



Nabespreking rondzending Complement



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Sanquin Diagnostiek B.V.

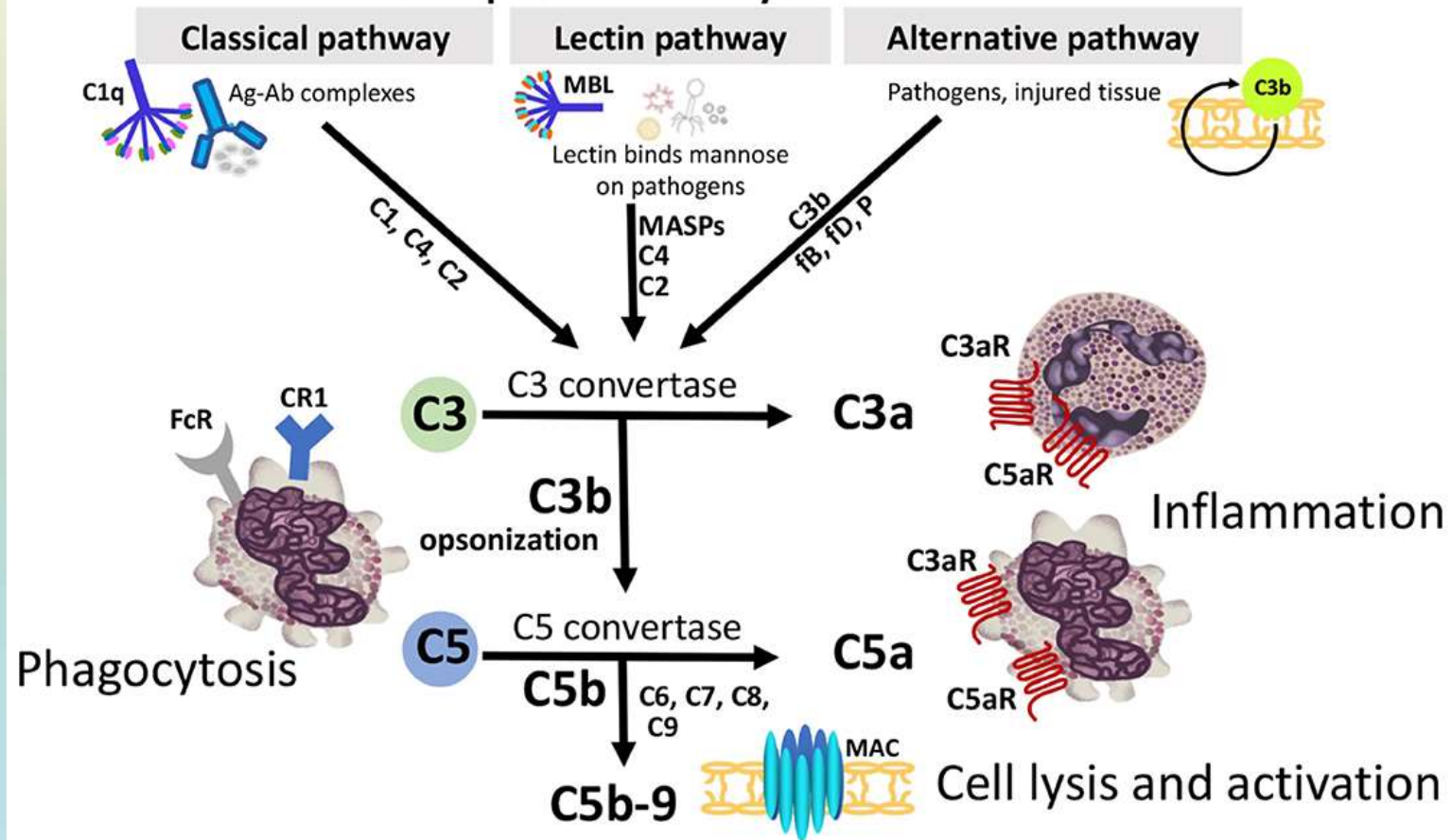


Complement

Hoe zat het ook alweer?



