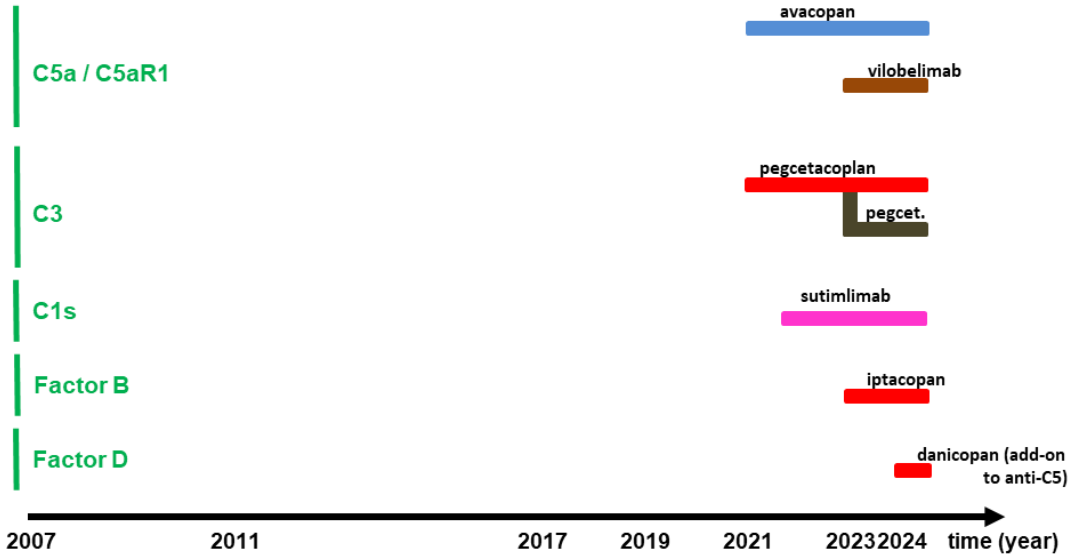
Disclosures of Christoph Schmidt

Company name	Research support	Employee	Consultant	Stockholder	Speakers bureau	Advisory board	Other
Takeda	yes						
Roche	yes						
Alexion					yes		
Vifor					yes		
Sobi					yes	yes	
Sanofi					yes		
OTHER							Registered inventor on patents describing novel complement inhibitors

COMPLEMENT: HEAT LABILE BUT NOT RESISTANT TO THERAPEUTICS

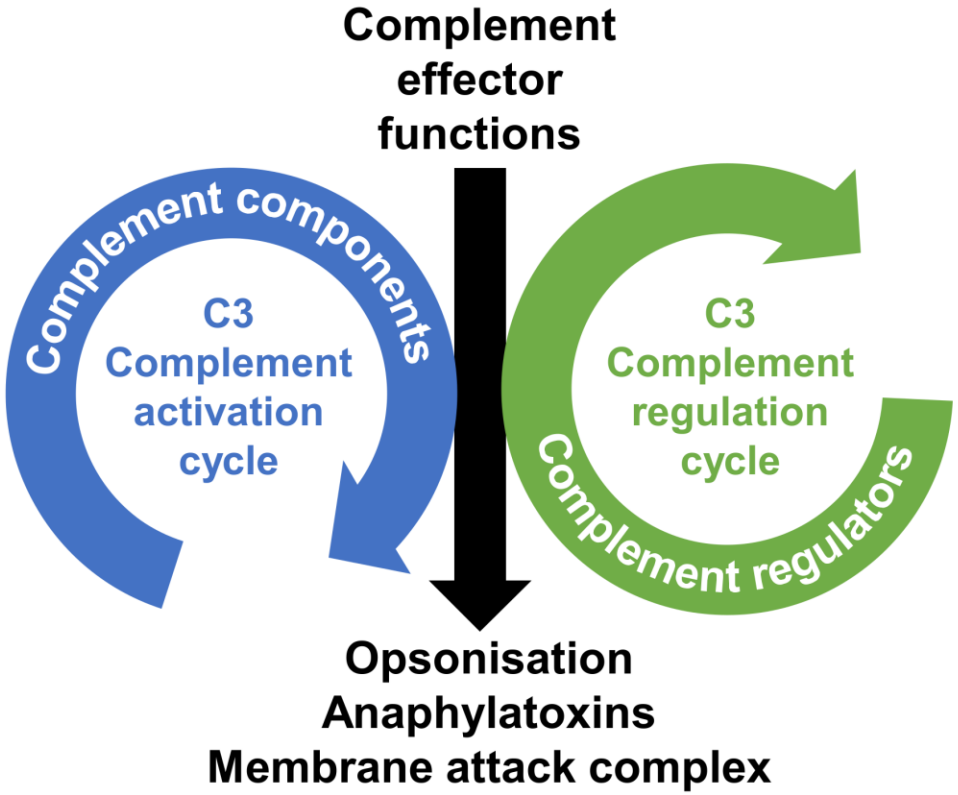


- Several targets
- Several indications



Adapted from Schmidt CQ & Smith RJH. *Immunol Rev.* 2023

COMPLEMENT SYSTEM – FUNCTIONS

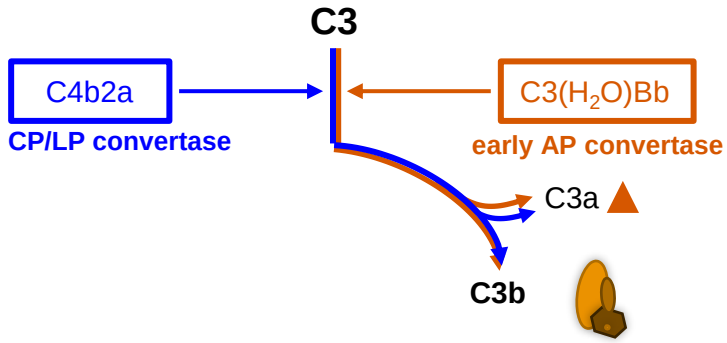


C3
in the centre of
the
complement
'universe'

Schmidt CQ et al. Blood. 2021

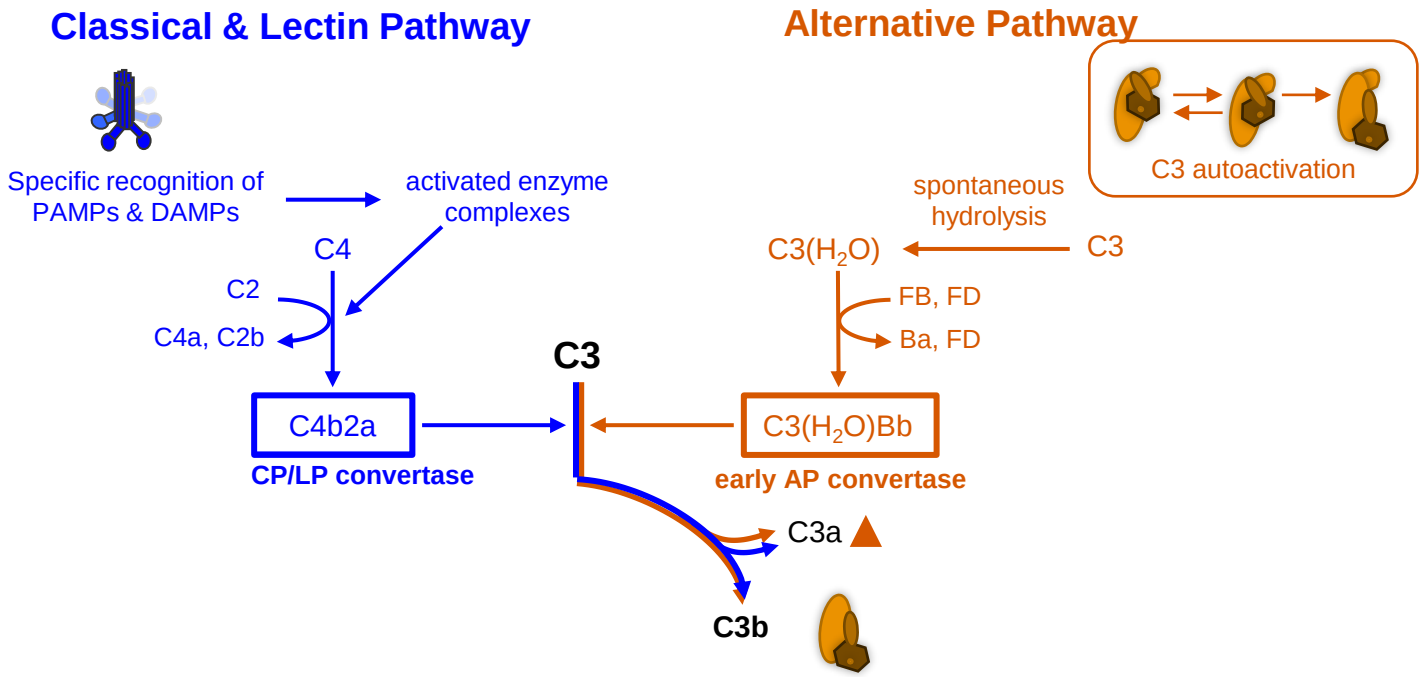
PROXIMAL COMPLEMENT ACTIVATION

Classical & Lectin Pathway **Alternative Pathway**



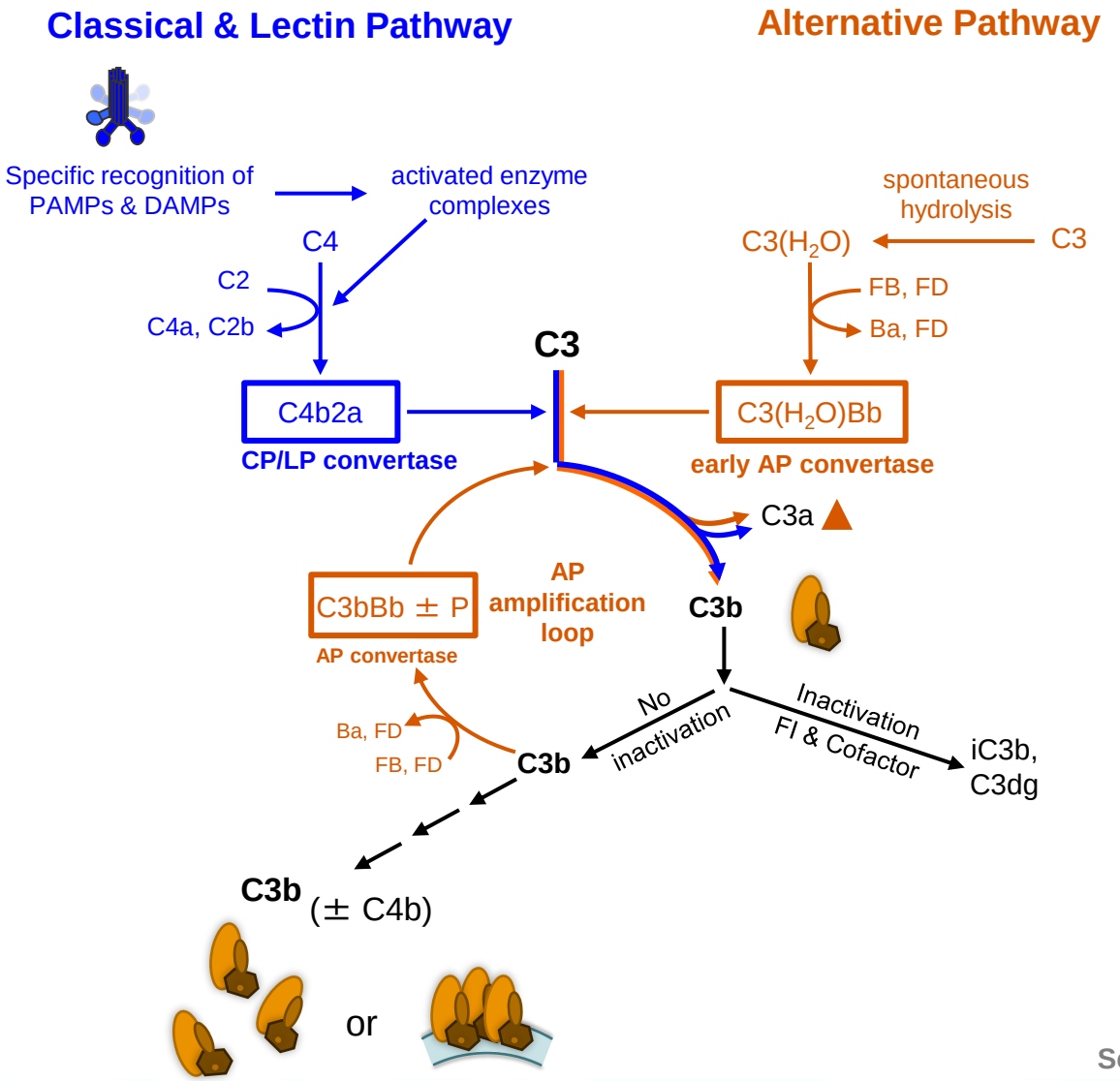
Mannes M et al. Blood 2021
Schmidt CQ et al. Blood 2022

PROXIMAL COMPLEMENT ACTIVATION



Mannes M et al. Blood 2021
Schmidt CQ et al. Blood 2022

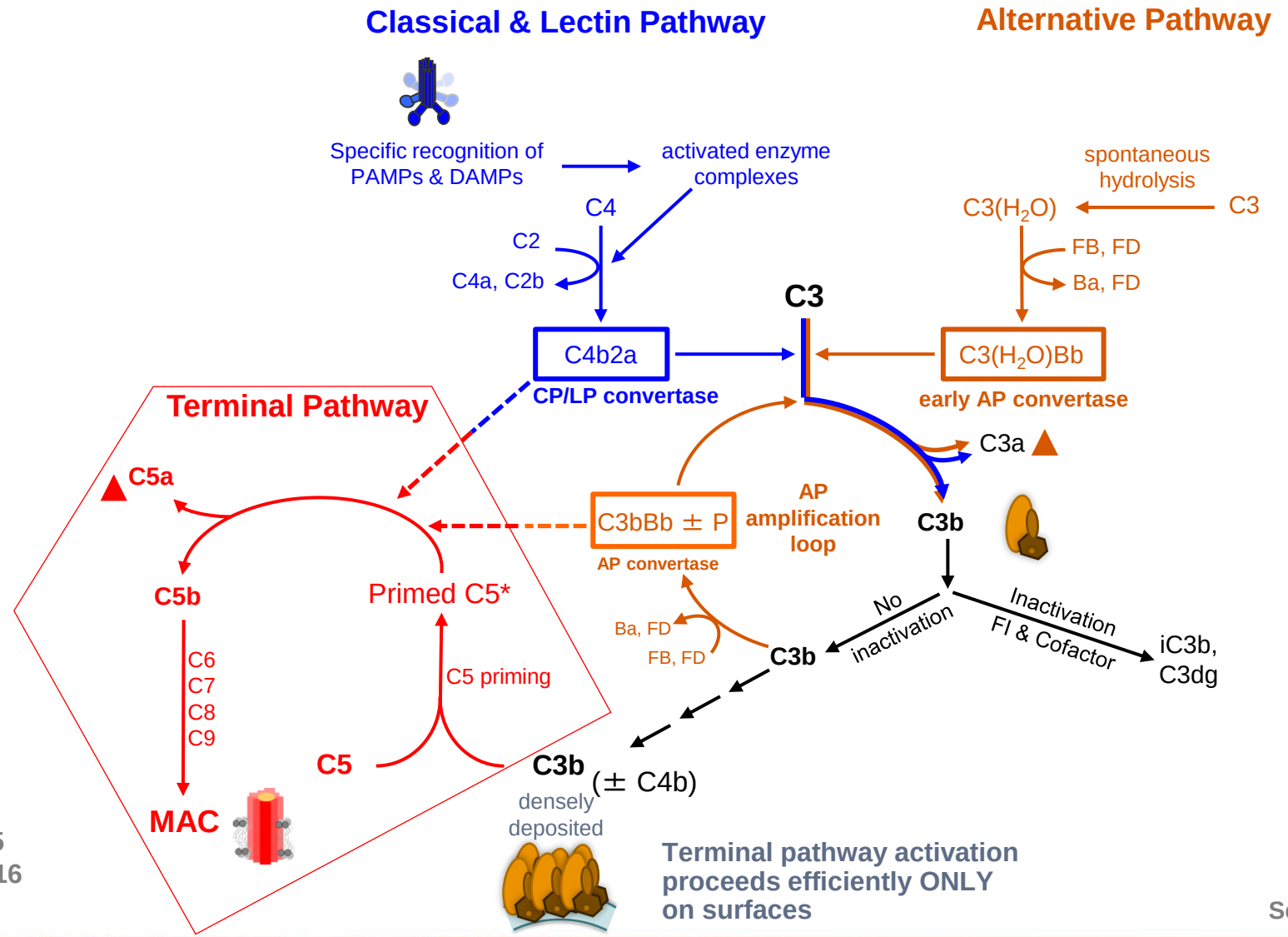
PROXIMAL COMPLEMENT ACTIVATION



Mannes M et al. Blood 2021
Schmidt CQ et al. Blood 2022

PROXIMAL & TERMINAL COMPLEMENT ACTIVATION

C3
in the centre of the complement ‘universe’



Inflammatory

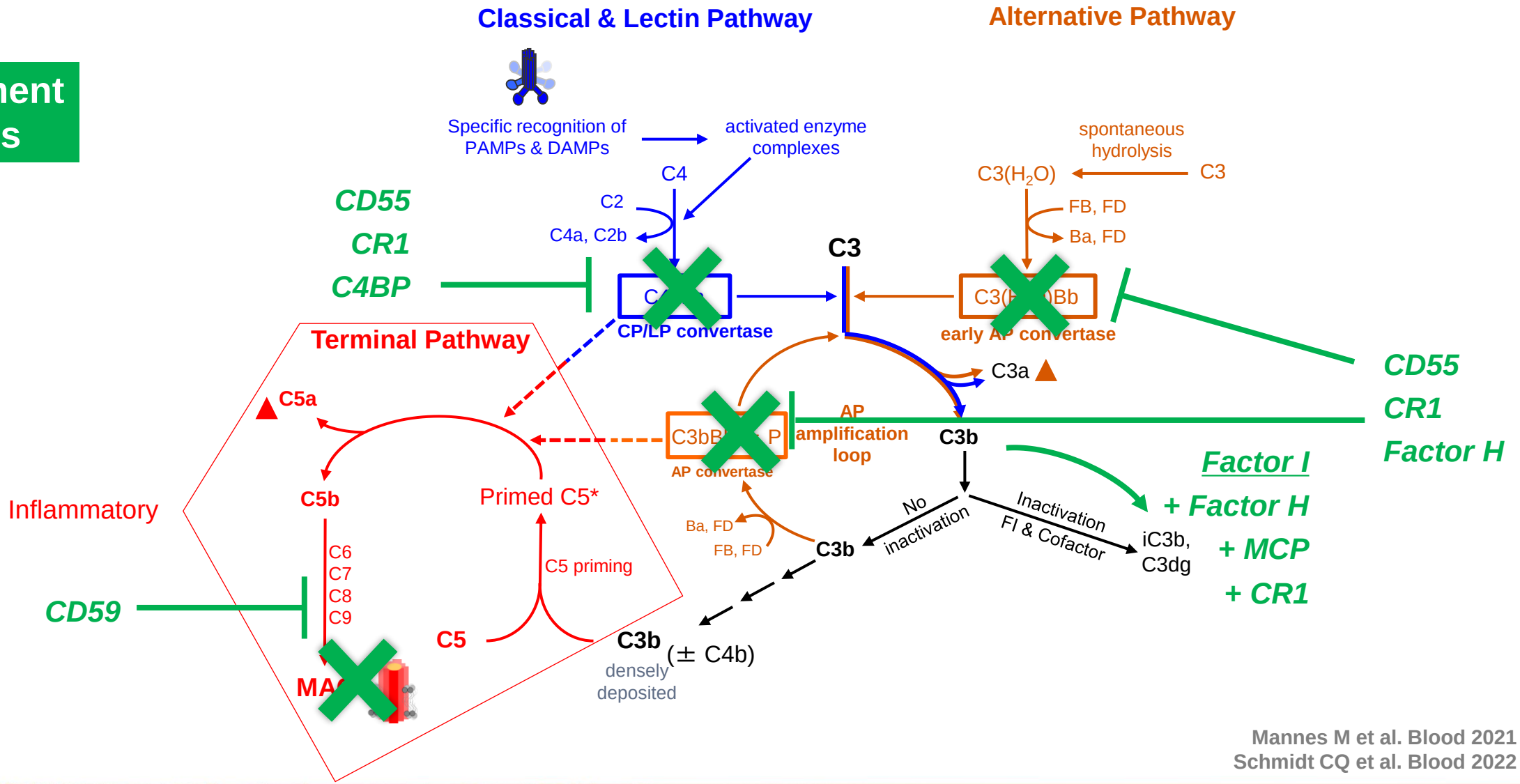
Terminal pathway activation proceeds efficiently ONLY on surfaces

Vogt W. et al. Immunology 1978
Berends ETM et al. BMC Biology 2015
Jore MM et al. Nat Struct Mol Biol. 2016
Harder MJ et al. Blood 2017

Mannes M et al. Blood 2021
Schmidt CQ et al. Blood 2022

COMPLEMENT CASCADE: UNDER CONTROL

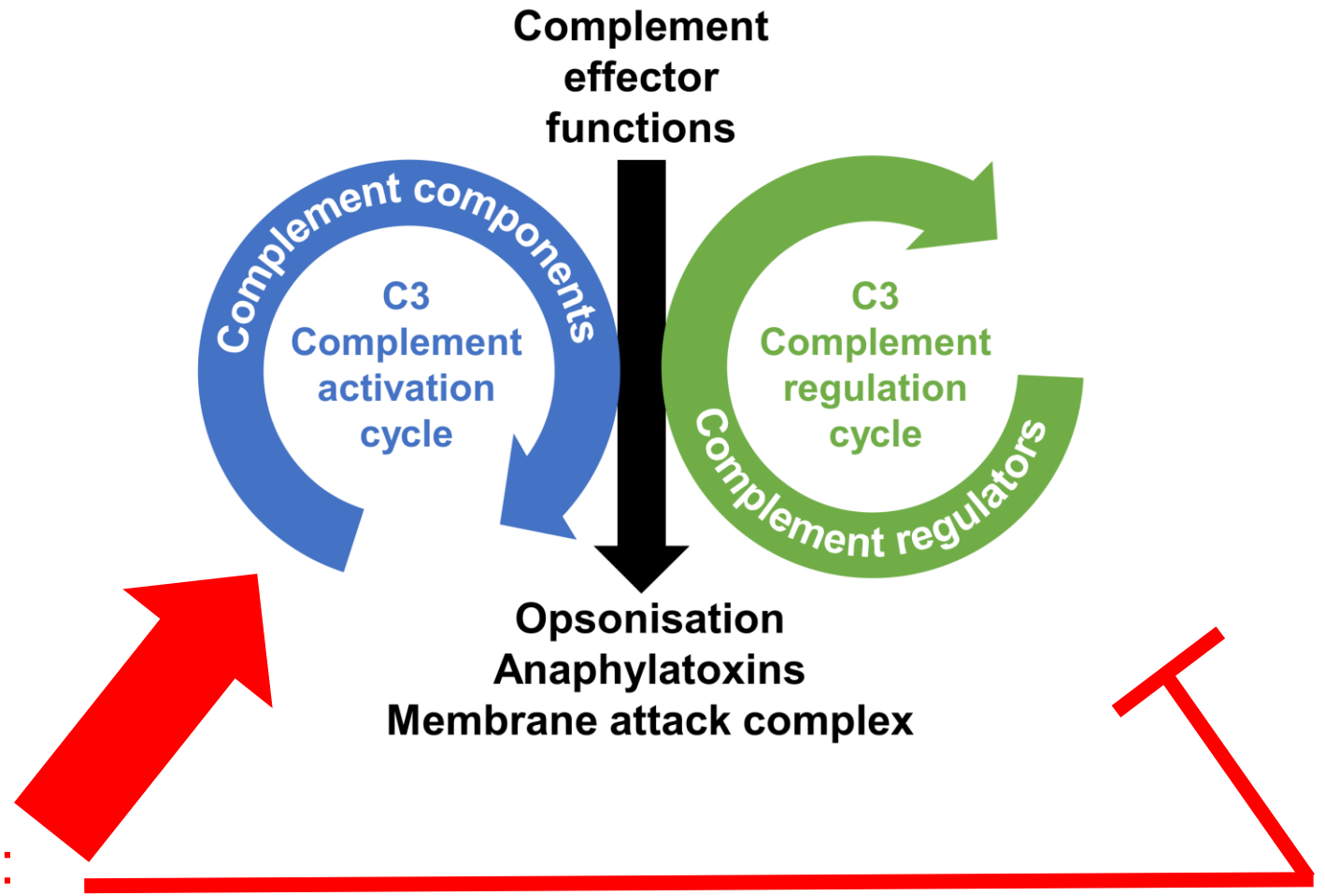
Complement regulators



MCP (= CD46)
CR1 (= CD35)

