

Grundlagenforschung und klinische Entwicklung

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Ulm, 06.03.2021



ulm university universität
ulm

Outline

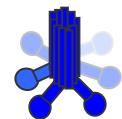
1. Komplement und PNH
2. Klinische Entwicklung – ein kurzer Überblick
3. PNH und Eculizumab „erklären“ Komplement
4. Ausblick

Outline

- 1. Komplement und PNH**
2. Klinische Entwicklung – ein kurzer Überblick
3. PNH und Eculizumab „erklären“ Komplement
4. Ausblick

Komplementschema

Klassischer Pathway (Pfad)
Lektin Pathway (Pfad)

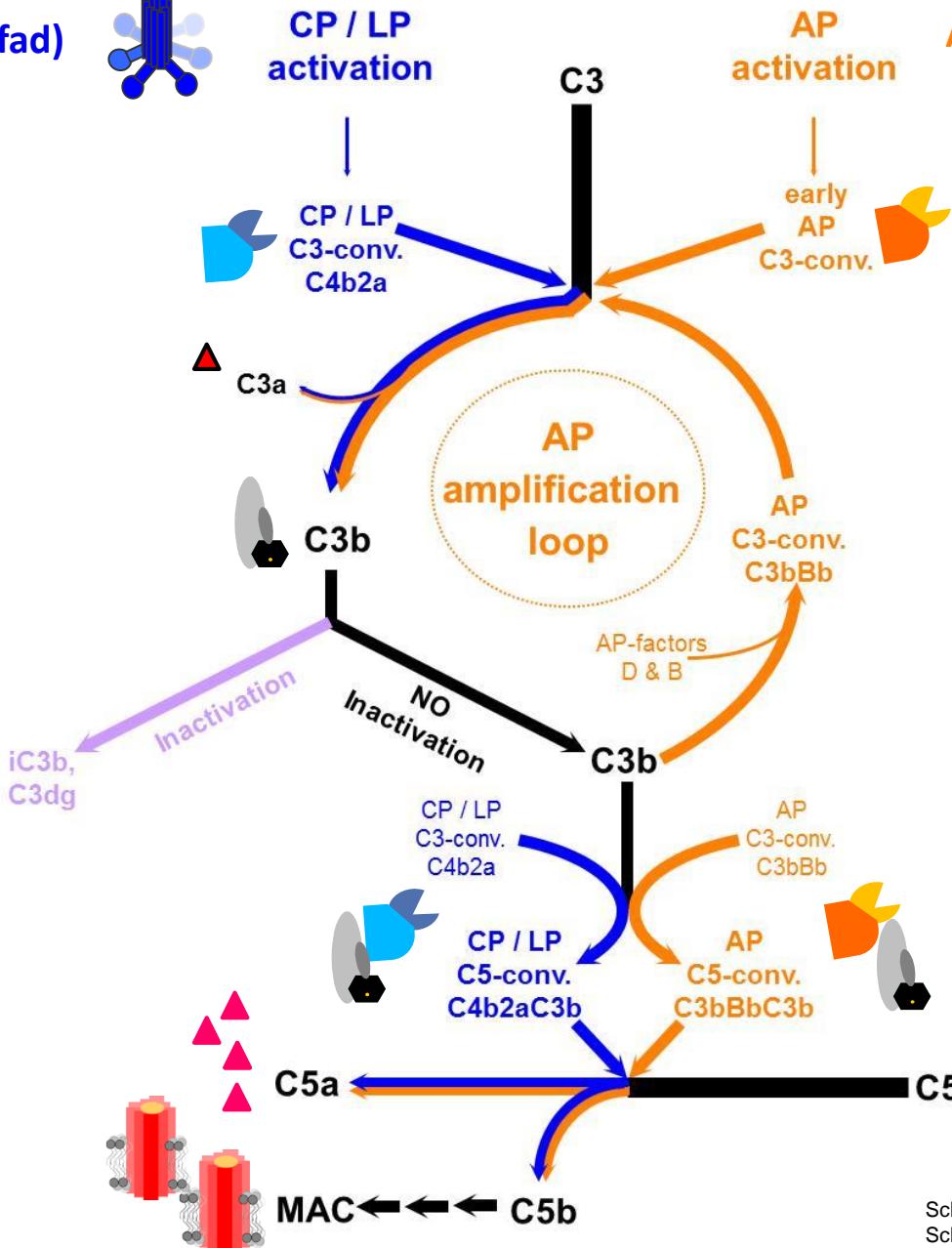


CP / LP activation

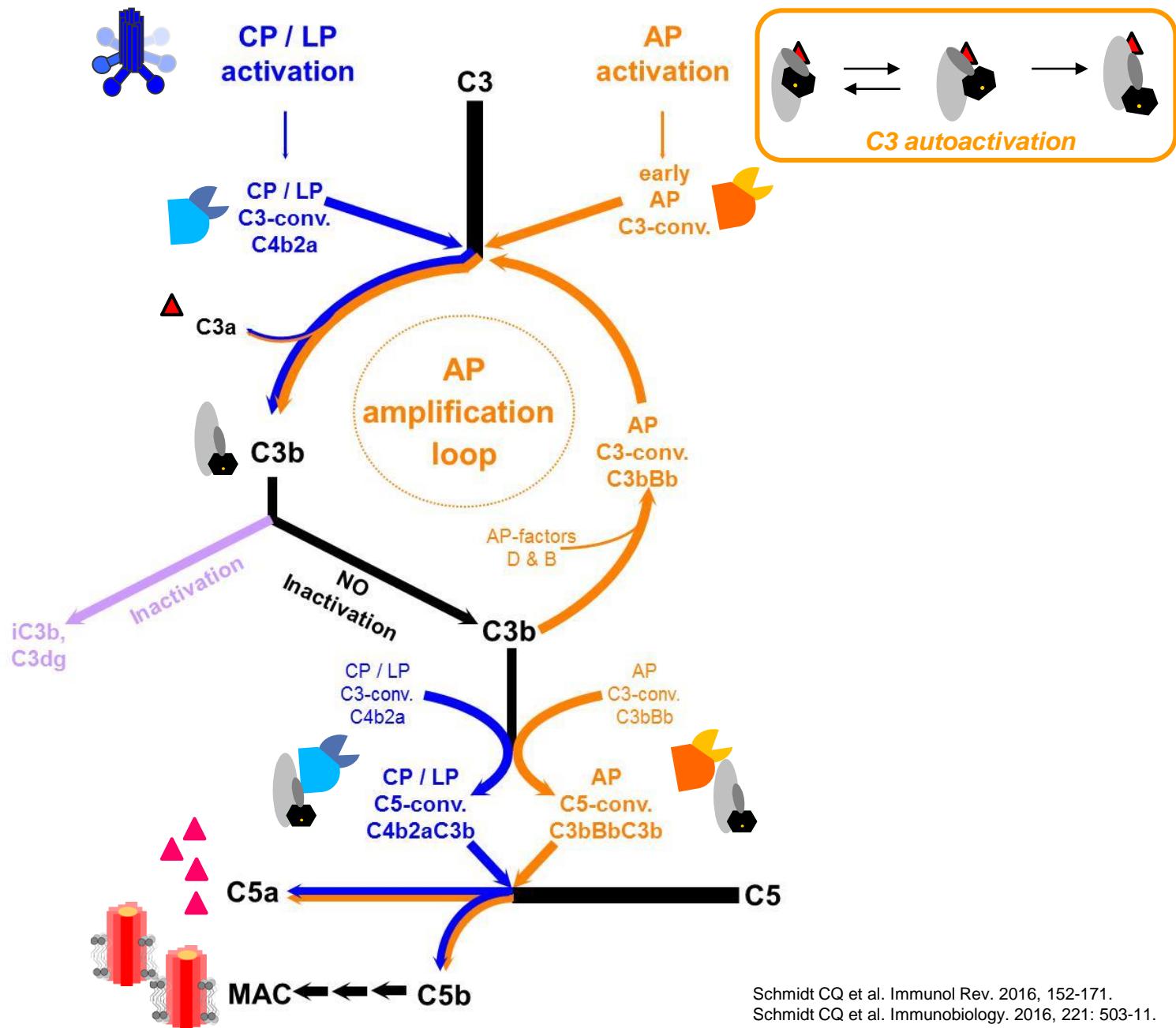
C3

AP activation

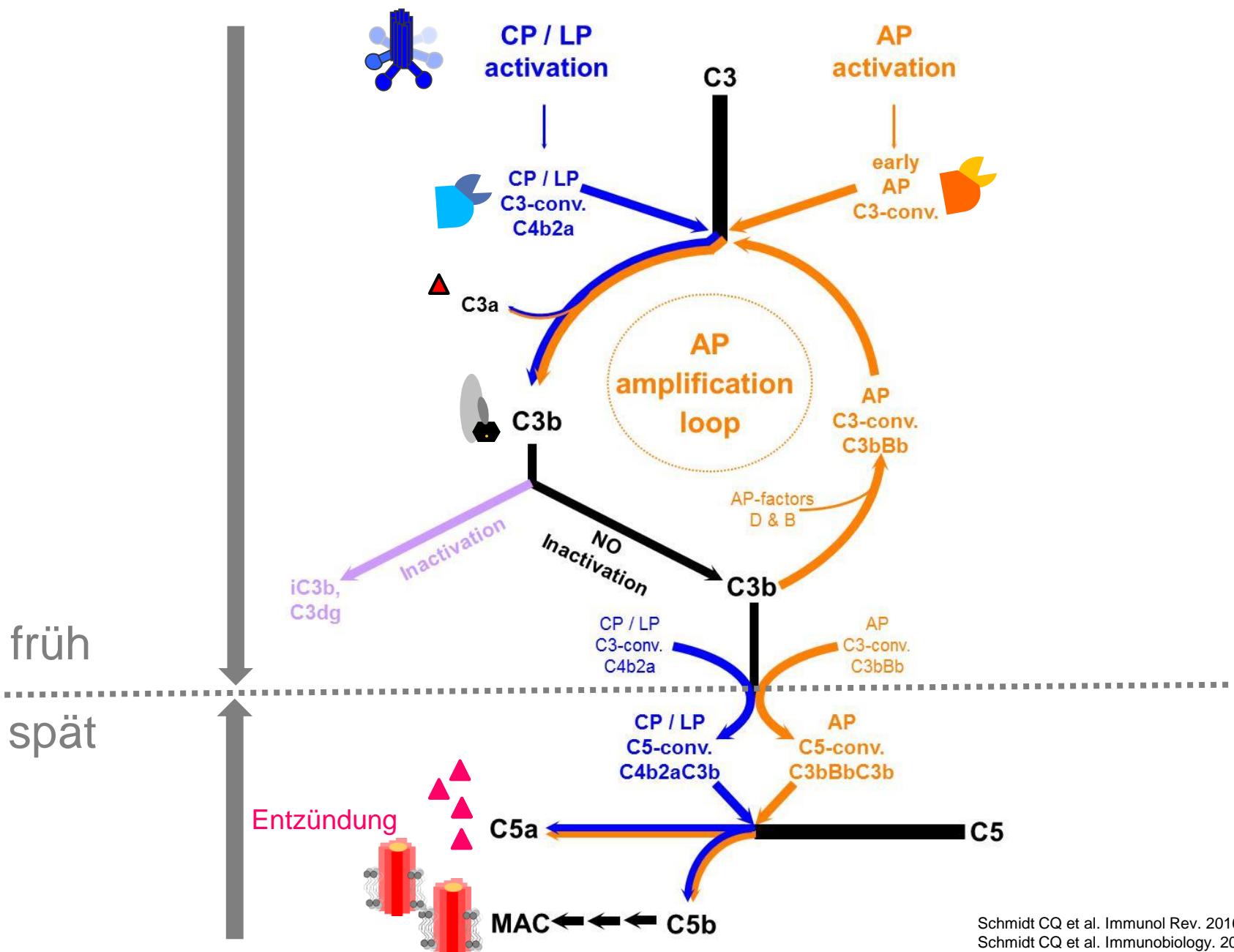
Alternativer Pathway (Pfad)



Komplementschema

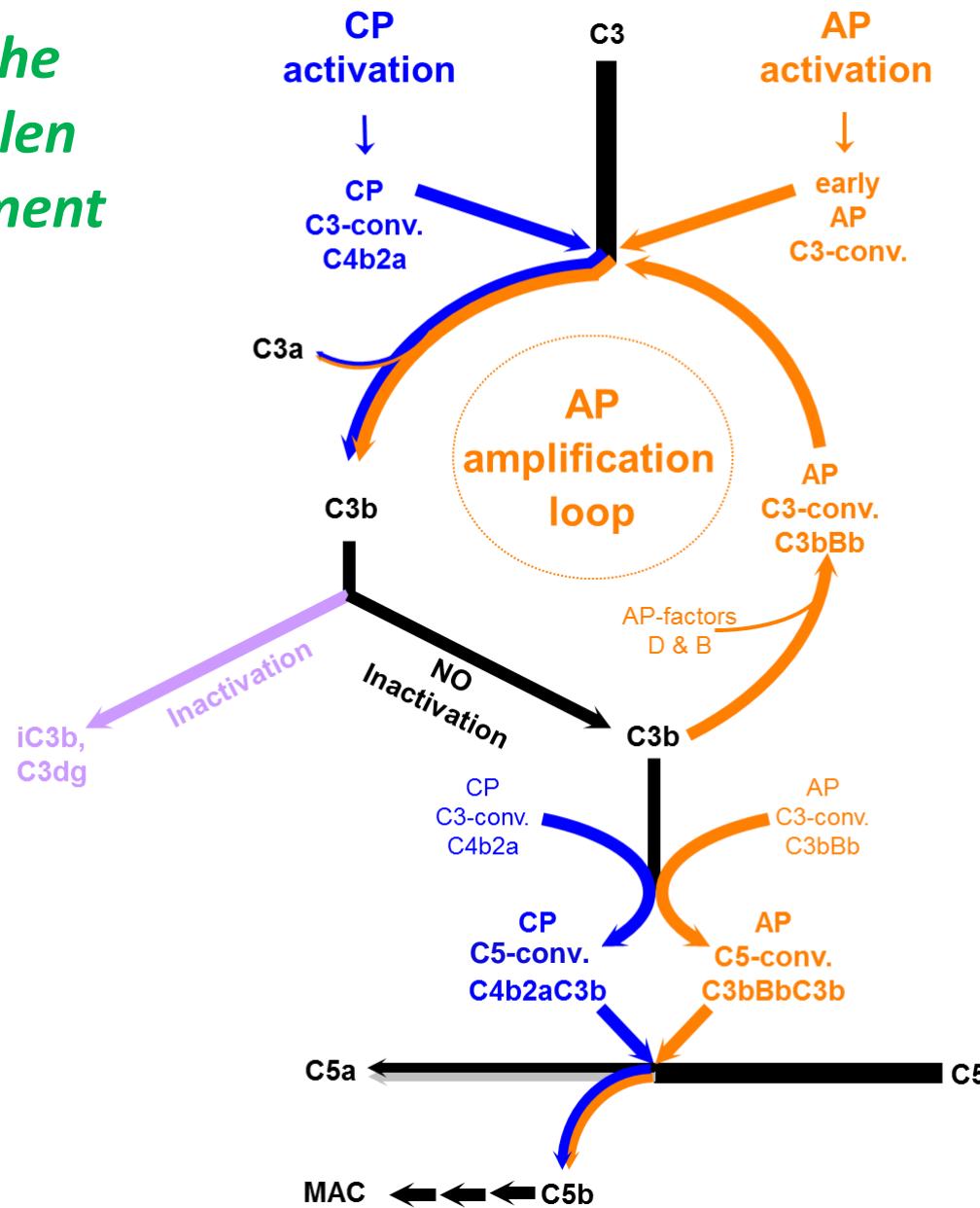


Komplementschema



Regulatorische Schlüsselstellen

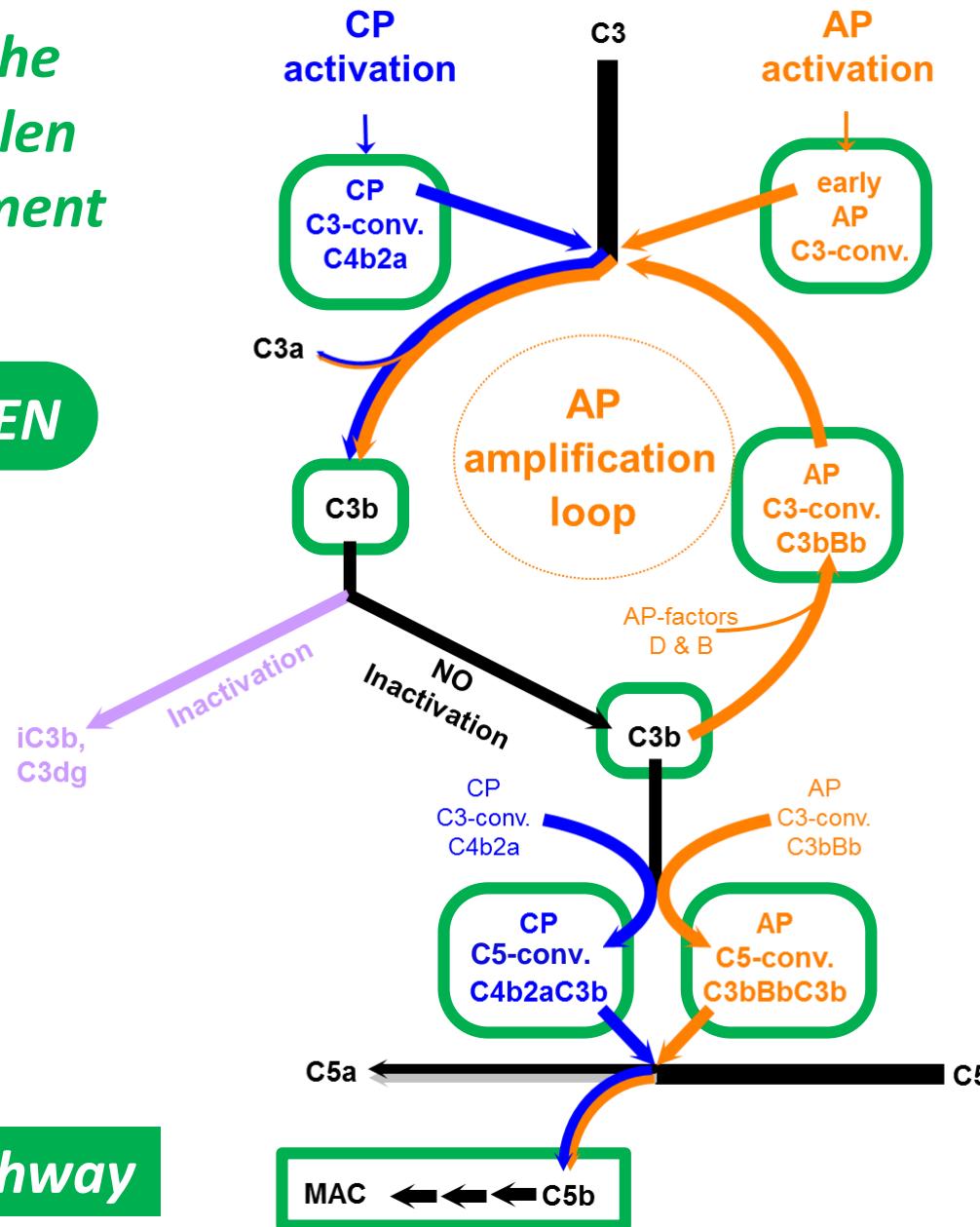
**Regulatorische
Schlüsselstellen
der Komplement
Kaskade:**