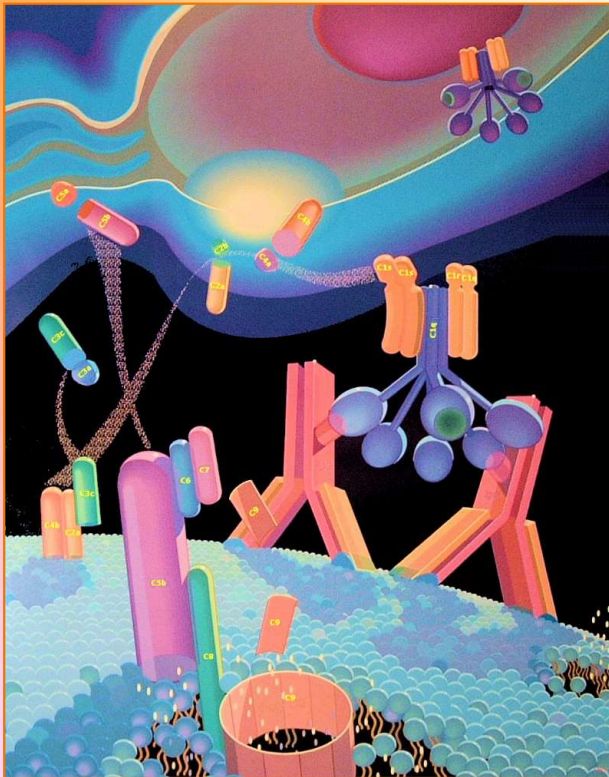
Complement system





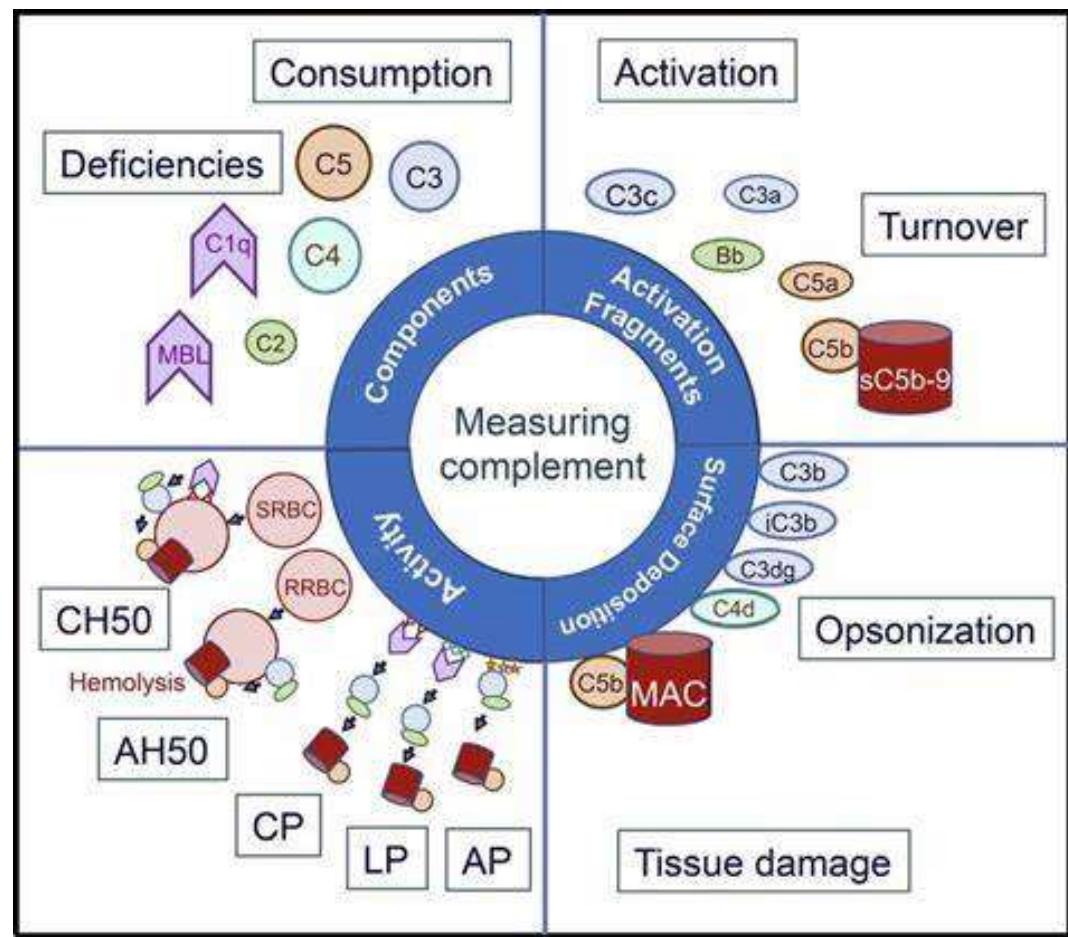
Wanneer complement diagnostiek?

- 1) Aangeboren/verkrege*n* deficiënties
- 2) Afwijkingen met complement activatie
- 3) Monitoring van therapie





Meten van complement



Rond- zending *2023*



- 6 samples (A-F)
- 4 verse monsters van gezonde donoren met verschillende vormen/concentraties van MBL
- Eén complement deficiëntie uit -80°C
- Een (SLE?) pool met verlaagd C3



Complement deficiencies

Klassieke route

Alternatieve route

Terminale route

Alternatieve route

Regulatoren

Complement protein	Effects of deficiency
C1, C2, C4	Immune-complex disease
C3	Susceptibility to capsulated bacteria
C5–C9	Only effect is susceptibility to <i>Neisseria</i>
Factor D, properdin (factor P)	Susceptibility to capsulated bacteria and <i>Neisseria</i> but no immune-complex disease
Factor I	Similar effects to deficiency of C3
DAF, CD59	Autoimmune-like conditions including paroxysmal nocturnal hemoglobinuria

AIZ

infecties

AIZ

Figure 9-9 The Immune System, 2/e (© Garland Science 2005)



Terminale route activatie

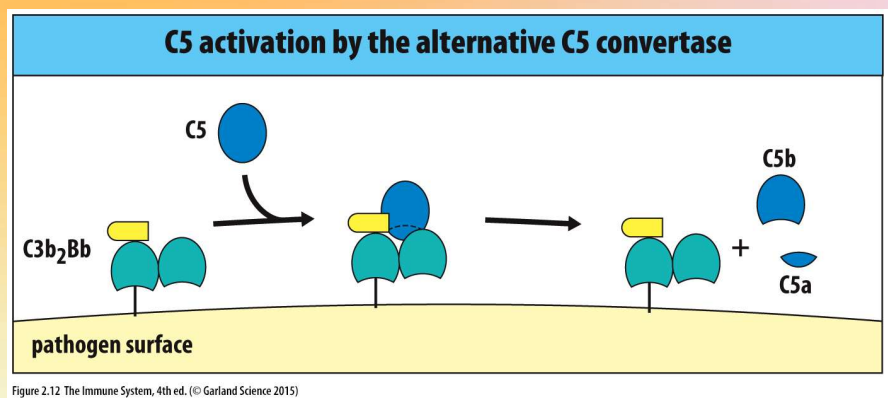


Figure 2.12 The Immune System, 4th ed. (© Garland Science 2015)

MAC
Membrane attack complex

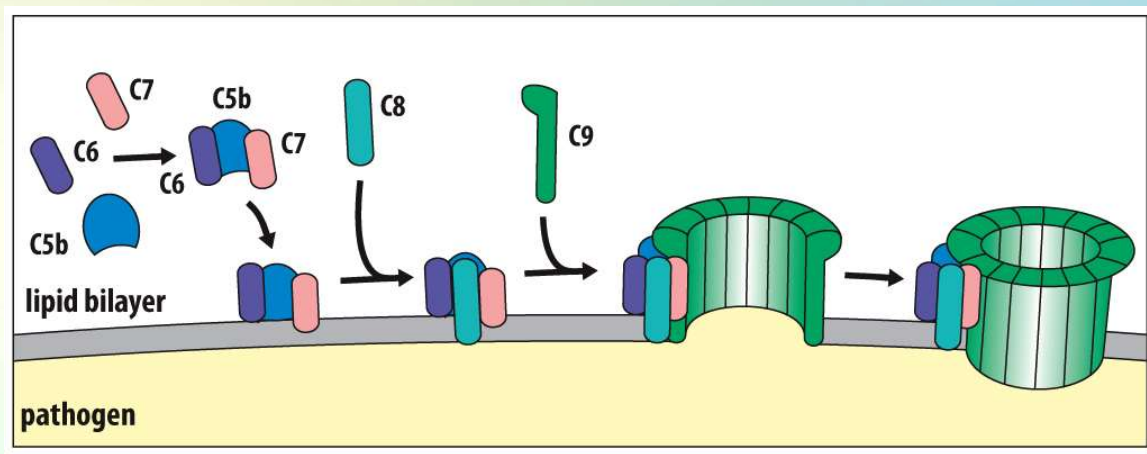
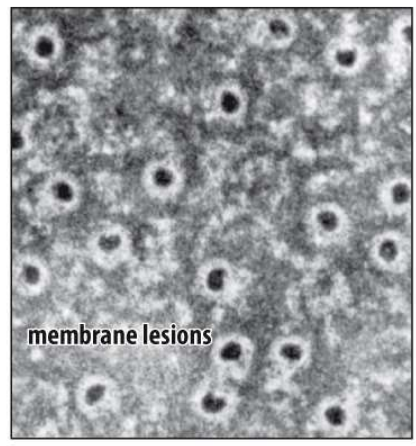