Mannes M et al. Blood 2021
Schmidt CQ et al. Blood 2022

COMPLEMENT SYSTEM – FUNCTIONS



Schmidt CQ et al. Blood. 2021

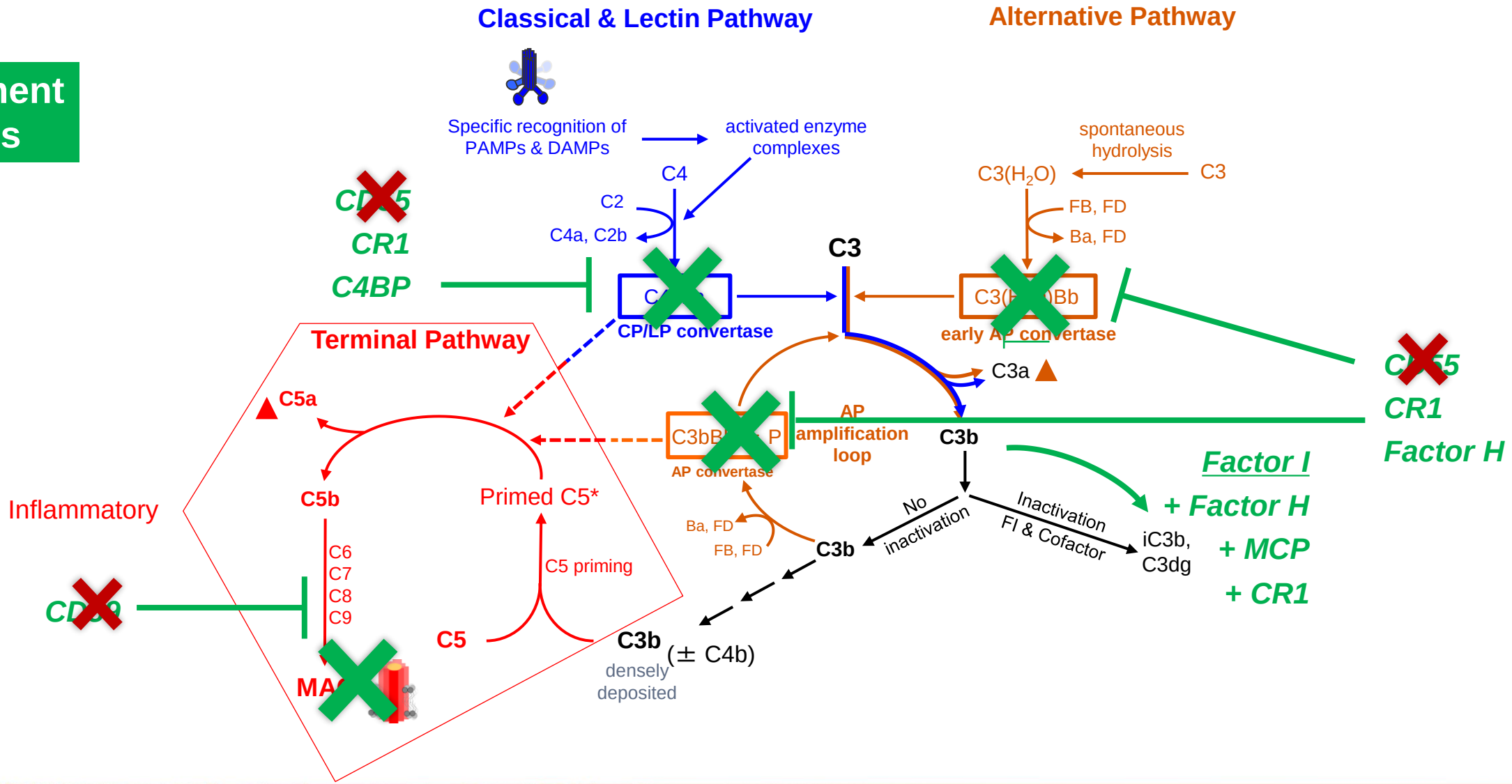
COMPLEMENT CASCADE: OUT OF CONTROL IN PNH

Mannes M et al. Blood 2021
Schmidt CQ et al. Blood 2022

COMPLEMENT CASCADE: OUT OF CONTROL IN PNH

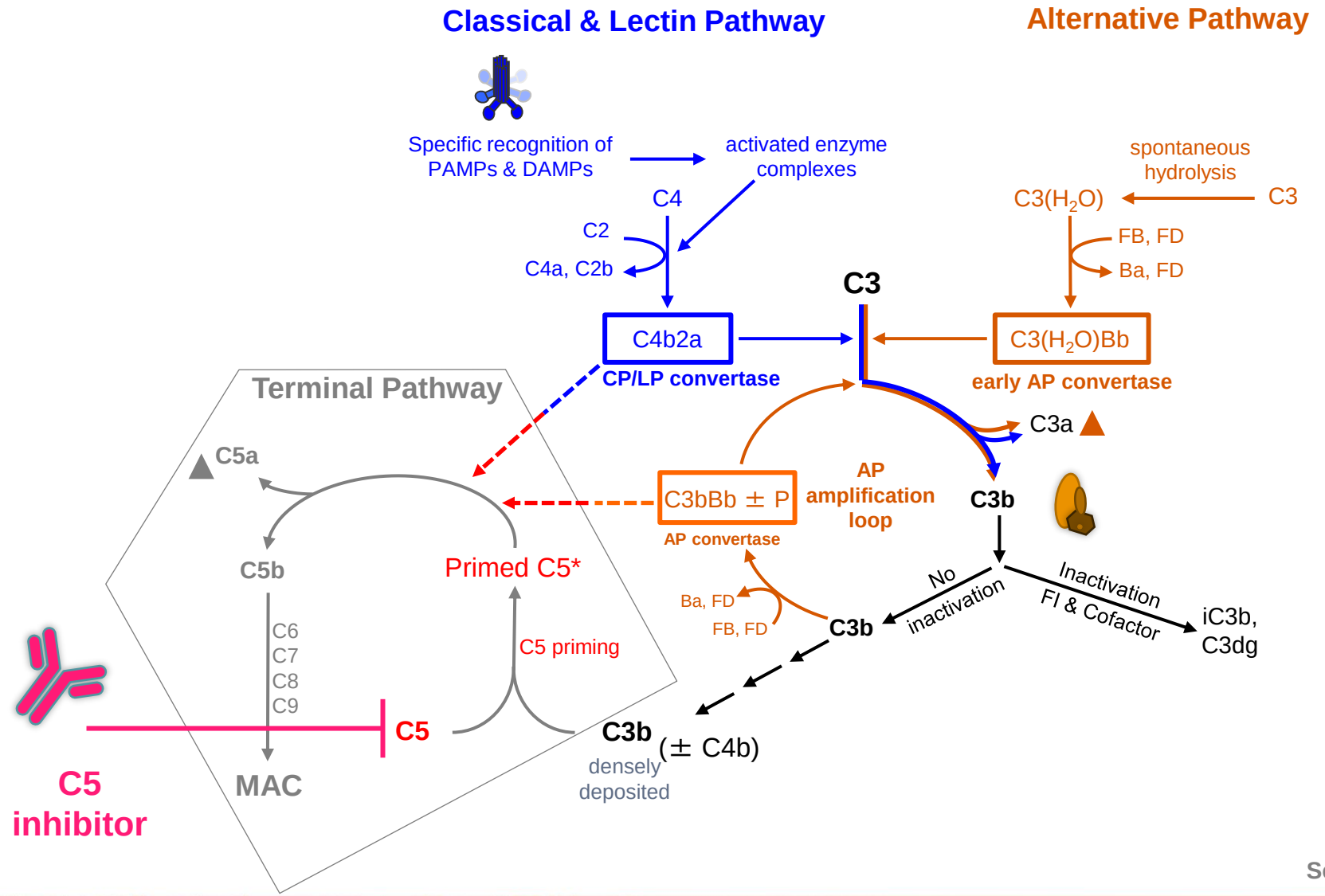
Complement regulators

PNH



MCP (= CD46)
CR1 (= CD35)

PNH & ANTI-C5 THERAPY



Therapeutic targeting of terminal pathway C5 'normalises' life expectancy

Mannes M et al. Blood 2021
Schmidt CQ et al. Blood 2022

THE FIRST COMPLEMENT INHIBITOR: ECULIZUMAB TARGETING C5

> ‘life transforming therapy’ approved for

- paroxysmal nocturnal haemoglobinuria (PNH)
- atypical haemolytic uraemic syndrome (aHUS)
- generalised myasthenia gravis (gMG)
- Neuromyelitis optica spectrum disorders (NMOSD)

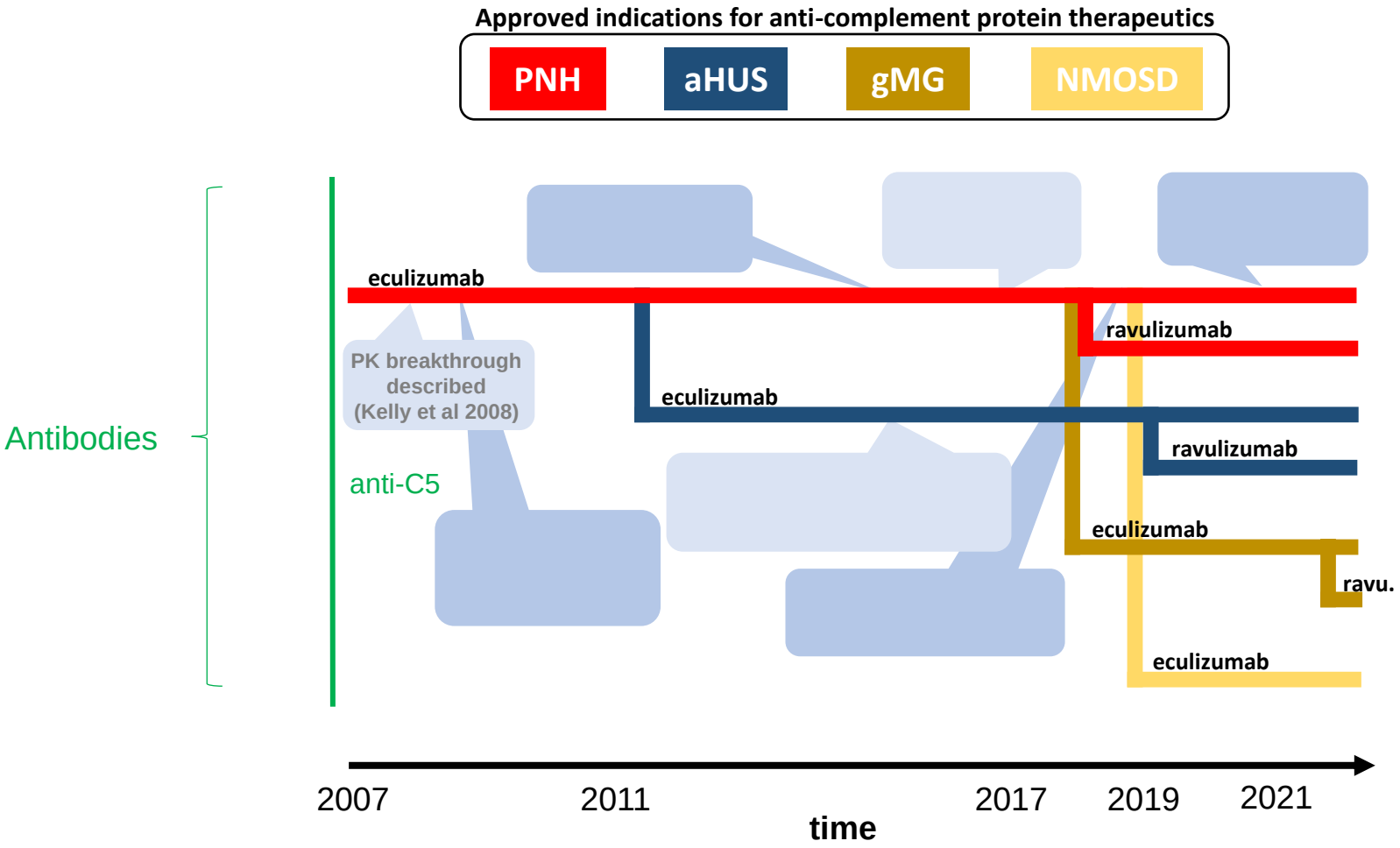
> cost of therapy: about 400 000 Euro per annum

> risk of meningococcal infection (despites vaccination)

> **not** all patients benefit fully (e.g. for some PNH patients transfusion dependency remains)

reviewed in Schmidt CQ et al. Eur J Immunol. 2024

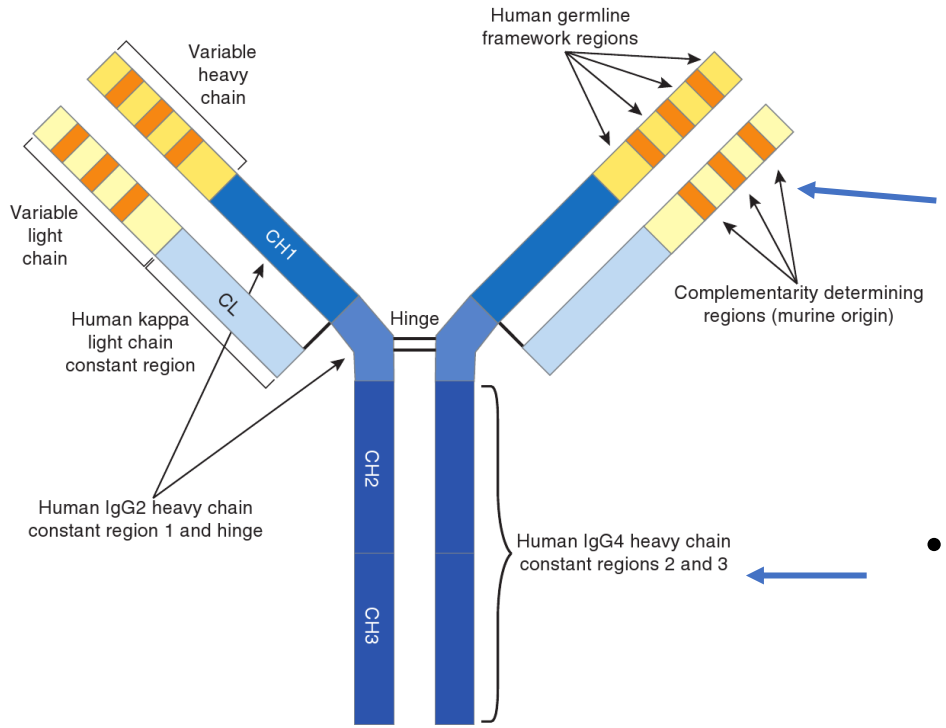
TIME COURSE OF APPROVED ANTI-C5 COMPLEMENT THERAPEUTICS:



Schmidt CQ et al. Immunol Rev. 2023

RAVULIZUMAB

- monoclonal humanized antibody based on Eculzumab
- 4 amino acids changed for improved FcRn cycling



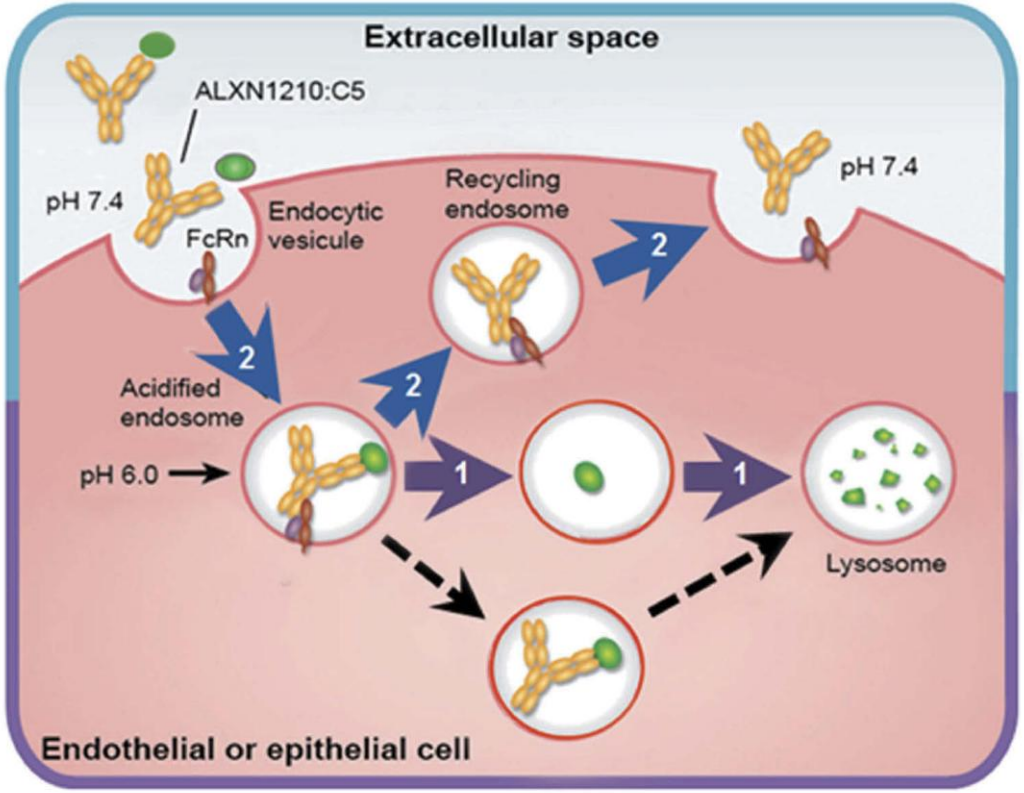
- 2 amino acid changes

- 2 amino acid changes

Lee JW, Kulasekararaj AG. Expert Opin Biol Ther. 2020

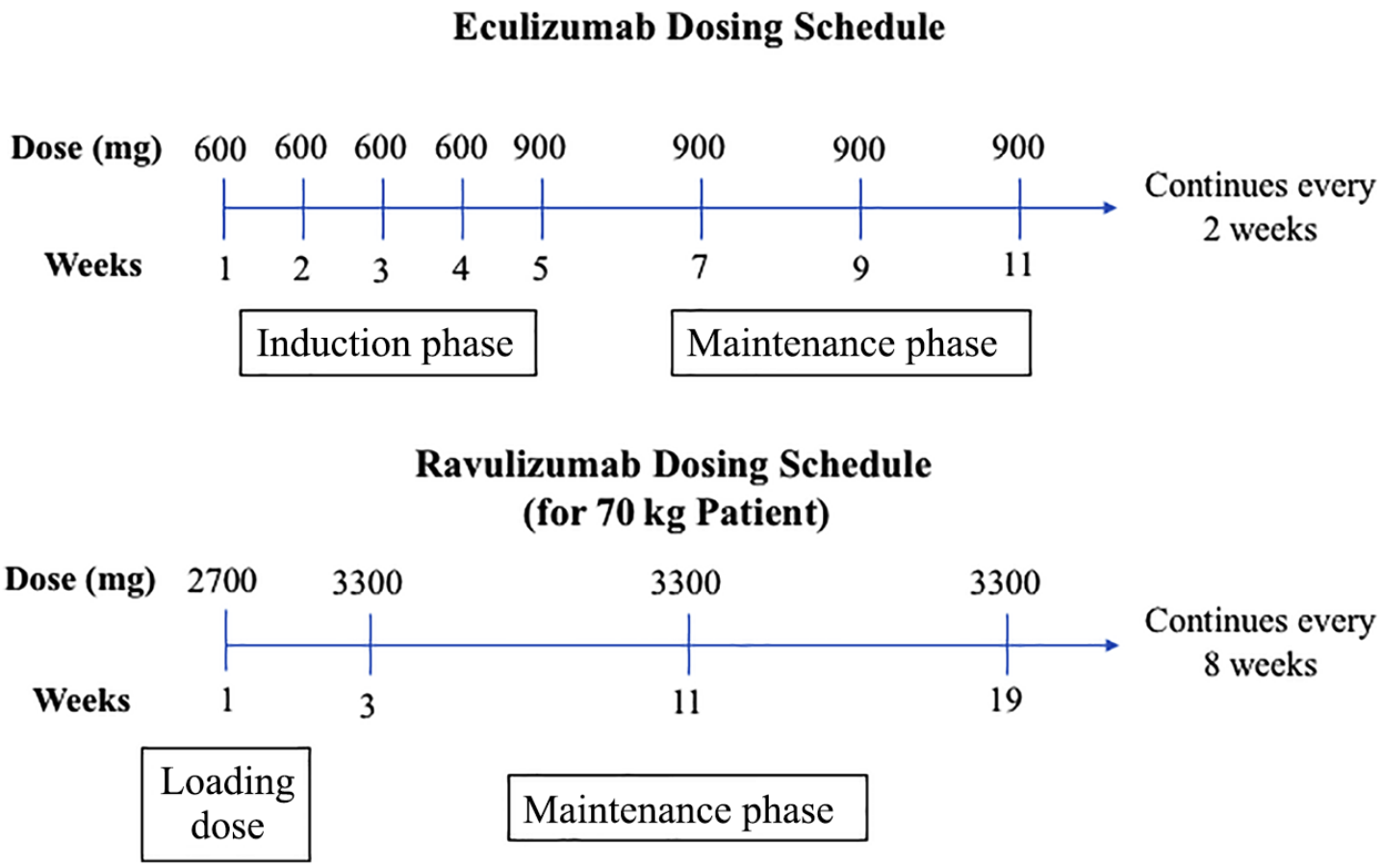
RAVULIZUMAB

- monoclonal humanized antibody based on Eculizumab
- 4 amino acids changed for improved FcRn cycling



Lee JW, Kulasekararaj AG. Expert Opin Biol Ther. 2020

RAVULIZUMAB VS. ECULIZUMAB DOSING IN PNH



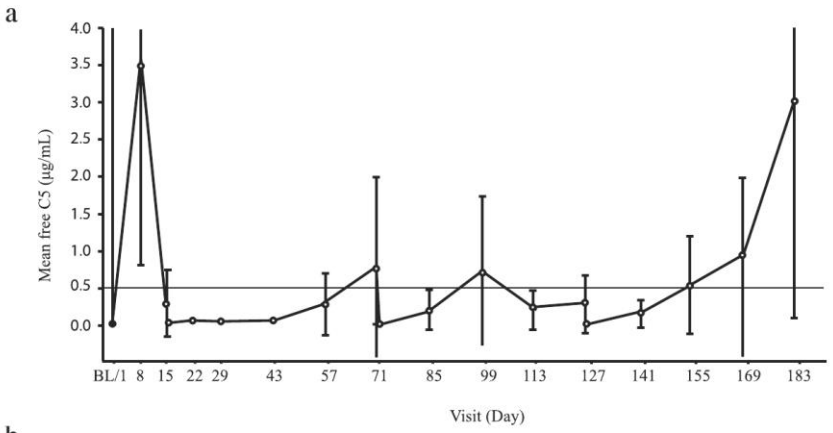
Stern RM, et al. Ther Adv Hematol. 2019

RAVULIZUMAB VS. ECULIZUMAB IN PNH: 301 & 302 STUDY

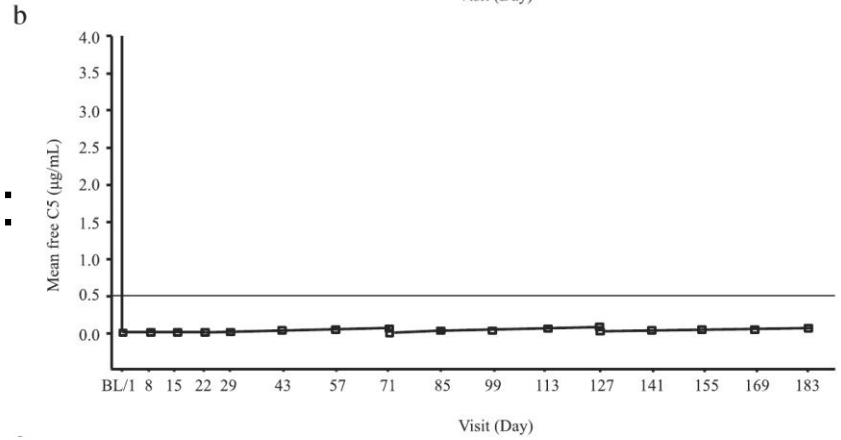
Measurement of free C5 in patient blood

301 study (Ecu or Ravu)