Regulatorische Schlüsselstellen

**Regulatorische
Schlüsselstellen
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Kaskade:**

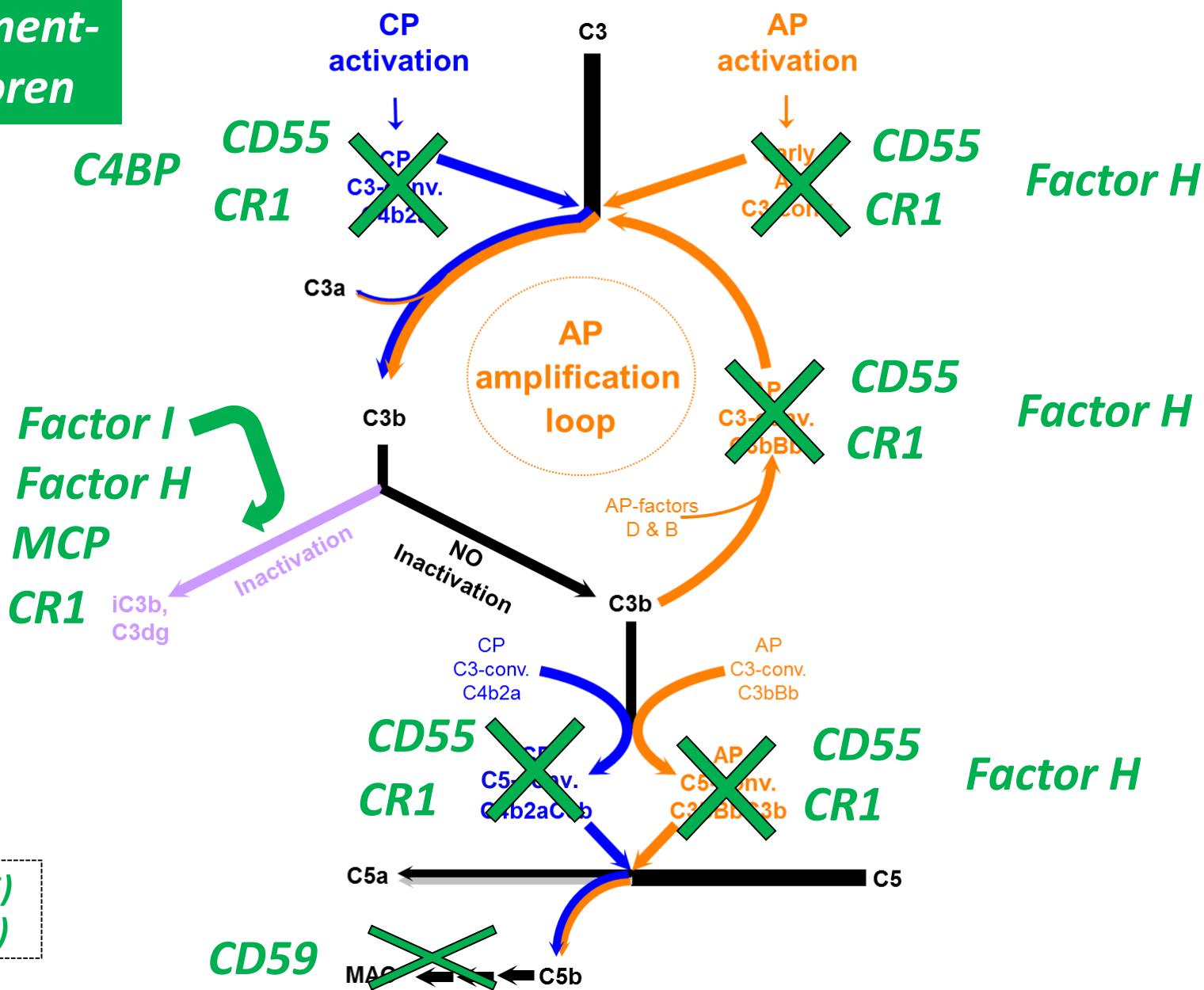
KONVERTASEN



Lytische Pathway

Komplement Kaskade: UNTER KONTROLLE

Komplement-Regulatoren

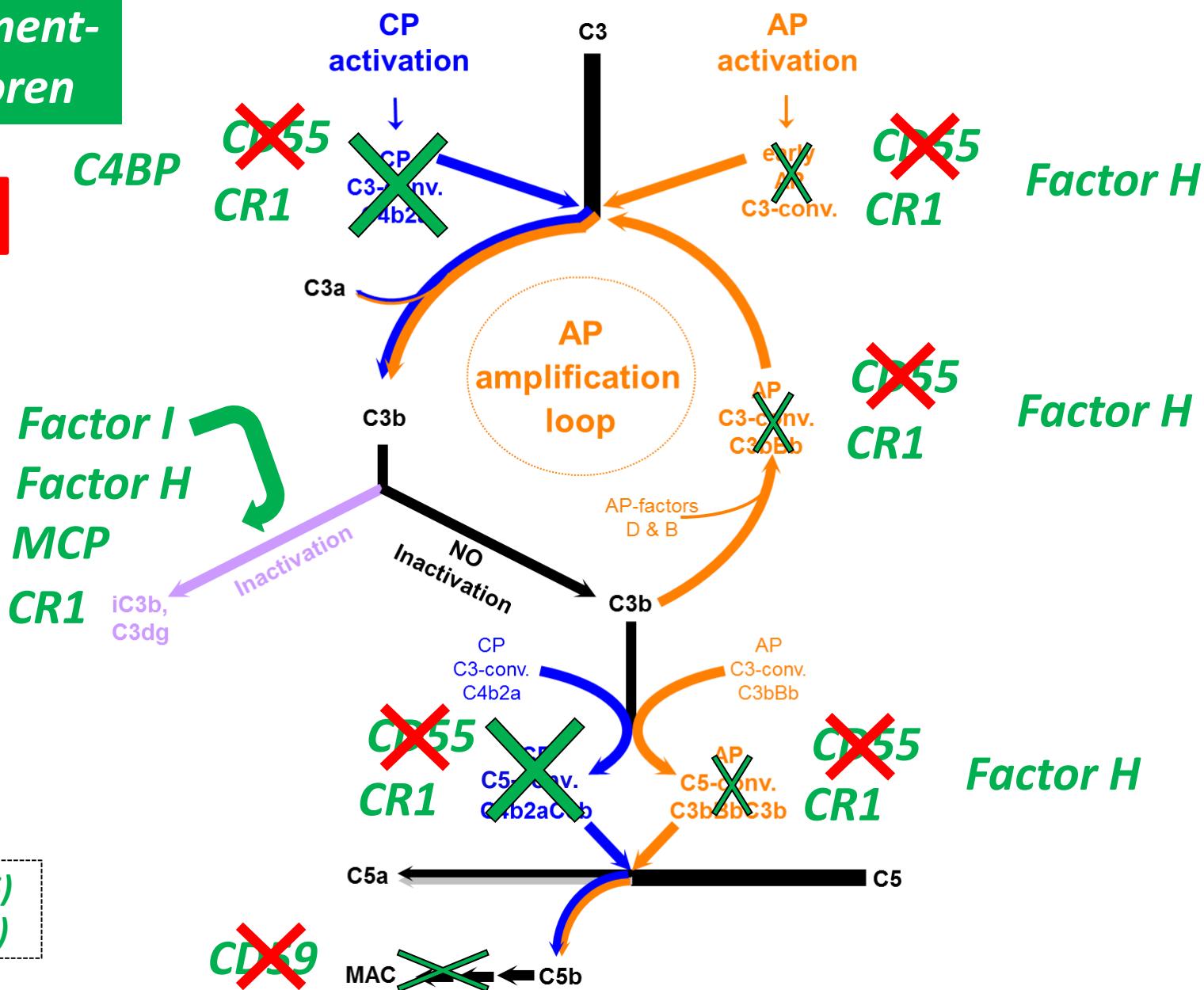


MCP (= CD46)
CR1 (= CD35)

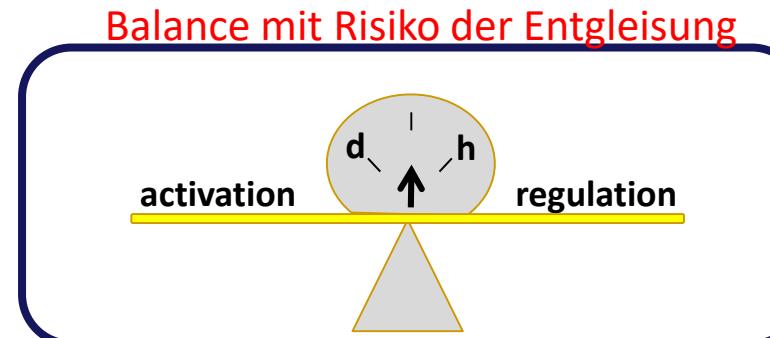
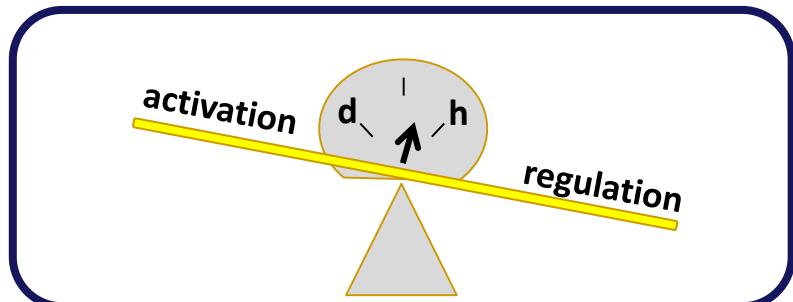
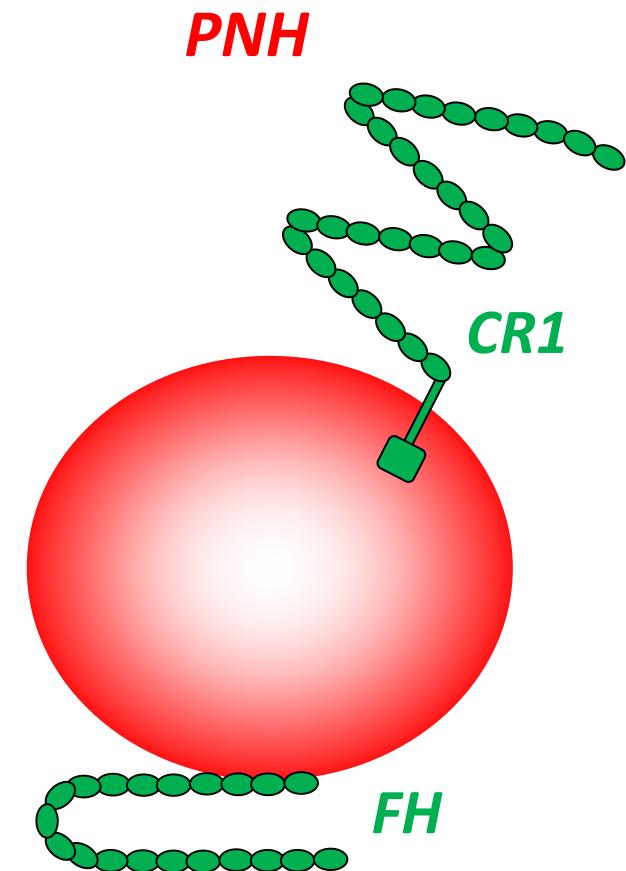
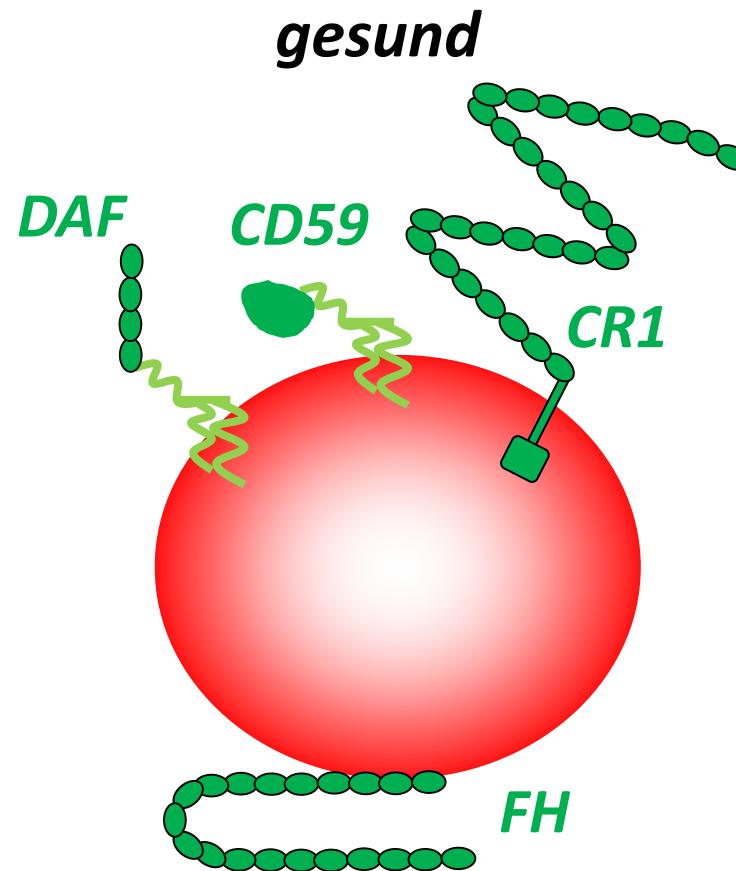
Komplement Kaskade: AUßER KONTROLLE

Komplement-Regulatoren

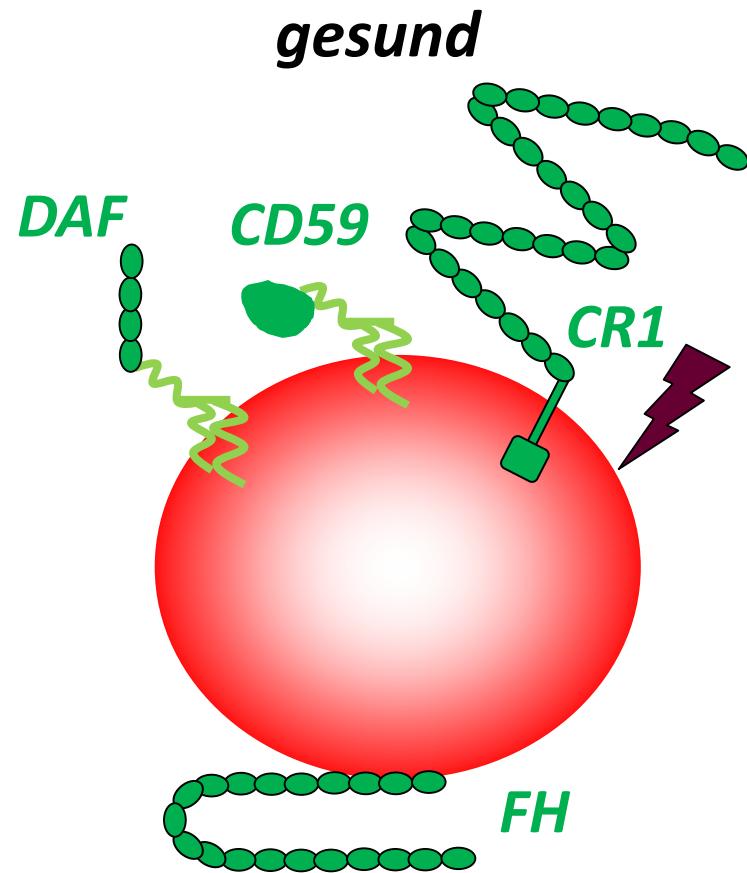
PNH



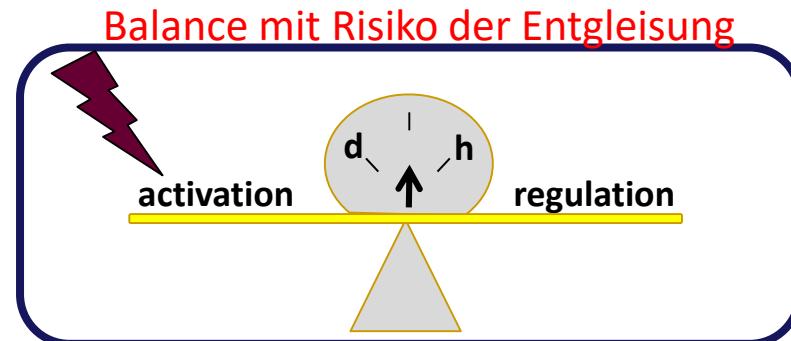
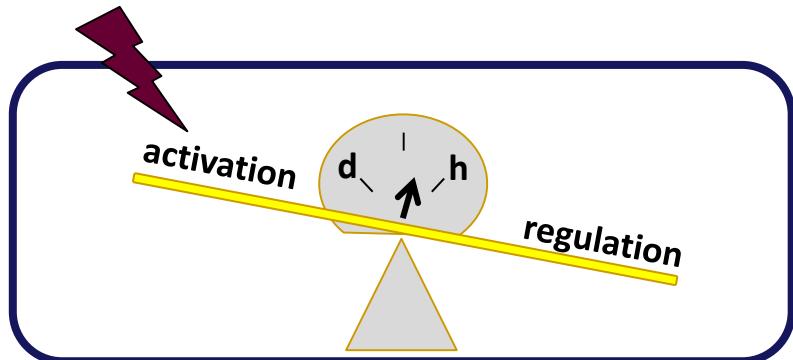
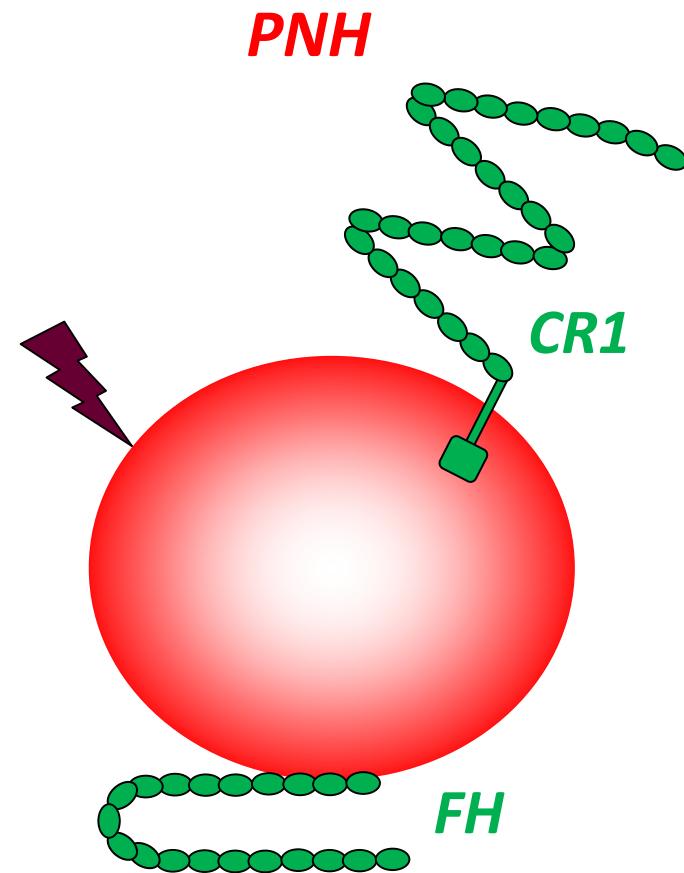
PNH Pathophysiologie