Figure 2.13 The Immune System, 4th ed. (© Garland Science 2015)

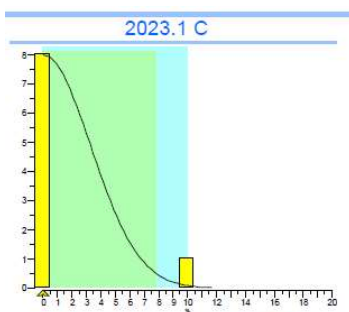




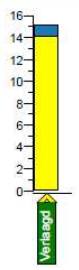
C6 deficiëntie

Sample C

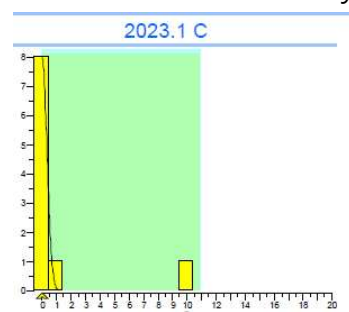
Classical Pathway (CP)



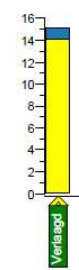
	cons.	meth.	ALTM	lab
gem.	0.0	0.0	0.0	0
SD	3.3	3.3	3.3	
n	9	9	9	
nu	0	0	0	
rec.				



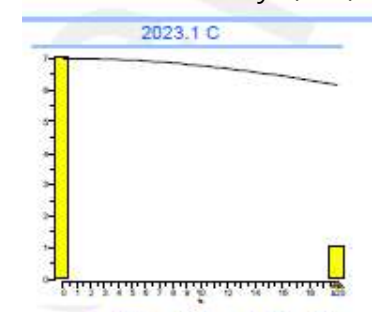
Alternative Pathway (AP)



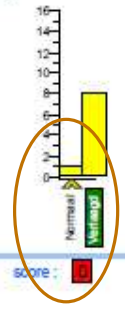
	cons.	meth.	ALTM	lab
gem.	0.0	0.0	0.0	0
SD	0.3	0.3	0.3	
n	10	10	10	
nu	1	1	1	
rec.				



Lectin Pathway (CP)



	cons.	meth.	ALTM	lab
gem.	0.00	0.00	0.00	111
SD	39.24	39.24	39.24	
n	8	8	8	
nu	0	0	0	
rec.				