Ecu:

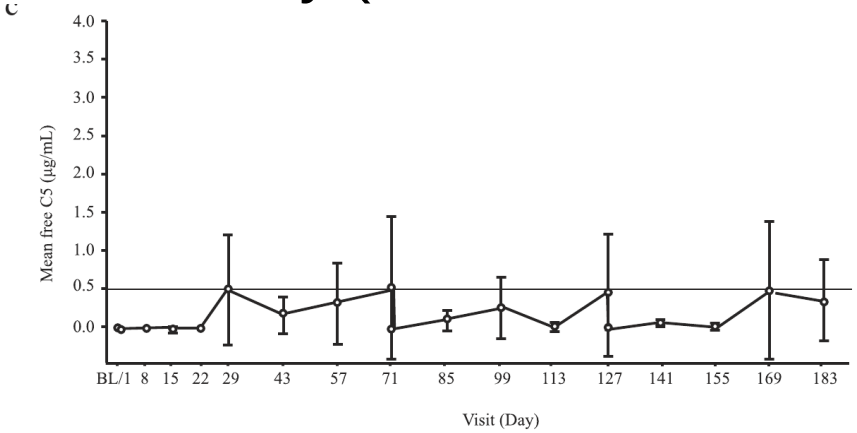


Ravu:

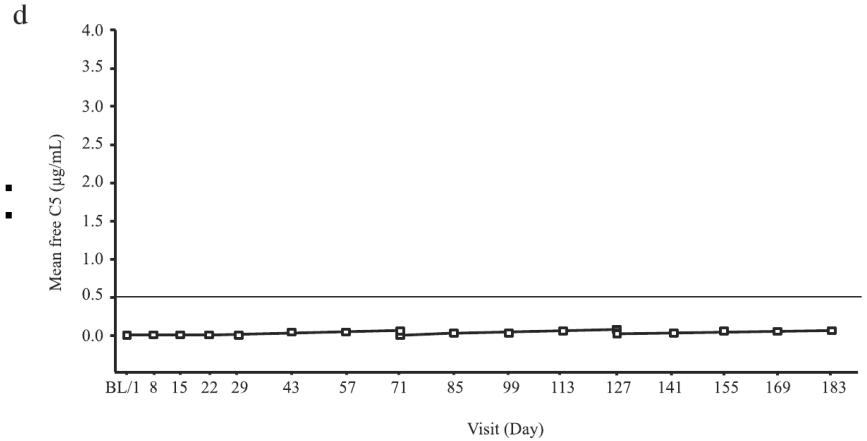


302 study (switch from Ecu to Ravu)

Ecu:

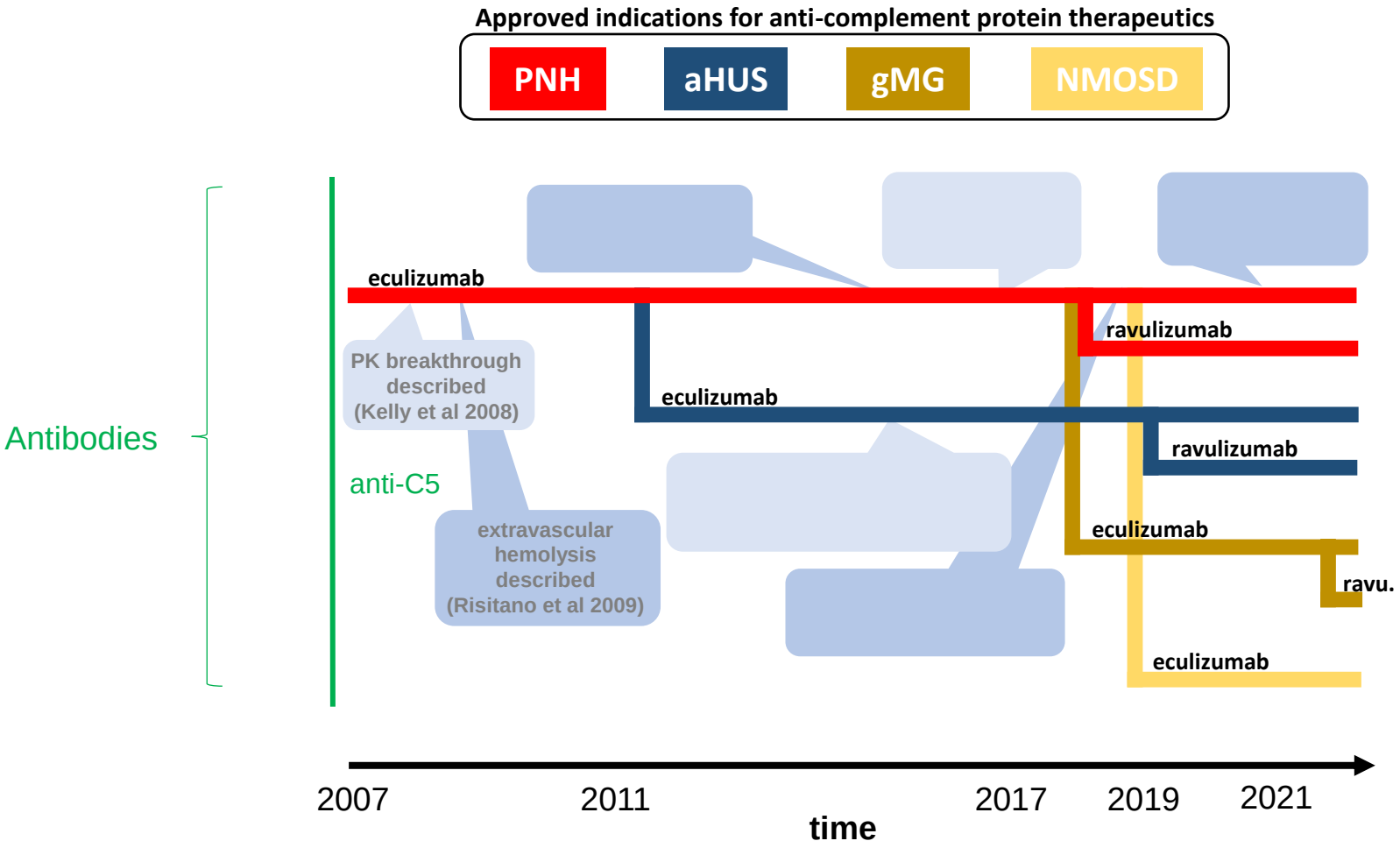


Ravu:



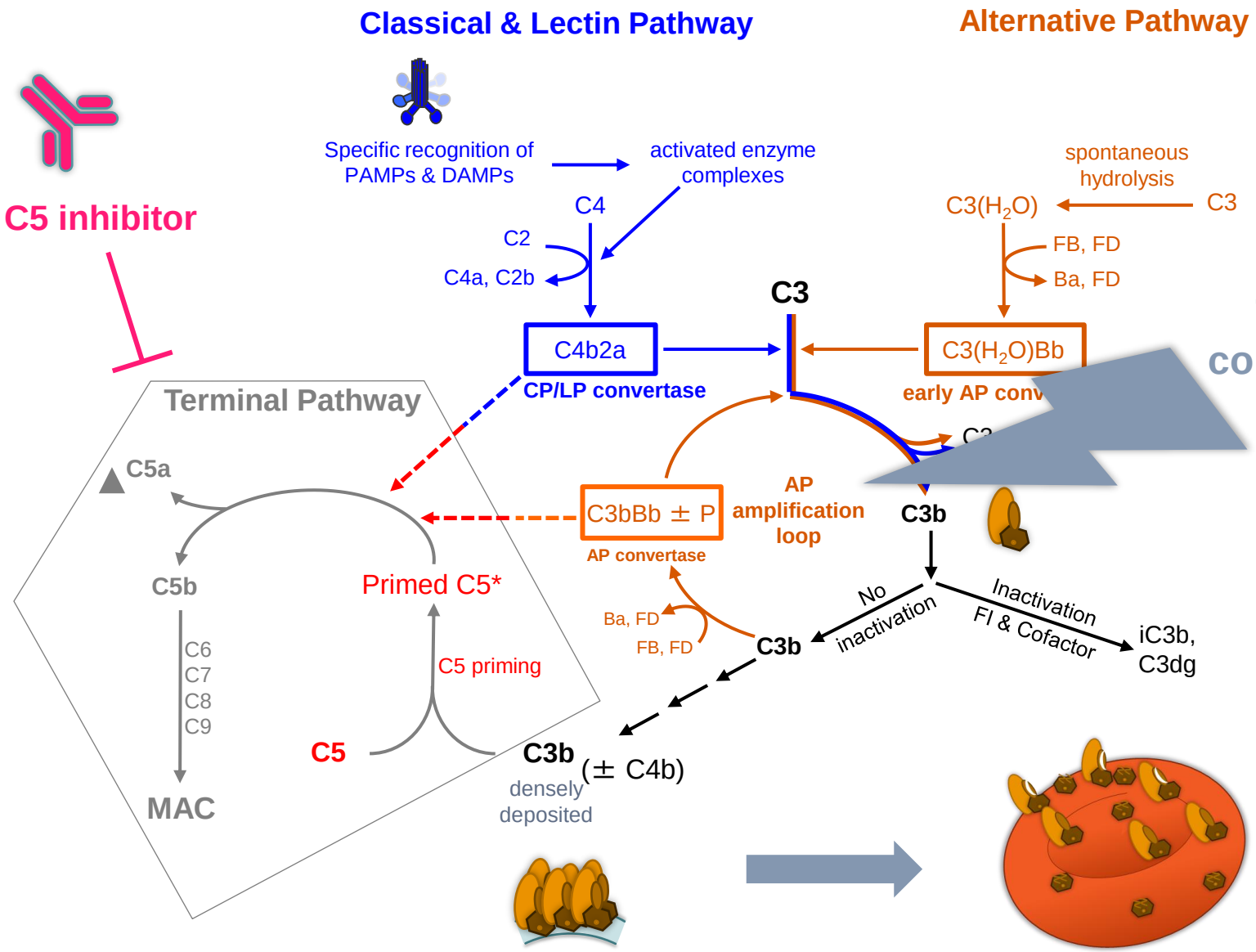
Lee JW, Kulasekararaj AG. Expert Opin Biol Ther. 2020

TIME COURSE OF APPROVED ANTI-C5 COMPLEMENT THERAPEUTICS:



Schmidt CQ et al. Immunol Rev. 2023

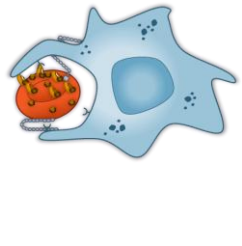
PROXIMAL CASCADE IS STILL ACTIVE UNDER C5 INHIBITION



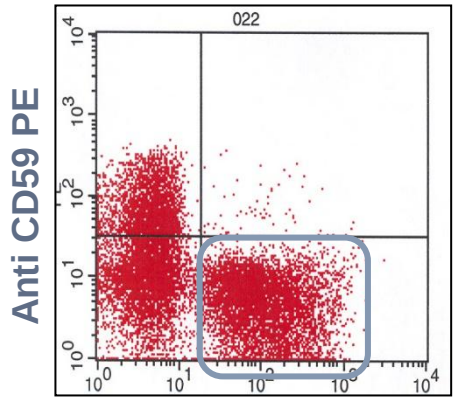
RES macrophages:

→ clearance of C3-opsonised PNH-RBCs:

→ extravascular haemolysis

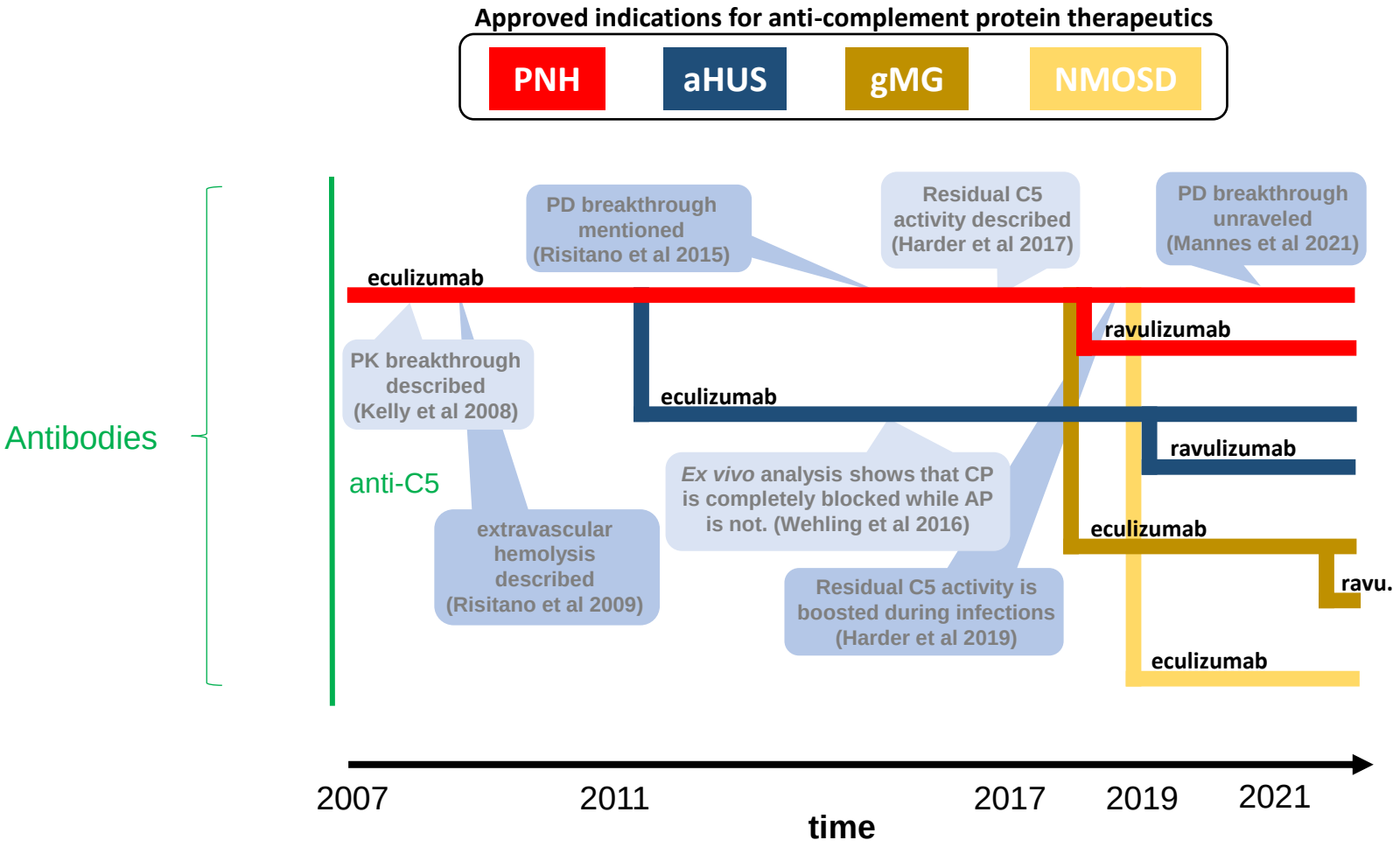


RBCs from eculizumab treated PNH patients

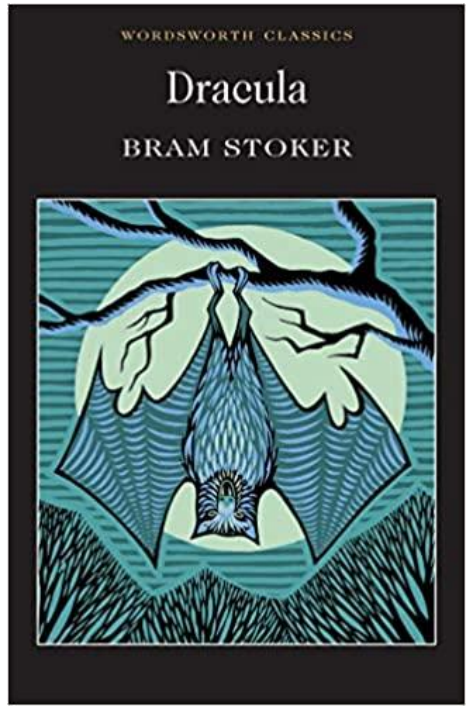


Risitano et al. Blood 2009
Hill et al. Haematologica 2010
Höchsmann et al. Vox Sang 2012

TIME COURSE OF APPROVED ANTI-C5 COMPLEMENT THERAPEUTICS:



…the unexpected always happens …



Schmidt CQ et al. Immunol Rev. 2023

RESIDUAL AP C5 ACTIVITY – LITERATURE EXAMPLES **IN/EX VIVO**

Clinical & Experimental Immunology
The Journal of Translational Immunology
British Society for immunology

Clinical and Experimental Immunology ORIGINAL ARTICLE doi:10.1111/cei.12890

Monitoring of complement activation biomarkers and eculizumab in complement-mediated renal disorders

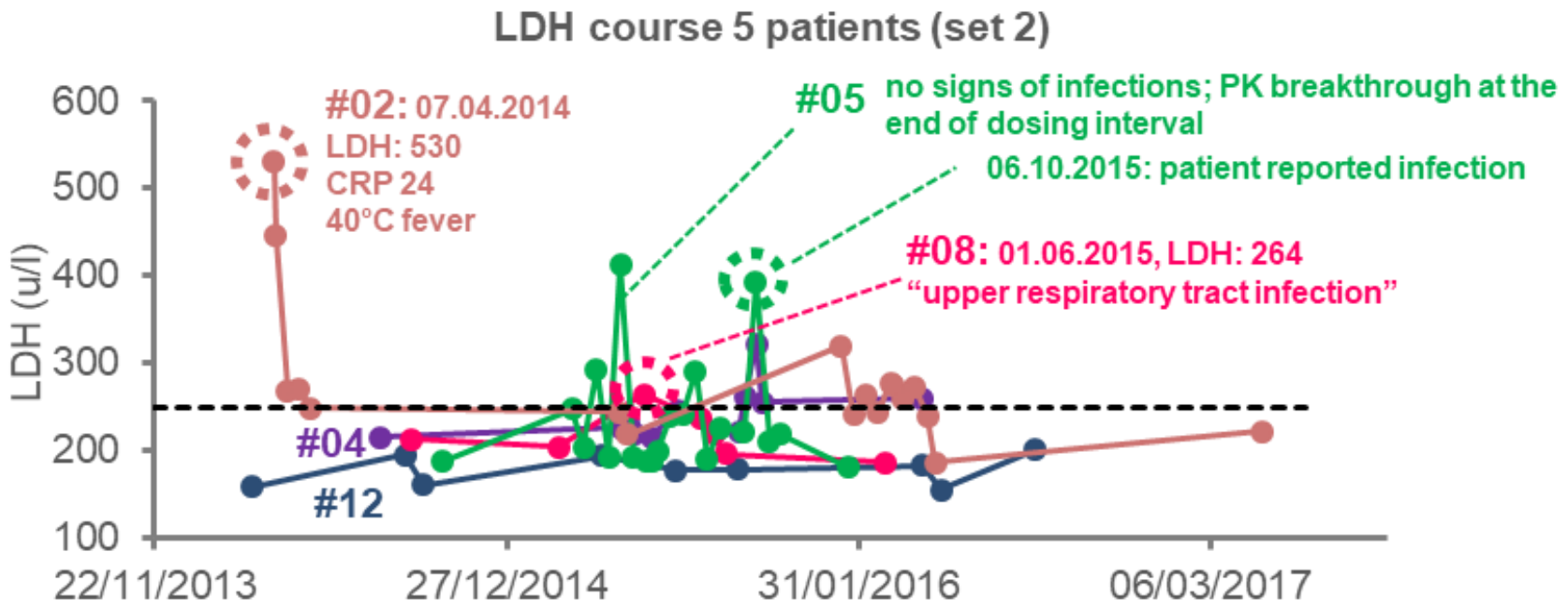
C. Wehling,* O. Amon,† M. Bommer,‡ B. Hoppe,§ K. Kentouche,¶ G. Schalk,** R. Weimer,†† M. Wiesener,‡‡ B. Hohenstein,§§ B. Tönshoff,¶¶ R. Büscher,*** H. Fehrenbach,††† Ö.-N. Gök‡‡‡ and M. Kirschfink*

(Fig. 4a). While the haemolytic activity of the classical pathway was constantly undetectable under treatment, a remaining haemolytic activity of the alternative pathway was observed, with APH50 values up to 20% (Fig. 4b). C3 levels

in most aHUS cases presented here the function of the classical and alternative pathway was inhibited completely, in some patients (e.g. aHUS patients 3 and 6 at T1) the alternative pathway in particular showed remaining haemolytic activity up to 67%, despite high concentrations of eculizumab.

WHAT WE DO NOT EXACTLY UNDERSTAND – ONE EXAMPLE

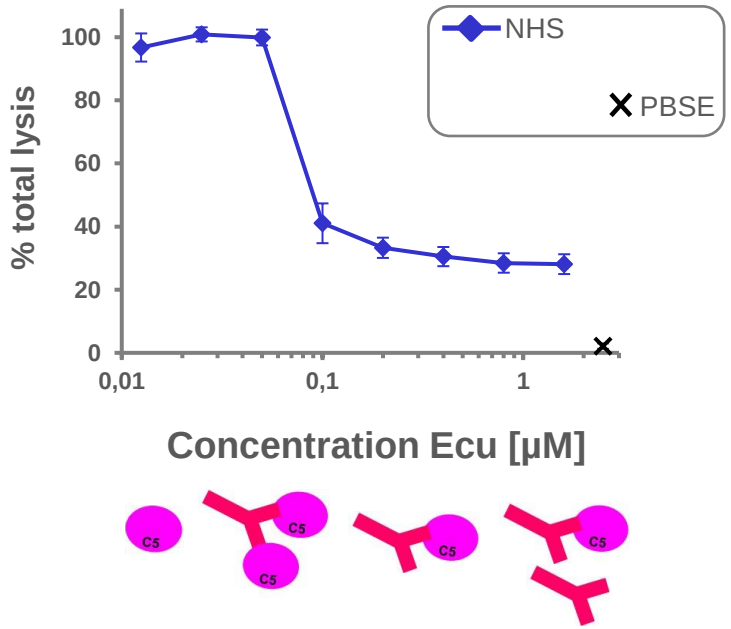
- there are two versions of breakthrough events under Eculizumab therapy: pharmacokinetic & pharmacodynamic

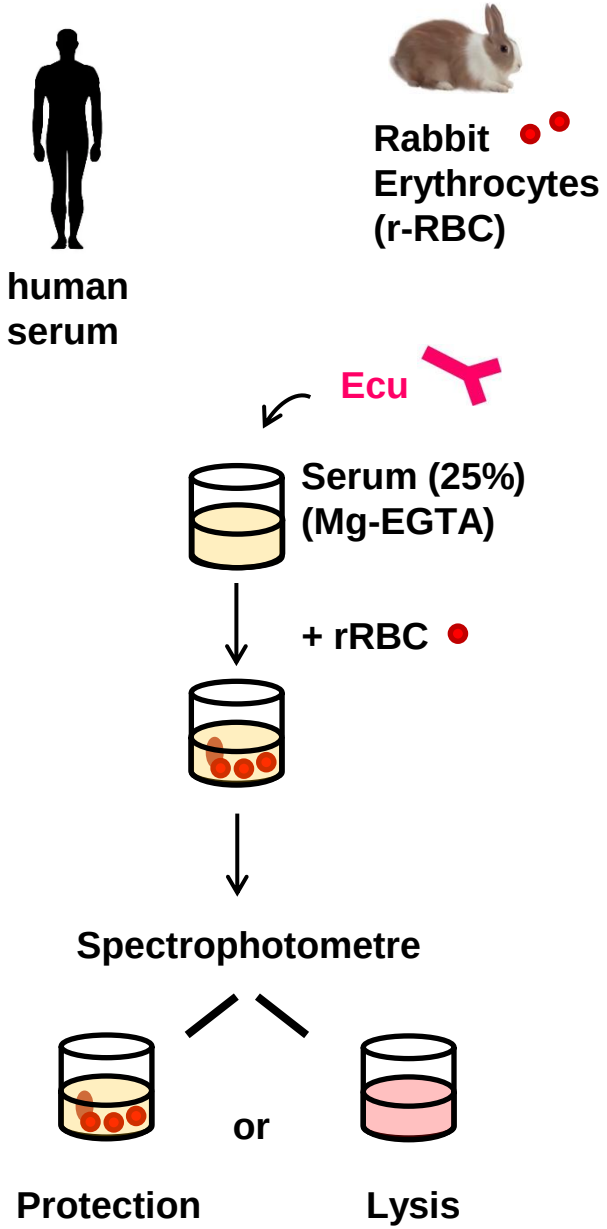


Harder MJ et al Front Immunol. (2019) 10:1639

Pharmacodynamic breakthrough of C5 inhibitors

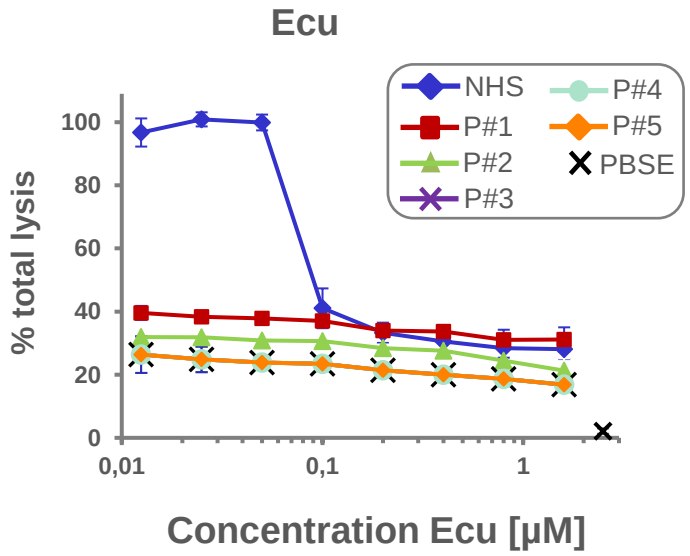
AP RABBIT-RBC ASSAY IN SERUM OF A HEALTHY INDIVIDUAL