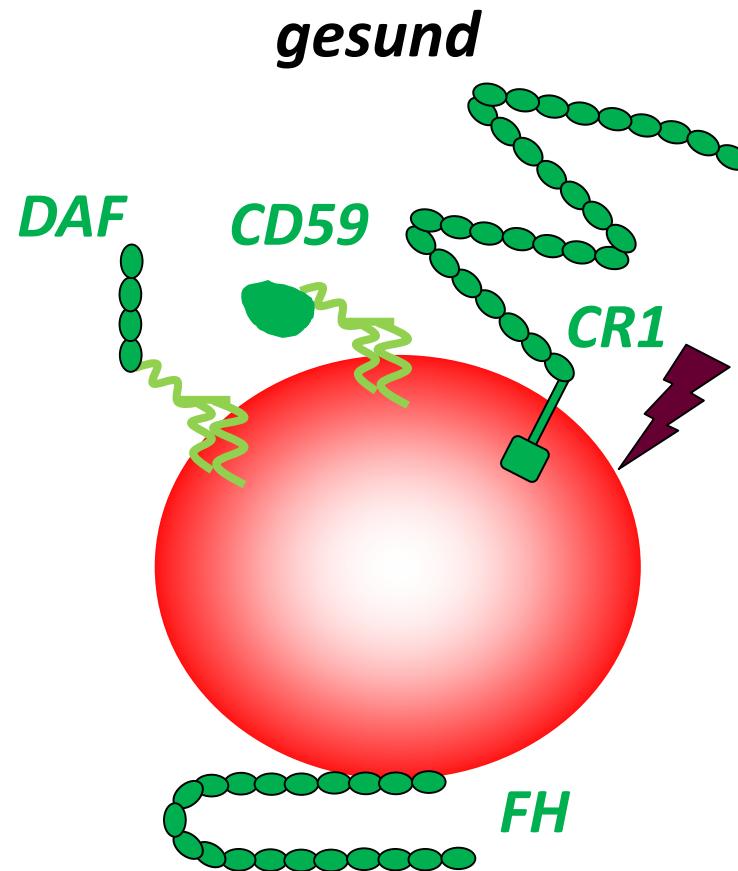
PNH Pathophysiologie



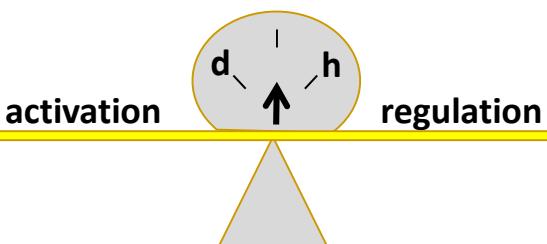
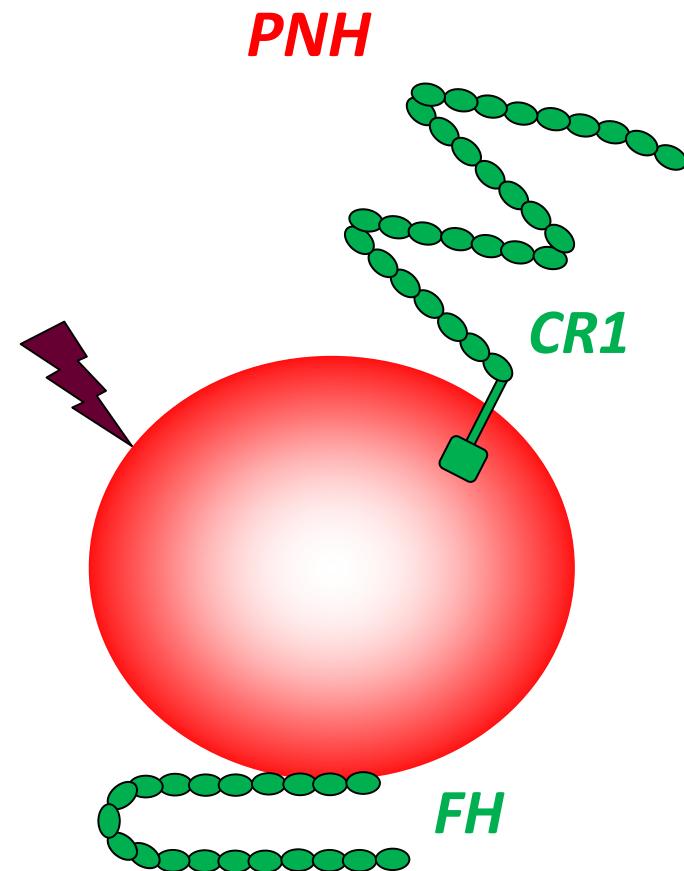
*Auslöser der
Komplement
Aktivierung
(e.g. Infektion,
Operation)*



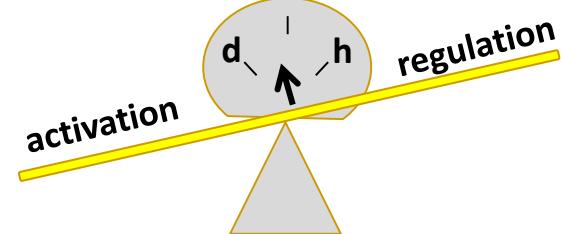
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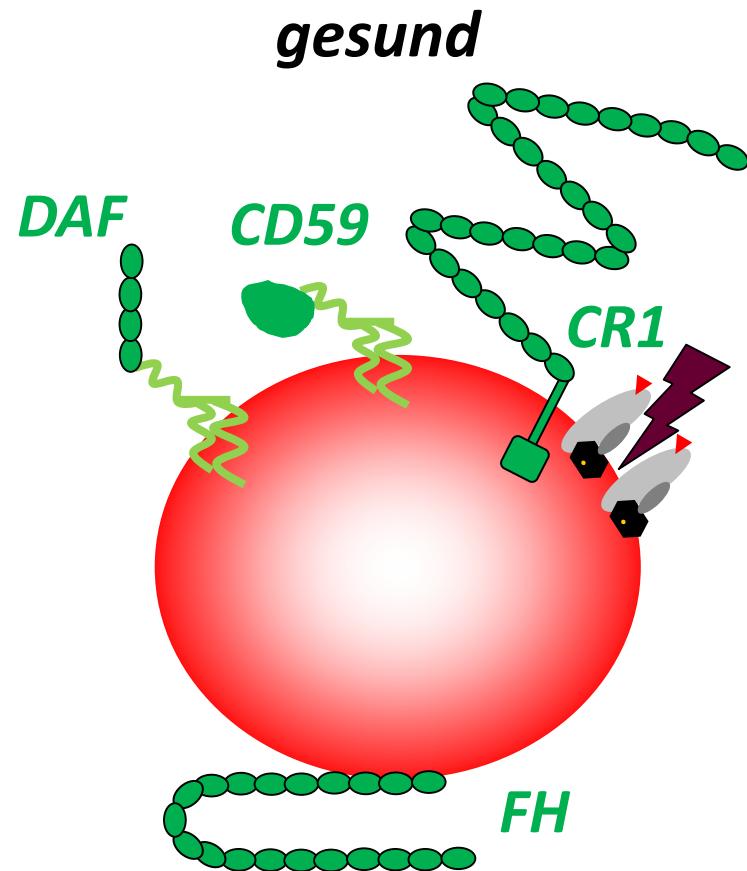
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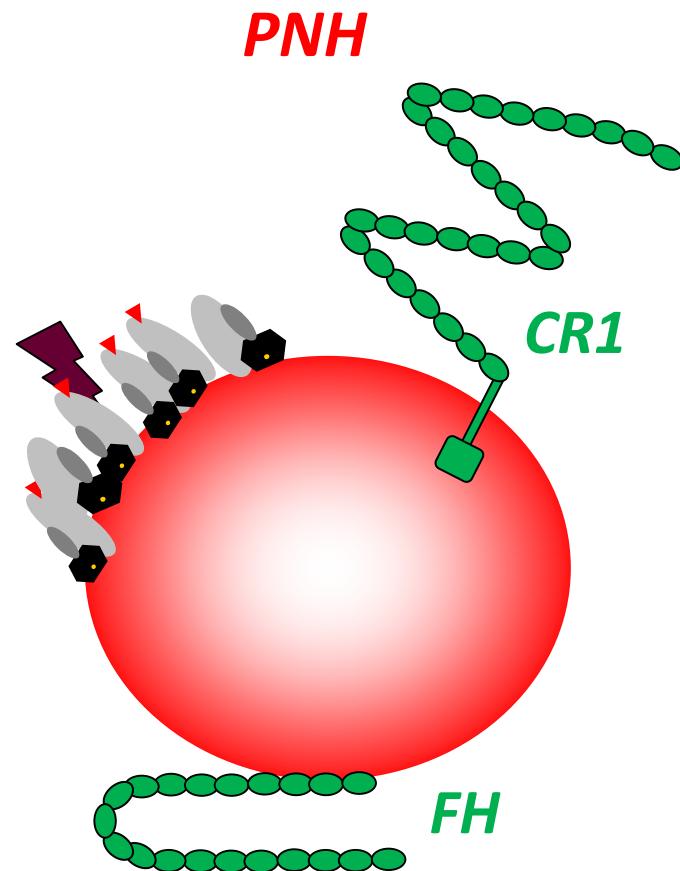
Balance entgleist



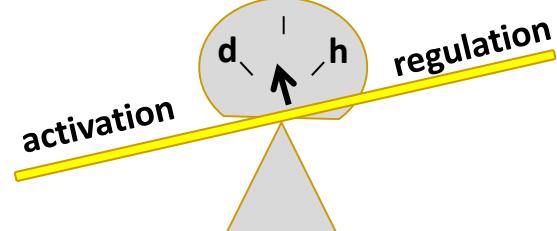
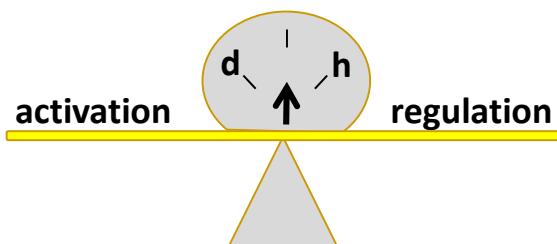
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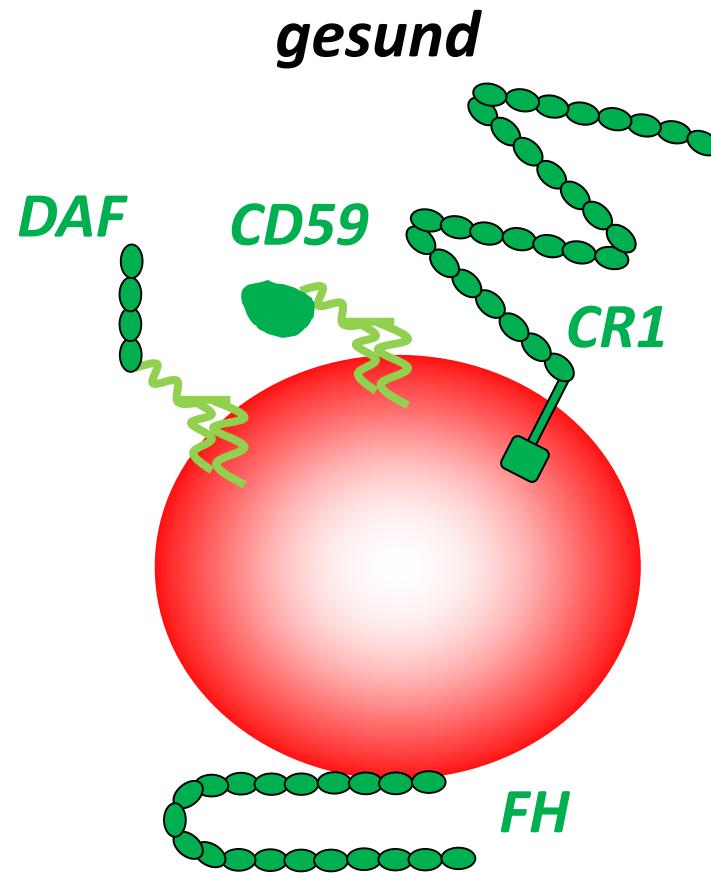
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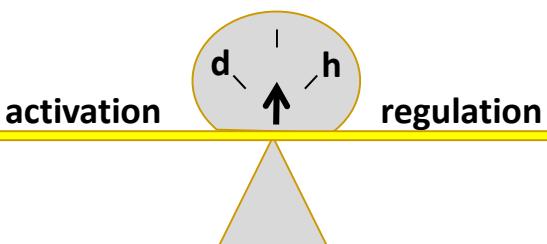
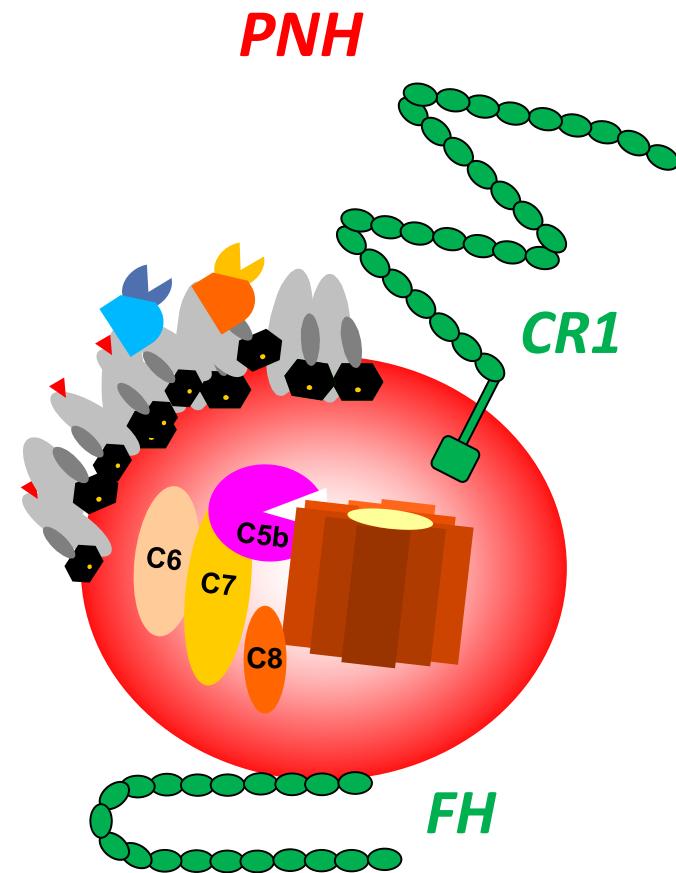
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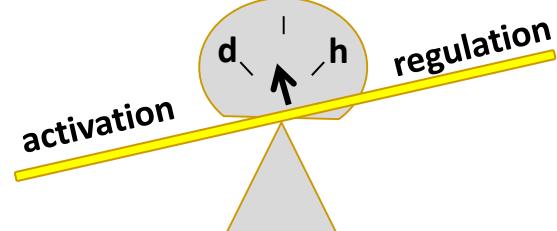
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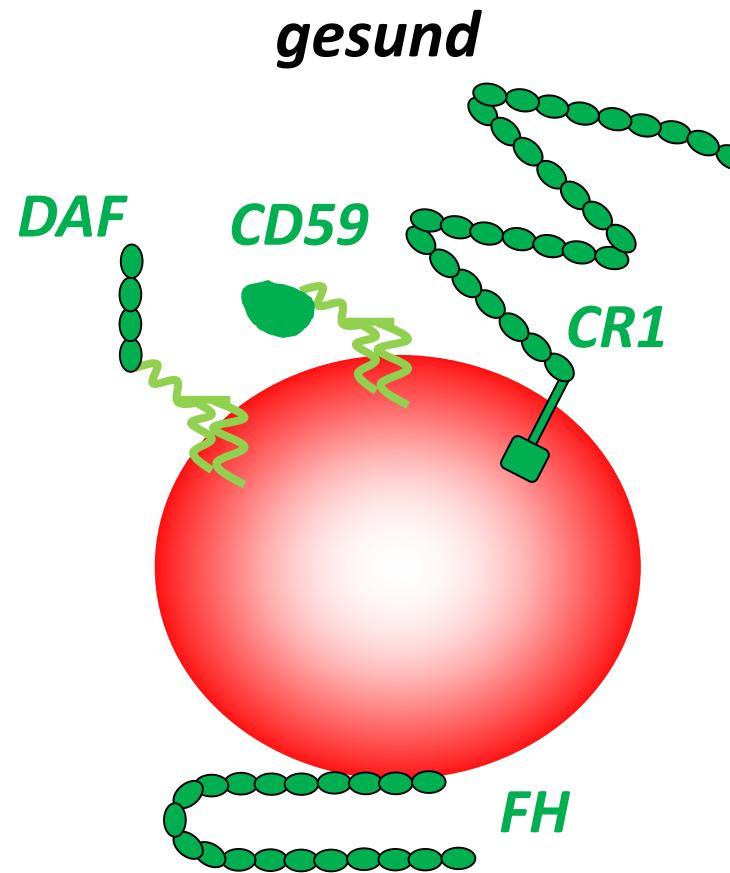
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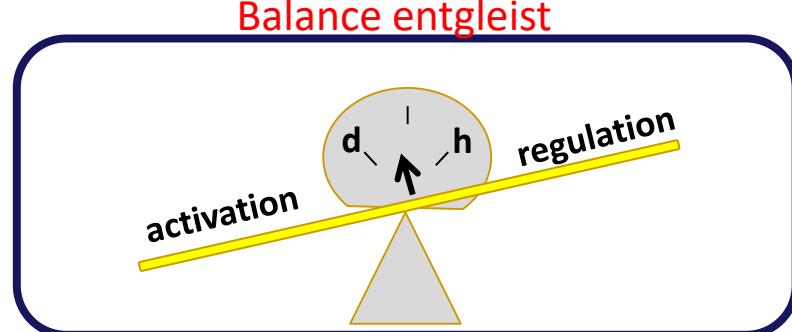
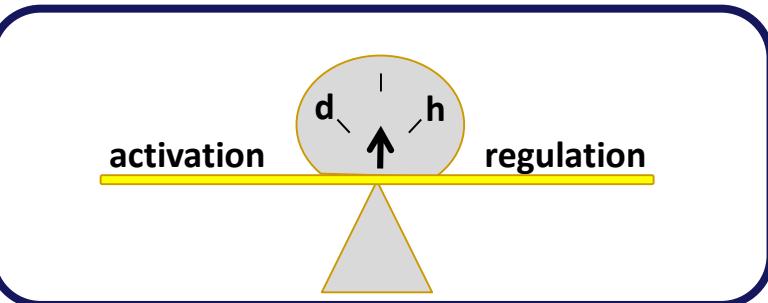
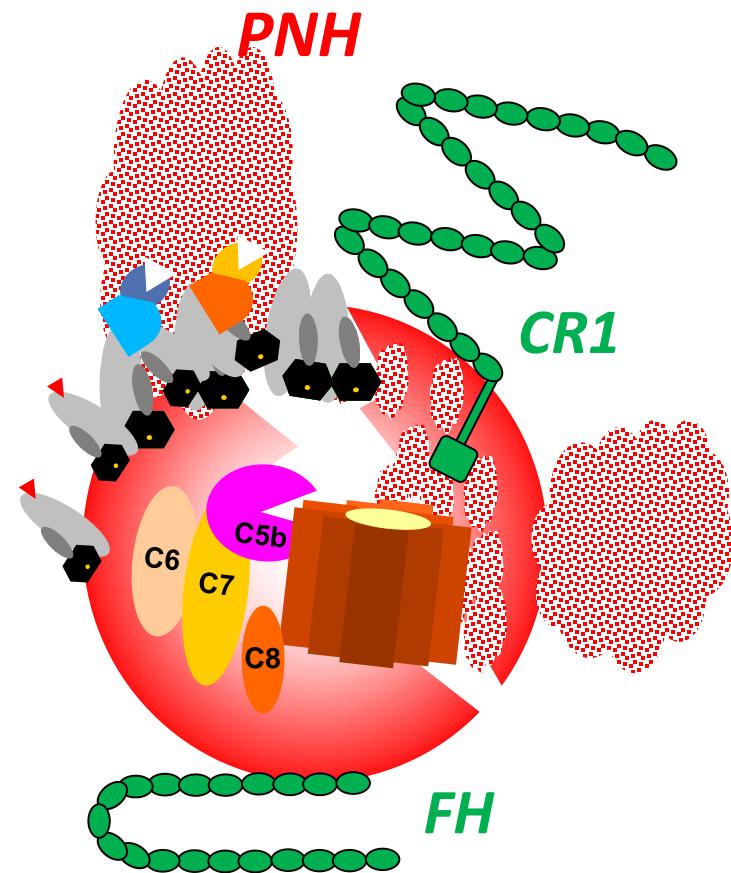
Balance entgleist