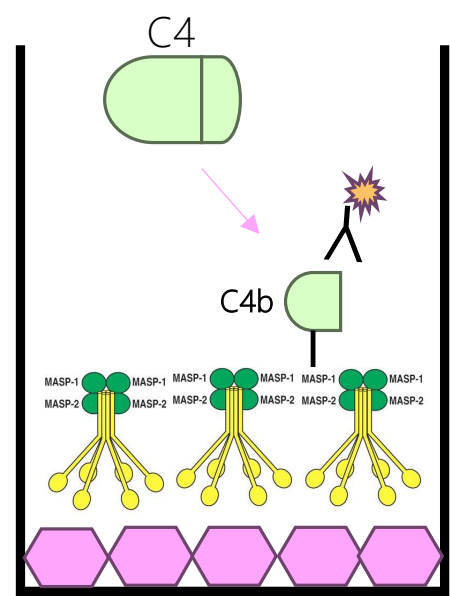
score: 1



LPact @ SQ

C4-depositie

LP activation ELISA
up to C4 dep

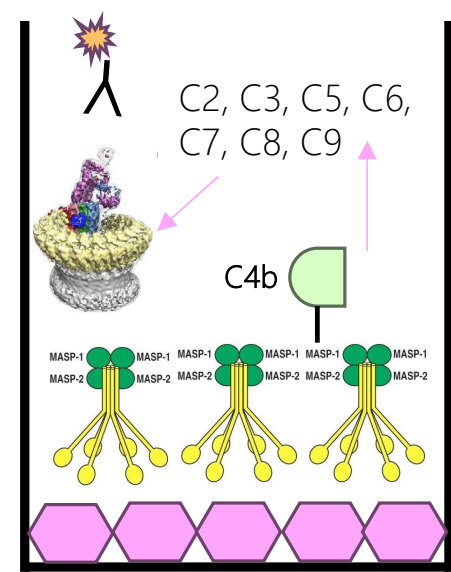


Anti-C4

MBL

Mannaan

LP activation ELISA
up to C5b-9



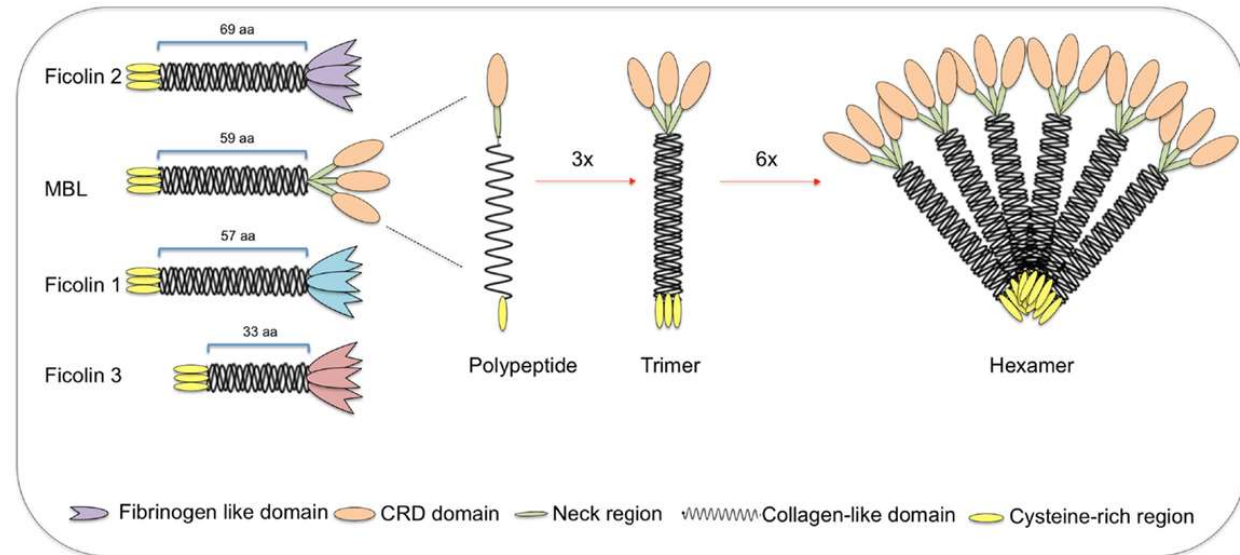
Anti-C5b-9
neoepitooop

MBL

Mannaan

MBL

varianten



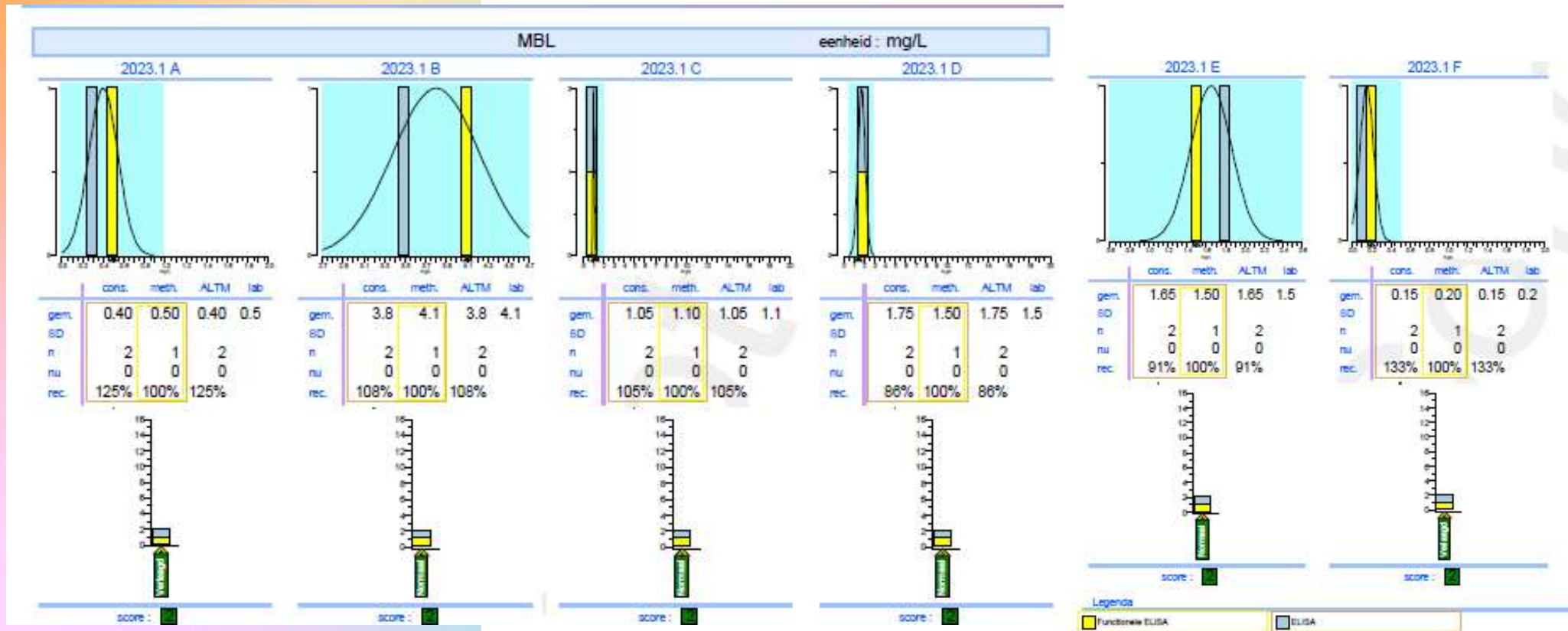
- Mutaties die structuur veranderen
- Mutaties in promotor die serum conc. beïnvloeden

→ 7 meest voorkomende haplotypes

Sommige maken veel MBL (*HYP A*, *LYQ A*)
 Anderen niks (*LYP B*, *LYQ C*, *HYP D*)