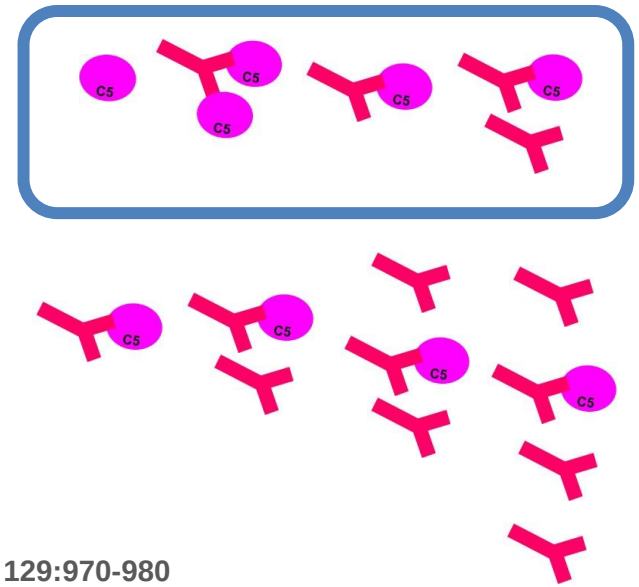




Harder MJ et al Blood. 2017 129:970-980
Mannes M et al. Blood. 2021. 137:443-455

AP RABBIT-RBC ASSAY IN NHS & SERA OF PNH PATIENTS ON ECU

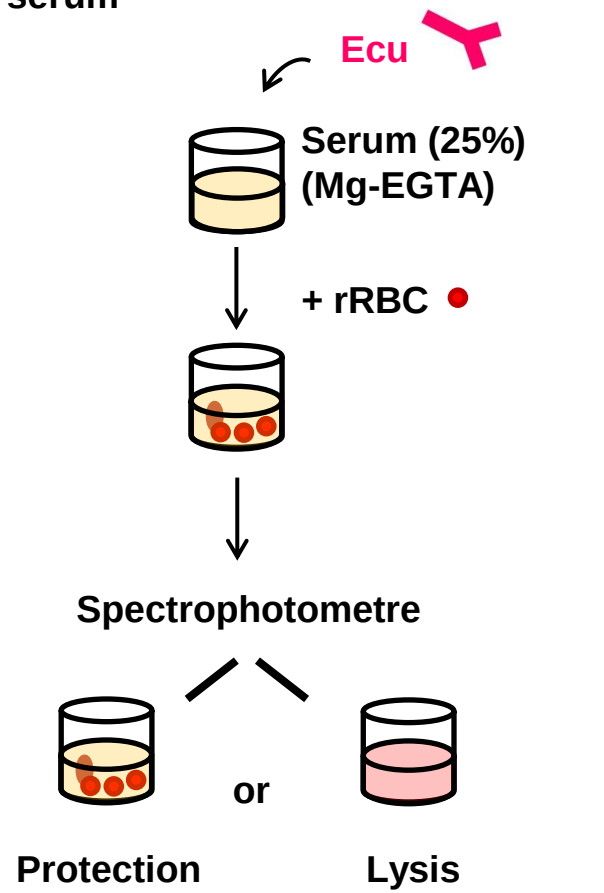




patient serum with Eculizumab

human serum

Rabbit Erythrocytes (r-RBC)



Harder MJ et al Blood. 2017 129:970-980
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RESIDUAL AP C5 ACTIVITY – LITERATURE EXAMPLES **IN VITRO**

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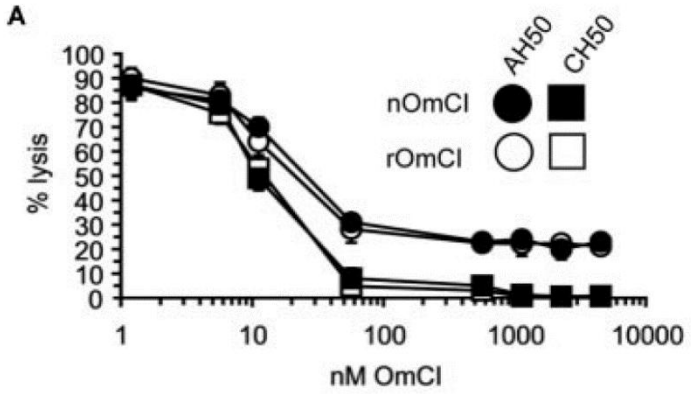
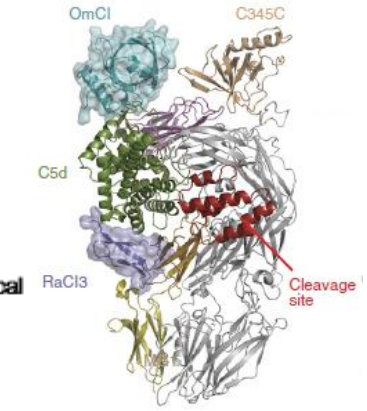
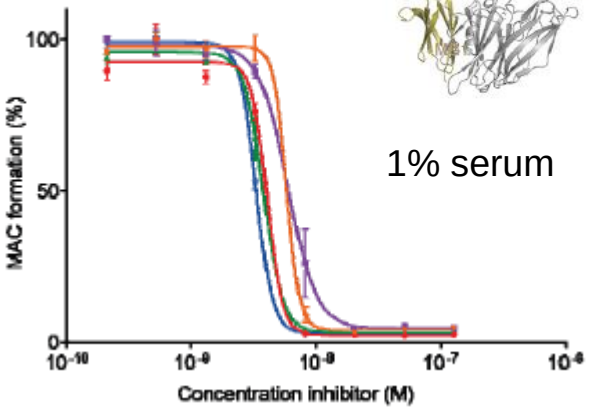
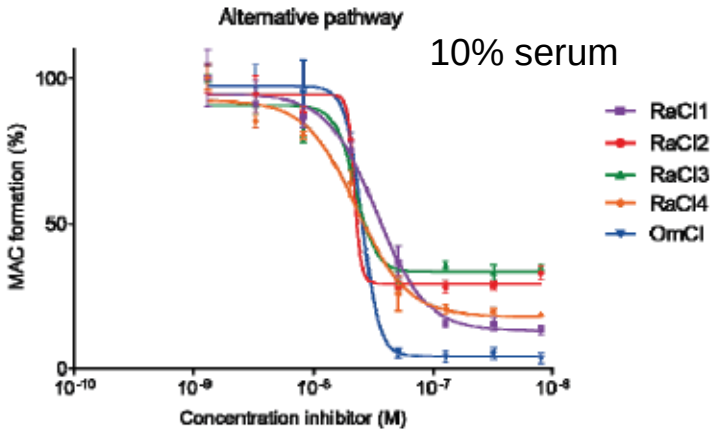


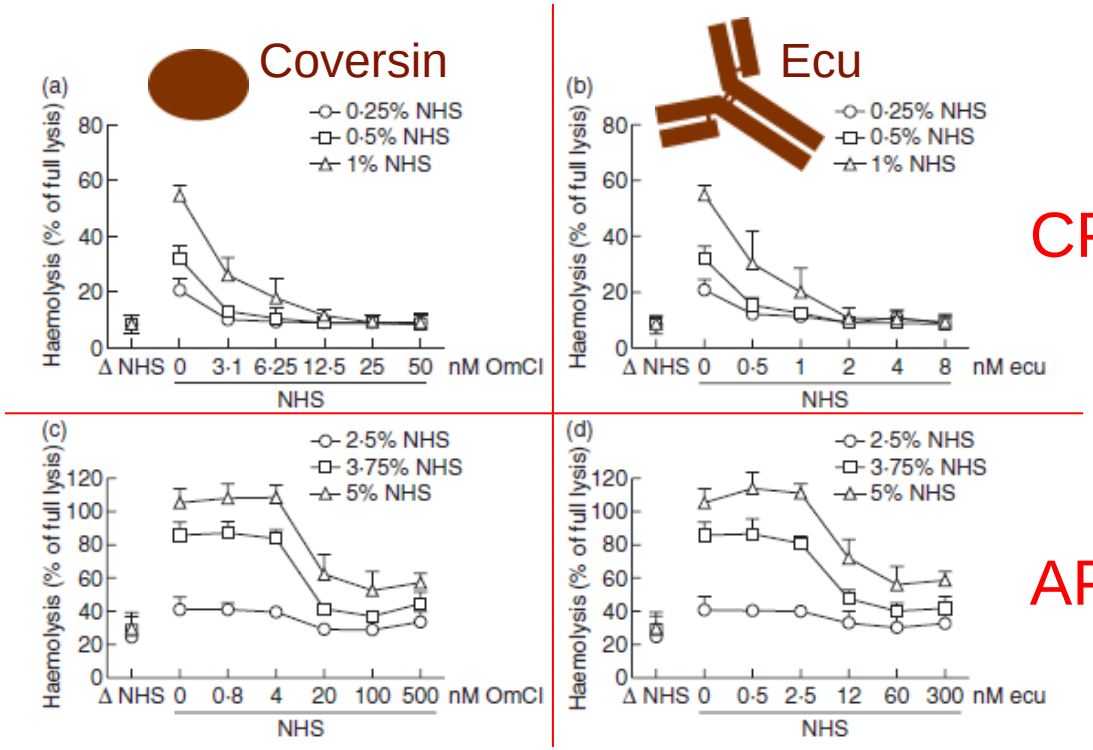
From: Nunn MA et al J Immunol. (2005) 174(4):2084-91

- Similar, residual C5 activity effects seen also by other laboratories







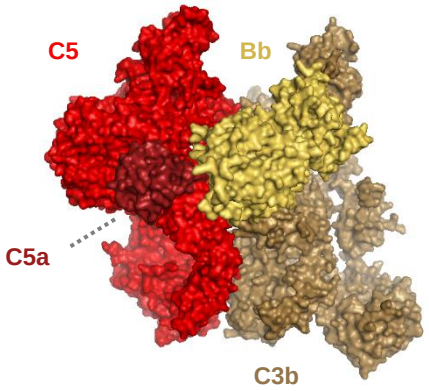


From: Blom AM et al Clin Exp Immunol. (2014) 178(1):142-53.

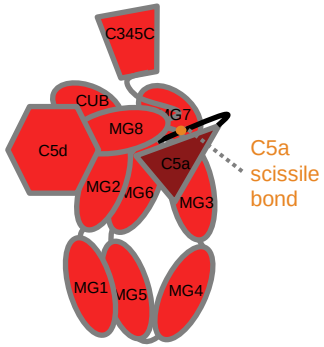
From: Jore MM et al Nat Struct Mol Biol. (2016) 23(5):378-386

STRUCTURAL KNOWLEDGE ABOUT C5 & ITS ACTIVATION IS PATCHY

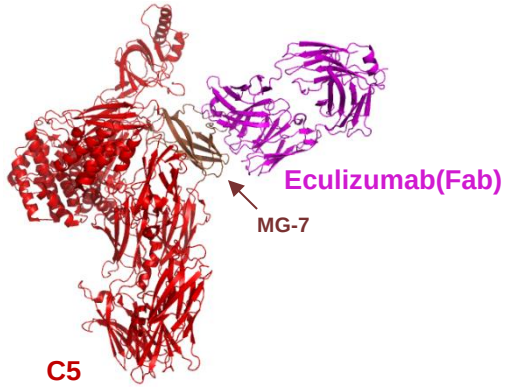
assumed engagement of C5 with C3bBb:



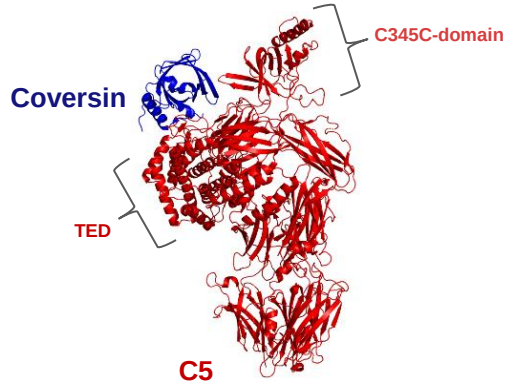
the problem:



C5:Ecu



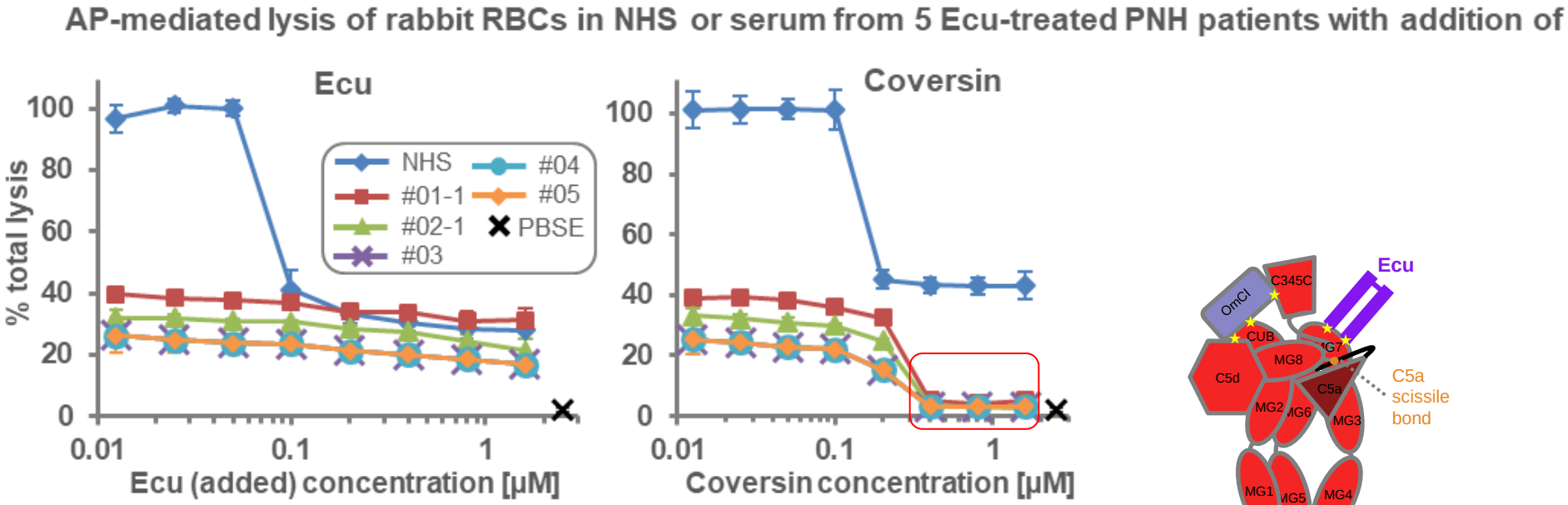
C5:Coversin



Schatz-Jakobsen JA et al J Immunol. (2016) 197(1):337-344.

Jore MM et al Nat Struct Mol Biol. (2016) 23(5):378-386

AP RABBIT-RBC ASSAY IN SERUM OF PNH-PATIENTS ON ECU



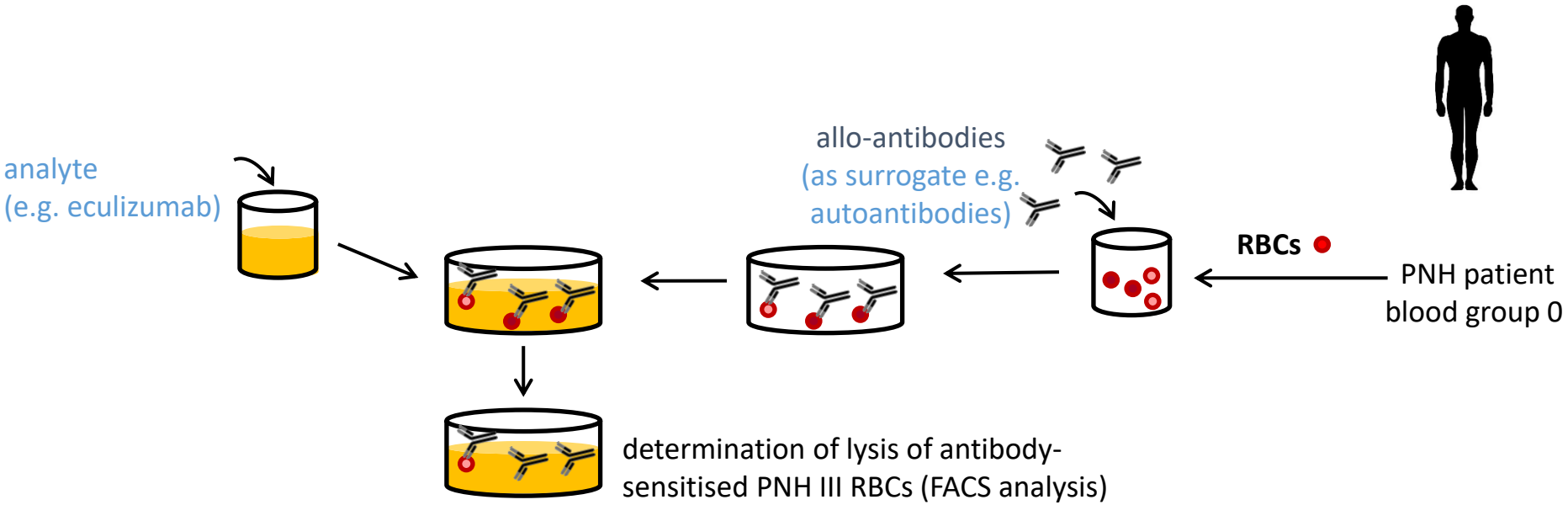
How severe can this residual C5 activity get?

> Sera from different PNH patients have different levels of residual haemolysis

> C5 double inhibition efficiently & completely inhibits C5 activation

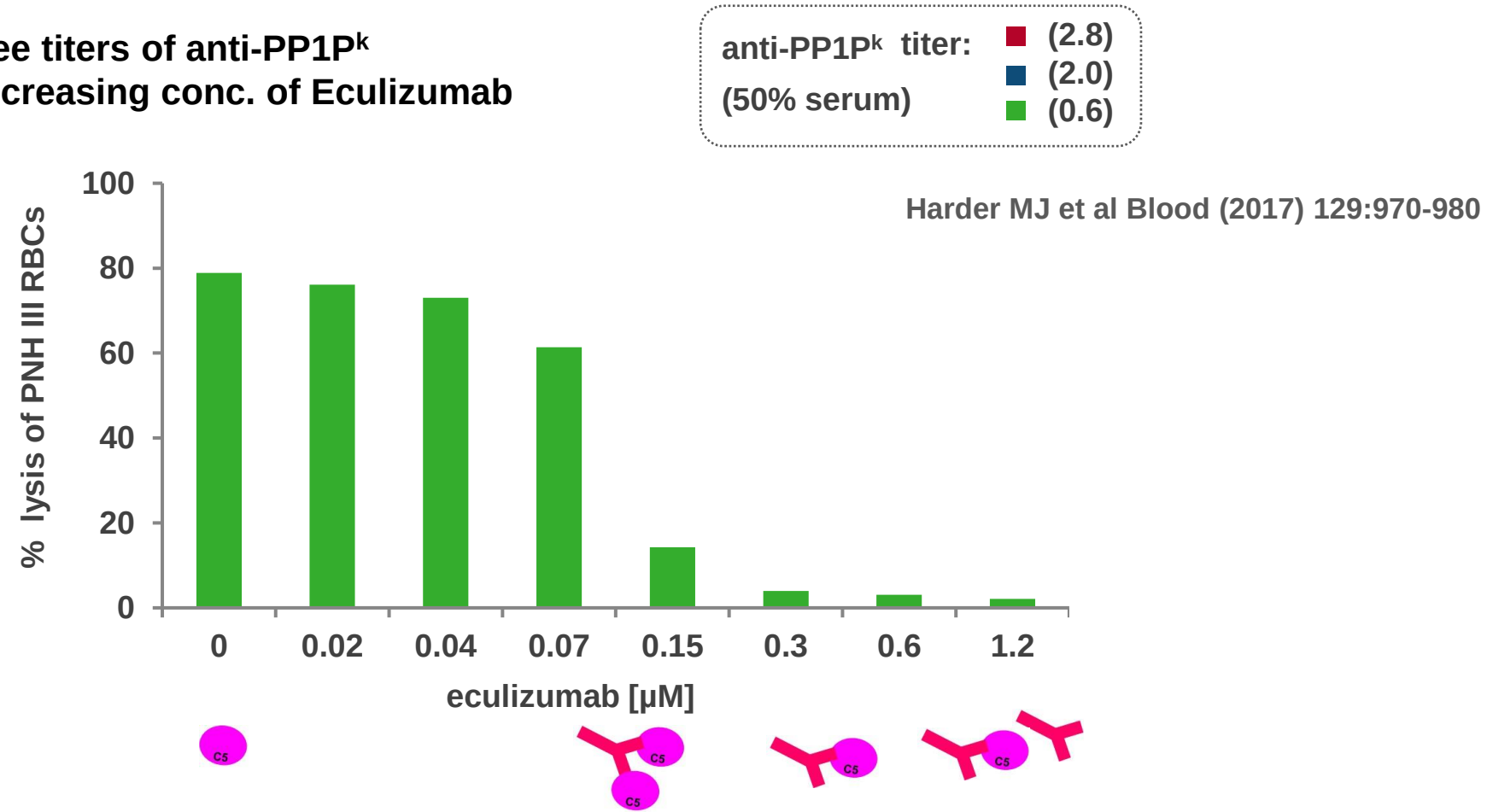
Harder MJ et al Blood. 2017 129:970-980; Schatz-Jakobsen JA et al J Immunol. (2016) 197(1):337-344.; Jore MM et al Nat Struct Mol Biol. (2016) 23(5):378-386