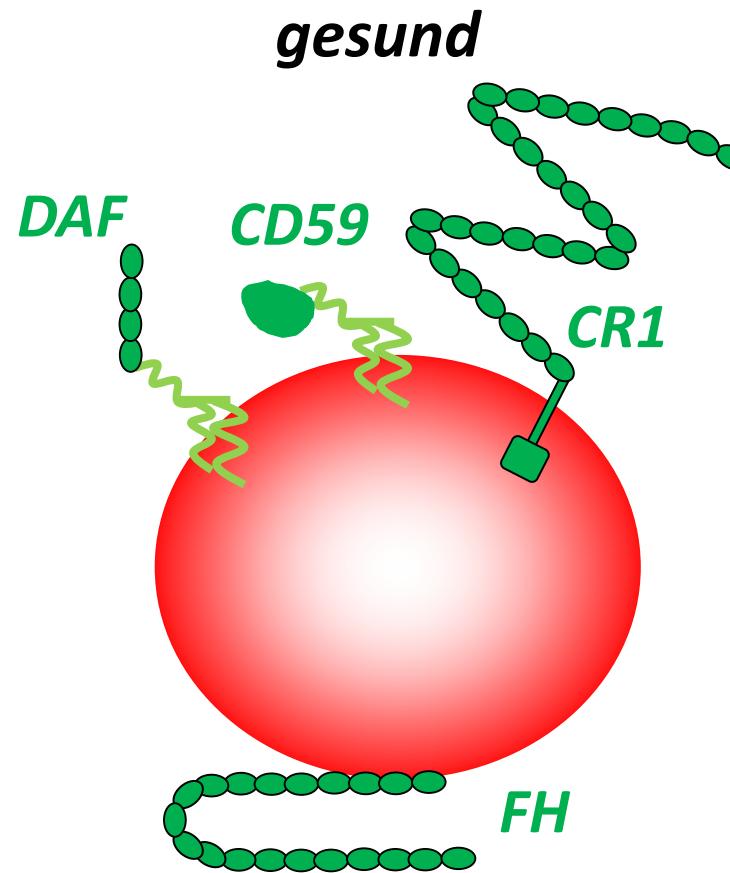
PNH Pathophysiologie



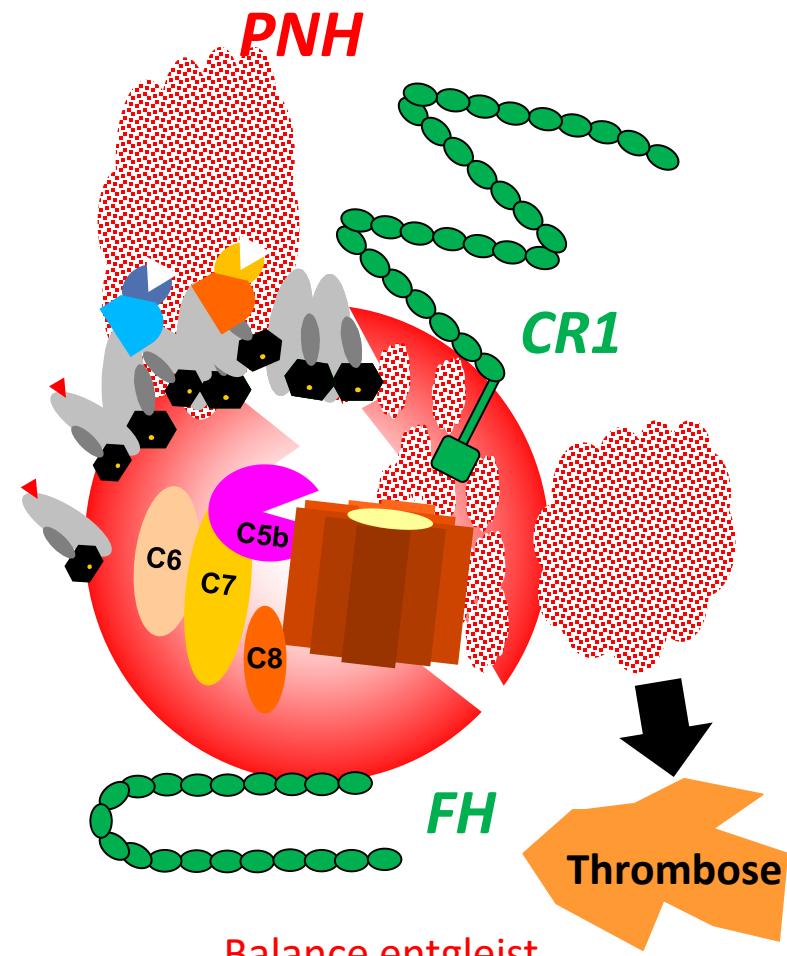
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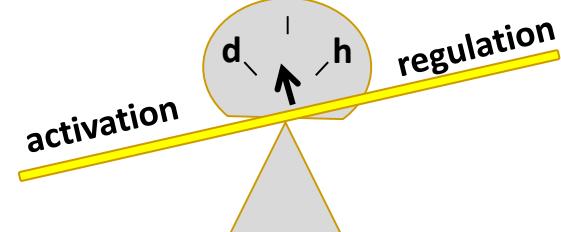
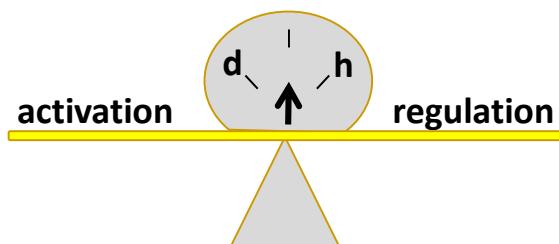
PNH Pathophysiologie



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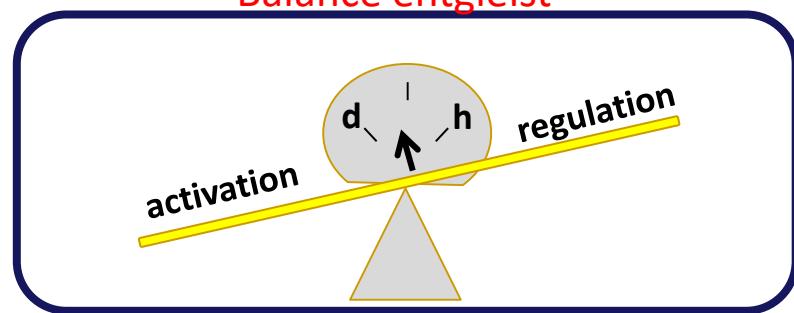
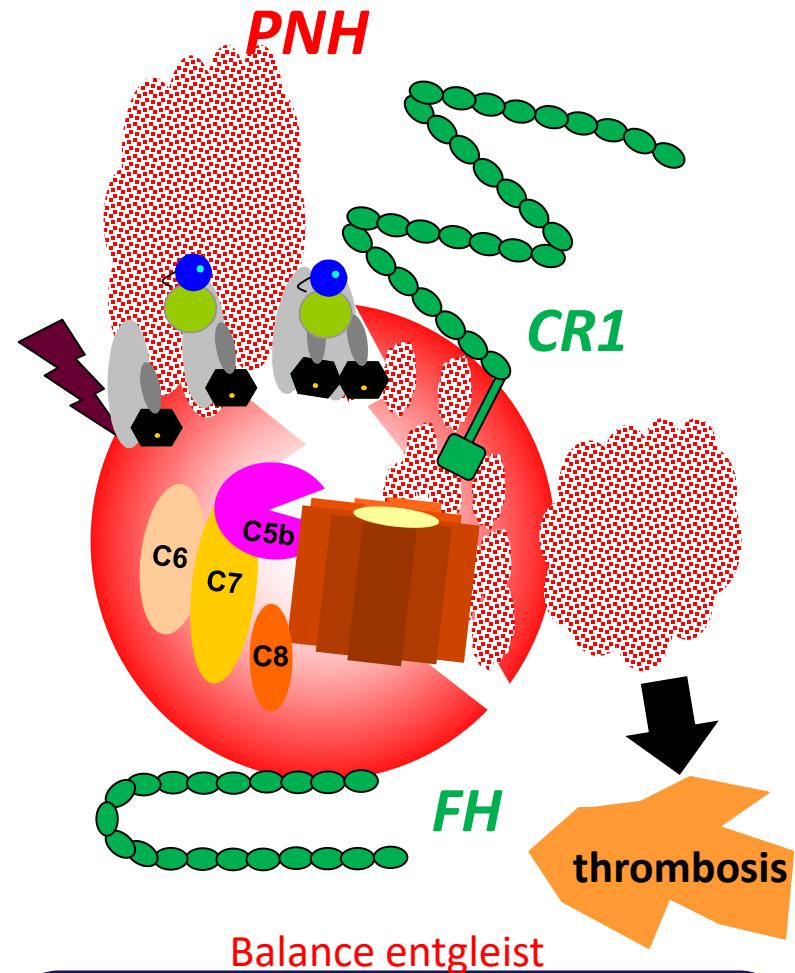


Balance entgleist

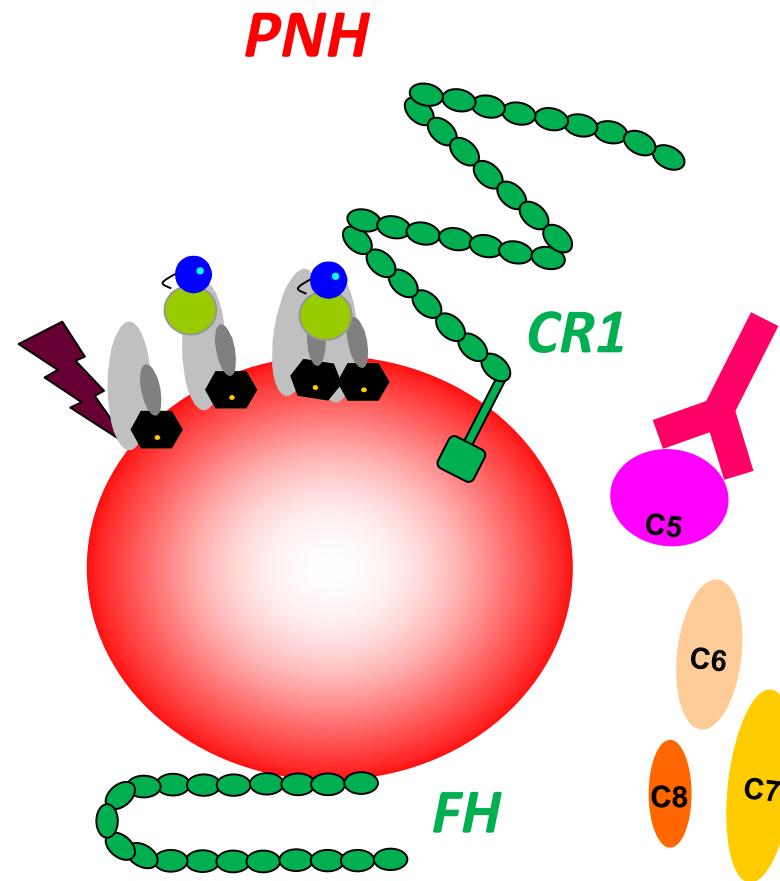


PNH Therapie (seit 2007)

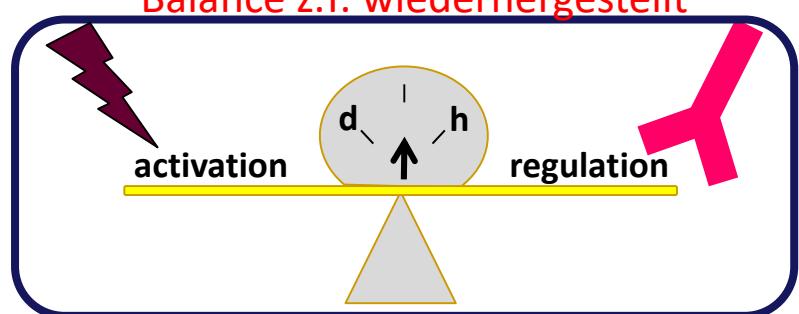
PNH Therapie (seit 2007)



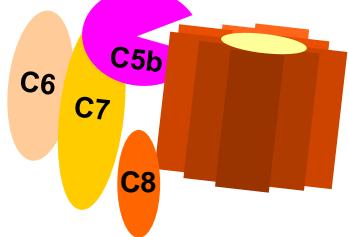
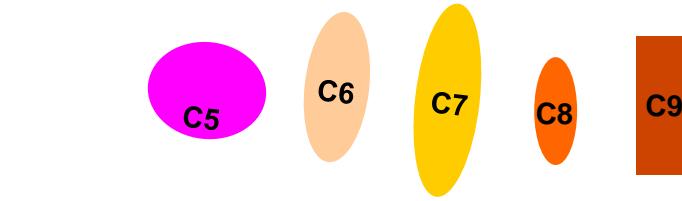
PNH Therapie (seit 2007)



Balance z.T. wiederhergestellt

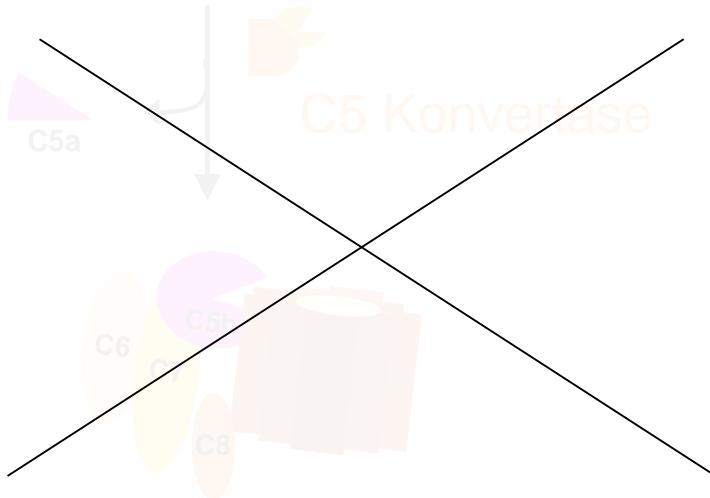
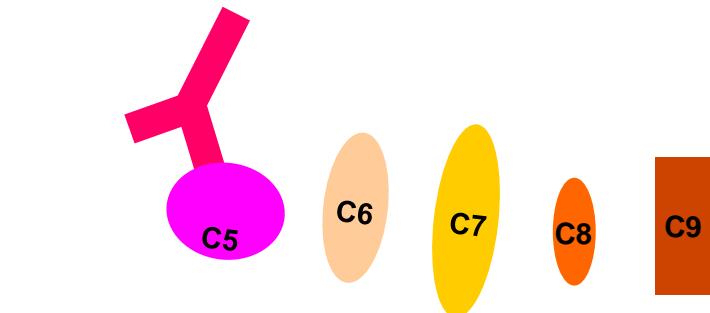