MBL conc

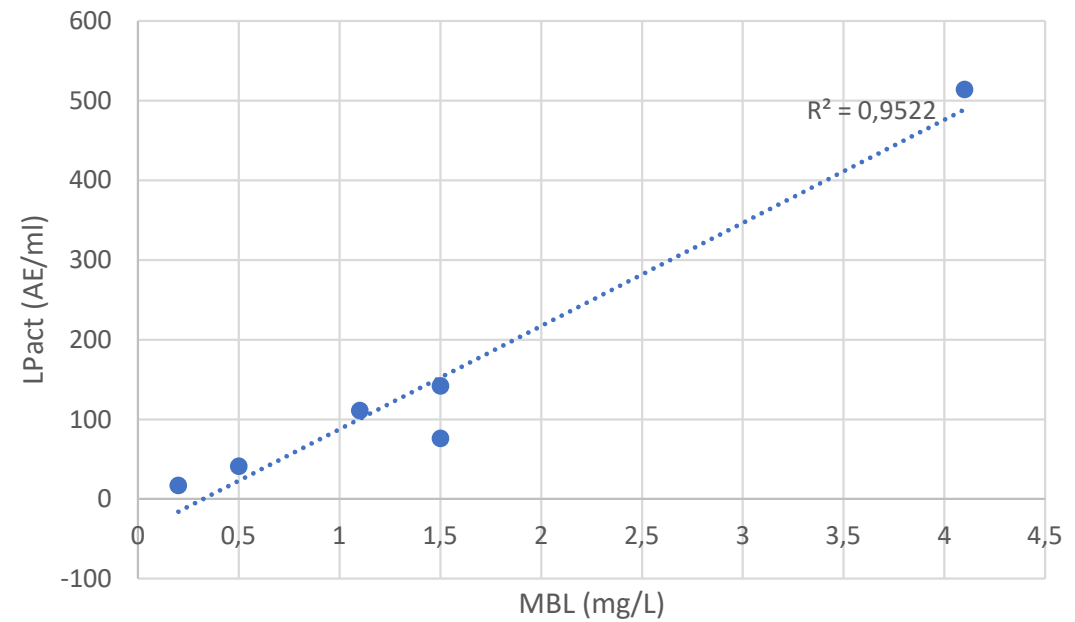




MBL vs LP

Sanquin

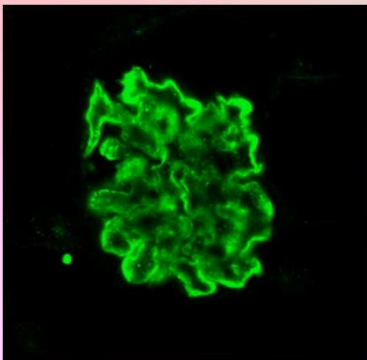
Monster	MBL	LPact (>50)
	mg/L	AE/ml
A	0,5	41
B	4,1	514
C	1,1	111
D	1,5	142
E	1,5	76
F	0,2	17



Complement consumptie

Human genetic deficiencies

C1q -	98% SLE
C4 -	70% SLE
C2 -	10% SLE
C3 -	5% SLE



C3 en C4 (en C1q) serum concentratie

C3 en C4 levels zijn een reflectie van

- Aanmaak (lever, acute fase respons)
- Verbruik (complement activatie)

Normaalwaarde intervallen C3 en C4 zijn breed:

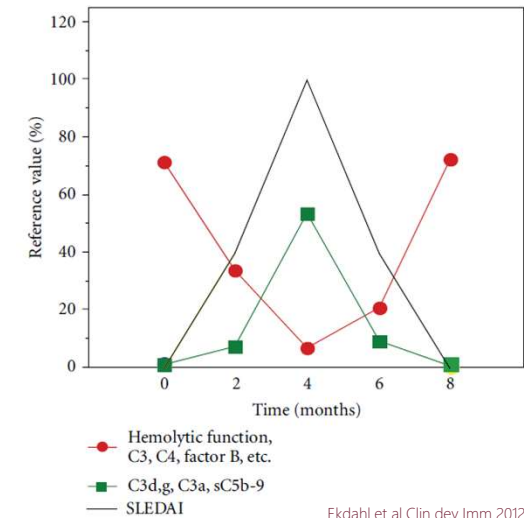
C3 0,9 – 1,8 g/L

C4 0,150 – 0,400 g/L

Een daling kan onopgemerkt blijven!

Verbruik kan gemeten worden met complement activatie producten

C3d, sC5b-9 (C5a, C3a)





Complement concentrations in SLE

Verlaagd

	C1q	C3	C4
<i>Spec</i>	96%	81%	83%
<i>Sens</i>	20%	78%	80%

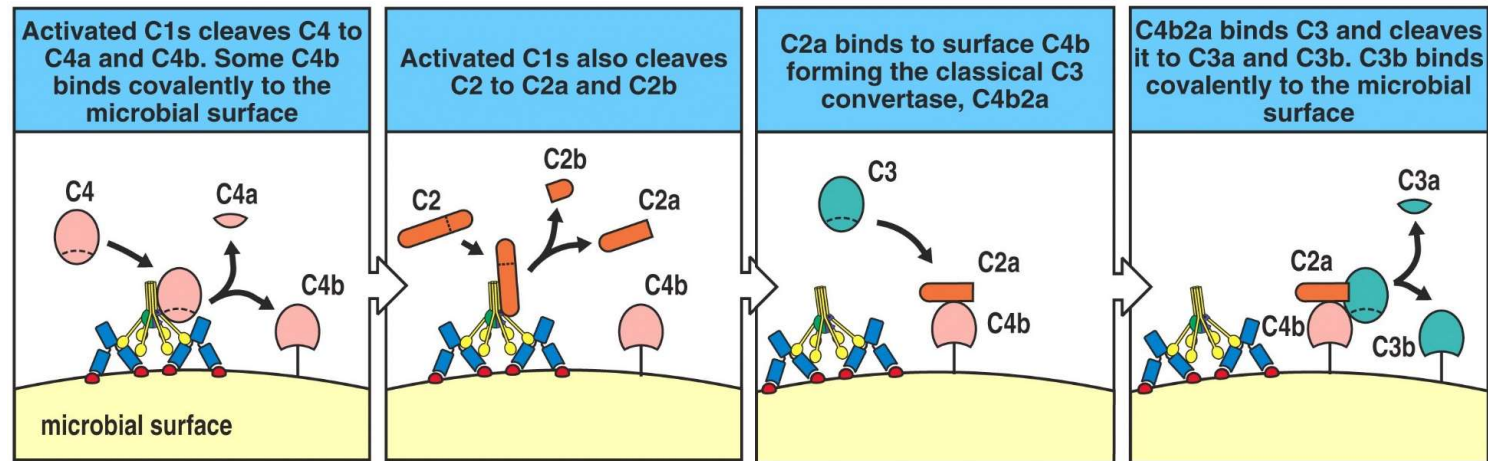


Figure 7-34 part 1 of 2 The Immune System, 2/e (© Garland Science 2005)

Figure 7-34 part 2 of 2 The Immune System, 2/e (© Garland Science 2005)



SLE patient

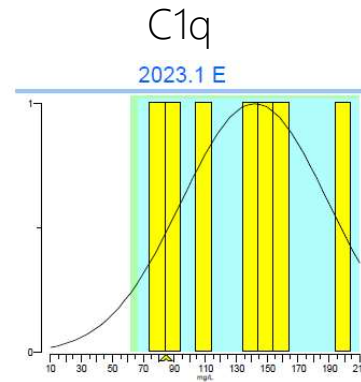
Sample E

				NW	>0,8 (mg/L)	68-133 (%)	67-128 (%)	>50 (AE/ml)	81-127 (AE/ml)	127-201 (mg/L)	0,9-1,8 (g/L)	100-400 (mg/L)
Monster	BD	materiaal	kleur	ISBT	MBL	CH50	AP50	LPact	C1q	(mg/L)	C3	C4
E (vers)	pool	serum		754717	1,48	47	54	43	56	88	0,78	151
E (rondz.)	pool	serum			1,50	55	53	76	54	85	0,77	154