CORRELATING STRENGTH OF C-ACTIVATION WITH RESIDUAL C5 ACTIVITY



CORRELATING STRENGTH OF C-ACTIVATION WITH RESIDUAL C5 ACTIVITY

Three titers of anti-PP1P^k
& increasing conc. of Eculizumab



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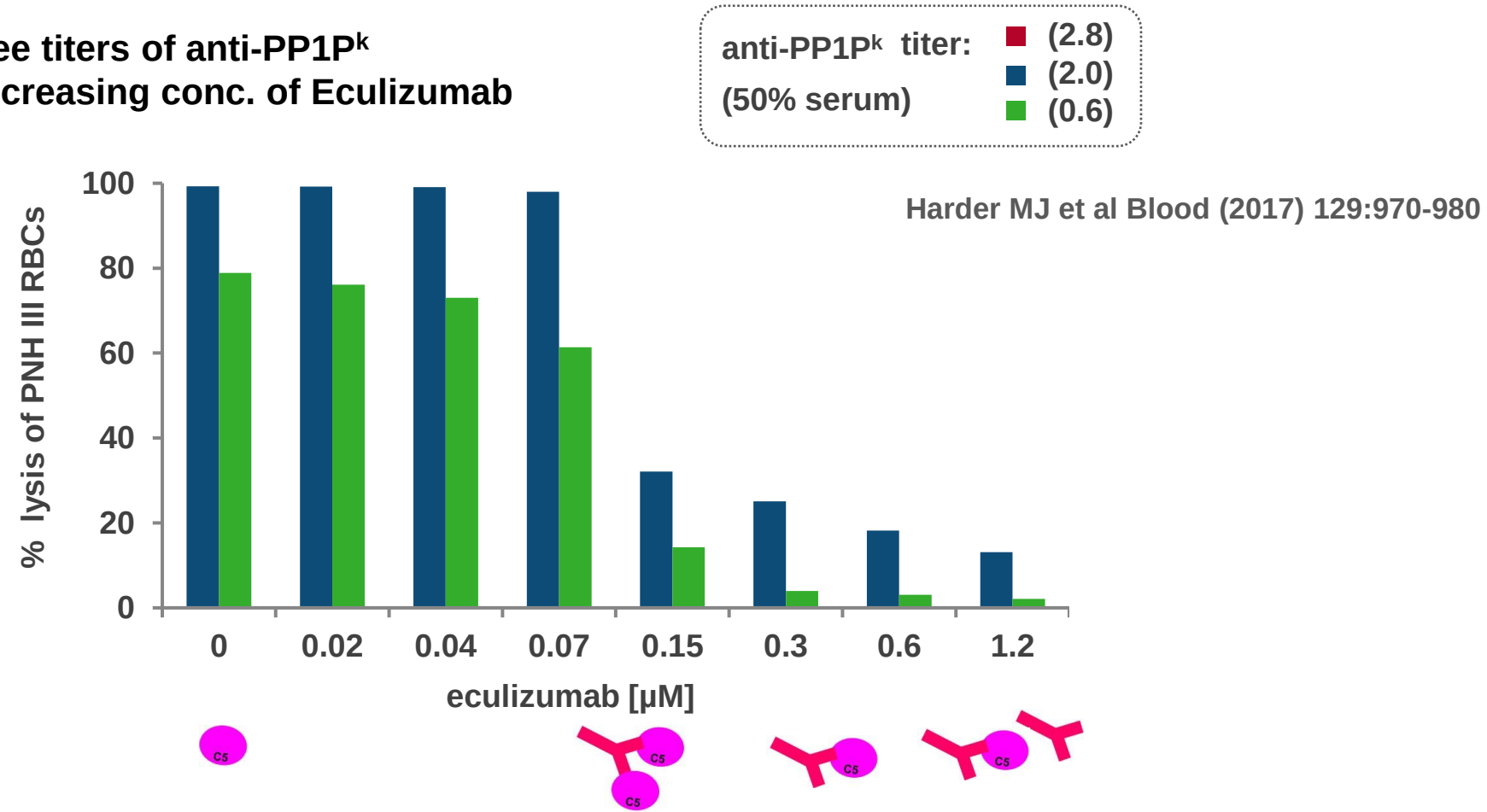


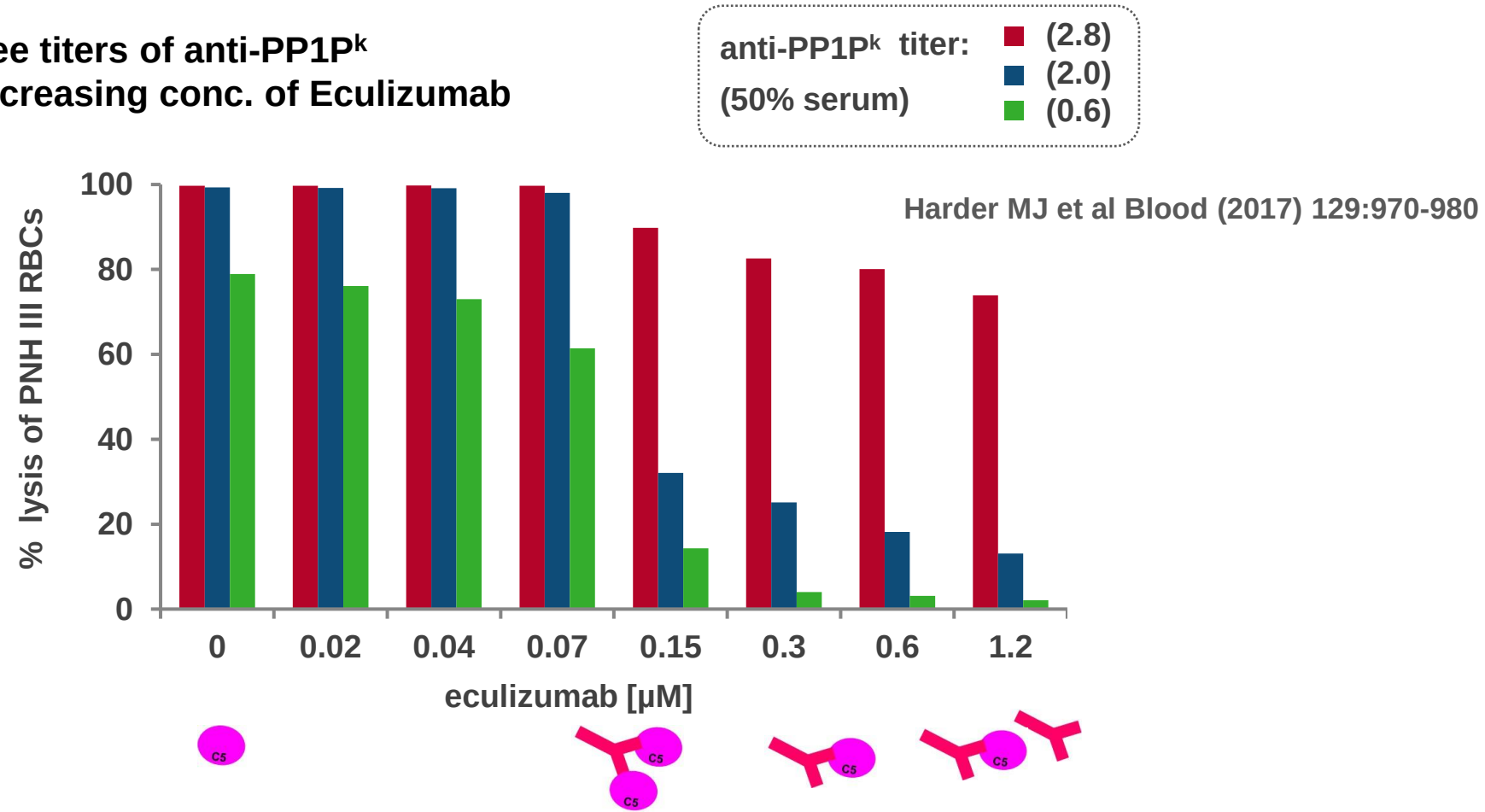
Harder MJ et al Blood (2017) 129:970-980

CORRELATING STRENGTH OF C-ACTIVATION WITH RESIDUAL C5 ACTIVITY

"pharmacodynamic breakthrough"

- depends on the strength of complement activation (C3b density)

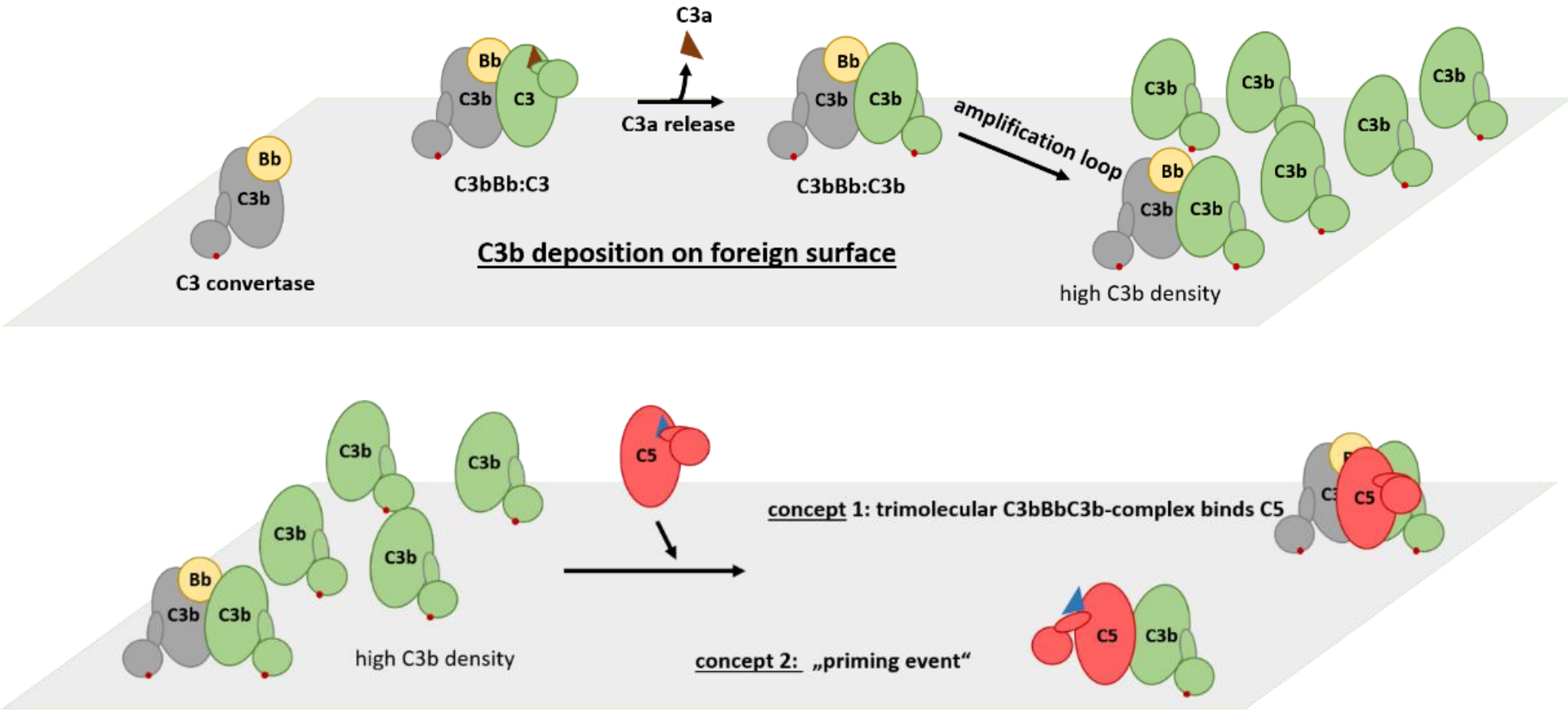
Three titers of anti-PP1P^k
& increasing conc. of Eculizumab



Harder MJ et al Blood (2017) 129:970-980

Molecular mechanism of activating the Complement component C5 and implication for its inhibition

TEXTBOOK KNOWLEDGE, QUESTIONS AND HYPOTHESIS



How is C5 activated?

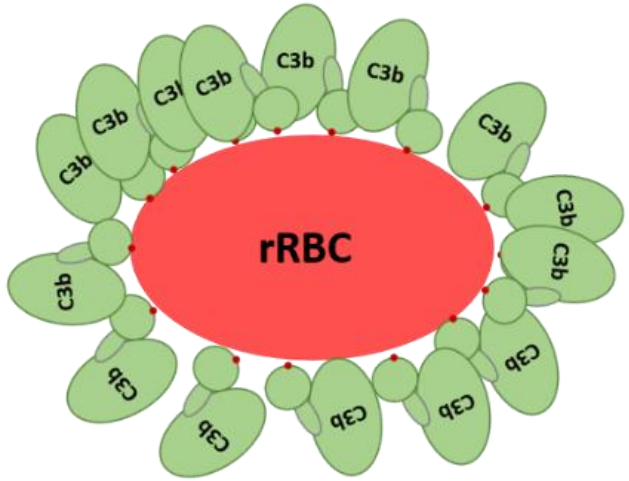
What is the molecular arrangement of the C5 convertase?

What implications do these questions have on Complement inhibition?

REQUIREMENTS FOR C5 ACTIVATION

Berends et al. BMC Biology. 2015: 13:93

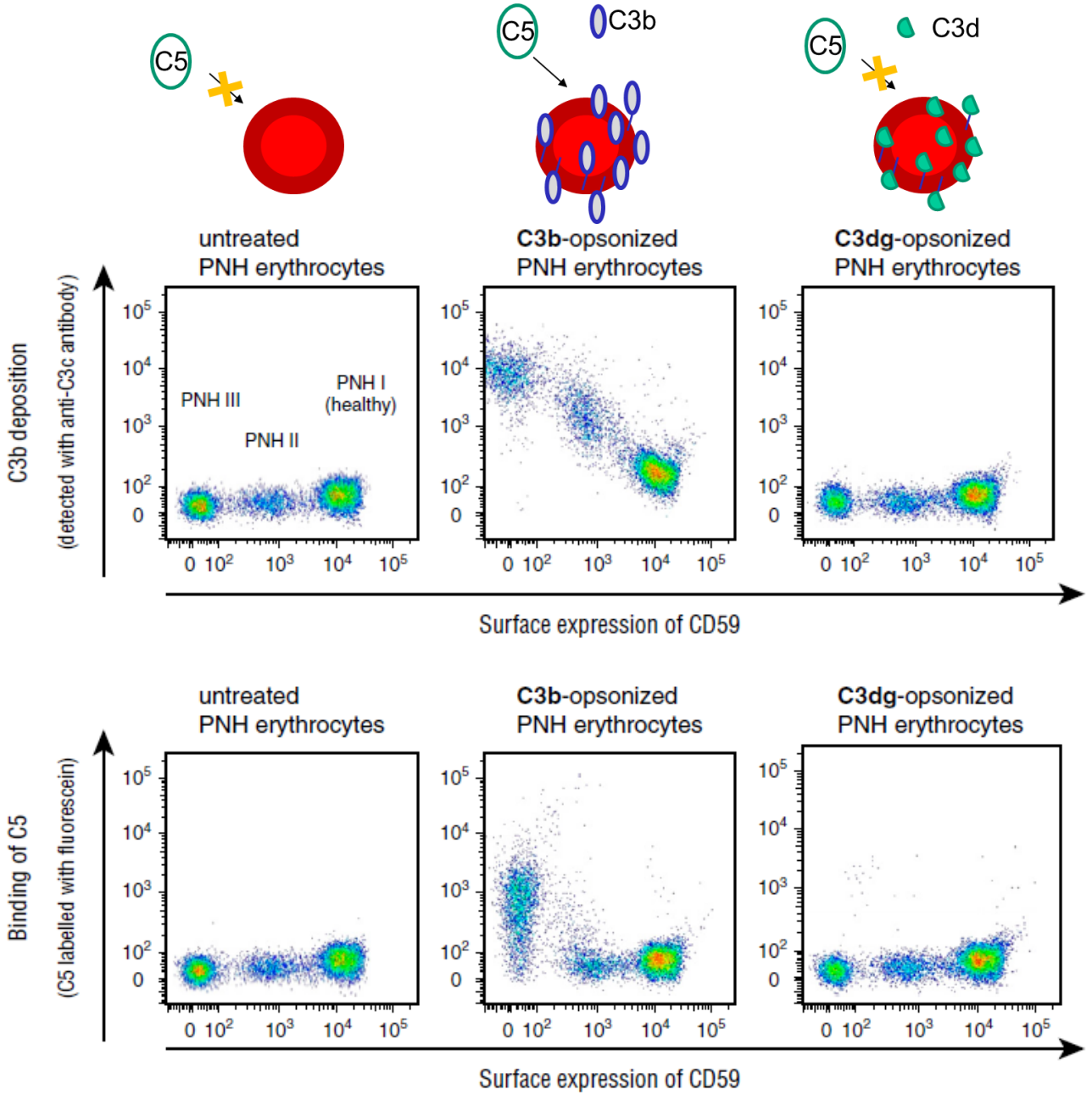
- Fluid phase: >> next to no C5 activation
  - High C3b density (on a surface) needed for C5 activation



→ Is a fluid phase convertase really sufficient?

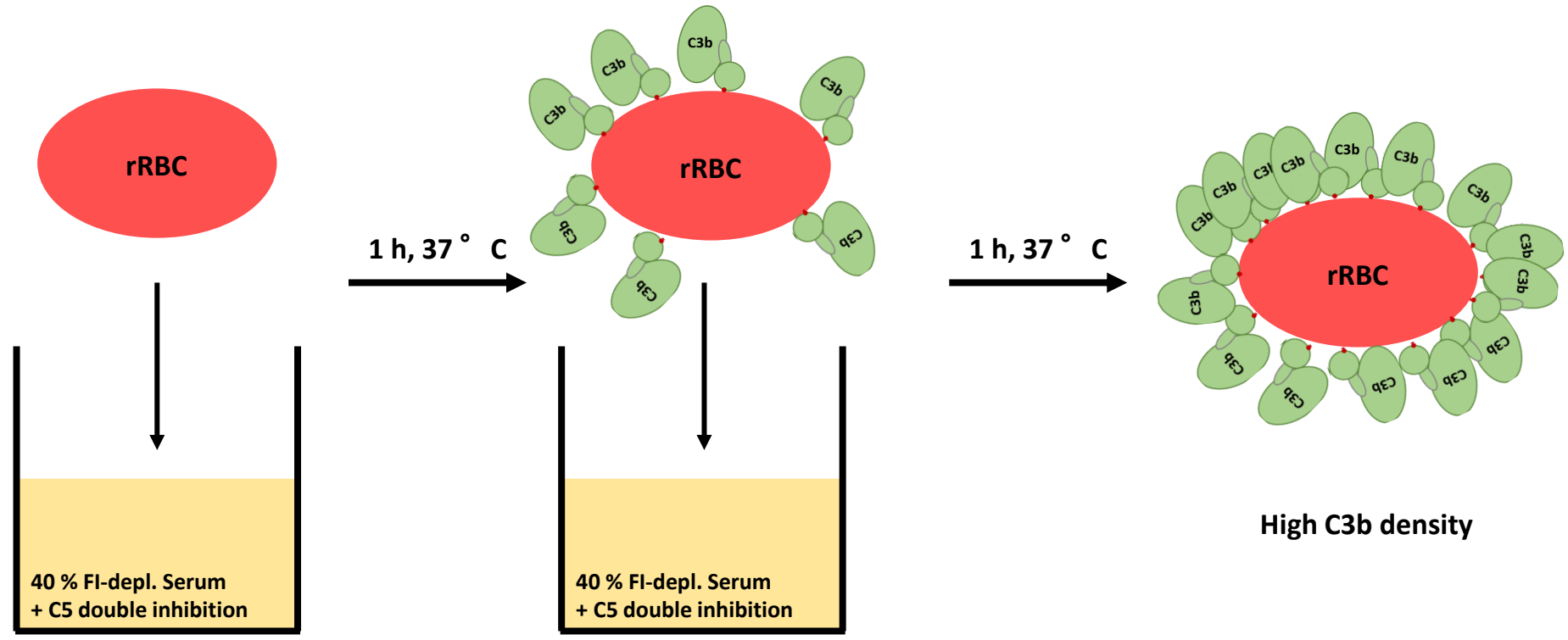
→ Is this convertase then bi- or trimolecular?

C5 BINDING TO C3B ON ERYTHROCYTES



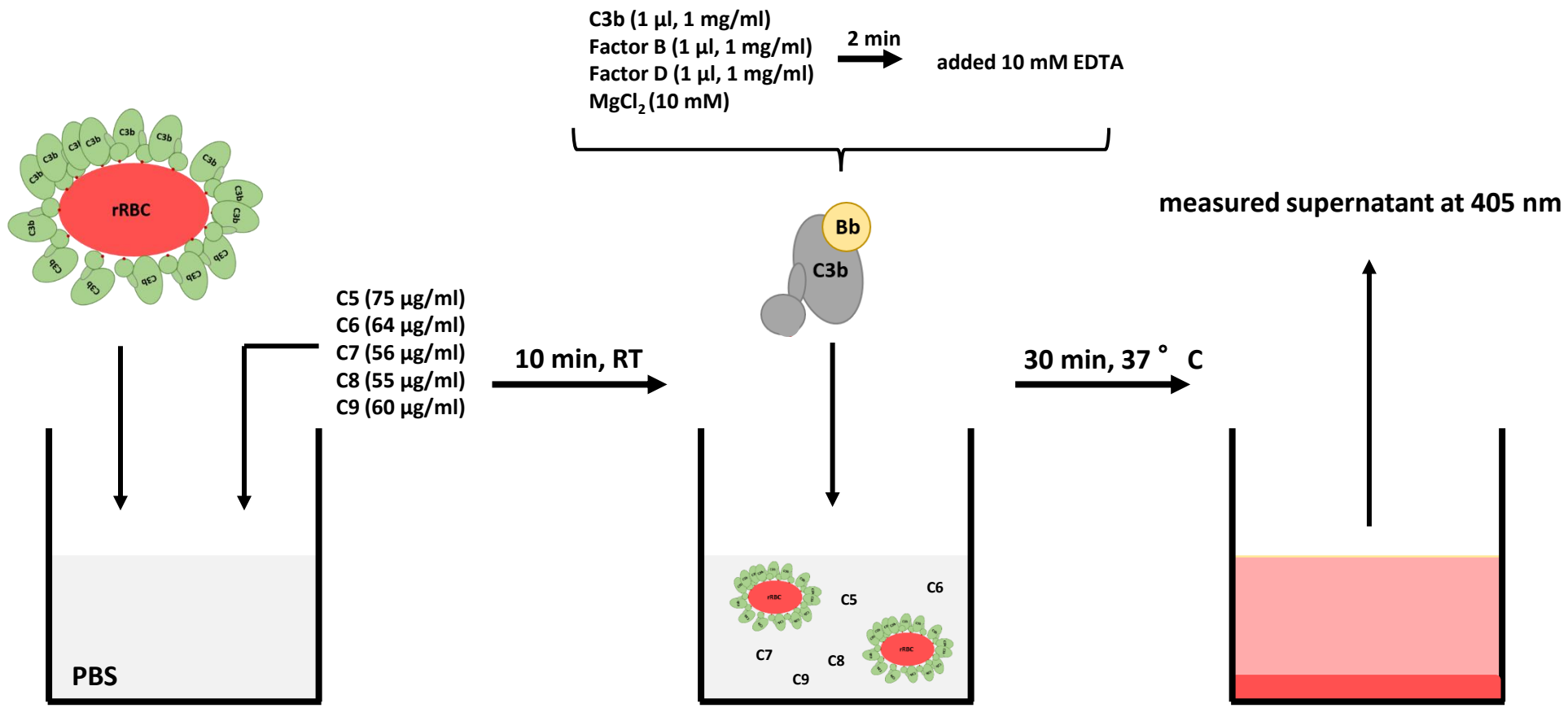
Harder MJ et al BLOOD (2017) 129(8):970-980

HEMOLYSIS POSSIBLE WITH FLUID PHASE CONVERTASE?



Mannes M et al. Blood. 2021. 137:443-455

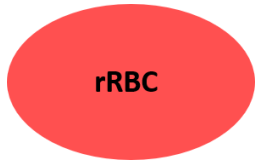
HEMOLYSIS POSSIBLE WITH FLUID PHASE CONVERTASE?

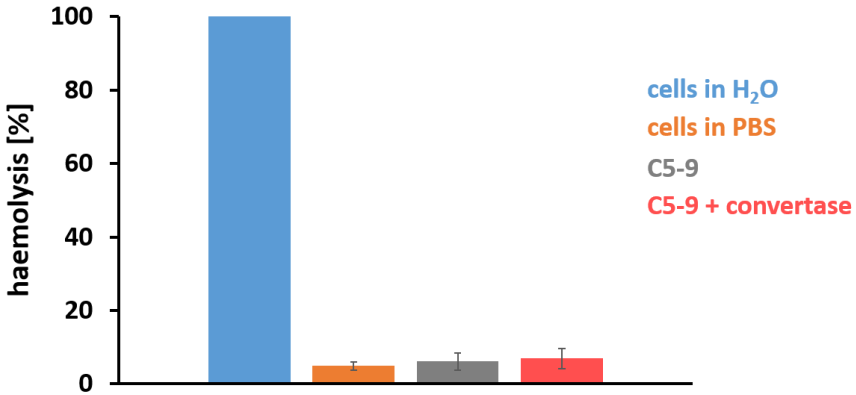


Mannes M et al. Blood. 2021. 137:443-455

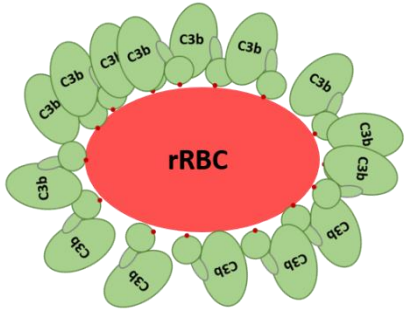
HEMOLYSIS POSSIBLE WITH FLUID PHASE CONVERTASE?