MAC: Membran-Angriffs-Complex



Therapeutische C5 Inhibition

Eculizumab

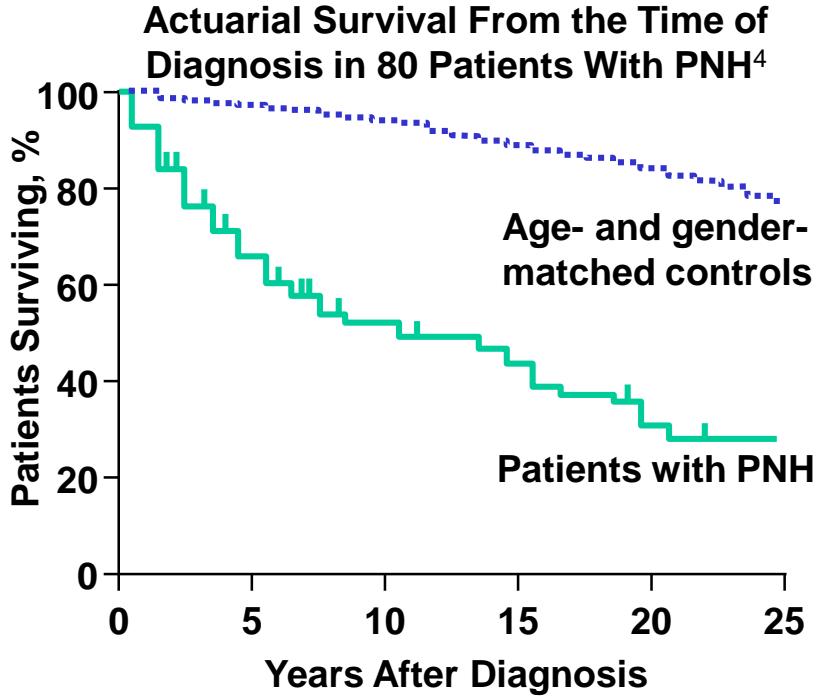


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3. PNH und Eculizumab „erklären“ Komplement
4. Ausblick

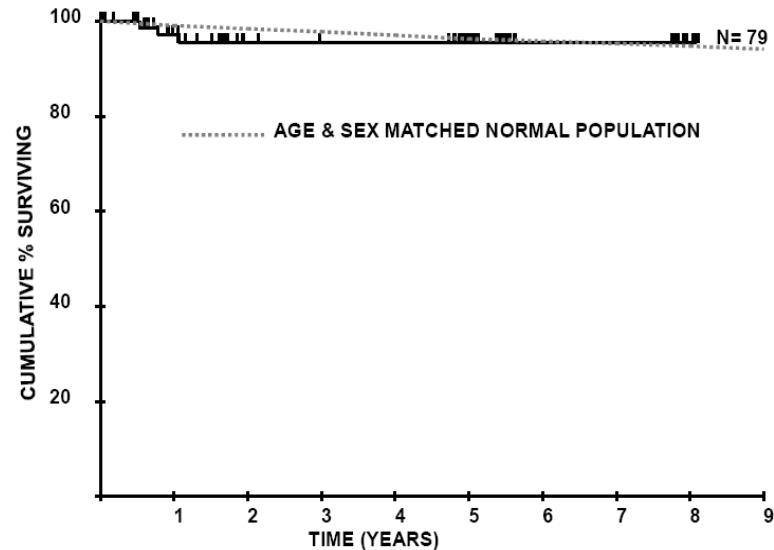
Eculizumab – eine Erfolgsgeschichte

> PNH: erste Indikation von Eculizumab („*first-in-class*“
Komplement Inhibitor in der Klinik)



1. Hill A, et al. *Blood*. 2006;108(11): 290a.
2. Nishimura JI et al. *Medicine*. 2004;83:193-207.
3. Socié G, et al. *Lancet*. 1996;348(9027):573-577.
4. Hillmen P, et al. *N Engl J Med*. 1995;333(19):1253-1258.

Eculizumab behandelte PNH Patienten versus normal Population:



Kelly RJ, Hill A, Arnold LM, Brooksbank GL, Richards SJ, Cullen M, Mitchell LD, Cohen DR, Gregory WM, Hillmen P. *Blood*. 2011;117:6786-92.

Andere Komplementinhibitoren in der Pipeline

stoichiometric

Table 2 | Complement therapeutics in clinical trials

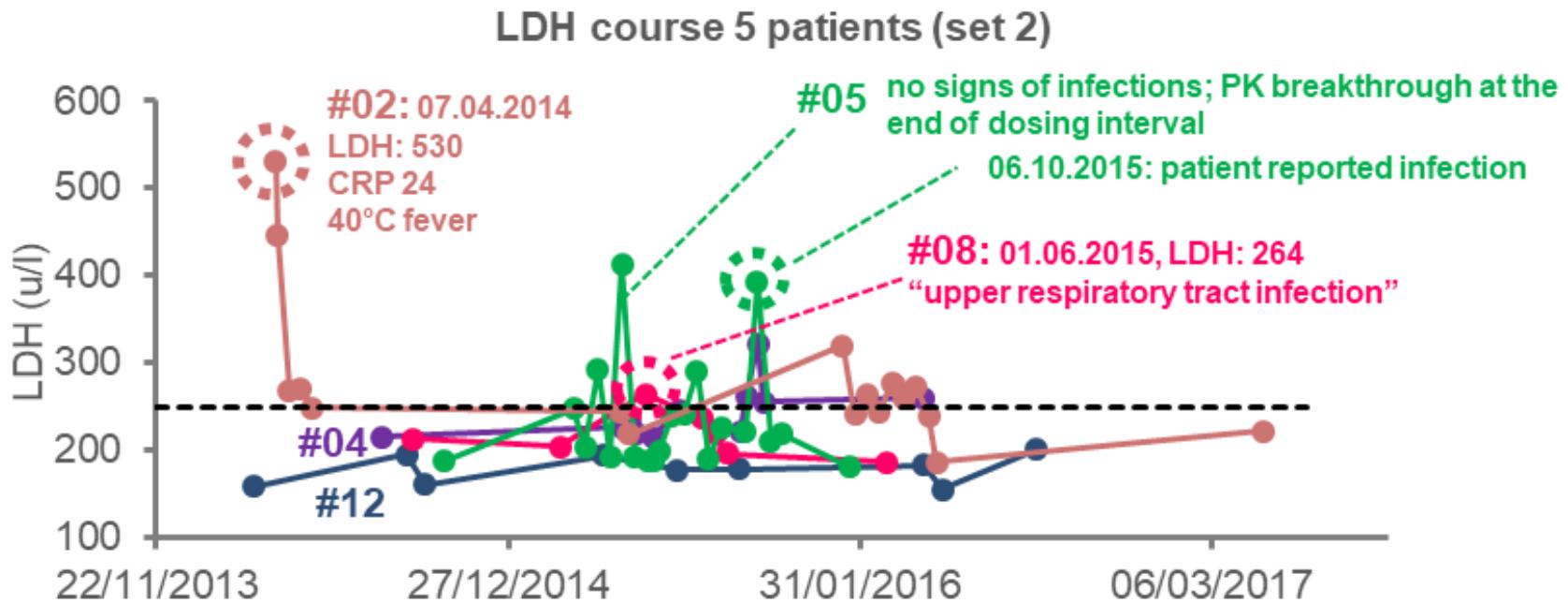
Target	Drug candidate (Company)	Entity	Clinical trial(s)		Indication(s)
			Phase	Trial number	
C1s	BIVV009 (Bioverativ)	Antibody	I	NCT02502903	Cold agglutinin disease
MASP2	OMS721 (Omeros)	Antibody	II	NCT02222545	Thrombotic microangiopathies
				NCT02682407	IgA nephropathy, LN, MN, C3G
			III	NCT03205995	aHUS
Properdin	CLG561 (Novartis)	Antibody	II	NCT02515942*	AMD and/or GA
C3	AMY-101 (Amyndas)	Peptide	I	NCT03316521	C3G
			II	NA	C3G, PNH, ABOi kidney transplantation, periodontitis
	APL-1 (Apellis)	Peptide	I	NA	COPD
			I	NCT02588833	PNH
	APL-2 (Apellis)			NCT02264639	PNH (add-on therapy)
				NCT02461771‡	AMD (CNV)
			II	NCT02503332	AMD and/or GA
				NCT03226678	wAIHA, CAD
			I	ACTRN12616000862448	PNH
FB	IONIS-FB-LRx (Ionis, GSK)	Oligonucleotide	I	2015-001837-25	AMD and/or GA
FD	Lampalizumab (Genentech)	Antibody	II	NCT02288559	AMD and/or GA
				NCT02745119	AMD and/or GA
				NCT02247531	AMD and/or GA
				NCT02247479	AMD and/or GA
			II	NCT03053102	PNH
Convertases	Mirococept (MRC)	Protein	III	ISRCTN49958194	Transplantation

Andere Komplementinhibitoren in der Pipeline

stoichiometric

Target	Drug candidate (Company)	Entity	Clinical trial(s)		Indication(s)
			Phase	Trial number	
C5a	ALXN1007 (Alexion)	Antibody	II	NCT02245412 ^{ll}	GVHD
				NCT02128269 ^{ll}	APS
	IFX-1 (InflaRx)	Antibody	II	NCT02246595 [‡]	Sepsis
				NCT02866825 [‡]	SIRS, complex cardiac surgery
				NCT03001622	Hidradenitis suppurativa
C5aR1	Avacopan; also known as CCX168 (ChemoCentryx)	Small molecule	II	NCT02464891 ^{ll}	aHUS
				NCT02384317 [‡]	IgA nephropathy
			III	NCT02994927	AAV
C5	Ravulizumab; also known as ALXN1210 (Alexion)	Antibody	I/II	NCT02598583	PNH
			II	NCT02605993	PNH
			III	NCT02946463	PNH (naive)
				NCT03056040	PNH (treated)
				NCT02949128	aHUS (naive)
	Tesidolumab; also known as LFG316 (Novartis and MorphoSys)	Antibody	I	NCT02878616 [‡]	Transplantation
			II	NCT02763644	Transplant-associated microangiopathy
				NCT01527500 [‡]	AMD and/or GA
				NCT02515942*	AMD
				NCT02534909	PNH
				NCT01526889	Uveitis and/or panuveitis
C5	SKY59; also known as RG6107 and RO7112689 (Chugai and Roche)	Antibody	I/II	NCT03157635	PNH
	REGN3918 (Regeneron)	Antibody	I	NCT03115996	PNH
	ABP959 (Amgen)	Antibody [§]	I	ACTRN12616000509460	PNH, aHUS
	GNR-045 (Generium)	Antibody [§]	I	ECU-PNH-I	PNH
	Coversin (Akari)	Protein	II	NCT02591862	PNH
	RA101495 (Ra Pharma)	Peptide	II	NCT03030183	PNH (poor responders)
				NCT03078582	PNH
	Zimura (Ophthotech)	Oligonucleotide	II	NCT02397954 [‡]	IPCV
			II/III	NCT02686658	AMD
	Cemdisiran (Alnylam)	Oligonucleotide	I/II	NCT02352493	PNH
			II	NA	aHUS

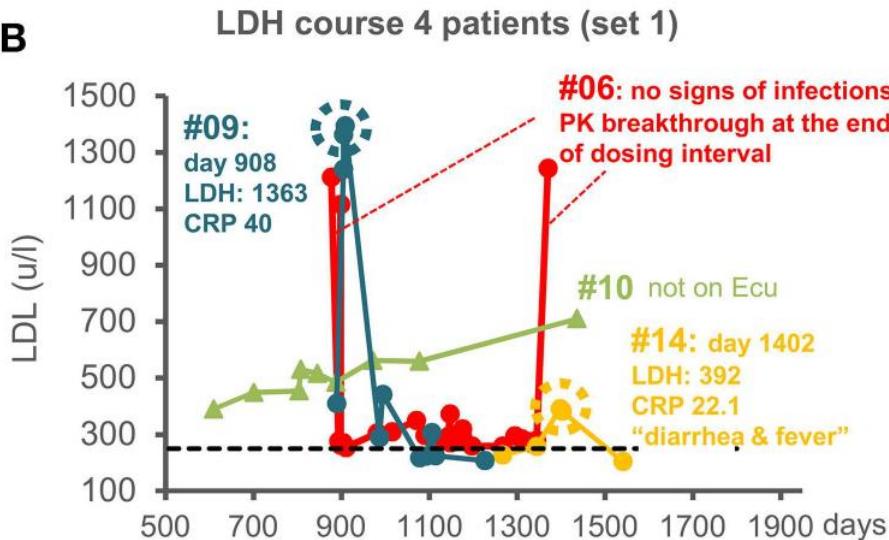
C5-Lyseaktivität trotz Eculizumab?



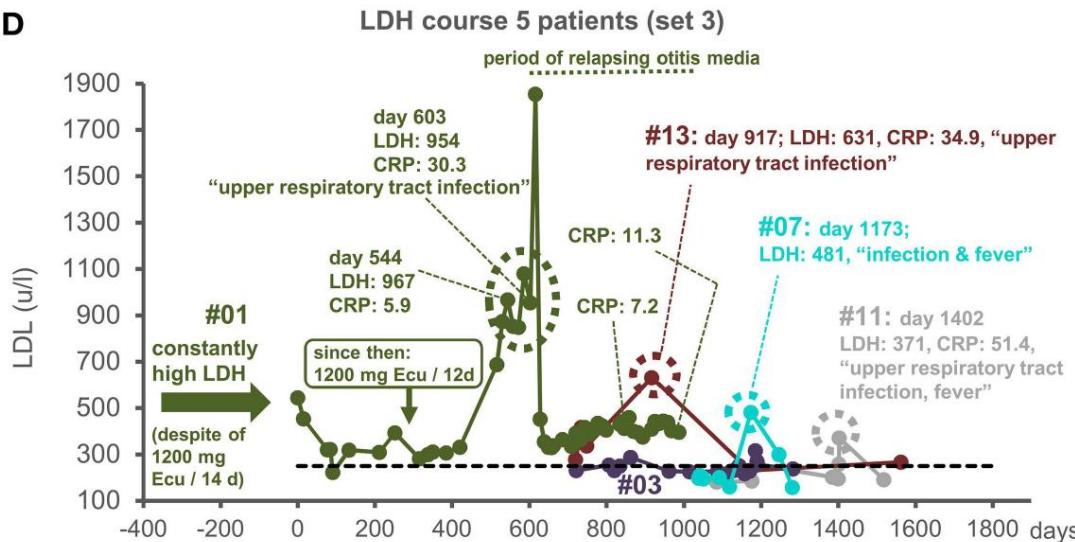
> Die verbleibende Komplement-C5-Aktivität verschlimmert sich während Infektionen und führt bei Eculizumab behandelten PNH-Patienten zu einer Durchbruchshämolyse

C5-Lyseaktivität trotz Eculizumab?

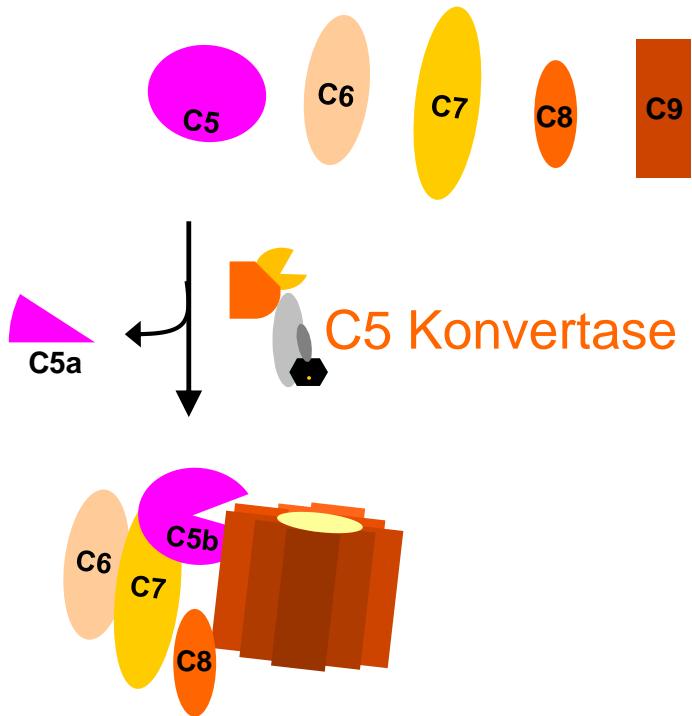
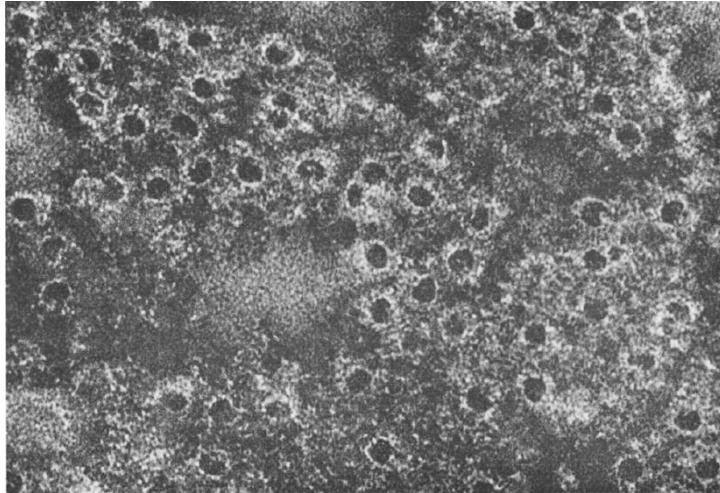
B



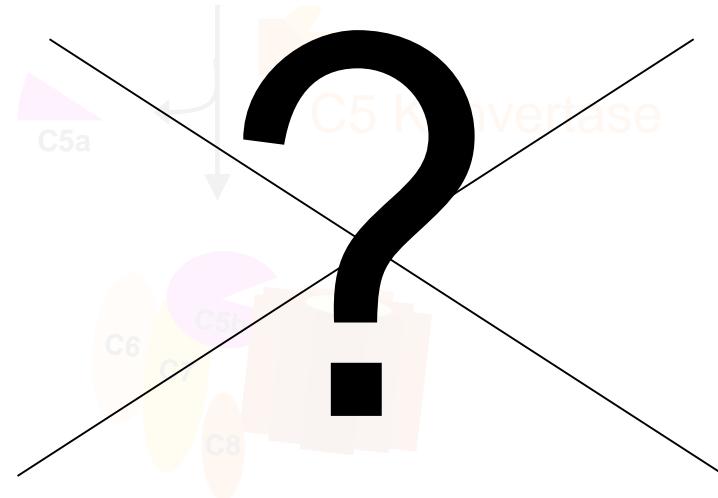
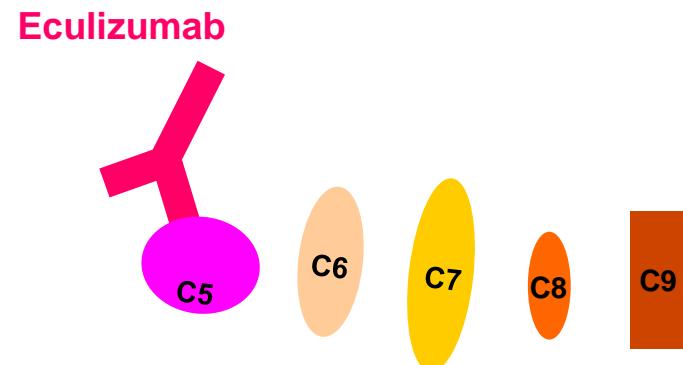
D