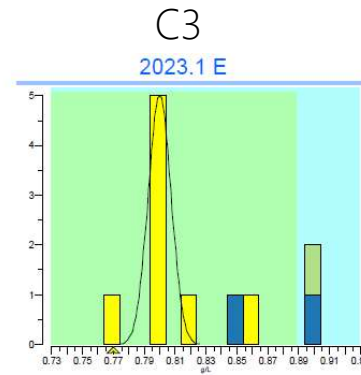
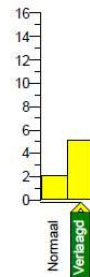


SLE patient

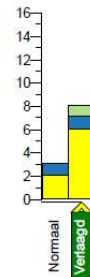
Sample E



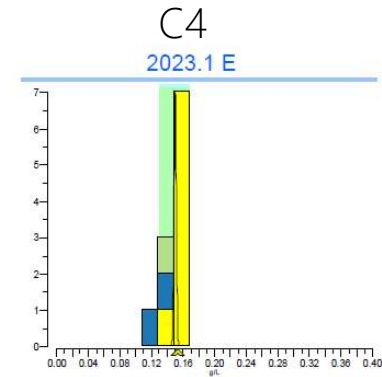
	cons.	meth.	ALTM	lab
gem.	142	142	142	85
SD	47	47	47	
n	7	7	7	
nu	0	0	0	
rec.	60%	60%	60%	



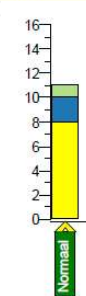
	cons.	meth.	ALTM	lab
gem.	0.80	0.80	0.80	0.77
SD	0.01	0.01	0.03	
n	8	8	11	
nu	2	2	2	
rec.	96%	96%	96%	



score :



	cons.	meth.	ALTM	lab
gem.	0.150	0.150	0.150	0.154
SD	0.001	0.001	0.006	
n	8	8	11	
nu	2	2	1	
rec.	103%	103%	103%	