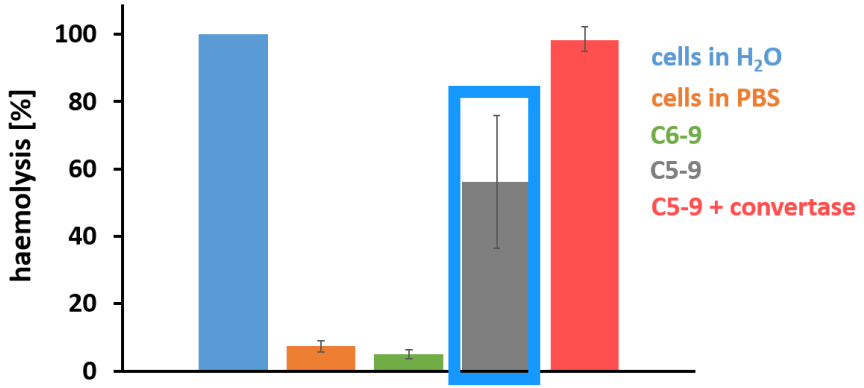
non-opsonized cells





C3b-opsonized cells





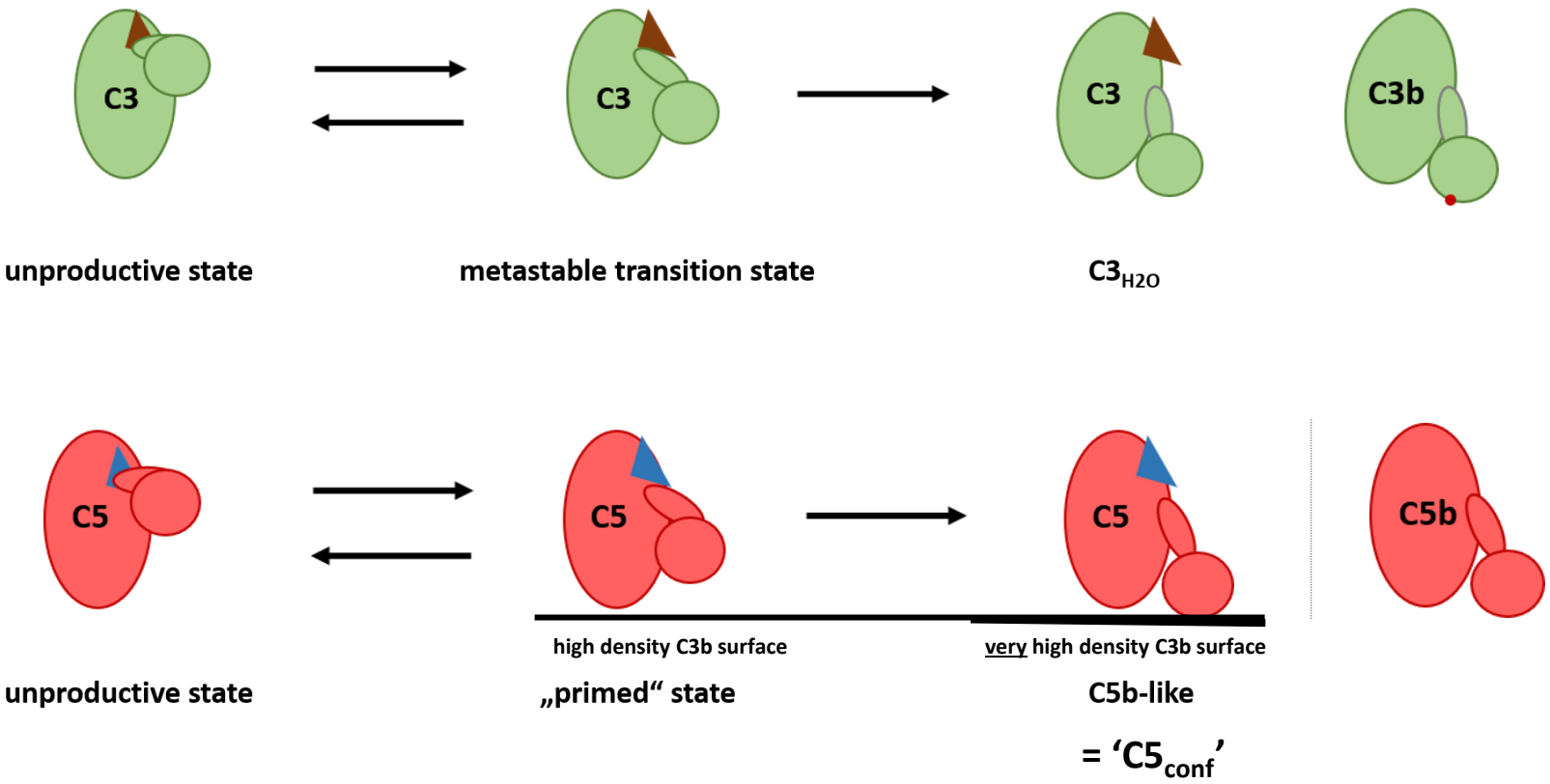
No convertase!!!!

→ Fluid phase convertase is sufficient for lysis

→ High C3b density cause lysis without convertase activity

Mannes M et al. Blood. 2021. 137:443-455

HYPOTHETICAL C5 CONFORMATION MODEL



Mannes M et al. Blood. 2021. 137:443-455

C5 BINDING TO C3B – CONCLUSIONS & LITERATURE

1. ***C5 can be cleaved*** (activated) only when in addition to the enzyme-generating components ***C3b is present on a solid surface***

2. Newly discovered ***property of surface-bound C3b***: C3b is capable of ***reversibly binding C5***

3. A ***special configuration*** of surface-fixed C3b ***prepares or modulates the substrate C5 to make it accessible for cleavage by (fluid) C3 convertases***

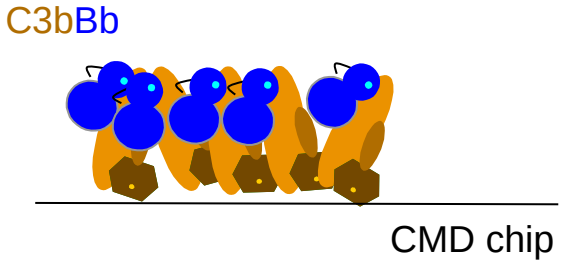
A new function of the activated third component of complement: binding to C5, an essential step for C5 activation

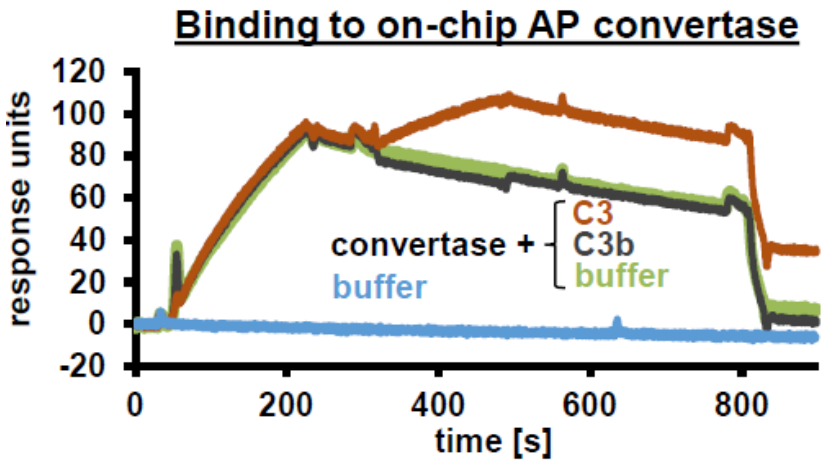
W. VOGT, GISA SCHMIDT, BEATE VON BUTTLAR & L. DIEMINGER *Max-Planck-Institut für experimentelle Medizin, Department of Biochemical Pharmacology, Göttingen, Germany*

Vogt W et al Immunology. 1978 Jan;34(1):29-40

IS THE C5 CONVERTASE A TRIMOLECULAR COMPLEX OF C3bBb3b?

SPR experiment with chip assembled convertases C3bBb:





Mannes M et al. Blood. 2021. 137:443-455

SUMMARY POINTS PHARMACODYNAMIC BREAKTHROUGH OF C5

1. Strong complement activation (high C3b densities) overrides the terminal pathway inhibition by eculizumab or other stoichiometric C5 inhibitors

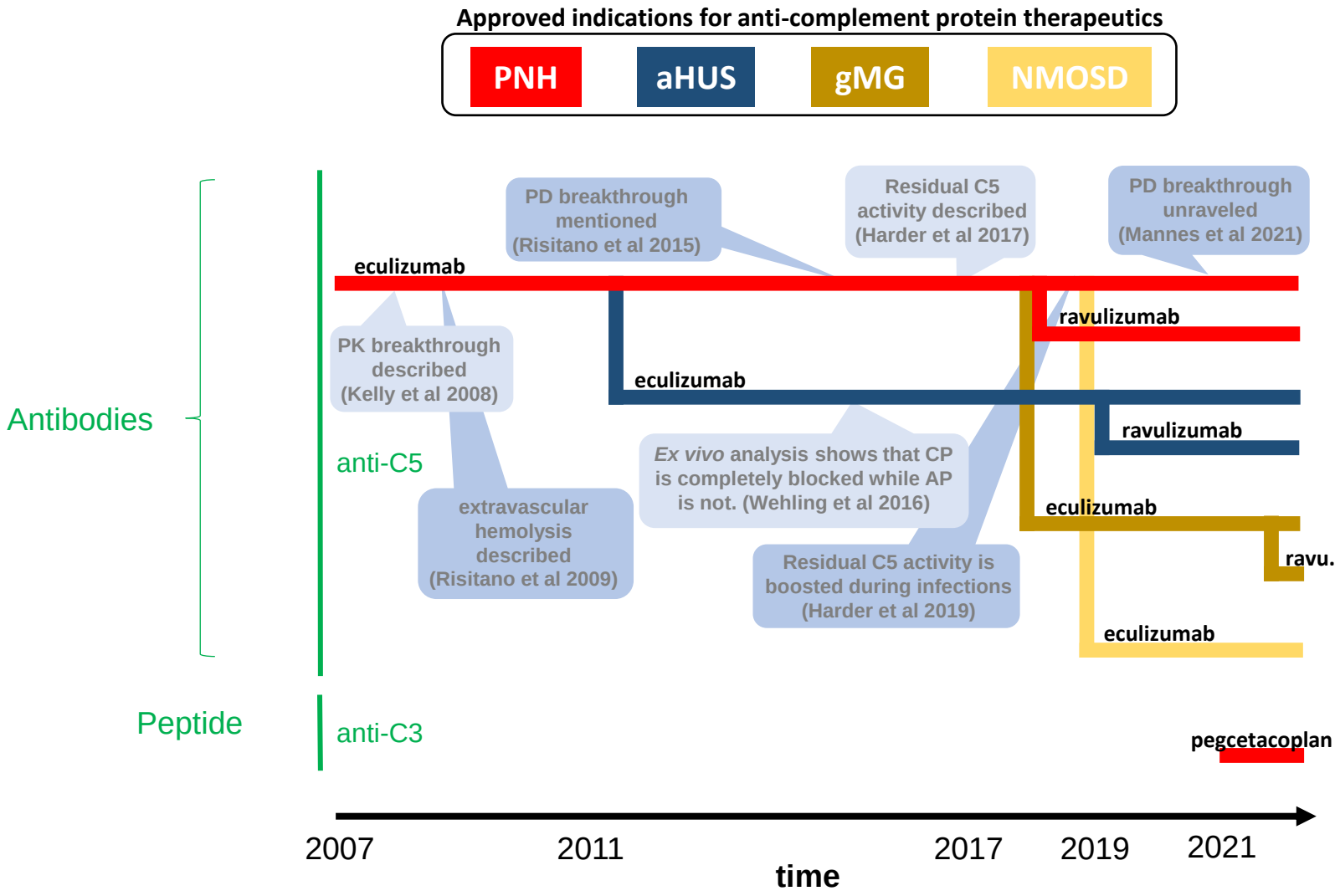
2. These C5 inhibitors reduce but do not abolish terminal complement activity (unless two orthogonal C5 inhibitors)

3. The more powerful complement is activated, the less effective is terminal pathway inhibition by diverse anti-C5 agents = pharmacodynamic breakthrough

IMPLICATIONS FOR THE COMPLEMENT CASCADE

Bimolecular (fluid phase) convertase is sufficient for C5 conversion after priming on a C3b opsonized surface

‘EVOLUTION’ OF APPROVED COMPLEMENT THERAPEUTICS:



C5i >>> C3i

Can these remaining problems be addressed by C3 inhibitors?

Schmidt CQ et al. Immunol Rev. 2023

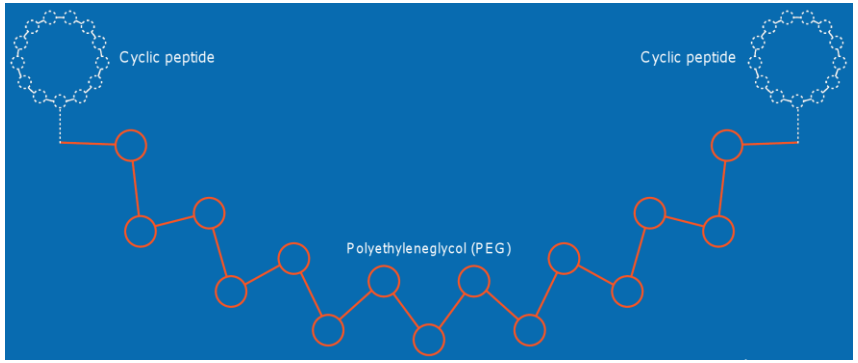
Other Complement inhibitors to overcome the short-coming of the C5 inhibiting approach

C3 PEPTIDE INHIBITORS : COMPSTATIN FAMILY

- PEGCETACOPLAN: Two compstatin Cp05 moieties are bridged by a 40 kDa polyethylene glycol (PEG)

(A)

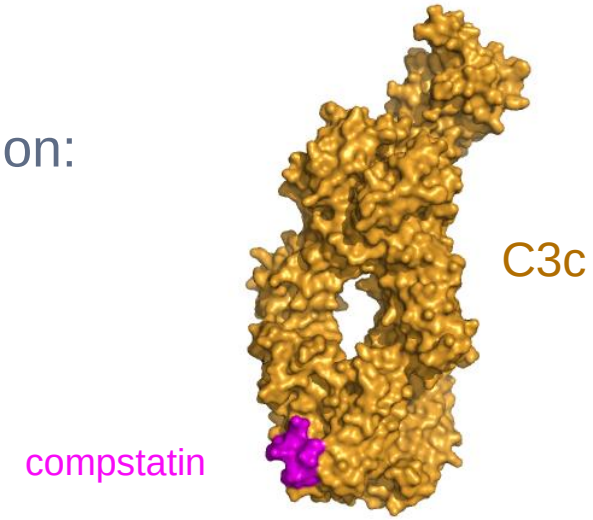
	1 2 3 4 5 6 7 8 9 10 11 12 13 14	K_D (nM)
Compstatin	I-[C-V-V----Q-D-W-G---H-H-R-C]-T	1600
Analog Cp01	Ac-I-[C-V-W----Q-D-W-G---A-H-R-C]-T	150
Analog Cp05	Ac-I-[C-V-1MeW-Q-D-W-G---A-H-R-C]-T	12
Analog Cp10	Ac-I-[C-V-1MeW-Q-D-W-Sar-A-H-R-C]-I	4.4
Analog Cp20	Ac-I-[C-V-1MeW-Q-D-W-Sar-A-H-R-C]-mI	2.3
Analog Cp40	y-I-[C-V-1MeW-Q-D-W-Sar-A-H-R-C]-mI	0.5
ABM2-Cp20	ABM2-I-[C-V-1MeW-Q-D-W-Sar-A-H-R-C]-mI	0.15
Cp40-KKK	y-I-[C-V-1MeW-Q-D-W-Sar-A-H-R-C]-mI-KKK	0.21

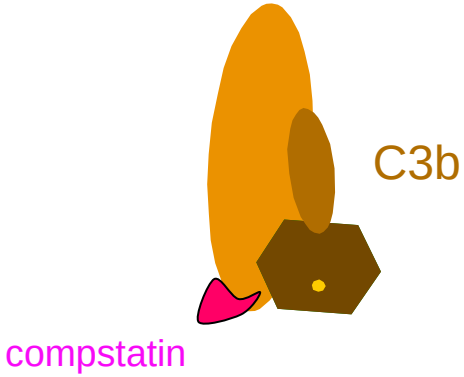


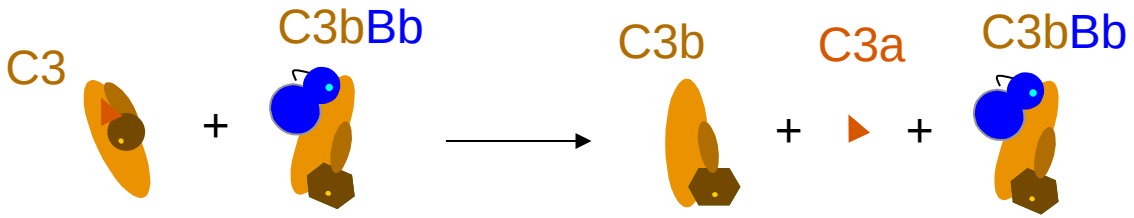
Lamers C et al. Trends in Pharmacological Sciences, 2022

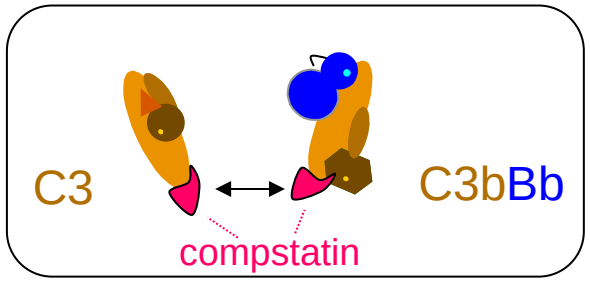
C3 PEPTIDE INHIBITORS : COMPSTATIN FAMILY

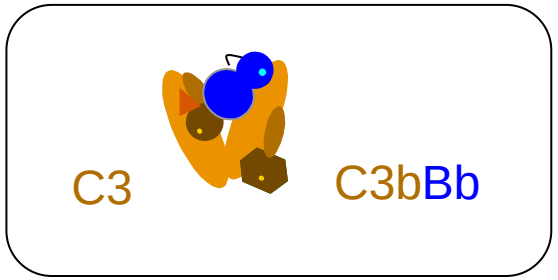
- Comstatins: Mode of action:







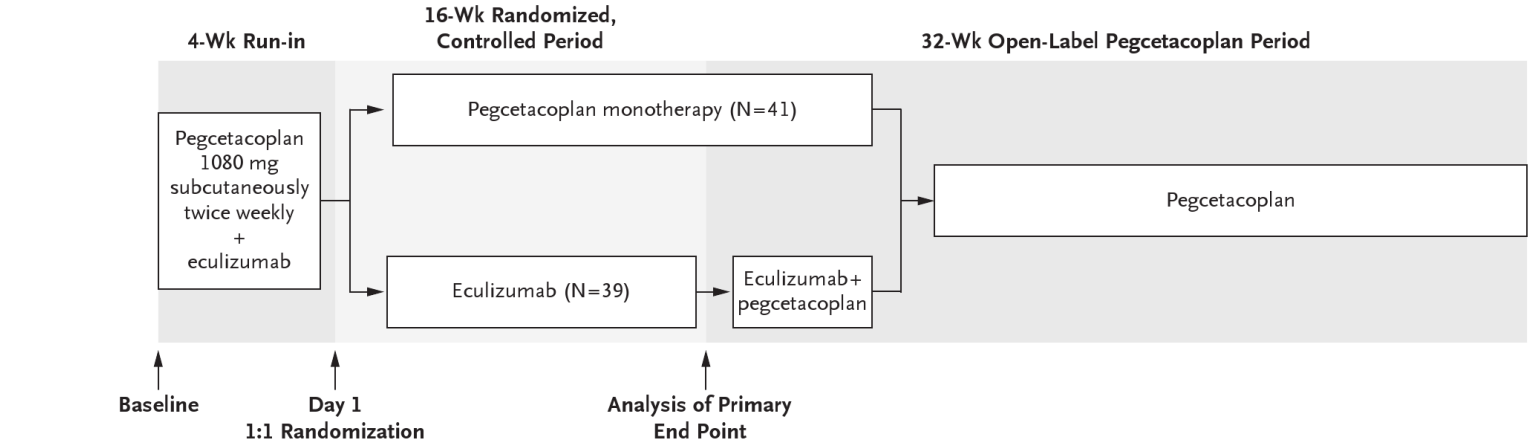


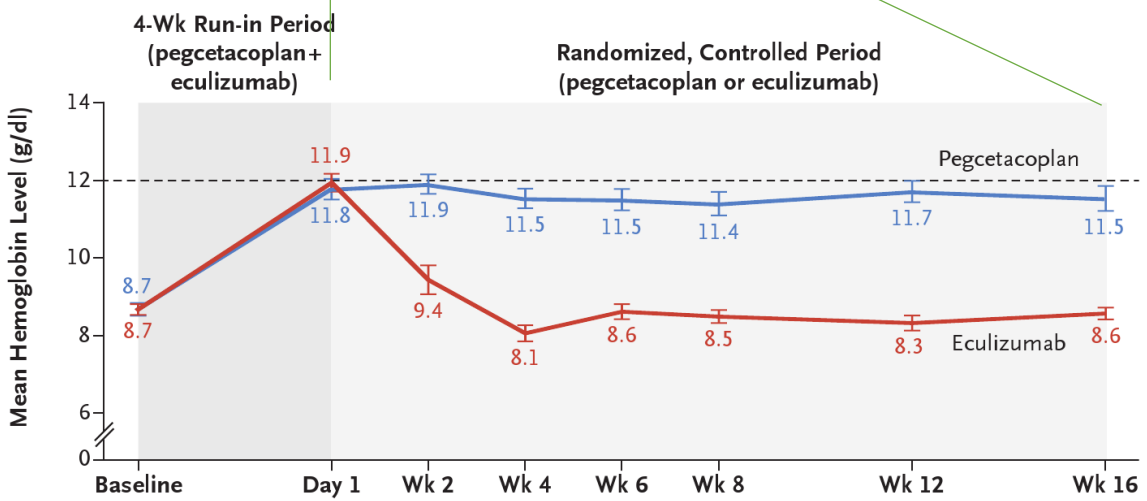


Janssen BJC et al. J Biol Chem. 2007

PNH & C3 INHIBITION BY PEGCETACOPLAN VS. ECU

PEGASUS
phase 3 clinical trial





No. with Available Data								
Pegcetacoplan	41	40	40	40	39	37	38	37
Eculizumab	39	37	38	39	36	39	39	38

Hillmen P. et al. N Engl J Med 2021

NEW GENERATION OF COMPLEMENT THERAPEUTICS: A PROXIMAL INHIBITOR

2021:

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Pegcetacoplan versus Eculizumab in Paroxysmal Nocturnal Hemoglobinuria

Peter Hillmen, M.B., Ch.B., Ph.D., Jeff Szer, M.B., B.S., Ilene Weitz, M.D., Alexander Röth, M.D., Britta Höchsmann, M.D., Jens Panse, M.D., Kensuke Usuki, M.D., Ph.D., Morag Griffin, B.M.Sc., M.B., Ch.B., Jean-Jacques Kiladjian, M.D., Ph.D., Carlos de Castro, M.D., Hisakazu Nishimori, M.D., Ph.D., Lisa Tan, R.N., Mohamed Hamdani, M.S., Pascal Deschatelets, Ph.D., Cedric Francois, M.D., Ph.D., Federico Grossi, M.D., Ph.D., Temitayo Ajayi, M.D., Antonio Risitano, M.D., Ph.D., and Régis Peffault de la Tour, M.D., Ph.D.

2022:

The NEW ENGLAND JOURNAL of MEDICINE

REVIEW ARTICLE

Dan L. Longo, M.D., *Editor*

Breakthrough Hemolysis in PNH with Proximal or Terminal Complement Inhibition

Rosario Notaro, M.D., and Lucio Luzzatto, M.D.