MAC: Membran-Angriffs-Complex



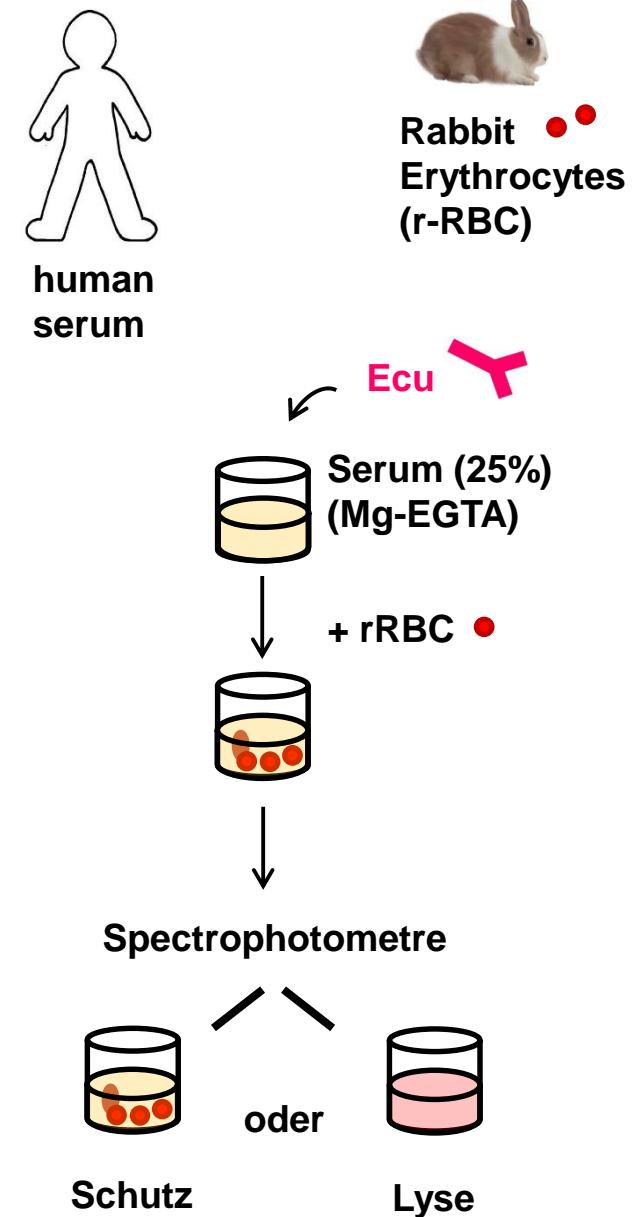
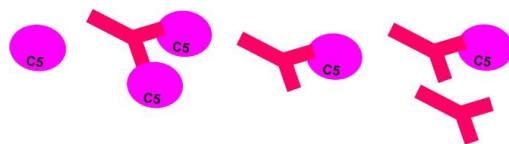
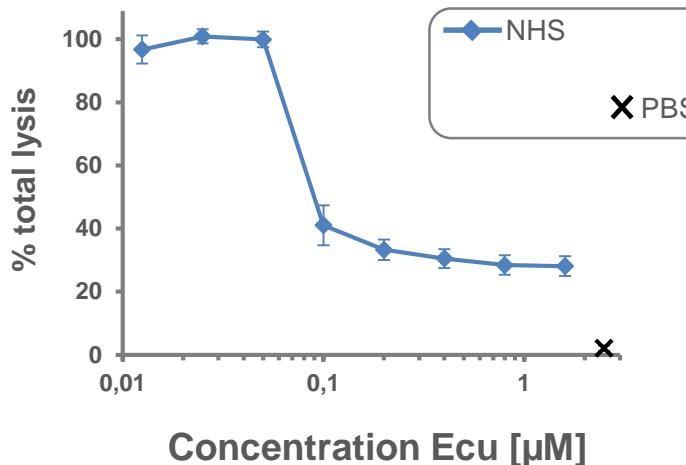
Therapeutische C5 Inhibition



Outline

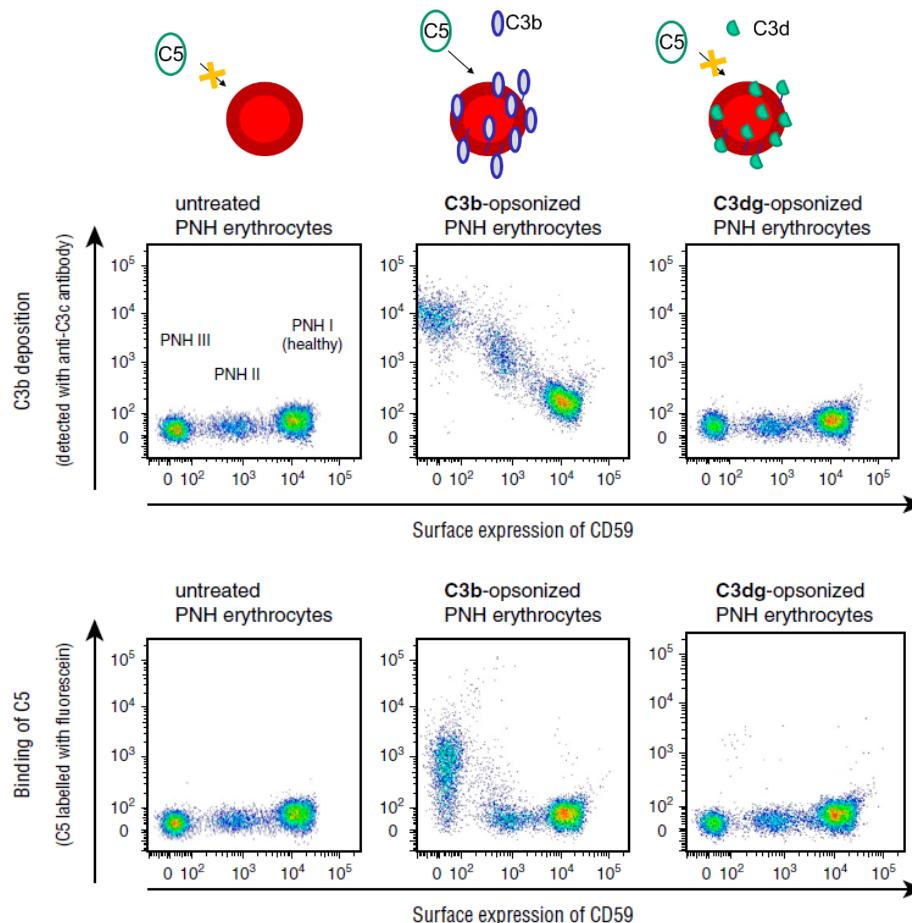
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AP r-RBC Assay mit Serum von Gesunden

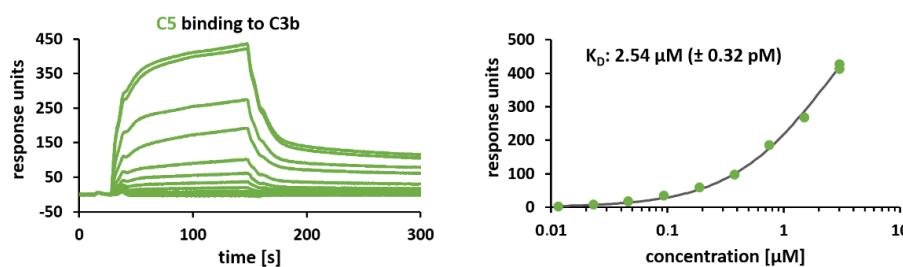


Einsichten in die Funktionsweise der C5 Konvertase

on cell surfaces:

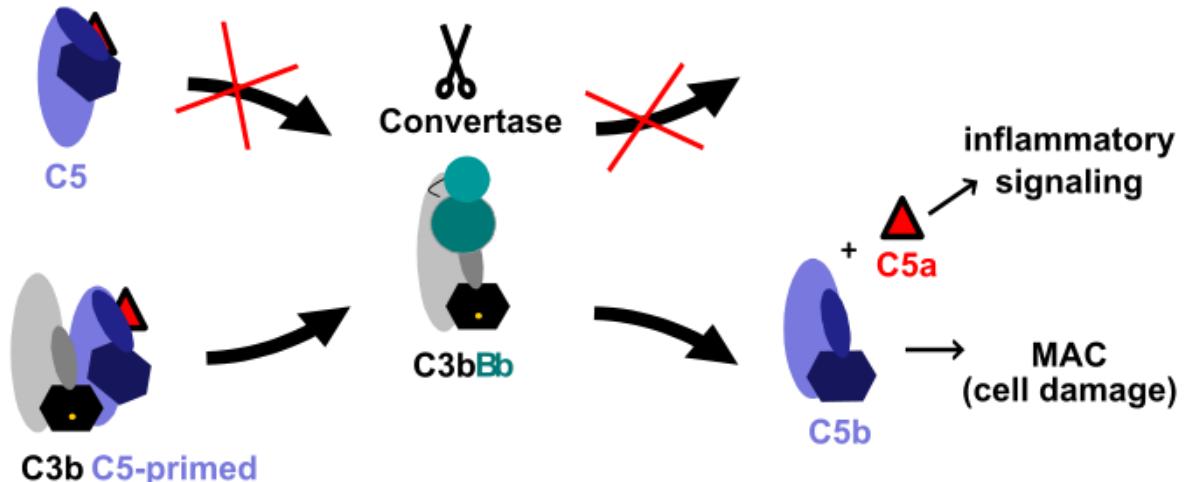


on purified proteins:

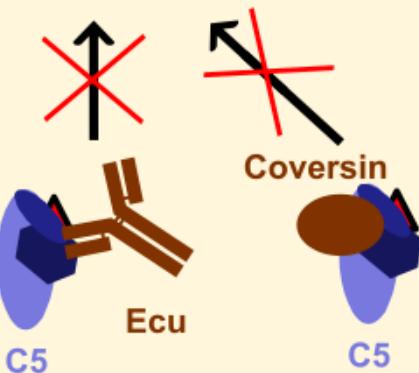
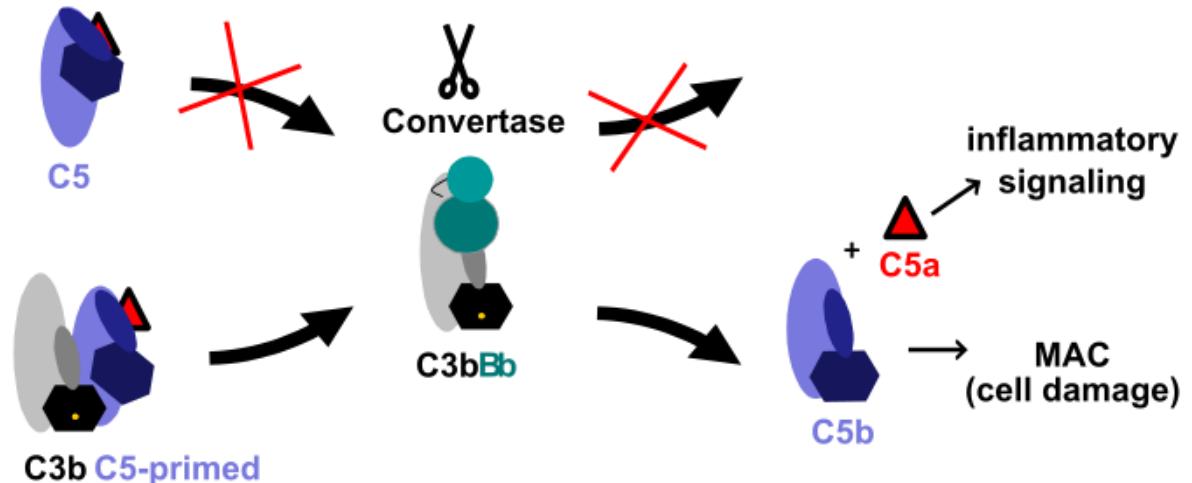


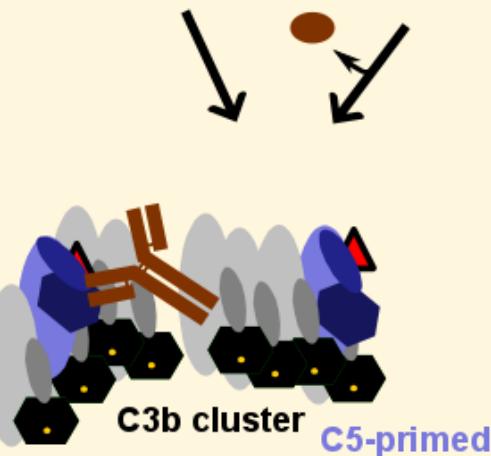
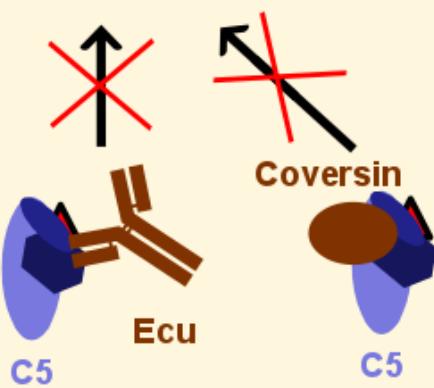
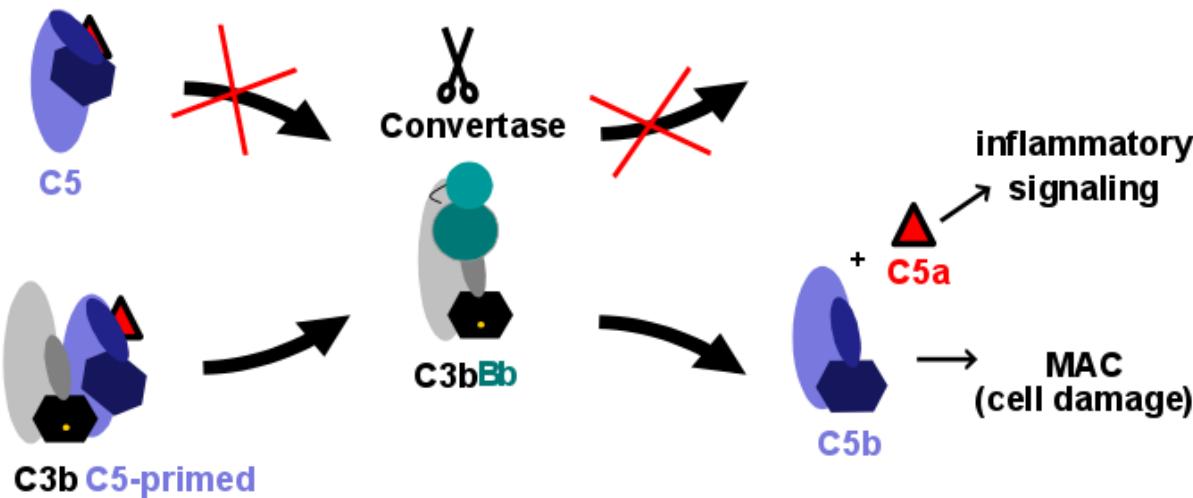
Harder MJ et al Blood (2017) 129:970-980

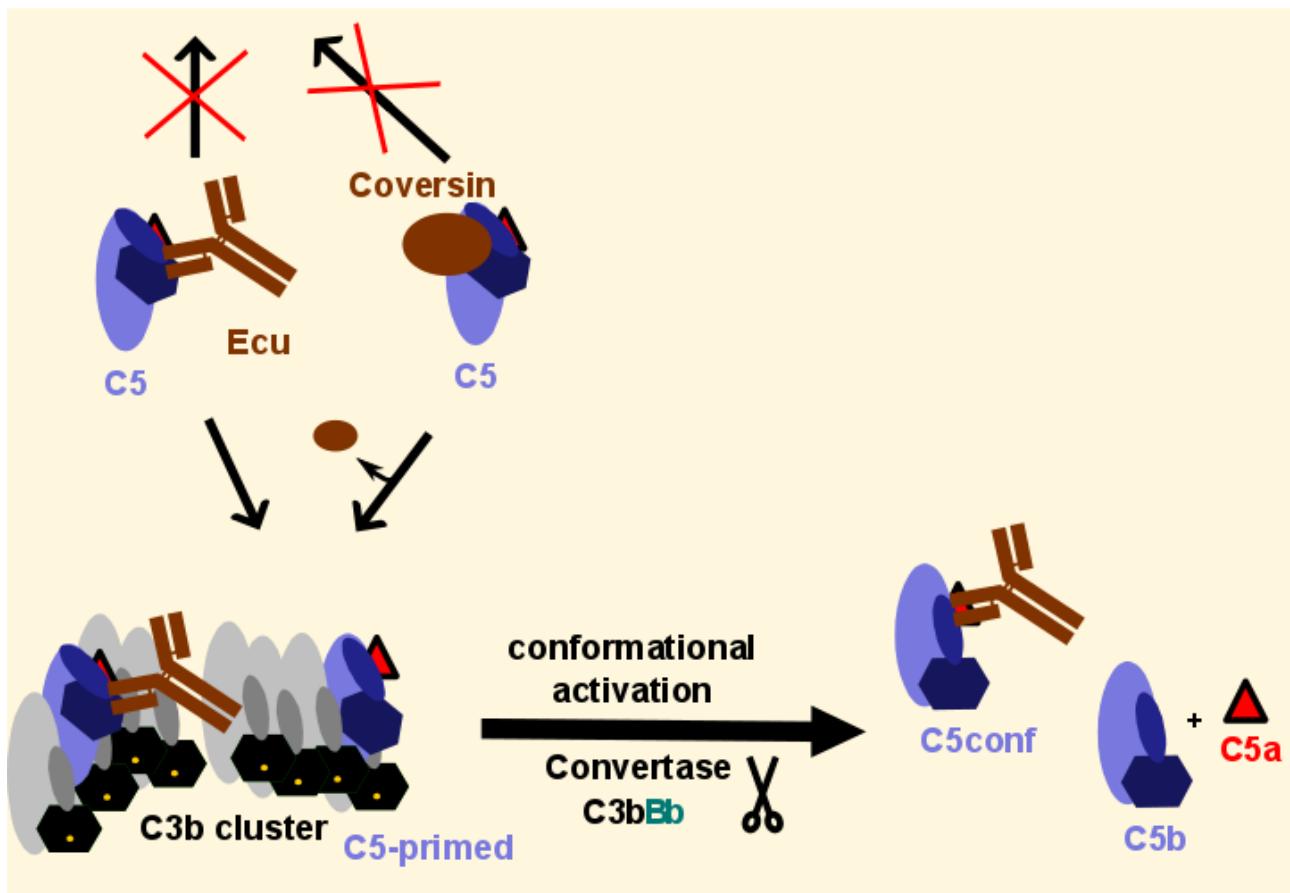
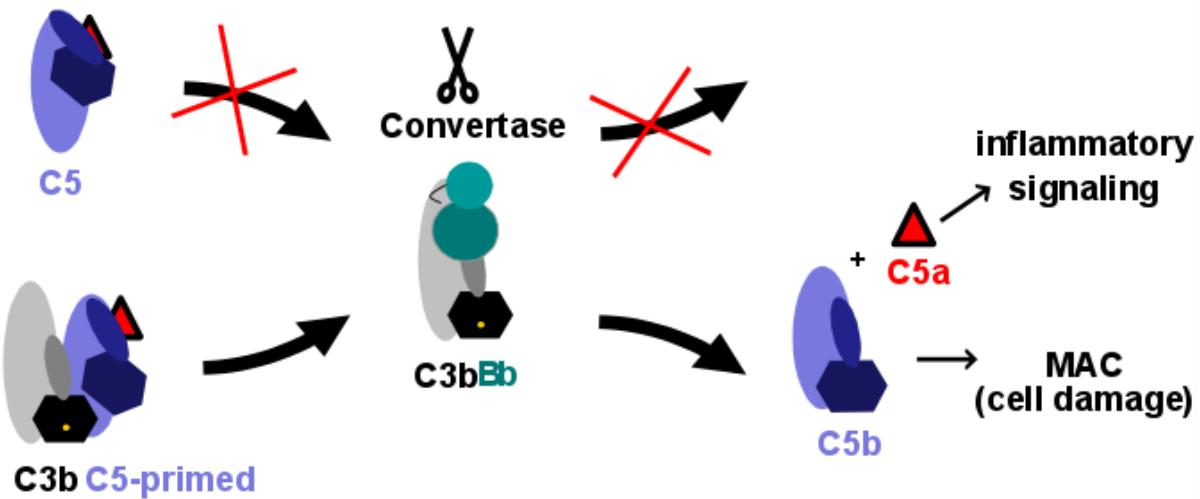
Mannes M et al Blood (2021) 137:443-455