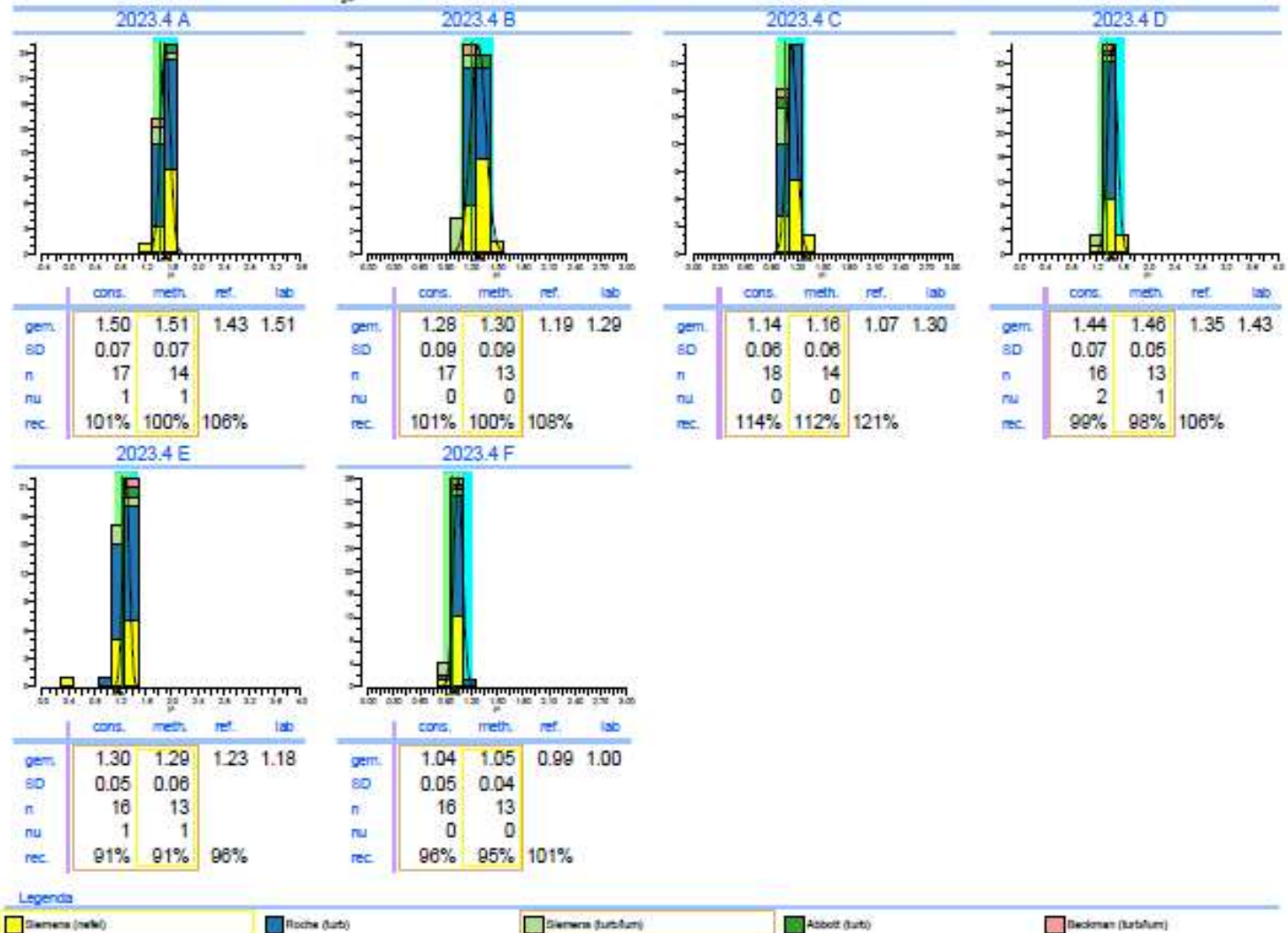
Legenda

- Siemens (nefel)
- Roche



C3

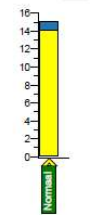
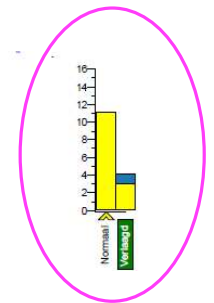
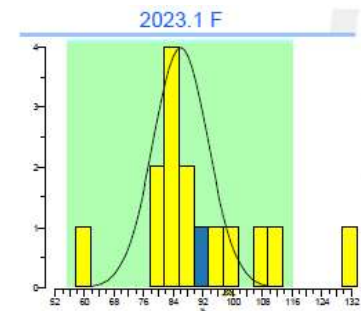
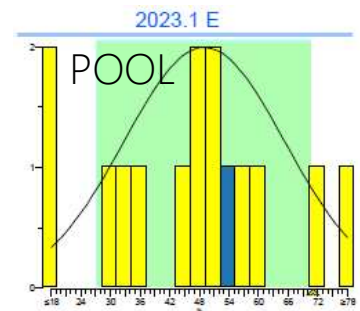
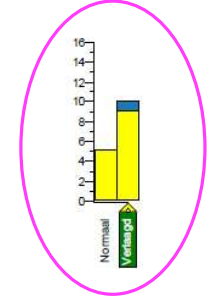
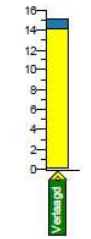
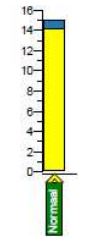
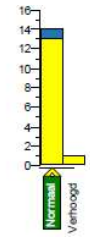
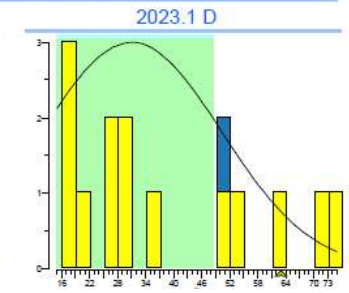
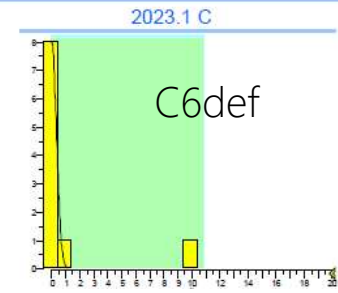
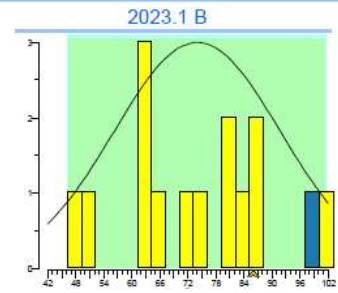
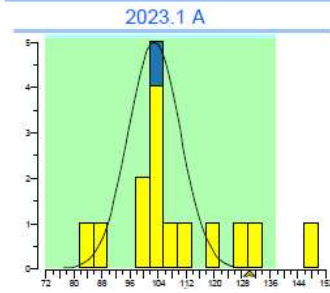
Plasma eiwitten



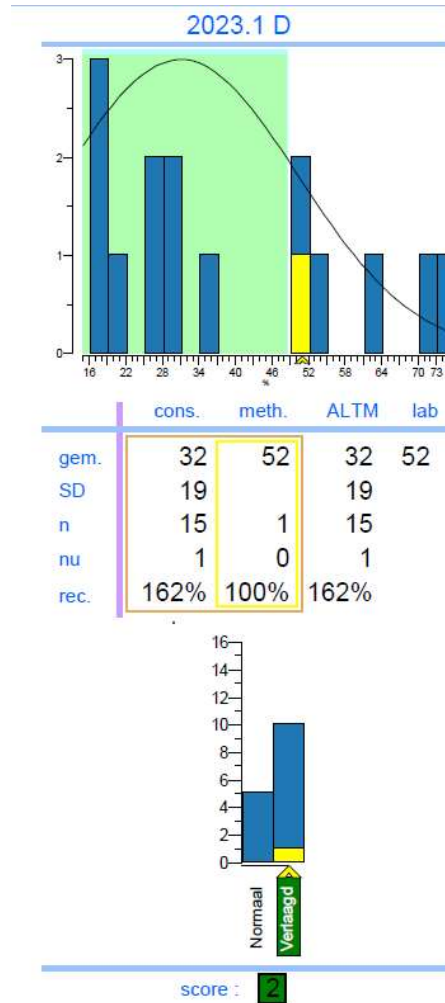


AP 4 HC's

AP eenheid : %



AP



Inlichten aanvragers:

- Wat betekenen die procenten nou precies?
- Als C3 verlaagd is, meer variatie?

Uit de bijsluiter

Performance characteristics

120 sera from blood donors were tested in the AP assay and the normal reference range was calculated. The values were expressed in % of the positive control. See Figure 1 and Table 1. In the study no blood donor was below 10 %.

Figure 1 AP assay.

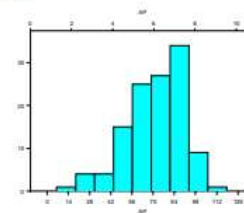
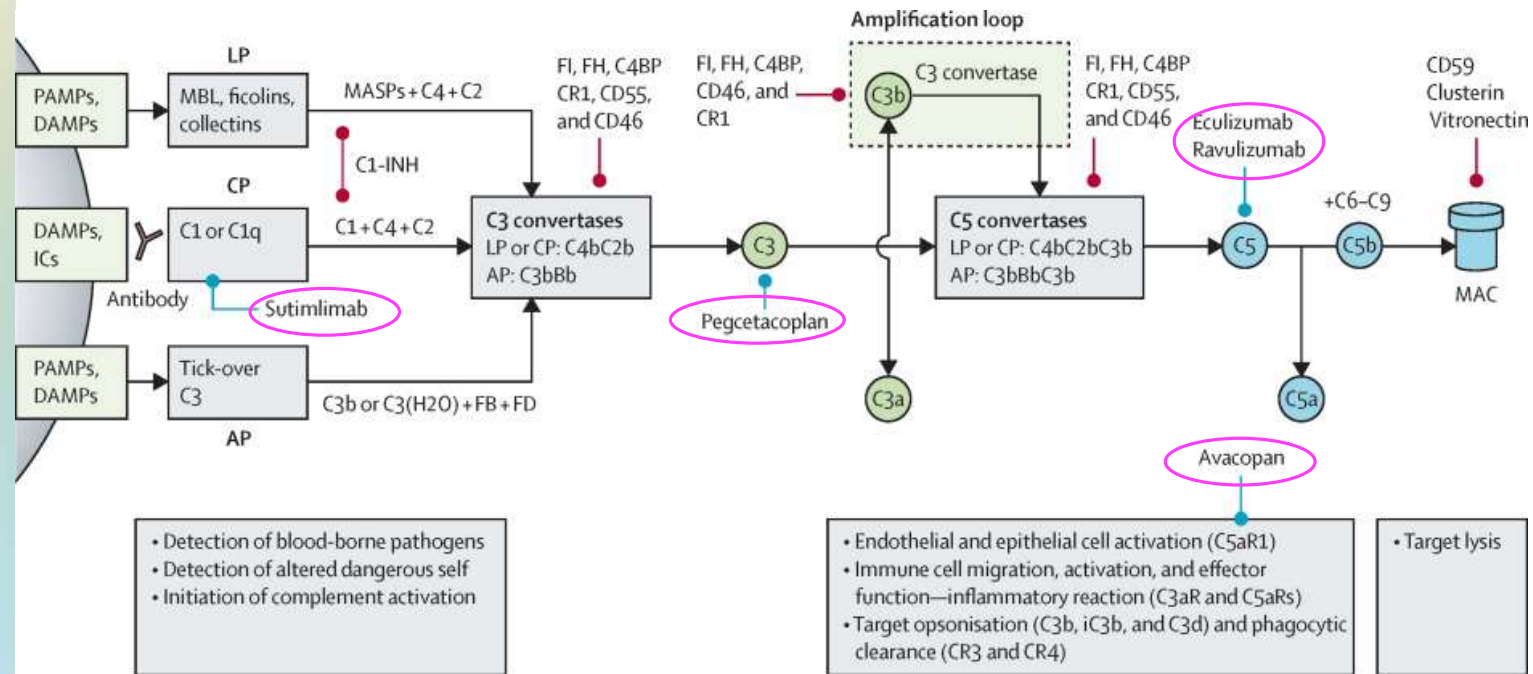