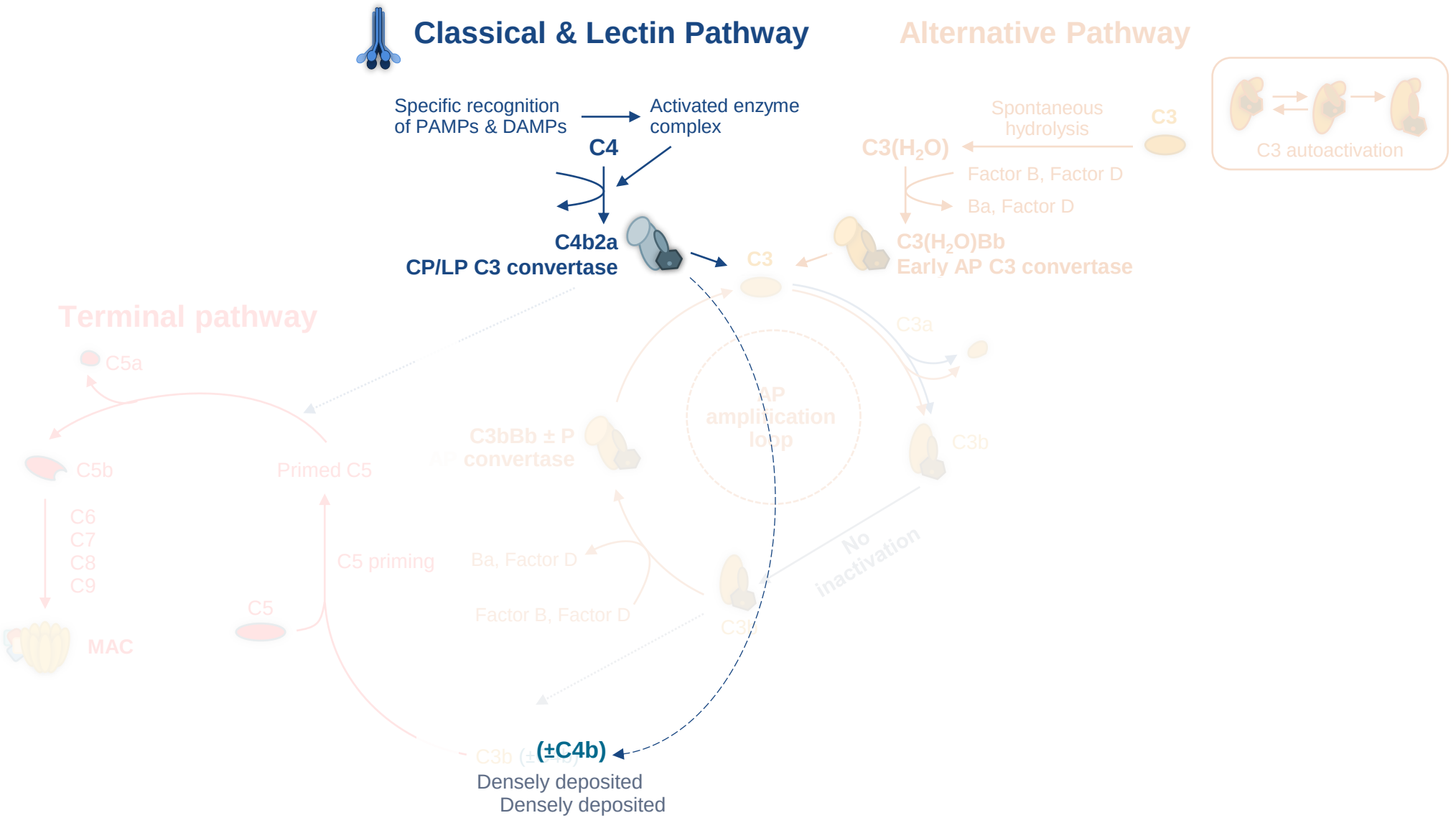
BREAKTHROUGH HAEMOLYSIS WITH PROXIMAL INHIBITORS

- Could it be pharmacokinetic BTH (PK-BTH)?

- Could it be pharmacodynamic BTH (PD-BTH)?
  - MAC-mediated erythrocyte lysis despite excess of C3 inhibitor over C3

Can there be a C5 convertase without C3b?

COMPLEMENT CASCADE UNDER C3 INHIBITION (1)



Mannes M et al. Blood. 2021

C5 ACTIVATION WITHOUT C3 (1)

REGULAR ARTICLE

blood advances

Absence of complement component 3 does not prevent classical pathway–mediated hemolysis

Lingjun Zhang,[1] Yang Dai,[1] Ping Huang,[1] Thomas L. Saunders,[2] David A. Fox,[3] Jijun Xu,[1,4] and Feng Lin[1,5]

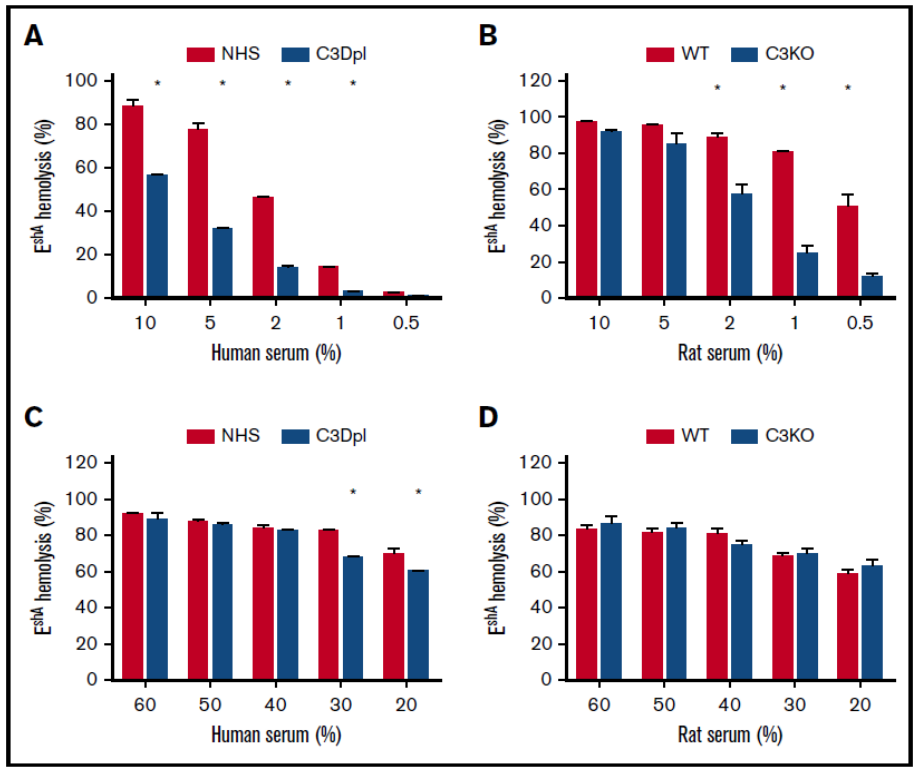
[1]Department of Inflammation and Immunity, Lerner Research Institute, Cleveland Clinic, Cleveland, OH; [2]Transgenic Animal Model Core and [3]Division of Rheumatology, University of Michigan, Ann Arbor, MI; and [4]Department of Pain Management, Anesthesiology Institute, and [5]Cole Eye Institute, Cleveland Clinic, Cleveland, OH

Key Points

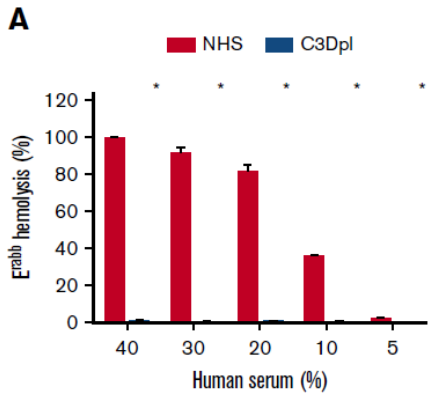
- Absence of C3 does not prevent classical pathway–mediated hemolysis.
- Absence of C3 abolishes alternative pathway–mediated hemolysis.

CP:

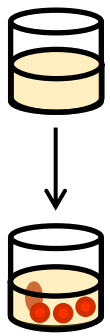
human rat



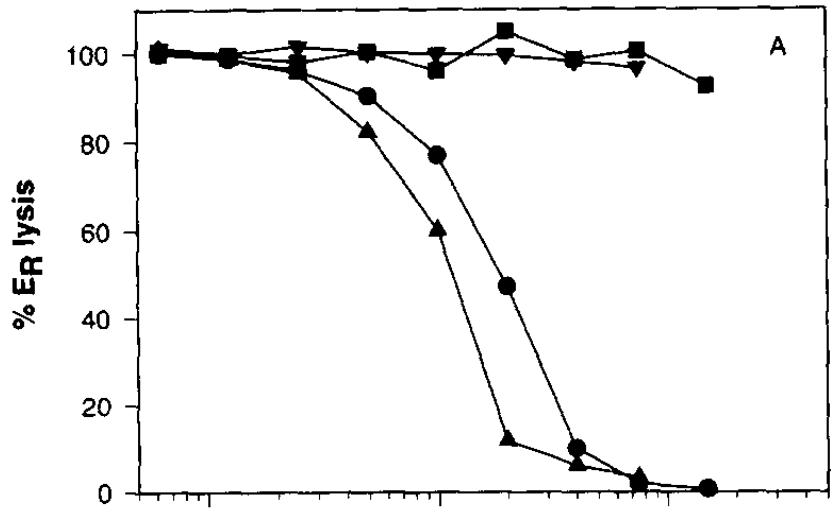
AP:



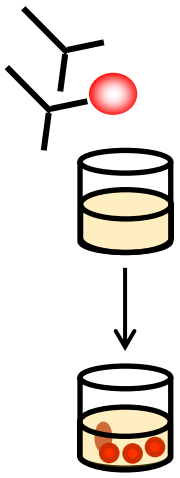
COMPSTATINS: C3 INHIBITING CYCLIC PEPTIDES – THE BEGINNINGS



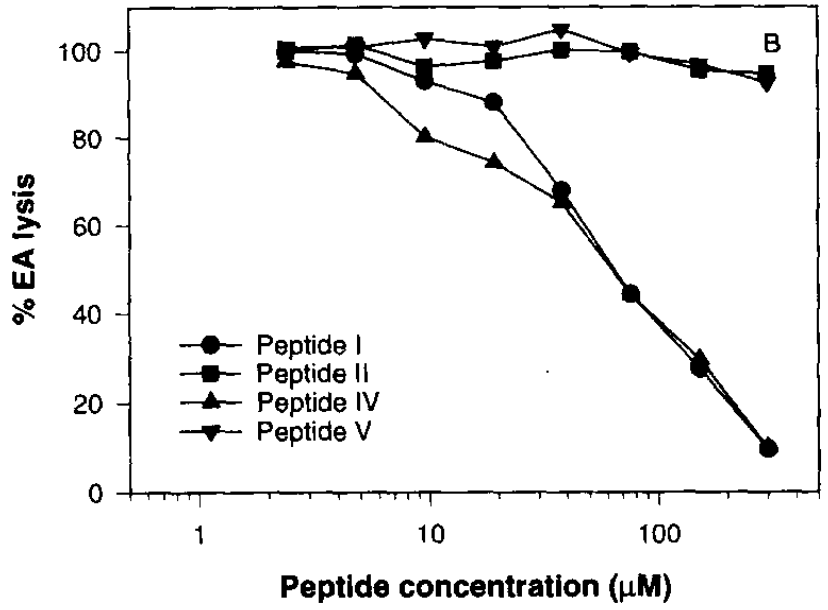
AP



serum = 5%



CP



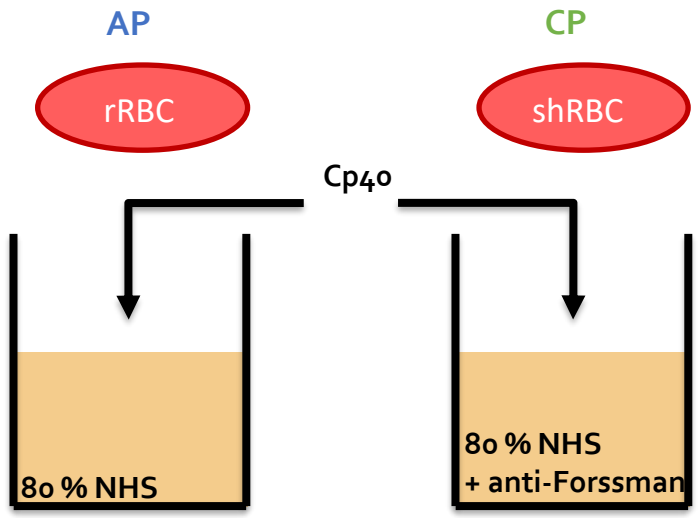
serum < 1%

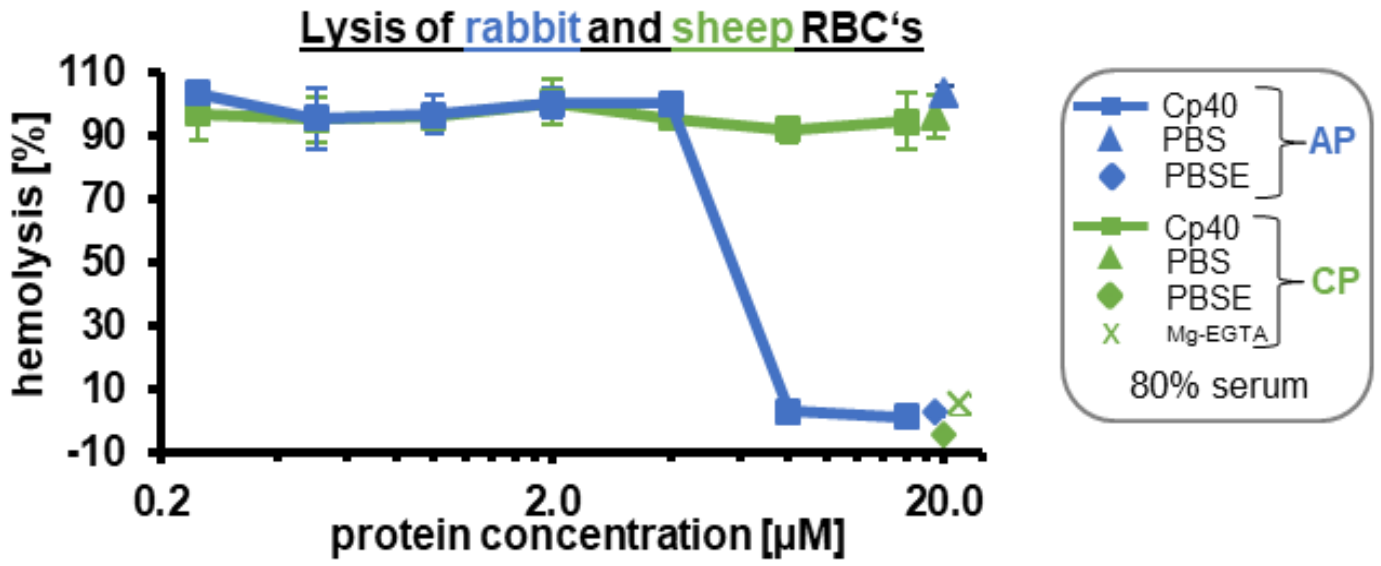
Sahu A et al J Immunol. 1996

Yes, there can be ‘a C5 convertase’ without C3b!

How does it work?

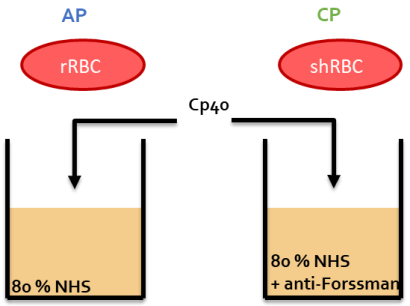
EFFECT OF C3 BLOCKAGE DURING STRONG AP / CP ACTIVATION



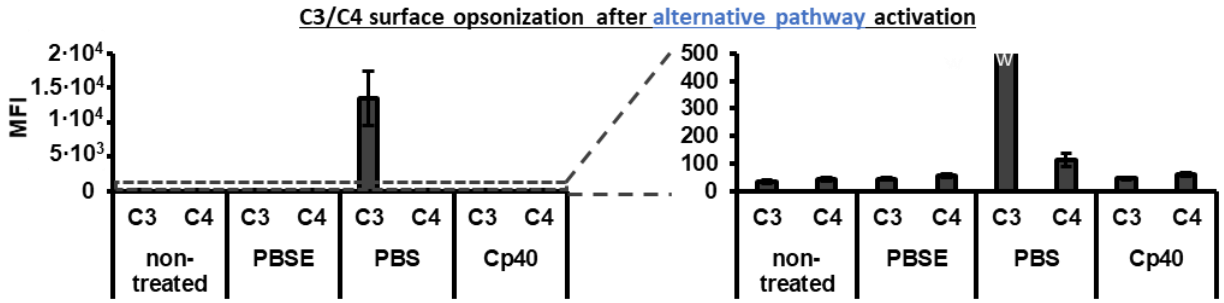


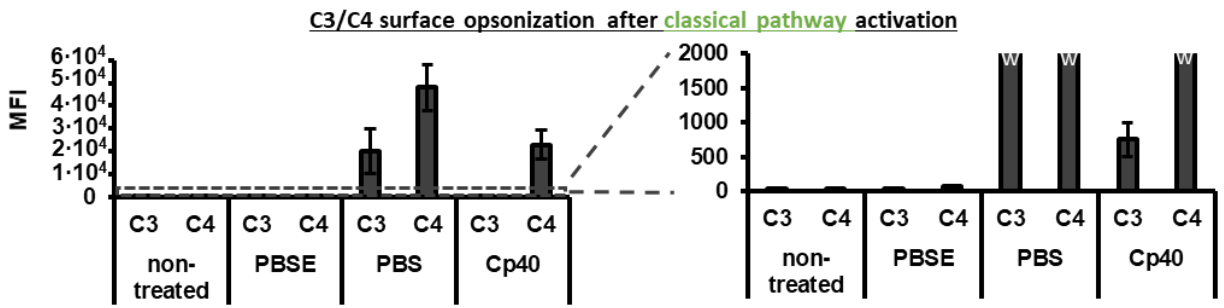
Mannes M et al. Blood. 2021

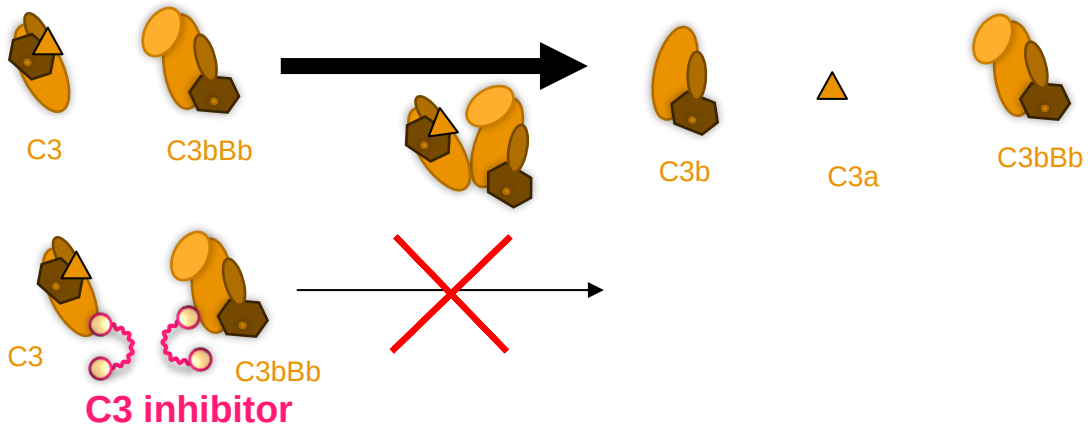
C3/C4 SURFACE DEPOSITION AFTER AP/CP ACTIVATION WITH C3 INHIBITORS



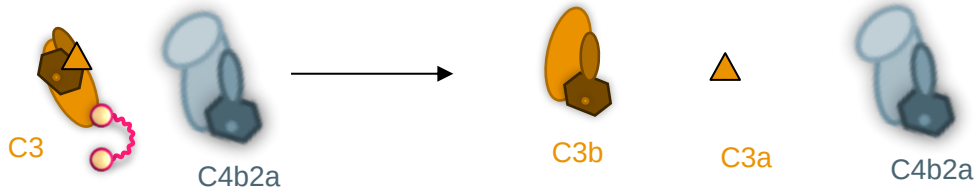
+ C5 double inhibition







- AP: complete C3 inhibition



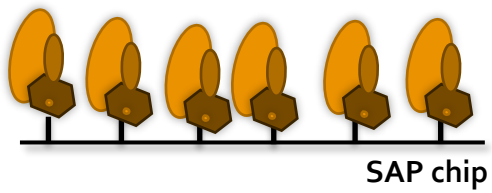
- CP: residual C3 deposition

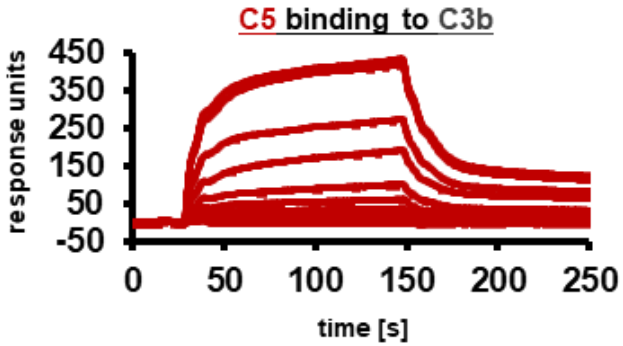
Mannes M et al. Blood. 2021

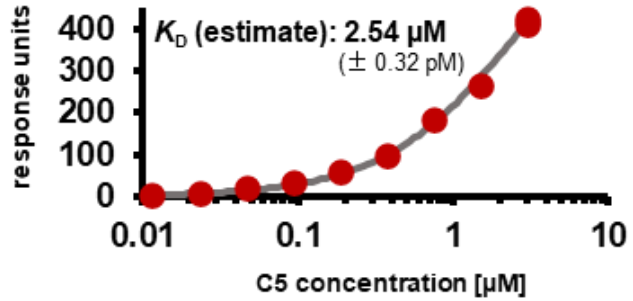
C4b BINDS C5 IN A SIMILAR MANNER TO C3b

SPR experiment with chip immobilised C3b or C4b:

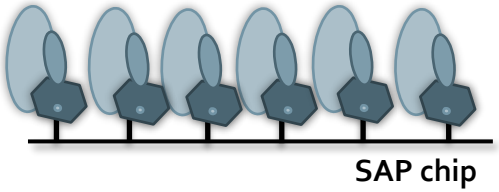
C3b

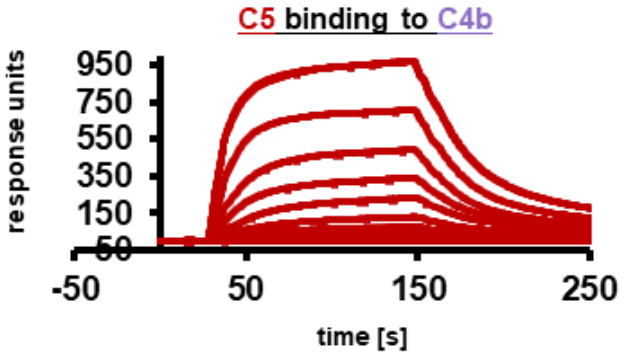


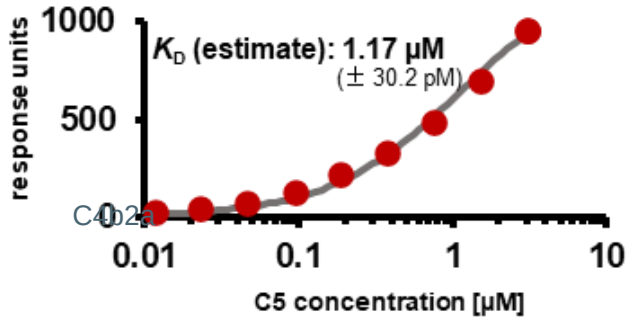




C4b

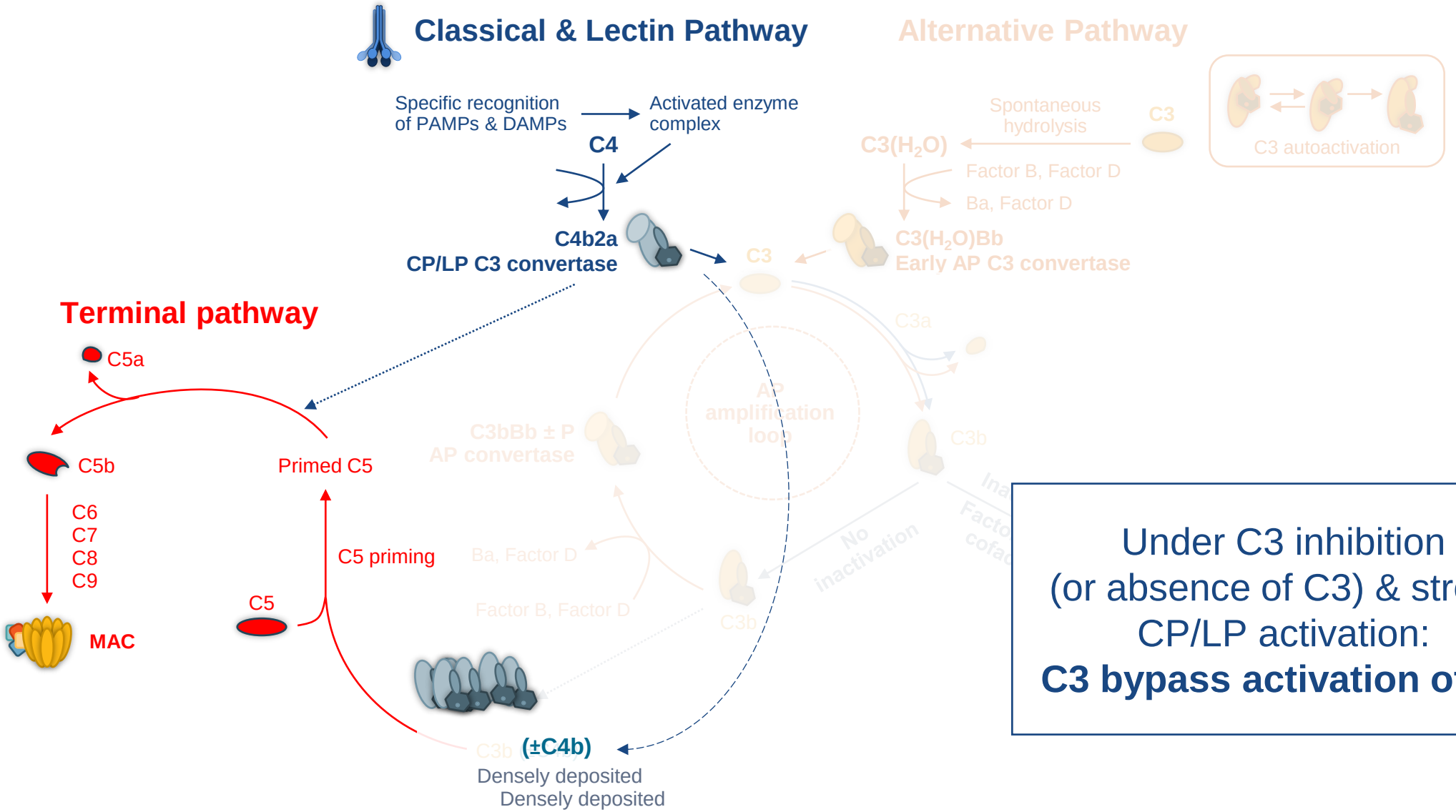






Mannes M et al. Blood. 2021

COMPLEMENT CASCADE UNDER C3 INHIBITION (2)



Under C3 inhibition
(or absence of C3) & strong
CP/LP activation:
C3 bypass activation of C5

Mannes M et al. Blood. 2021

C3 BYPASS IN PRECLINICAL MODELS – ‘HISTORIC REPORTS’

C3 BYPASS IN PRECLINICAL MODELS – ‘HISTORIC REPORTS’

Detection of C5 activation products in C3 knockout or C3-depleted animals:
(often attributed to extrinsic pathway activation)

Huber-Lang M, Sarma JV, Zetoune FS, et al.
Generation of C5a in the absence of C3: a new complement activation pathway.
Nat. Med. 2006;12(6):682–687.