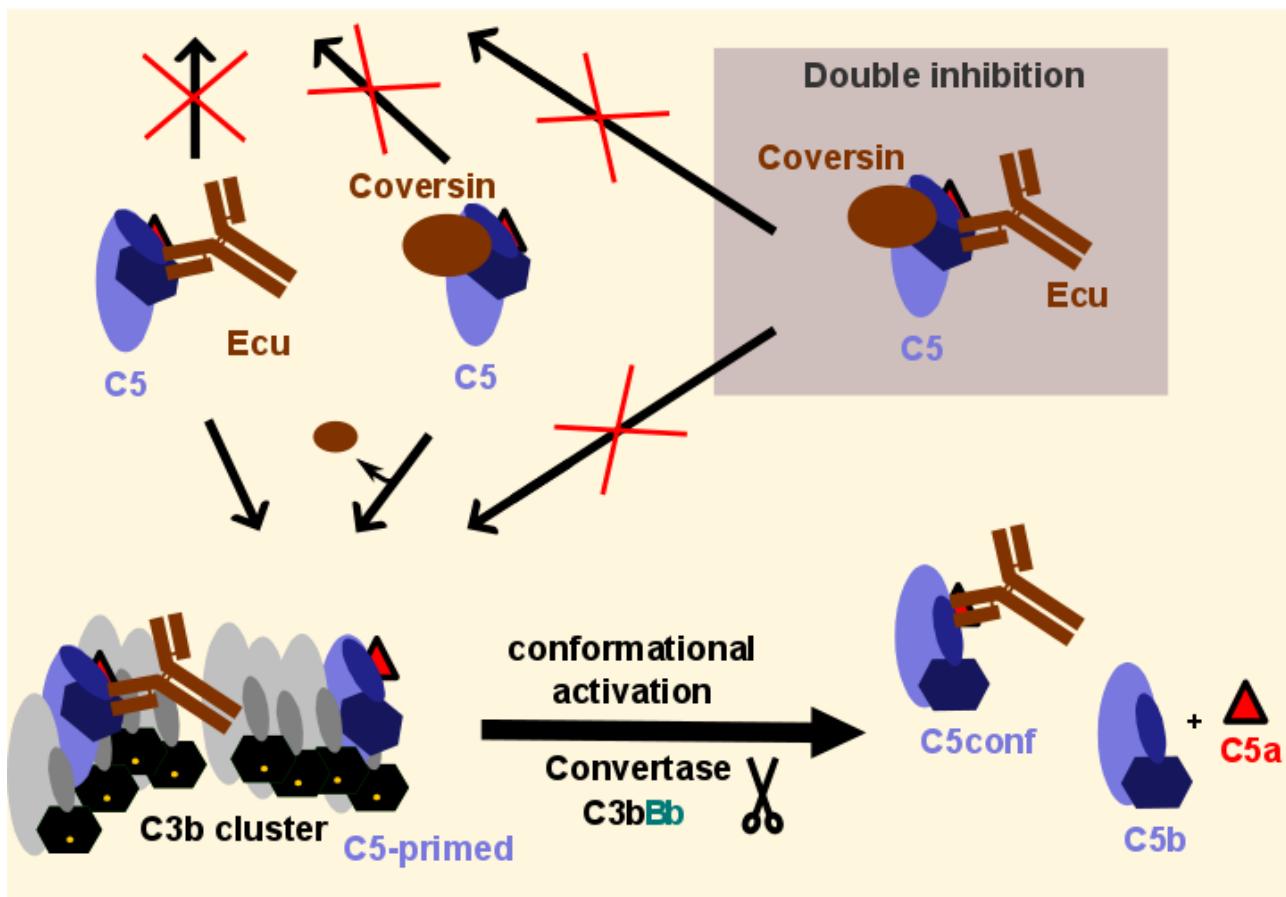
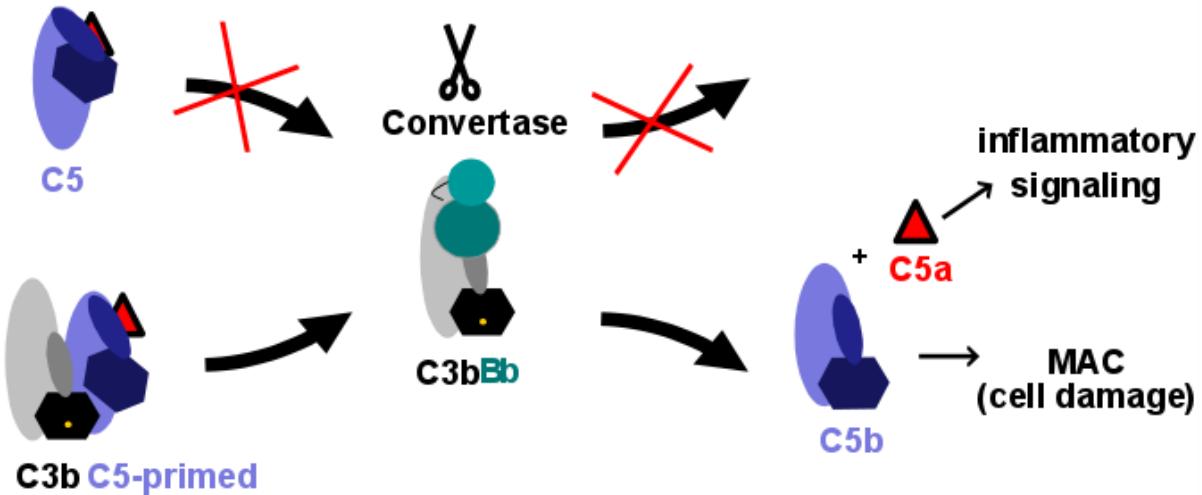
trimolecular
C5 Convertase





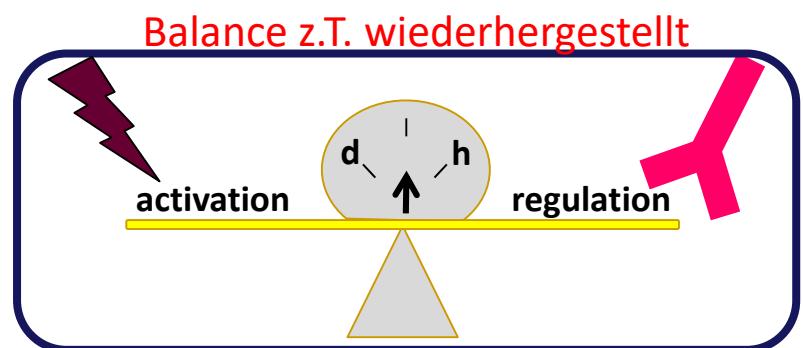
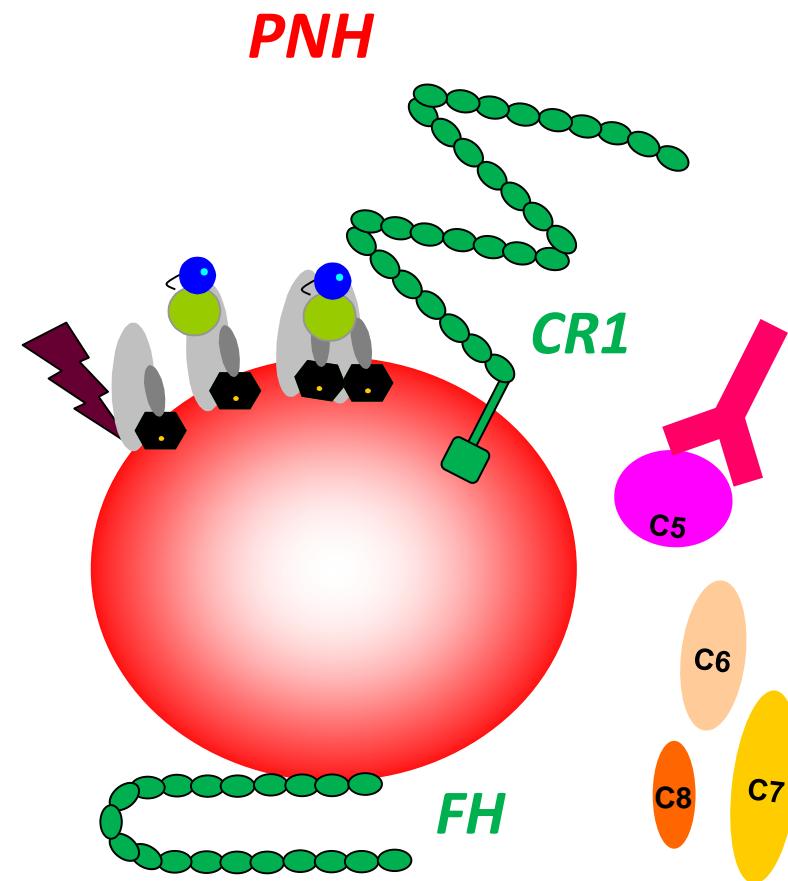
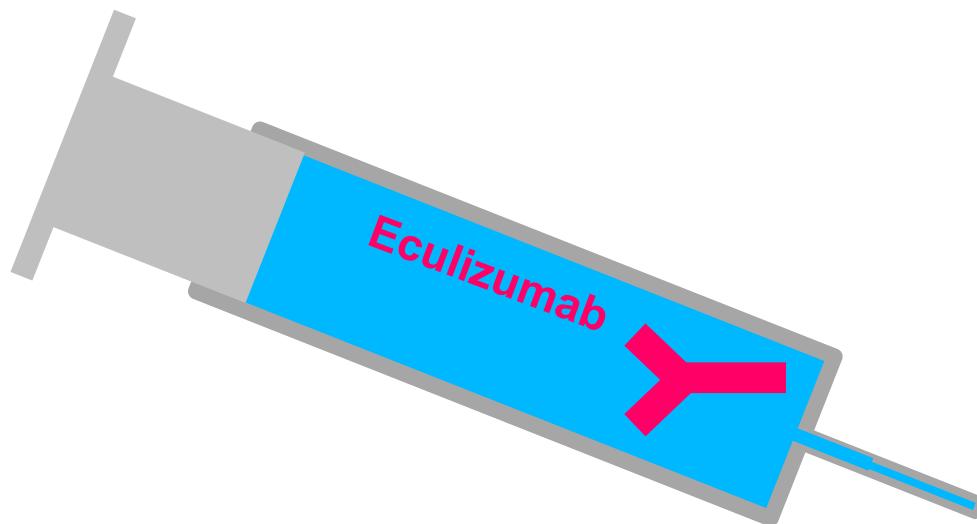


Harder MJ et al Blood (2017) 129:970-980
Mannes M et al Blood (2021) 137:443-455

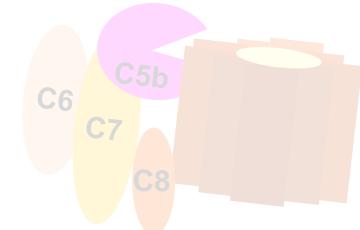
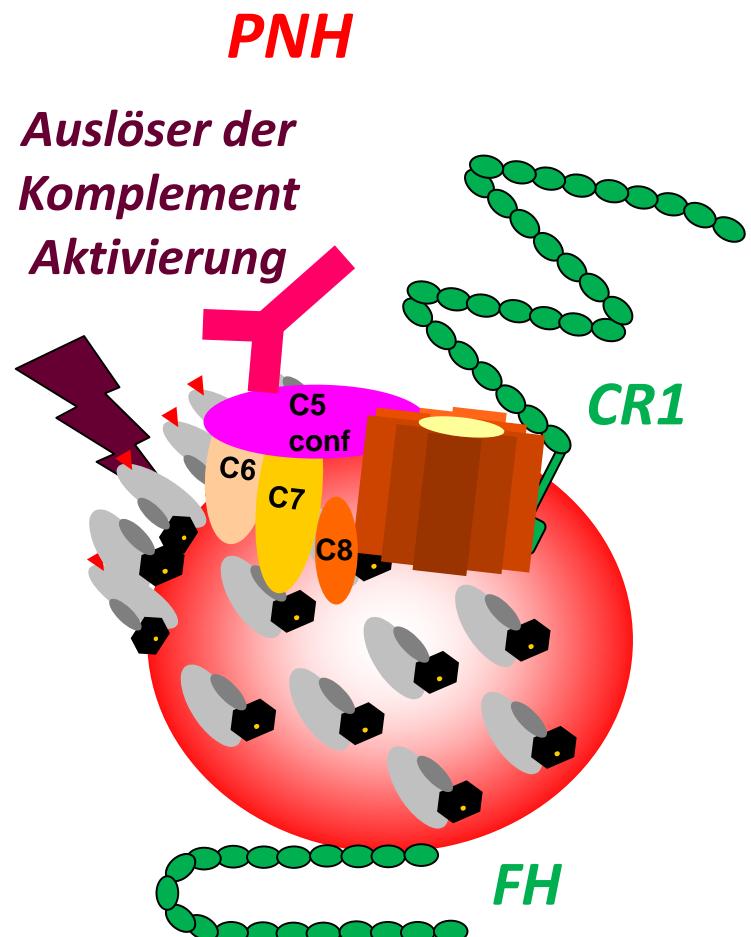
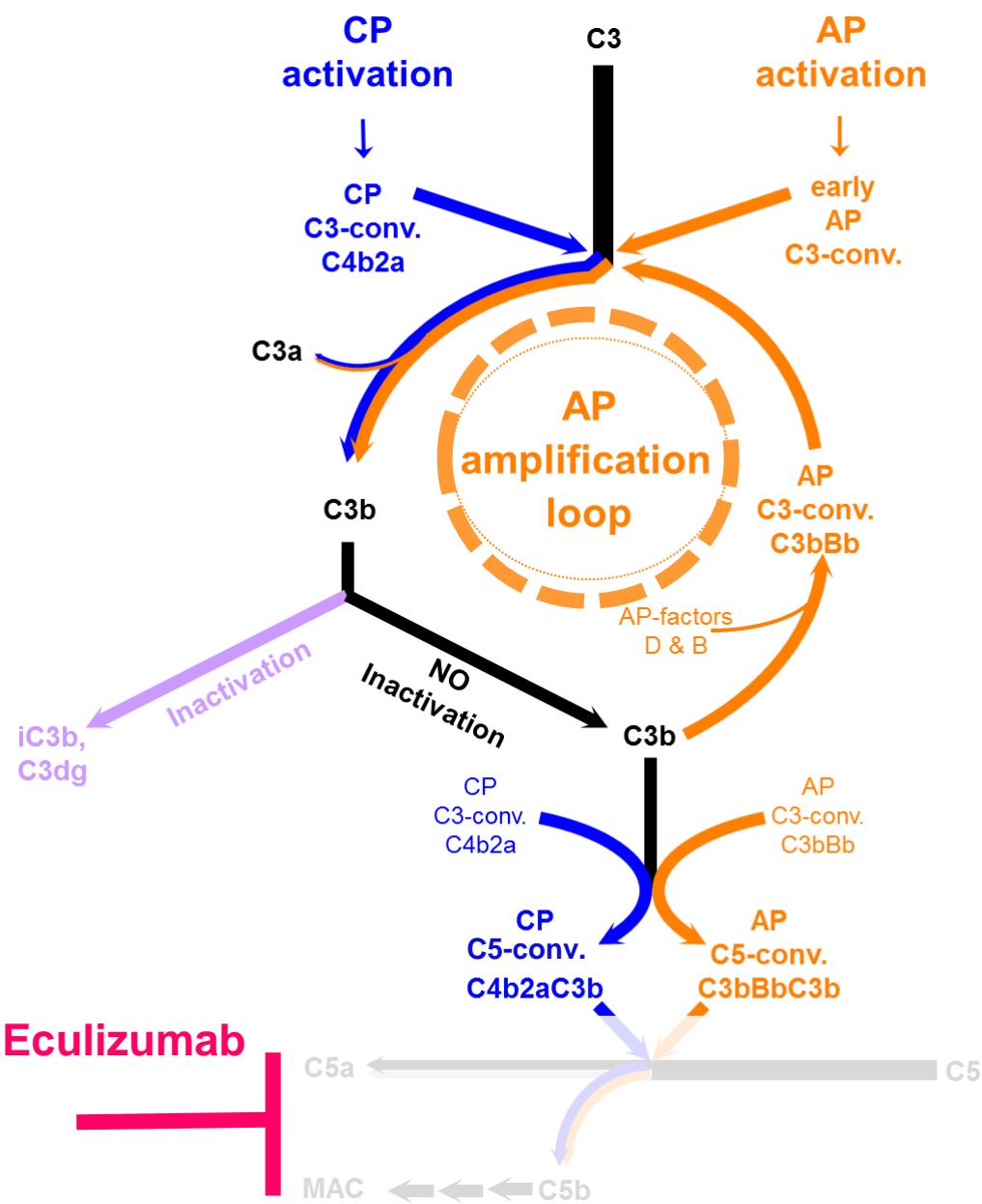