Table 1.

	n	Mean (%)	±2SD (%)	Median (%)
Alternative pathway	120	71	30-113	73



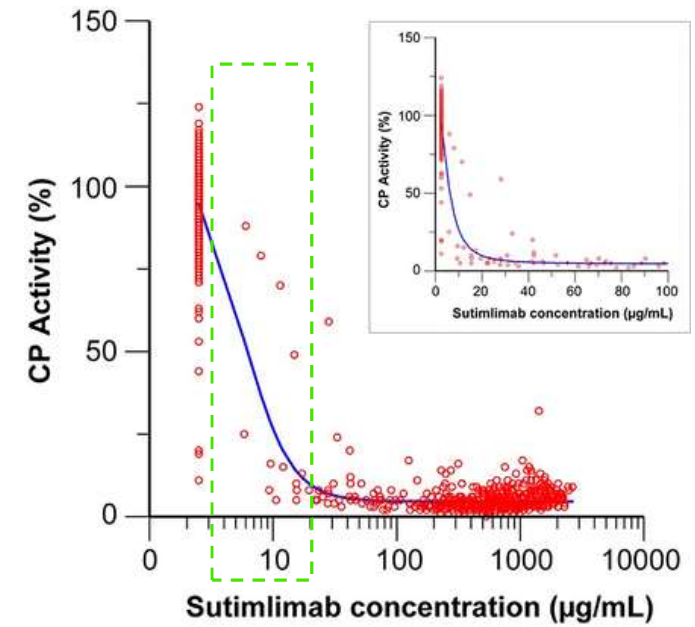
Complement drugs



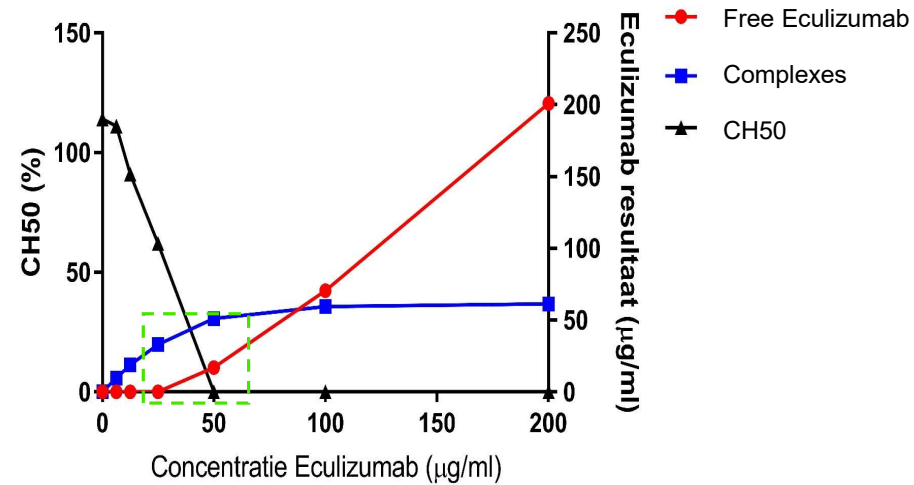
PK/PD en personalized dosing



Sutimlimab = anti-C1s
Eculizumab = anti-C5



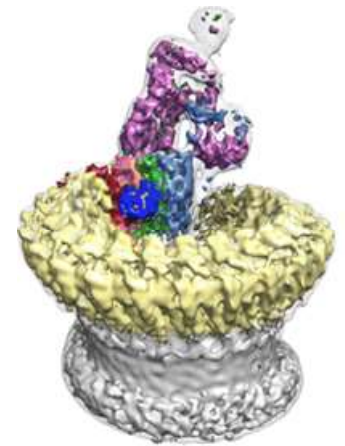
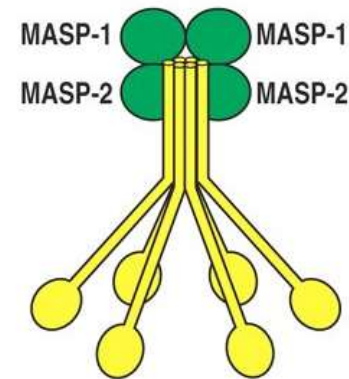
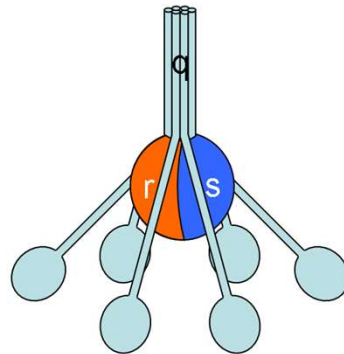
<https://jpet.aspetjournals.org/>





Conclusie

- Ken uw assay in de gebruikte context
- AP assays lijken gevoelig voor variatie bij verlaagde C3 concentraties
- We doen het best goed!!





Sanquin

For Life.