Ramos TN, Darley MM, Weckbach S, et al.
The C5 convertase is not required for activation of the terminal complement pathway in murine experimental cerebral malaria.
J. Biol. Chem. 2012;287(29):24734–24738.

Auger JL, Haasken S, Binstadt BA.
Autoantibody-mediated arthritis in the absence of C3 and activating Fcγ receptors: C5 is activated by the coagulation cascade.
Arthritis Res. Ther. 2012;14(6):R269.

CLINICAL MEANING OF C3 BYPASS: EXAMPLE AMY-101 IN SEVERE COVID-19

CLINICAL MEANING OF C3 BYPASS: EXAMPLE AMY-101 IN SEVERE COVID-19

SCIENCE ADVANCES | RESEARCH ARTICLE

CORONAVIRUS

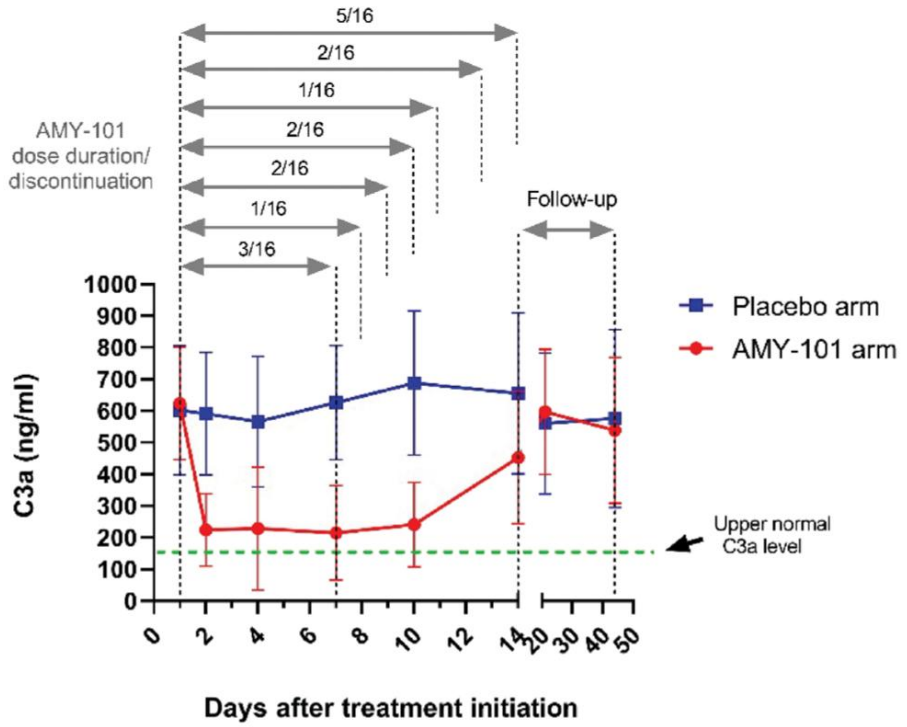
Complement C3 inhibition in severe COVID-19 using compstatin AMY-101

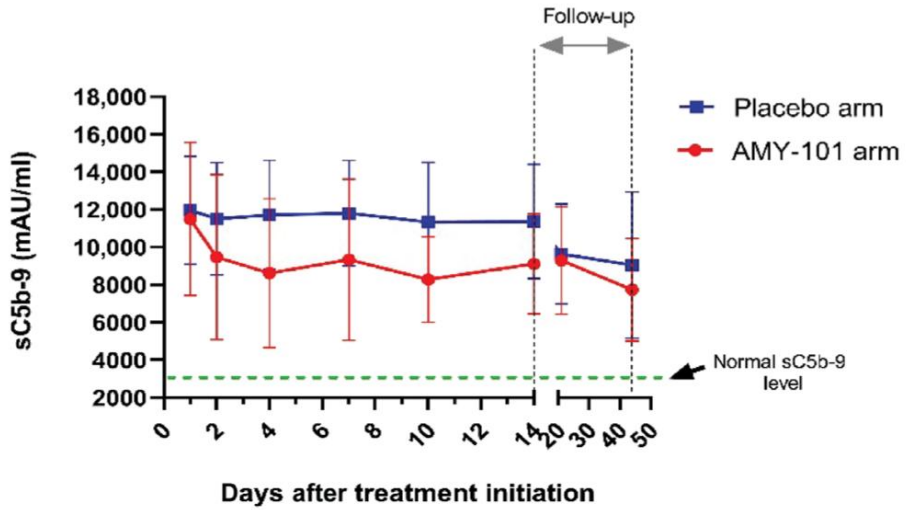
Panagiotis Skendros[1], Georgios Germanidis[2], Dimitrios C. Mastellos[3], Christina Antoniadou[1], Efstratios Gavriilidis[1], Georgios Kalopitas[2], Anna Samakidou[4], Angelos Liontos[5], Akrivi Chrysanthopoulou[1], Maria Ntinopoulou[1], Dionysios Kogias[1], Ioanna Karanika[2], Andreas Smyrlis[1], Dainora Cepaityte[2], Iliana Fotiadou[1], Nikoleta Zioga[1], Ioannis Mitroulis[1], Nikolaos K. Gatselis[4], Charalampos Papagoras[1], Simeon Metallidis[2], Haralampos Milionis[5], George N. Dalekos[4], Loek Willems[6], Barbro Persson[7], Vivek Anand Manivel[7], Bo Nilsson[7], E. Sander Connolly[8], Simona Iacobelli[9], Vasileios Papadopoulos[1], Rodrigo T. Calado[10], Markus Huber-Lang[11], Antonio M. Risitano[12], Despina Yancopoulou[13], Konstantinos Ritis[1], John D. Lambris[14]*

Complement C3 activation contributes to COVID-19 pathology, and C3 targeting has emerged as a promising therapeutic strategy. We provide interim data from ITHACA, the first randomized trial evaluating a C3 inhibitor, AMY-101, in severe COVID-19 (PaO2/FiO2 ≤ 300 mmHg). Patients received AMY-101 ($n = 16$) or placebo ($n = 15$) in addition to standard of care. AMY-101 was safe and well tolerated. Compared to placebo (8 of 15, 53.3%), a higher, albeit nonsignificant, proportion of AMY-101–treated patients (13 of 16, 81.3%) were free of supplemental oxygen at day 14. Three nonresponders and two placebo-treated patients succumbed to disease-related complications. AMY-101 significantly reduced CRP and ferritin and restrained thrombin and NET generation. Complete and sustained C3 inhibition was observed in all responders. Residual C3 activity in the three nonresponders suggested the presence of a convertase-independent C3 activation pathway overriding the drug's inhibitory activity. These findings support the design of larger trials exploring the potential of C3-based inhibition in COVID-19 or other complement-mediated diseases.

CLINICAL MEANING OF C3 BYPASS: EXAMPLE AMY-101 IN SEVERE COVID-19

- good C3 inhibition
- some C5 inhibition





Skendros P et al. Sci Adv. 2022

CONCLUSIONS: C3 BYPASS ACTIVATION OF C5

- ‘historic’ preclinical models in C3-deficient animals reported data that are consistent with a C3 bypass activation of C5

- first indications that such bypass may exist in the clinic

CONCLUSIONS: STOICHIOMETRIC C3 INHIBITORS

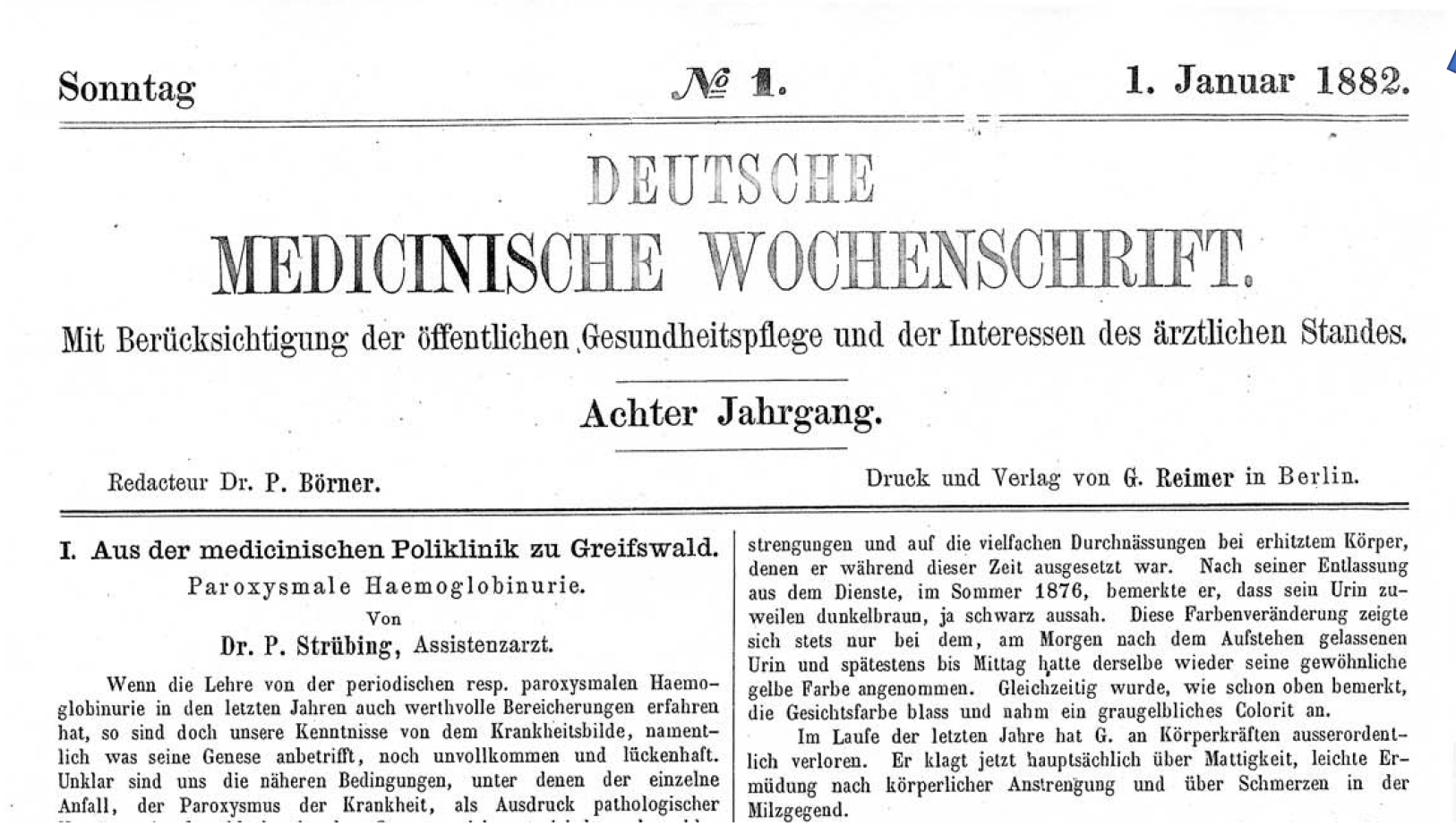
- **complete** inhibition of **AP**-mediated C5 activation

- **insufficient** inhibition of **CP**-mediated C5 activation

→ potential implications for PD breakthrough events with proximal complement inhibitors in the clinic

Complement cascade: historic milestones

‘First’ description of PNH



Sonntag № 1. 1. Januar 1882.

DEUTSCHE
MEDICINISCHE WOCHENSCHRIFT.

Mit Berücksichtigung der öffentlichen Gesundheitspflege und der Interessen des ärztlichen Standes.

Achter Jahrgang.

Redacteur Dr. P. Börner. Druck und Verlag von G. Reimer in Berlin.

I. Aus der medicinischen Poliklinik zu Greifswald.

Paroxysmale Haemoglobinurie.

Von

Dr. P. Strübing, Assistenzarzt.

Wenn die Lehre von der periodischen resp. paroxysmalen Haemoglobinurie in den letzten Jahren auch werthvolle Bereicherungen erfahren hat, so sind doch unsere Kenntnisse von dem Krankheitsbilde, namentlich was seine Genese anbetrifft, noch unvollkommen und lückenhaft. Unklar sind uns die näheren Bedingungen, unter denen der einzelne Anfall, der Paroxysmus der Krankheit, als Ausdruck pathologischer

strengungen und auf die vielfachen Durchnässungen bei erhitztem Körper, denen er während dieser Zeit ausgesetzt war. Nach seiner Entlassung aus dem Dienste, im Sommer 1876, bemerkte er, dass sein Urin zuweilen dunkelbraun, ja schwarz aussah. Diese Farbenveränderung zeigte sich stets nur bei dem, am Morgen nach dem Aufstehen gelassenen Urin und spätestens bis Mittag hatte derselbe wieder seine gewöhnliche gelbe Farbe angenommen. Gleichzeitig wurde, wie schon oben bemerkt, die Gesichtsfarbe blass und nahm ein graugelbliches Colorit an.

Im Laufe der letzten Jahre hat G. an Körperkräften ausserordentlich verloren. Er klagt jetzt hauptsächlich über Mattigkeit, leichte Ermüdung nach körperlicher Anstrengung und über Schmerzen in der Milzgegend.

Complement cascade: historic milestones

Fodor (1887): Die faehigkeit des Bluts bakterien zu vernichten. Deutsch. Med. Wschr. 13, 745

Nuttall (1888): Experimente uber die bacterienfeindlichen Einfluesse des thierischen Korpers. Z. Hyg. Infectionskir. 4, 353.

Buchner (1889, 1891): Uber die nahere Natur der bakterientodtenden Substanz in Blutserum. Zbl. Bakt. (Naturwiss.) 6, 561. >>> "heat labile substance in blood" Alexine

Bactericidal activity in serum

Hans Ernst August Buchner (1850 – 1902)
German bacteriologist (Munich)

https://en.wikipedia.org/wiki/Hans_Ernst_August_Buchner

Bordet (1895): Immune lysis by of two factors: a heatlabile lytic factor (similar to alexin) and a heat-stable factor kills Vibrios; heat stable factor was termed sensitiser (antibody)

Bordet & Ehrlich (1898/1899): Immune lysis of erythrocytes by of two factors; Ehrlich coined 'Complement'

Lachmann P. *Mol Immunol.* 2006;43:496–508
Nesargikar PN, Spiller B, Chavez R. *Eur J Microbiol Immunol (Bp).* 2012;2:103–111

Complement cascade: historic milestones

European Journal of Immunology
Clinical·Basic·Translational

HIGHLIGHTS

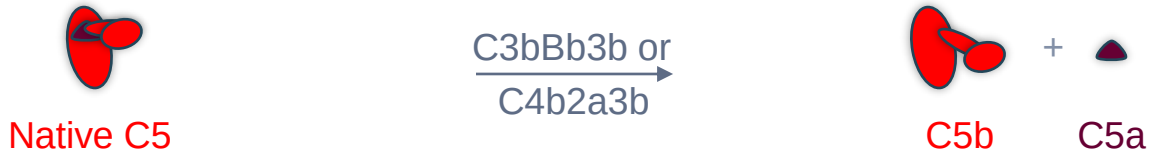
REVIEW

The complement model disease paroxysmal nocturnal hemoglobinuria

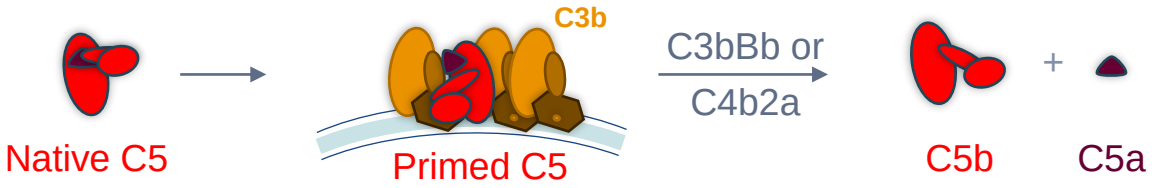
Christoph Q. Schmidt[1], *Britta Höchsmann*[2,3] *and Hubert Schrezenmeier*[2,3]

GRAPHICAL SUMMARY: UNEXPECTED RESULTS >>> NEW COMPLEMENT INSIGHTS

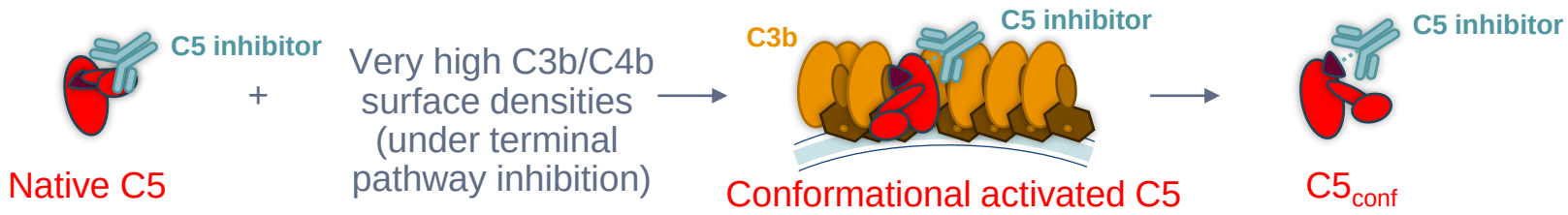
Traditional mechanism:
Trimolecular C5 convertases



Novel mechanism:
Bimolecular C5 convertases
& C5 priming



In presence of C5 inhibitors:
Conformational activation → $C5_{conf}$

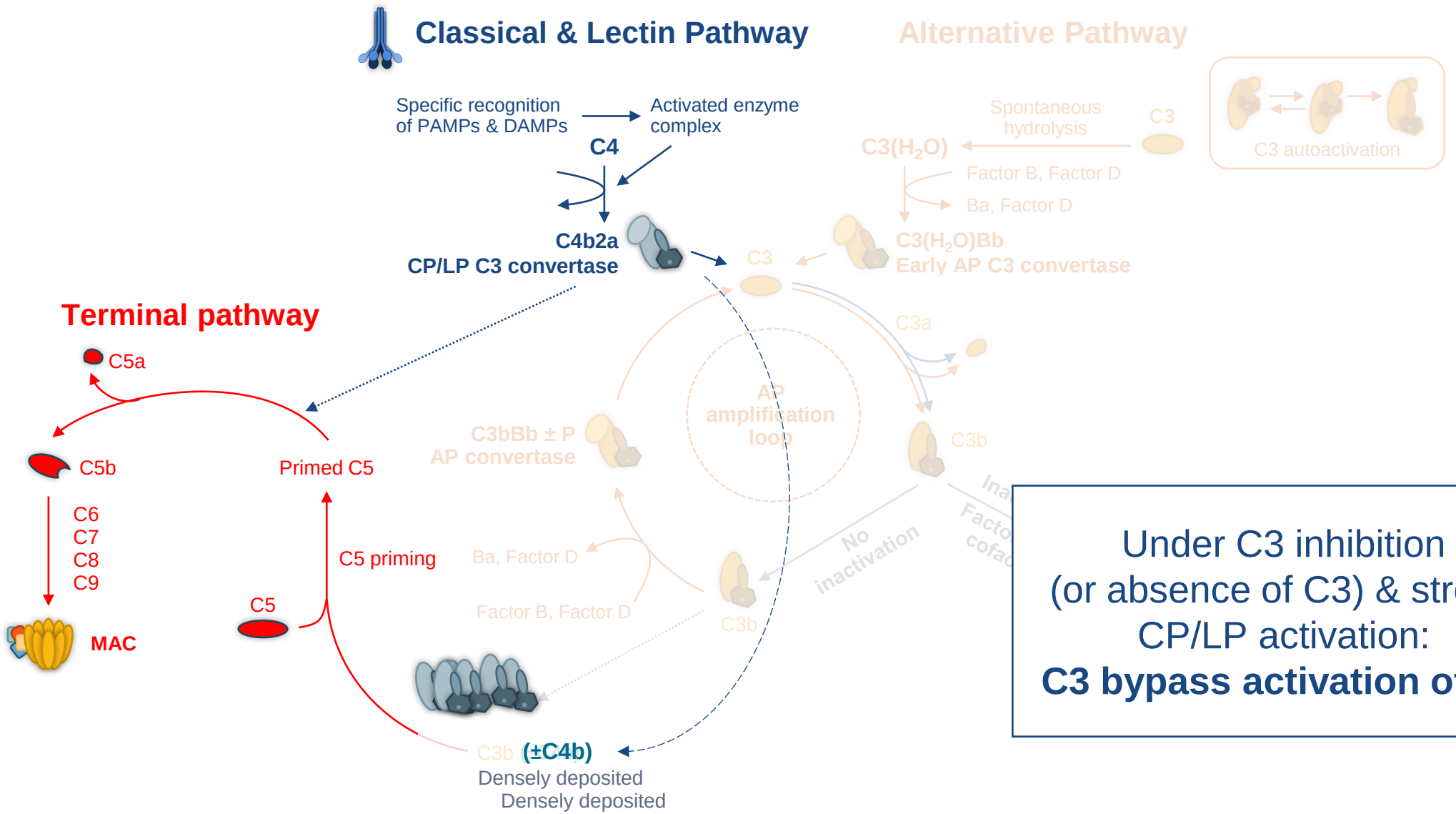


In absence of functional C3 & with strong CP/LP activation: C3 bypass

Mannes et al. *Blood* 2021
Schmidt & Smith. *Immunol Rev* 2023.

THANK YOU FOR YOUR ATTENTION

COMPLEMENT CASCADE UNDER C3 INHIBITION (2)



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Mannes M et al. Blood. 2021