Harder MJ et al Blood (2017) 129:970-980
Mannes M et al Blood (2021) 137:443-455

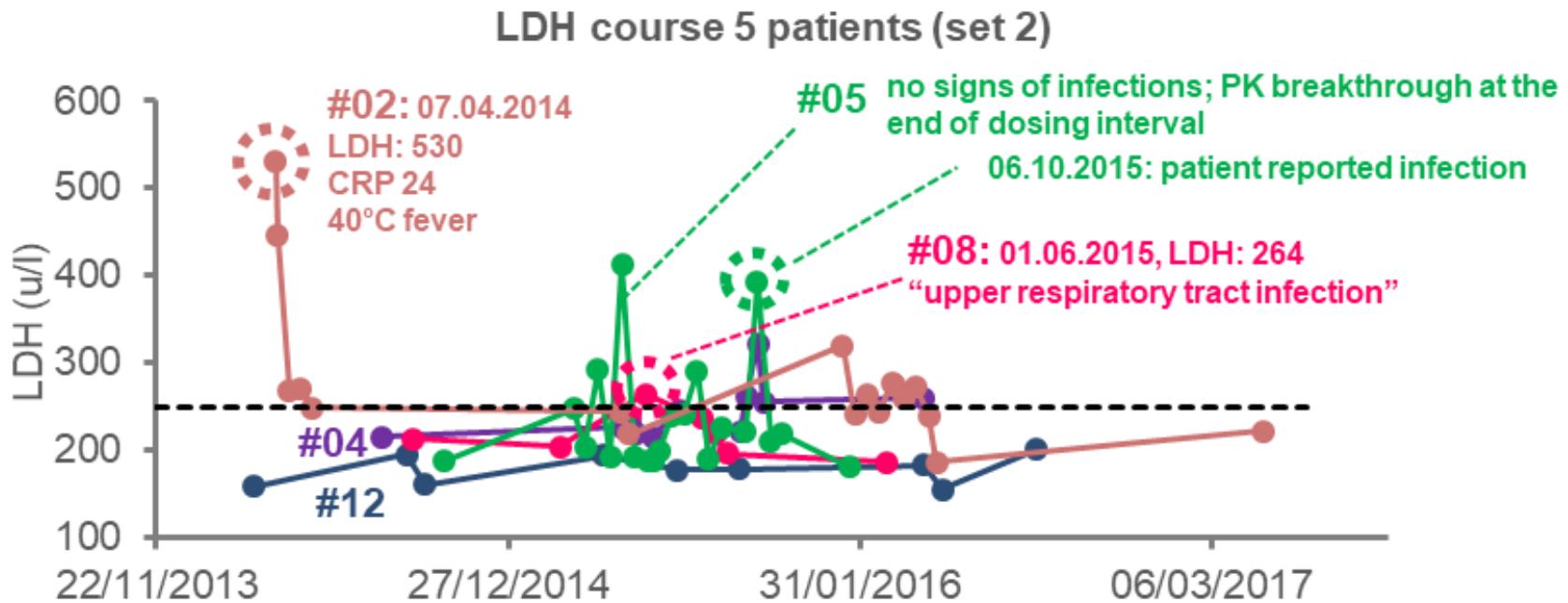
Eculizumab verhindert intravaskuläre Hämolyse



Eculizumab: Proximale Kaskade immer noch aktiv



C5-Lyseaktivität trotz Eculizumab?

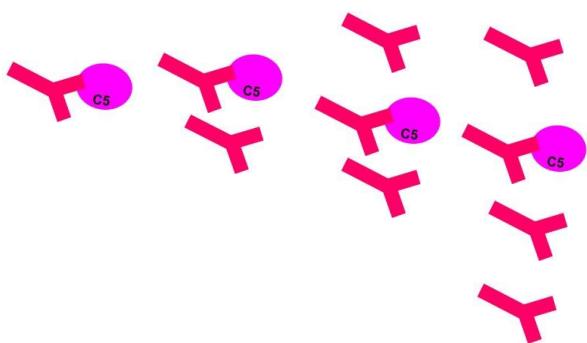
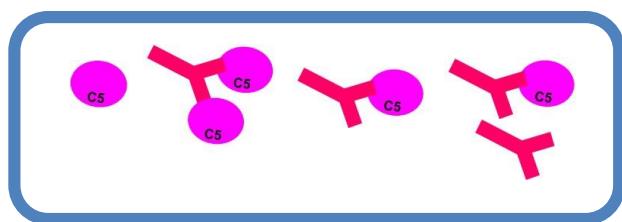
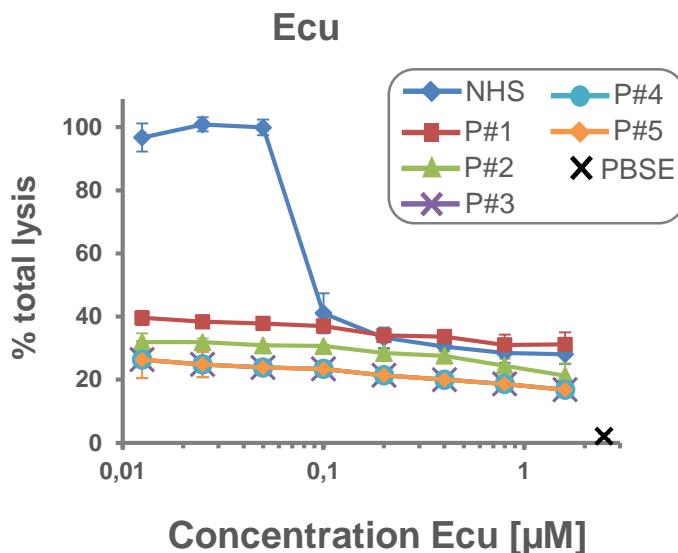


> Die verbleibende Komplement-C5-Aktivität verschlimmert sich während Infektionen und führt bei Eculizumab behandelten PNH-Patienten zu einer Durchbruchshämolyse

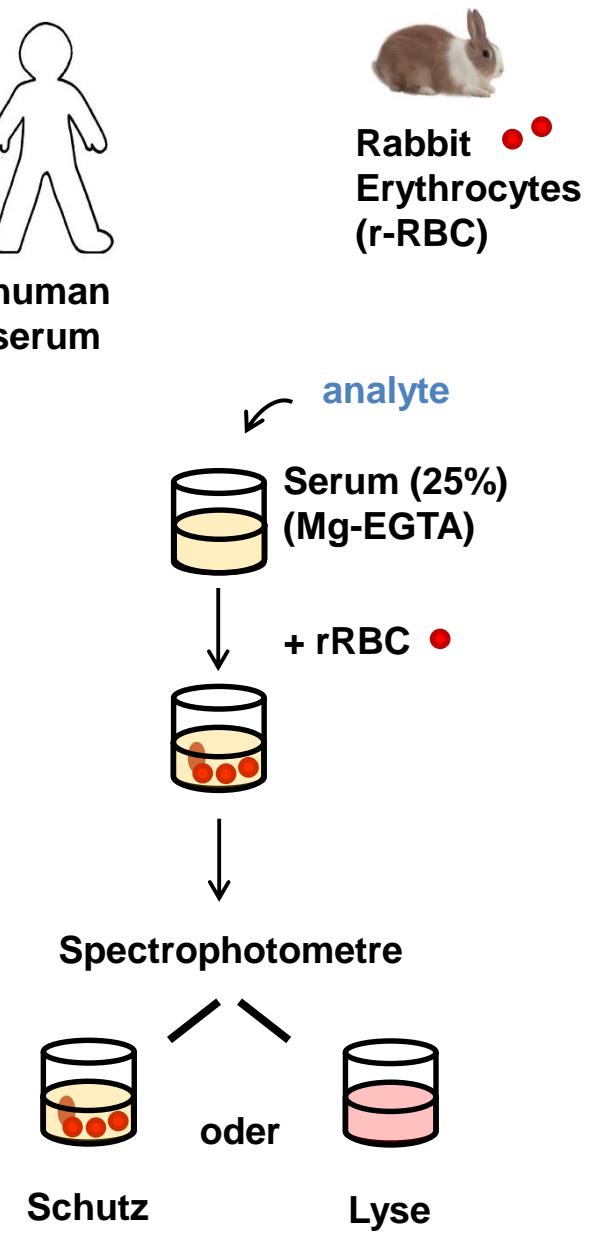
Outline

1. Komplement und PNH
2. Klinische Entwicklung – ein kurzer Überblick
3. PNH und Eculizumab „erklären“ Komplement
4. Ausblick

AP r-RBC Assay mit Serum von PNH-Patienten mit Ecu

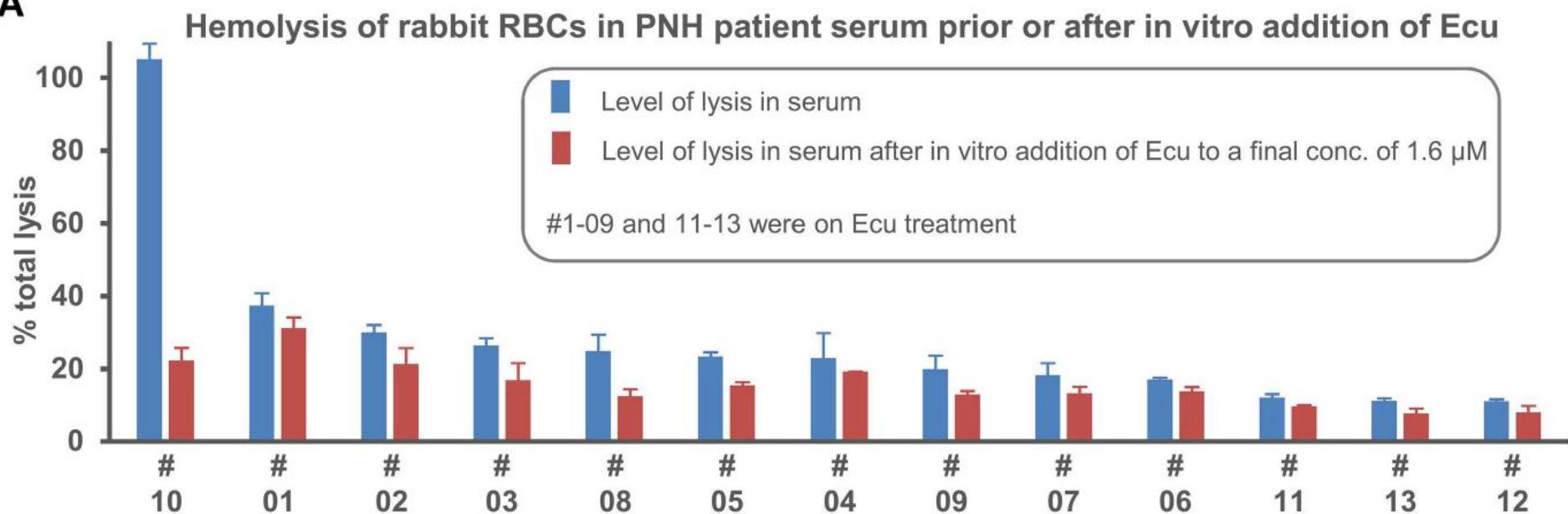


Rabbit
Erythrocytes
(r-RBC)



AP r-RBC Assay mit Serum von PNH-Patienten mit Ecu

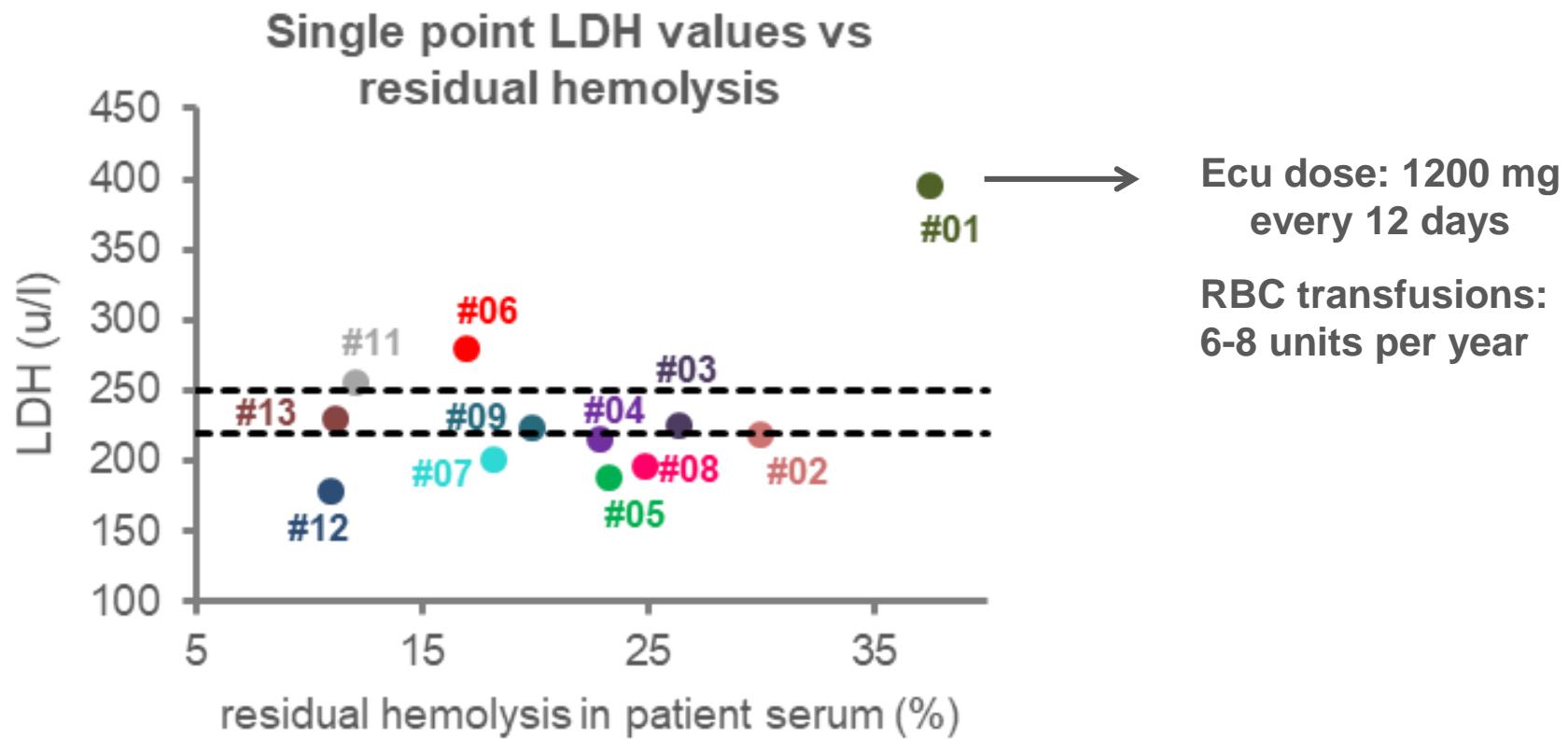
A



- unterschiedliche residuale C5 Aktivitäten im Serum von PNH Patienten unter Eculizumab-Therapie

unpublished

AP r-RBC Assay mit Serum von PNH-Patienten mit Ecu

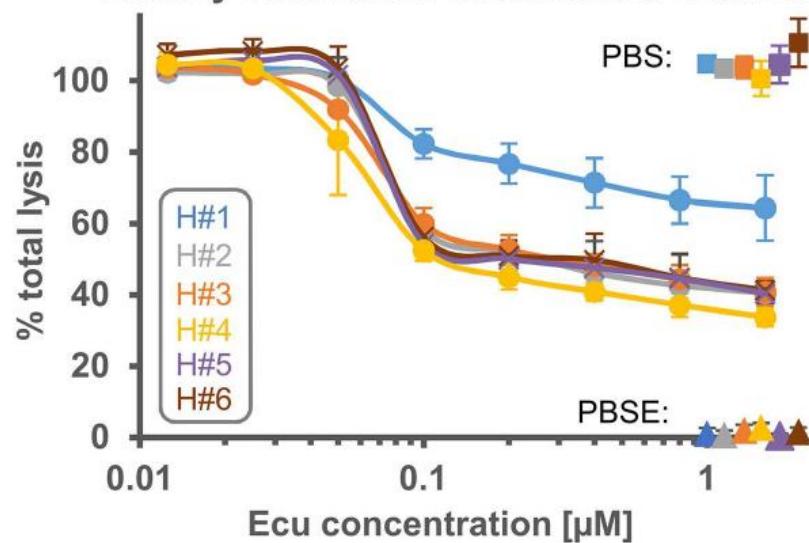


> Leidet Patient #01 (und andere) immer noch an einer geringen aber merkbaren intravaskulären Resthämolyse?

AP r-RBC Assay mit Serum von PNH-Patienten mit Ecu

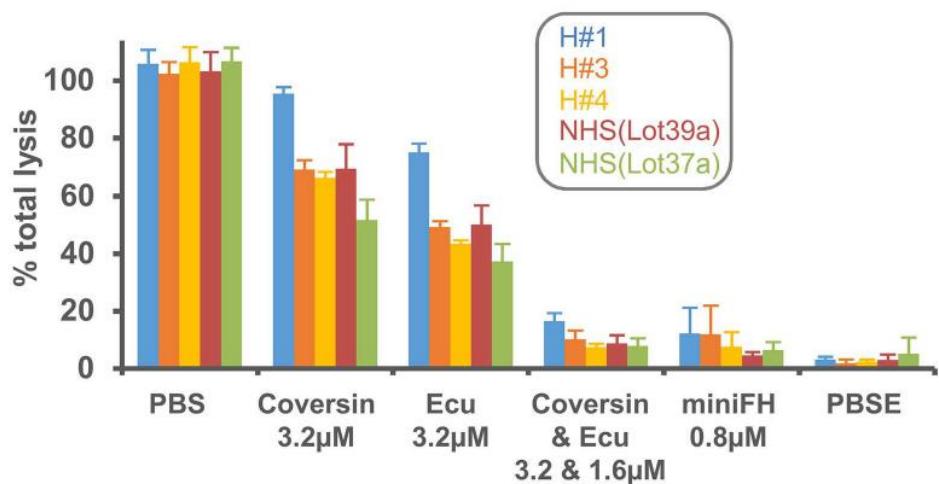
B

Hemolysis of rabbit RBCs in serum of 6 healthy volunteers substituted with Ecu



C

Hemolysis of rabbit RBCs in different sera from volunteers in presence of various inhibitors



> Phänomen sowohl in Patienten als auch Patienten bestätigt

>> klinische Relevanz?

- unterschiedliche residuale C5 Aktivitäten im Serum von gesunden Spendern

**Danke für Ihre
Aufmerksamkeit!**

